Dynamical Modeling and Analysis of Epidemics

edited by
Zhien Ma & Jia Li

World Scientific

Dynamical Modeling and Analysis of Epidemics

This page intentionally left blank

Dynamical Modeling and Analysis of Epidemics

edited by

Zhien Ma
Xi'an Jiaotong University, China

Jia Li
University of Alabama in Huntsville, USA

World Scientific

NEW JERSEY • LONDON • SINGAPORE • BEIJING • SHANGHAI • HONG KONG • TAIPEI • CHENNAI

Published by

World Scientific Publishing Co. Pte. Ltd.
5 Toh Tuck Link, Singapore 596224
USA office: 27 Warren Street, Suite 401-402, Hackensack, NJ 07601
UK office: 57 Shelton Street, Covent Garden, London WC2H 9HE

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

DYNAMICAL MODELING AND ANALYSIS OF EPIDEMICS

ISBN-13 978-981-279-749-0
ISBN-10 981-279-749-1

Typeset by Stallion Press
Email: enquiries@stallionpress.com

Printed in Singapore.

Preface

The spread of infectious diseases has always been of big concerns and poses a threat to public health, as well as the economic and social developments of the human society. Thus, its prevention and control become extremely important. Quantitative studies on mechanisms of disease transmissions provide a foundation for such prevention and control, and the fundamental aim of *Epidemic Dynamics* is to investigate the transmission dynamics of infectious diseases. It formulates mathematical models, based on the occurrence and progressions of diseases and the surroundings, to characterize the infectious agents, to describe the transmission processes, to analyze origins of the diseases and factors involved in the transmissions, and to predict the prevalence of the diseases and their patterns. With deep understanding and the knowledge that we obtain from the *Epidemic Dynamics* studies, and good estimates of important factors and parameters, prevention and control strategies can be made. *Epidemic Dynamics* can employ well-developed modern dynamic theory to better characterize the inherent patterns and to investigate long-term behavior of disease transmissions. Further qualitative and quantitative studies, and sensitivity analysis on model parameters can help us to make more realistic simulations and reliable transmission prediction which may not be feasible by experiments or field studies. Moreover, the combination of epidemic dynamics, epidemiologic theory, biostatistics, and computer simulations will significantly contribute to further improvement of our knowledge of transmission patterns of epidemics, development of epidemiology, and more effective methods in controlling infectious diseases.

The Mathematical Biology group of Xi'an Jiaotong University led by Professor Zhien Ma, collaborating with Dr. Jia Li, Professor of University of Alabama in Huntsville, USA and Guest Professor of Xi'an Jiaotong University, has been working on the mathematical modeling of infectious diseases and epidemic dynamics since 1995. The Mathematical Biology group of Xi'an Jiaotong University has been assigned and achieved four important national research projects and an international collaborative

project. This book is based on what we have learned and gained throughout the course in our research.

The focus of this book is on the qualitative analysis of mathematical epidemic models. It consists of six chapters. Basic mathematical disease models, the ideas for the modeling, and fundamental concepts and techniques for the model analysis are given in Chapter 1. They are the foundations for beginners. Introductions and more advanced studies on models based on ordinary differential equations, delayed differential equations, impulse differential systems, and structured models, are provided in Chapters 2 to 5, respectively. Models on SARS (severe acute respiratory syndrome), HIV (human immunodeficiency virus) and AIDS (acquired immune deficiency syndrome), and TB (tuberculosis) are introduced and investigated to show the applications of *Epidemic Dynamics* to specific diseases in Chapter 6.

This book aims to lead the reader, who is interested in *Epidemic Dynamics*, from the fundamentals to the research frontier of the filed. It provides references that the authors have collected and the results from their research projects during the past few years. The content of the book is intended to be written as easy-to-digest and comprehensive for the beginner, as well as advanced for the researcher to pursue further development. In this book, an attempt has also been made to give more rigorous descriptions of basic concepts, to emphasize modeling ideas, to introduce widely used and newly developed methods and techniques throughout well-thought and selected models, and to provide useful and detailed biological interpretations of the mathematical conclusions from the models. We believe that this book is a vital reading for applied mathematicians, public health workers, epidemiologists, and graduate students in those disciplines.

Based on planning as a whole, the book was written cooperatively as follows: Chapter 1 by Zhien Ma and Jia Li, Chapter 2 by Jianquan Li, Chapter 3 by Wendi Wang, Chapter 4 by Zhen Jin, and Chapters 5 and 6 by Yicang Zhou. Jia Li did a final edit of the book.

We would like to express our sincere appreciation to Professor Daqian Li, Member of Chinese Academy of Sciences, for his support and Professor Zhongqing Xu for his recommendation. The work of Jia Li was partially supported by U.S. National Science Foundation grant DMS-0412386.

Considering the vast literature, to select suitable materials and references for a book devoted to *Epidemic Dynamics* is a very difficult task. It is certain that many important parts have been missing or omitted, for that we bear full responsibility.

The authors

List of Contributors

Zhien Ma
Department of Applied Mathematics
Xi'an Jiaotong University
Xi'an, 710049
China
E-mail address: zhma@mail.xjtu.edu.cn

Jia Li
Department of Mathematical Sciences
University of Alabama in Huntsville
Huntsville, AL 35899
USA
E-mail address: li@math.uah.edu

Jianquan Li
Department of Applied Mathematics and Physics
Air Force Engineering University
Xi'an, 710051
China
E-mail address: jianqli@263.net

Wendi Wang
School of Mathematics and Statistics
Southwest University
Chongqing, 400715
China
E-mail address: wendi@swu.edu.cn

Zhen Jin
Department of Mathematics
Northern University of China
Taiyuan, 030051
China
E-mail address: jinzhn@263.net

Yicang Zhou
Department of Applied Mathematics
Xi'an Jiaotong University
Xi'an, 710049
China
E-mail address: zhouyc@mail.xjtu.edu.cn

Contents

This page intentionally left blank

Chapter 1

Basic Knowledge and Modeling on Epidemic Dynamics

Zhien Ma and Jia Li

1.1. Introduction

The spread of infectious diseases has always been of concerns and a threat to public health. It has caused serious problems for the survival of human beings and other species, and for the economic and social development of the human society. The Antonine Plague, 165–180 AD, was an ancient pandemic, either of smallpox or measles, brought back to the Roman Empire by troops returning from campaigns in the Near-East. The epidemic invaded the Roman Empire, claimed the lives of two Roman emperors and caused drastic population reduction and economic hardships which led to disintegration of the empire because of disorganization that facilitated invasions of barbarians [Wikipedia (2008)]. In the early 1500s, smallpox was introduced into the Caribbean by the Spanish armies led by Cortez, from where it spread to Mexico, Peru, and Brazil. It is probable that smallpox was one of the factors that resulted in widespread deaths among the Incas. The population of Mexico was reduced from up to 30 million to less than 2 million during a period of 50 years after the Spanish invasion, smallpox being the principal cause of death [Brauer and Castillo-Chavez (2001); Geddes (2006)]. The Black Death (bubonic plague) had spread four times in Europe. It had caused the death of more than 10 000 people every day and a half of the population there in 600 AD, and the death of as much as one-third of the population between 1346 and 1350. The disease recurred regularly in various parts of Europe and, particularly, led to the death of one-sixth of the population in London between 1665 and 1666. The last outbreak of the bubonic plague happened between 1720 and 1722 in France,

which had taken the lives as much as a half of the population in Marseilles, 60% nearby Toulon, 44% in Arles, and 30% in Aix and Avignon [Brauer and Castillo-Chavez (2001); Snell (2008)].

The fighting with infectious diseases has had a long history, and great progresses had been achieved, especially during the 20th century. While smallpox outbreaks have occurred from time to time for thousands of years, the disease is now eradicated after a successful worldwide vaccination program [HHS (2008)]. In 1991, World Health Assembly passed a resolution to eliminate leprosy as a public health problem by the year 2000, where elimination of leprosy as a public health problem is defined as a prevalence rate of less than one case per 10 000 persons. The target was achieved on time [WHO (2008a)]. Poliomyelitis (polio) is a highly infectious viral disease, which mainly affects young children. When the Global Polio Eradication Initiative was launched in 1988, wild poliovirus was endemic in more than 125 countries on five continents, paralyzing more than 1000 children every day. As a result of the Global Polio Eradication Initiative — the single largest, internationally coordinated public health project to date — by the end of 2006, only four countries remained which had never interrupted endemic transmission of wild poliovirus (Nigeria, India, Pakistan, and Afghanistan). In 2006, less than 2000 cases were reported [WHO (2008c)]. There are some other infectious diseases, such as diphtheria, measles, pertussis, and tetanus (lockjaw), that can be serious and fatal, but have been significantly under control in many countries.

While the great achievement and progresses in the prevention and control of infectious diseases are promising and inspiring, there is a long way to go to completely eradicate infectious diseases in the world.

An estimated 1.5 million people died from tuberculosis in 2006 [WHO (2007)]. Malaria is by far the world's most important tropical parasitic disease. Approximately, 40% of the world's population, mostly those living in the world' poorest countries, are at risk of malaria. Every year, more than 500 million people become severely ill with malaria, and between 1 and 1.5 million people die from it. Malaria kills more people than any other communicable disease except tuberculosis [WHO (2008b)]. Over 22 million people have died from AIDS. The United Nations estimates that, currently, there are 14 million AIDS orphans and that there will be 25 million by 2010 [UNTIL (2008)].

To prevent and to control infectious diseases more effectively, it is important to first fully understand the mechanism of the spread and the

transmission dynamics of the diseases, and then provide useful predictions and guidance so that better strategies can be established.

The research in infectious diseases can be basically classified as descriptive, analytic, experimental, and theoretic. Epidemic dynamics study is an important theoretic approach to investigate the transmission dynamics of infectious diseases. It formulates mathematical models to describe the mechanisms of disease transmissions and dynamics of infectious agents. The mathematical models are based on population dynamics, behavior of disease transmissions, features of the infectious agents, and the connections with other social and physiologic factors. Through quantitative and qualitative analysis, sensitivity analysis, and numeric simulations, mathematical models can give us good understanding of how infectious diseases spread, discover general principles governing the transmission dynamics of the diseases, and identify more important and sensitive parameters, to make reliable predictions and provide useful prevention and control strategies and guidance.

Compared to the classic statistic analysis in epidemic research, employing the well-developed modern theory of dynamic systems and utilizing high-speed computing facilities, epidemic dynamics studies provide deeper understanding of transmission mechanisms and global analysis of transmission dynamics. Further qualitative and quantitative investigations, and sensitivity analysis on model parameters can help us to make more realistic simulations and reliable long-term transmission prediction which may not be feasible by experiments or field studies. Moreover, the combination of epidemic dynamics, epidemiologic theory, biostatistics, and computer simulations will significantly contribute to further improvement of our knowledge of transmission patterns of epidemics, development of epidemiology, and more effective methods in controlling infectious diseases.

While mathematical modeling of infectious diseases can be traced back to 1760 when Bernoulli used mathematical models for smallpox [Bernouilli (1760)], the research on infectious diseases, using deterministic mathematical models, actually began in the 20th century. Hamer formulated a discrete-time model for the spread of measles in 1906. A physician, Dr. Ross, used a differential equation model to describe the transmissions of malaria between human beings and mosquitoes in 1911, and determined that there exists a threshold of the size of mosquitoes below which the spread of malaria can be controlled. It was because of his outstanding contributions in the research of the transmission dynamics of malaria, Dr. Ross was awarded his second Nobel Prize in medicine. Kermack and

McKendrick formulated a well-known and well-recognized SIR (susceptible–infective–recovered) compartmental model, in 1926, to study the outbreak of Black Death in London during the period of 1665–1666, and the outbreak of plague in Mumbai in 1906. They later, in 1932, formulated an SIS compartment model and, based on the investigation of this model, formally introduced the concept of thresholds that determines whether a disease spreads in a given population [Kermack and McKendrick (1932)]. The concept of thresholds established the fundamentals of the theory of epidemic dynamics. More intensive studies on epidemic dynamics took place after the middle of the 20th century. A remarkable and landmark publication is the book by Bailey with the first edition in 1957, and the second edition in 1975.

More developments and progresses have been particularly made during the past 20 years. Massive mathematical models have been formulated and developed to study various infectious diseases, ranging from more theoretic, general ones [Waltman (1974); Burnett and White (1974); Hoppensteadt (1975); Frauenthal (1980); Anderson and May (1982); Evans (1982); Webb (1985); Kranz (1990); Busenberg and Cooke (1993); Capasso (1993); Isham and Medley (1996); Daley and Gani (1999); Diekman and Heesterbeek (2000)] to more specific ones especially for measles, malaria, tuberculosis, sexually transmitted diseases (STD), or AID/HIV [Hethcote and Yorke (1984); Hethcote (2000); Hyman and Stanley (1988); Brauer and Castillo-Chavez (2001); Brauer *et al.* (2008)]. The modeling of infectious diseases has shown rich dynamic behavior and phenomena.

From the perspective of transmission mechanisms, those models have included a variety of factors. For example, contact, vertical, and vector transmissions have been considered. Models incorporating incubation or latent periods, isolations, quarantines, vaccination with or without immunity loss, and infection within groups or between groups, or different population dynamics that epidemic modeling bases on have been formulated. More sophisticated models with age structure, infection-age structure, or spatial structure have also been studied.

From the perspective of mathematical structures of the models, while most deterministic models are based on ordinary differential equations, first- and second-order partial differential equations and delayed differential equations have been used for age-structured, spatial-structured, or reaction–diffusion models, and models with latent or incubation periods, respectively. Impulse differential systems have also been applied to evolution processes with a short-term perturbation.

As the deterministic epidemic models based on dynamic systems are developed and applied extensively, the functional extreme value problems from the theories of optimal control and optimization have been used for finding the best strategies in prevention and control of disease transmissions. Moreover, stochastic epidemic modeling and network epidemiologic models have also been employed.

Mathematical models can also be categorized, based on the described diseases, populations, and environments, as linear, nonlinear, autonomous, or nonautonomous models. There exist, moreover, modeling variations in each category.

The analysis of deterministic mathematical models has been focused on the wellposedness of the models and their solutions, persistence of diseases, existence and stability of steady states, which characterize the diseases spreading or being endemic, existence and stability of periodic solutions, which describe the oscillations of disease transmissions, and occurrence of bifurcations or chaotic behavior.

In earlier deterministic mathematical models for epidemic transmissions, a constant population size was usually assumed. It took the advantage of the tractability of the mathematical analysis. Those models are also good approximations for short-term predictions in closed populations or in the cases where the birth and death are relatively balanced and/or the disease-induced deaths are negligible. As progresses are being made in epidemic modeling, more advanced mathematical tools have been developed and are ready to be applied. More realistic mathematical models for infectious diseases have been dramatically developed lately. More specifically, (1) factors and structures, such as latent periods and time delays, age, infection-age, gender, other physiologic structures, and effects of isolations, quarantine, vaccination, or treatment, have been further included; (2) the dimensions of the models have been greatly increased, which allows for studying epidemic transmission dynamics between populations and species in depth; (3) more thorough and detailed investigations have been conducted on specific infectious diseases, such as AIDS/HIV and vector-borne diseases. Nevertheless, as the epidemic models become closer to reality and more biological and social factors are included, the model features and behavior become more complex. Hence, more advanced mathematical techniques, such as the theories of bifurcation, chaos, degree, and semigroup, have been broadly employed and utilized in the model analysis, and high-speed computers have also been used for more complicated simulations.

The theory of epidemic dynamics is so rich that it is impossible for us to cover all of its aspects. We only introduce basic mathematical disease models, the ideas for modeling, and fundamental concepts and techniques for the model analysis in this chapter. More sophisticated models and techniques will be gradually provided in later chapters.

1.2. The Fundamental Forms of Epidemic Models

1.2.1. *Two fundamental dynamic models of epidemics*

Dynamic models for infectious diseases are mostly based on compartment structures that were initially proposed by Kermack and McKendrick (1927, 1932) and developed later by many other biomathematicalians.

To formulate a dynamic model for the transmission of an epidemic disease, the population in a given region is often divided into several different groups or compartments. Such a model describing the dynamic relations among these compartments is called a **compartment model**.

1.2.1.1. *Kermack–Mckendrick SIR compartment model*

In the compartment model studied by Kermack and Mckendrick in 1927, the population is divided into three compartments: a **susceptible compartment**, labeled S, in which all the individuals are susceptible if they contact with a disease; an **infected compartment**, labeled I, in which all the individuals are infected by the disease and infectious; and a **removed compartment**, labeled R, in which all the individuals are removed or recovered from the infection. Denote the numbers of individuals in the compartments S, I, and R, at time t, as $S(t)$, $I(t)$, and $R(t)$, respectively. The following three assumptions were made by them:

1. The disease spreads in a closed environment; that is, there is no emigration nor immigration, and neither birth nor death in the population, so that the total population remains a constant K for all t, that is, $S(t) + I(t) + R(t) \equiv K$.
2. The number of susceptibles who are infected by an infected individual per unit of time, at time t, is proportional to the total number of susceptibles with the proportional coefficient (**transmission coefficient**) β, so that the total number of newly infectives, at time t, is $\beta S(t)I(t)$.
3. The number removed (recovered) individuals from the infected compartment per unit time is $\gamma I(t)$ at time t, where γ is the recovery rate coefficient, and the recovered individuals gain permanent immunity.

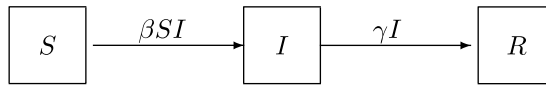


Fig. 1.1. Flow chart of the SIR model without vital dynamics.

Based on these assumptions, the flow chart of the model is shown in Fig. 1.1, and the corresponding model equations are given in the system

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - \gamma I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I. \end{aligned} \tag{1.1}$$

Because the equation for variable R is decoupled from the first two equations of system (1.1), we only need to consider the system

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - \gamma I. \end{aligned} \tag{1.2}$$

While system (1.2) is oversimplified, useful information can still be obtained as shown below.

From Eq. (1.2), we have

$$\frac{\mathrm{d}I}{\mathrm{d}S} = -1 + \frac{\rho}{S}, \tag{1.3}$$

where $\rho = \gamma/\beta$. The solution curves of Eq. (1.3) in the SI phase plane are shown in Fig. 1.2. All curves of $I(S)$ reach the maximum when $S = \rho$.

It follows from Fig. 1.2 that there is a threshold $S = \rho$ such that if the initial number of susceptibles $S(0) = S_0 > \rho$, the number of infectives increases; if $S(0) = S_0 < \rho$, the number of infectives decreases. Define

$$R_0 = \beta \frac{1}{\gamma} S_0 = \frac{S_0}{\rho},$$

then the epidemic spreads when $R_0 > 1$ and dies out when $R_0 < 1$.

We note that γI is the number of recovered individuals who move from the infected compartment I, per unit of time, at time t. Hence after the period of time $1/\gamma$, all the infectives $I(t)$ recover. Therefore, $1/\gamma$ is actually

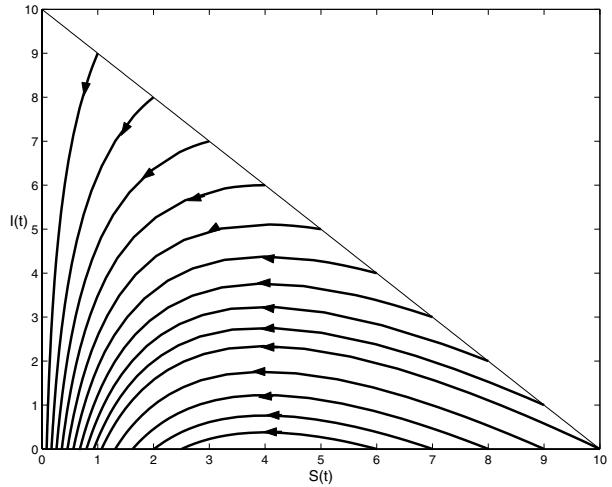


Fig. 1.2. The solution orbits of Eq. (1.3) are shown in the SI plane, where $\gamma = 4$ and $\beta = 1$.

the mean duration of infection, and $R_0 = \beta S_0/\gamma$ is the number of newly infectives infected by an infected individual during the whole infection period when all of the individuals in the population are initially susceptible. This quantity R_0 determines the thresholds for disease transmissions. The number of infectives decreases if $R_0 < 1$ and increases if $R_0 > 1$. Therefore, to control the spread of an epidemic, one of the key factors is to estimate the value of R_0 and then reduce it to < 1.

The estimation of R_0 is not an easy task in practice because it involves biological parameters some of which may not be easily measured. We introduce an approximate method and use the model governed by system (1.1) to illustrate the method as follows.

The solution of Eq. (1.3) with the initial value (S_0, I_0) is

$$I - I_0 = -(S - S_0) + \rho \ln \frac{S}{S_0}. \tag{1.4}$$

It follows from the second equation of (1.2) that $I(t) \to 0$, as $t \to \infty$, if $R_0 < 1$. Then since $S(t)$ is monotone decreasing and bounded below, $\lim_{t\to\infty} S(t) = S_\infty$. Writing $S_0 + I_0 = K$ and taking the limit in (1.4), we have

$$K - S_\infty + \rho \ln \frac{S_\infty}{S_0} = 0. \tag{1.5}$$

It is easy to verify that there is one and only one positive real root S_∞ to Eq. (1.5). It follows also from Eq. (1.5) that

$$\rho = \frac{K - S_\infty}{\ln S_0 - \ln S_\infty}. \tag{1.6}$$

Suppose that S_0 and S_∞ are measured clinically. Then we can determine the quantity ρ by (1.6) and then R_0 from $R_0 = S_0/\rho$. If the average infection period $1/\gamma$ is estimated, then the transmission coefficient β can be also determined by $\beta = \gamma/\rho$.

For example, the village of Eyam near Sheffield, England suffered an outbreak of bubonic plague in 1665–1666 [Brauer and Castillo-Chavez (2001)]. Preserved records show that the initial numbers of susceptibles and infectives were 254 and 7 in the middle of May 1666, respectively. and only 83 persons survived in the middle of October 1666. Hence, the parameters in (1.6) can be estimated as $S_0 = 254$, $S_\infty = 83$, and $K = 261$, so that $\rho = 153$ and $R_0 = S_0/\rho = 1.66$. The records also show that the infective period was 11 days such that

$$\beta = \frac{\gamma}{\rho} = \frac{1}{11} \times \frac{1}{153} = 0.000594(1/\text{day}) = 0.0178(1/\text{month}).$$

It follows from (1.3) that the number of infectives I reaches the maximum as $S = \rho$. Thus from (1.4), we estimate the number of the infectives at the high peak of the epidemic to be

$$\begin{aligned} I_m &= I_0 + S_0 - \rho + \rho \ln \frac{\rho}{S_0} \\ &= K - \rho(1 + \ln R_0) = 261 - 153(1 + \ln 1.66) = 31(\text{persons}). \end{aligned}$$

1.2.1.2. *Kermack–Mckendrick SIS compartment model*

For viral diseases, such as influenza, measles, and chickenpox, the recovered individuals, in general, gain immunity to the same virus. Then the SIR model described in Sec. 1.2.1.1 is applicable. However, for bacterial diseases, such as encephalitis, and gonorrhea, the recovered individuals gain no immunity and can be reinfected. To study the transmission dynamics of these diseases, Kermack and Mckendrick (1932) proposed an SIS model. The flow chart of an SIS model is shown in Fig. 1.3, and the corresponding

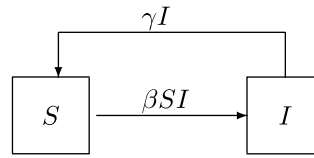


Fig. 1.3. Flowchart for an SIS model without vital dynamics.

model equations are given:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta SI + \gamma I, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI + \gamma I. \end{aligned} \tag{1.7}$$

Since $S + I \equiv K$, system (1.7) can be reduced to

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \beta(K - S)(\rho - S), \quad \text{where } \rho = \frac{\gamma}{\beta}. \tag{1.8}$$

Then it is easy to see that when $\rho \geq K$, Eq. (1.8) has only one equilibrium $S = K$, which is globally asymptotically stable, such that $S(t)$ with any initial value $S_0 \in (0, K)$ increases monotonically to K, and $I(t)$ decreases monotonically to zero. Hence the epidemic dies out.

When $\rho < K$, Eq. (1.8) has two positive equilibria, $S = K$ and $S = \rho$. $S = K$ is unstable and $S = \rho$ is globally asymptotically stable. Solution $S(t)$ starting from any initial value $S_0 \in (0, K)$ tends to ρ as $t \to \infty$, and $I(t)$ tends to $K - \rho$. In this case, the epidemic persists and the infectives eventually approach $(1 - \rho)$. Hence the disease becomes endemic.

Let $R_0 = K/\rho = \beta K/\gamma$. Then it is easy to see that this R_0 has the same biological meaning as the R_0 in the SIR model in Sec. 1.2.1.1.

1.2.2. *Fundamental forms of compartment models*

Fundamental forms of epidemic compartment models can be classified as the following types. We list them by their flow charts.

1.2.2.1. *Models without vital dynamics*

When a disease, such as influenza, measles, rubella, or chickenpox, spreads in a population rapidly, for a relatively short time, usually the vital dynamic

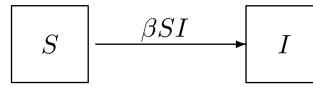


Fig. 1.4. Flow chart of the SI model without vital dynamics.

factors, such as birth and natural death of the population, can be neglected in the models.

Models without latent periods. In these models, infected individuals become infectious immediately.

SI model In this model, the infectives cannot be recovered from infection. The flow chart of the transmission dynamics is shown in Fig. 1.4.

SIS model The infectives are recovered but gain no immunity after recovery. The flow chart is shown in Fig. 1.3.

SIR model The infectives obtain permanent immunity to the disease after recovered from infection. The flow chart is shown in Fig. 1.1.

SIRS model The recovered individuals have only temporary immunity after they recovered from infection. The immunity will be lost eventually. If the number of individuals who lose their immunity per unit time is $\delta R(t)$ at time t, they enter the susceptible compartment again. The flow chart is shown in Fig. 1.5, where $1/\delta$ is the mean immunity period.

SIRI model For some diseases, such as tuberculosis, infectives cannot get permanent recovery after infection. The individuals who recover temporarily may get recurrence under some conditions, say, tiredness. Suppose that the recurrence rate coefficient is δ, then the flow chart of the SIRI model is shown in Fig. 1.6.

Remark 1.1. The difference between the SIRS and the SIS models is the following. For the SIS model, the individuals of infectives become susceptible again immediately after they are recovered from the infection,

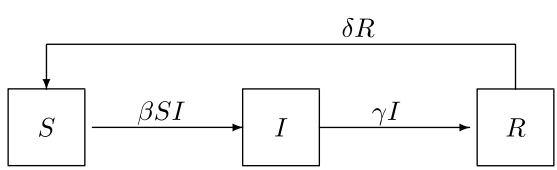


Fig. 1.5. Flow chart of the SIRS model without vital dynamics.

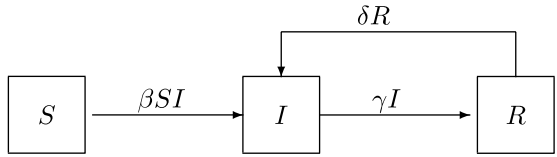


Fig. 1.6. Flow chart of the SIRI model without vital dynamics.

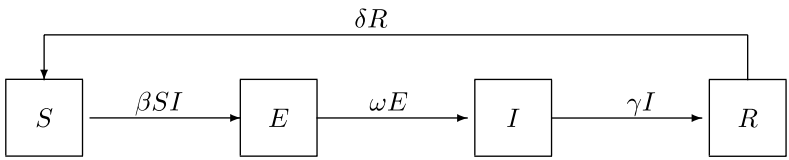


Fig. 1.7. Flow chart for the SEIRS model without vital dynamics.

but for the SIRS model, the recovered individuals are not susceptible to the same disease until they lose their immunity.

Models with latent periods. In these models, an exposed compartment, in which all of the individuals have been infected but have not yet infectious, is introduced. Let $E(t)$ denote the number of individuals in the exposed compartment at time t. Corresponding to the above models without latent periods, we may introduce SEI, SEIS, SEIR, and SEIRS models with latent periods, respectively. For example, the flow chart in Fig. 1.7. illustrates an SEIRS model with a latent period, where ω is the progression rate coefficient for individuals from compartments E to I, such that $1/\omega$ is the mean latent period.

1.2.2.2. *Models with vital dynamics*

Constant population size. If we assume that the birth and death rates of a population are equal during the epidemic period of a disease, and that there is no disease-induced death, then the population size in a closed environment keeps constant, denoted by K. Two examples for this case are given below:

SIR model without vertical transmission In this model, we assume that the disease is not inherited from parents to their new generations, so that all the newborns are susceptible. The corresponding flow chart of the model is shown in Fig. 1.8.

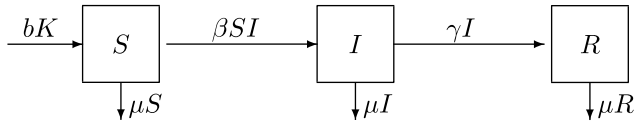


Fig. 1.8. Flow chart of the SIR model without vertical transmission.

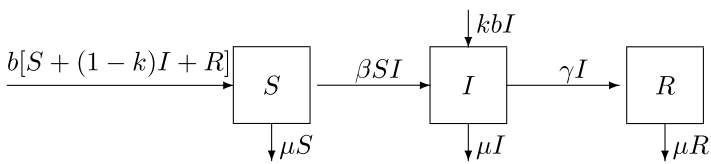


Fig. 1.9. Flow chart of the SIR model with vertical transmission.

SIR model with vertical transmission For many diseases, such as AIDS, hepatitis B, and hepatitis C, newborns from the infected individuals can be infected as well. Such transmission is called **vertical transmission**. Suppose that a fraction, k, of newborns is infected, and the rest is only susceptible to the disease. Then the flow chart of the model is shown in Fig. 1.9.

Variable population size. If the birth and death rates of a population are different, there is a migration to the population, or there is a disease-induced death to the population, then the population size varies. We give two examples as follows:

SIS model with vertical transmission, input, output, and disease-induced death The flow chart of the model is shown in the Fig. 1.10, where b is the birth rate coefficient, μ the natural death rate coefficient, α the coefficient of death rate caused by the disease, A the input rate of the total population, B the output rate coefficient of the susceptibles and the infected, and the other coefficients are the same as before.

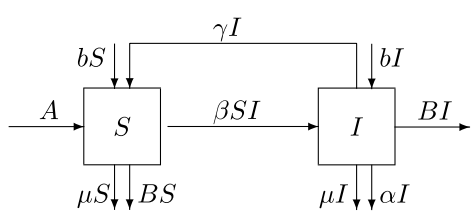


Fig. 1.10. Flow chart of the SIS model with vertical transmission, input, output and disease-induced death.

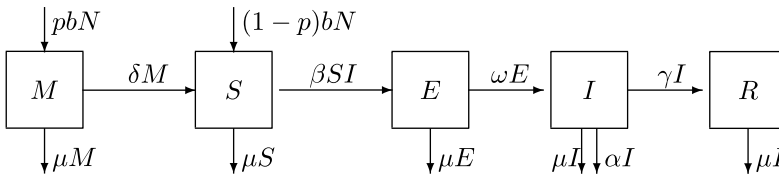


Fig. 1.11. Flow chart of the MSEIR model with passive immunity.

MSEIR model with passive immunity Here we introduce a new compartment M, in which all newborns have passive immunity, which means that the newborns have several months congenital immunity coming from their maternal antibodies, but they become susceptible after these months. Suppose that the fraction of newborns with passive immunity is p such that the mean period of passive immunity is $1/\delta$. The flow chart of the corresponding model is shown in Fig. 1.11.

1.3. Basic Concepts of Epidemiologic Dynamics

1.3.1. *Adequate contact rate and incidence*

An infectious diseases is, in general, transmitted through direct contacts. The number of individuals contacted by an infective per unit of time is called a **contact rate** of the infection, denoted by $U(N)$. It usually depends on the population size N in a given environment. If the individuals contacted by an infective are susceptible, they may be infected. Suppose that the probability of infection by each contact is β_0. Then the function $\beta_0 U(N)$ is called an **adequate contact rate**, which describes the infection strength of the infectives and usually depends on the toxicity of the virus or bacterium and the situation of the environment. Because diseases are only transmitted to susceptibles by contacting with infectives, and the fraction of the susceptibles in the population is S/N, the mean adequate contact rate of an infected individual to a susceptible is $\beta_0 U(N)S/N$. This rate is called an **infection rate**. Then the total new infectives infected by all individuals in the infected compartment, per unit of time, at time t is $\beta_0 U(N)SI/N$, which is called an **incidence** of the disease.

There are two types of incidence often used in disease modeling:

If $U(N) = kN$, that is, the contact rate is proportional to the total population size, the incidence is $\beta S(t)I(t)$, where $\beta = \beta_0 k$ is called the **transmission coefficient**. This type of incidence is called **bilinear incidence** or **simple mass action incidence**.

If $U(N) = k'$, that is, the contact rate is a constant, in this case, the incidence becomes $\beta SI/N$, where $\beta = \beta_0 k'$, and it is called **standard incidence**. For instance, in modeling of STDs in most circumstances, the standard incidence is often used, due to the fact that the number of sexual contacts per individual is approximately constant.

As Anderson and May (1986) pointed out, the standard incidence may be more suitable for human beings, or animals who live in groups. The incidence formed by $\beta N^{\alpha} SI/N$ was used in modeling of five types of infectious diseases in a human community which has 1000 to 400 000 people. Their results showed that α was estimated as between 0.03 and 0.07 [Anderson and May (1982, 1986)], closer to be 0 rather than 1. This study shows that, for many infectious diseases, the size of a human population where a disease is transmitted has little effects to the incidence. Hence the standard incidence is more suitable than the bilinear form for diseases transmitted in human populations, although the incidence $\beta N^{0.05} SI/N$ was used and its suitability was confirmed in [Anderson and May (1982)].

The so-called saturation contact rate, $U(N) = \alpha N/(1 + \omega N)$, is also used, which is between the proportional and constant contact rates [Dietz (1982)]. When the population size N is small, function $U(N)$ is close to $U(N) = \alpha N$, and it tends to the saturation value α/ω for large N. Moreover, Heesterbeek and others considered some stochastic factors in the contacts and proposed the following form of contact rate: $U(N) = \alpha N/(1 + bN + \sqrt{1 + 2bN})$ [Heesterbeek and Metz (1993)]. All of the contact rates listed above satisfy the following conditions:

(H_1): $U(N)$ is a nonnegative nondecreasing continuous function as $N \geq 0$ and is continuously differentiable for $N > 0$.

(H_2): $D(N) = U(N)/N$ is a nonincreasing continuously differentiable function as $N > 0, D(0^+) \neq 0$ and $U'(N) + |D'(N)| \neq 0$.

Therefore, we can also consider a contact rate in a more general form $U(N)$, and assume that it satisfies conditions H_1 and H_2, and the saturation condition: $\lim_{N \to +\infty} U(N) = U_0$.

To describe transmission dynamics of diseases in more details, and understand mechanism of transmissions of diseases, other nonlinear incidences are also proposed. These incidences are more plausible for some special cases. Capasso and Serio (1978) used a saturated incidence of the form of $\beta IS/(1 + \beta\delta I)$, Liu and his coworkers (1986, 1987) proposed nonlinear incidences of the form of $kI^p S/(1 + \alpha I^q)$ and $\beta I^p S^q$. More generalized

incidences $\beta g(I)S$ and $\beta g(I)S^p/N$ were also used [Wang (2006a); Hethcote and van den Driessche (1991); Alexander and Moghadas (2004, 2005)].

In short, what type of incidence is more suitable and to be chosen, when we investigate a specific epidemic, depend on the disease and the environment, and is determined by real data we obtained. Many forms of functional responses used in the studies of population dynamics may inspire us to construct different forms of contact rates for various diseases and environments.

1.3.2. *Basic reproductive number and modified reproductive number*

1.3.2.1. *Basic reproductive number*

We have seen a very important number, R_0, in the study of Kermack–Mckendrick SIR and SIS models in Sec. 1.2.1. A disease dies out if $R_0 < 1$ and spreads if $R_0 > 1$. To better understand this number R_0, we first provide the following two examples, through which we also introduce a qualitative method which is often used in planar differential systems for disease transmission dynamics.

Example 1.1. Consider the SIR model demonstrated in Fig. 1.8 in Sec. 1.2.2. The corresponding model is

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= bK - \beta SI - \mu S, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - \mu I - \gamma I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R, \end{aligned} \tag{1.9}$$

where we assume $b = \mu$. Since the variable R is not included in the first two equations of (1.9), and we are only interested in the spread of the disease, we only investigate the system consisting of the first two equations

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu K - \beta SI - \mu S := P(S, I), \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= (\beta S - \mu - \gamma)I := Q(S, I), \end{aligned} \tag{1.10}$$

where $(S, I) \in D = \{(S, I) : S > 0, I \geq 0, S + I \leq K\}$.

Equilibria of system (1.10) can be solved by letting the right side of each of the equations equal zero, so that possible equilibria of the system

(1.10) are

$$E_0(K,0) \quad \text{and} \quad E_1\left(\frac{\mu+\gamma}{\beta}, \frac{\mu[\beta K-(\mu+\gamma)]}{\beta(\mu+\gamma)}\right).$$

We then discuss the dynamics of these equilibria as follows:

(1) Assume $\beta K/(\mu+\gamma) < 1$. Then there is only one equilibrium E_0 in region D. The Jacobian matrix of (1.10) at this equilibrium, E_0, is given by

$$J(E_0) = \begin{pmatrix} -\mu & -bK \\ 0 & \beta K-\gamma-\mu \end{pmatrix}.$$

It is easy to see that $J(E_0)$ has two eigenvalues $\lambda_1 = -\mu < 0$ and $\lambda_2 = \beta K-(\gamma+\mu)$.

Since $\lambda_2 < 0$ for $\beta K/(\mu+\gamma) < 1$, equilibrium E_0 is locally asymptotically stable. Because there is only one equilibrium M_0 in the region D in this case, it is impossible to have a closed orbit of system (1.10), and we note that region D is positively invariant for system (1.10) such that all orbits of (1.10) started inside D cannot go out of D. Then equilibrium E_0 is globally asymptotically stable in D. This implies that no matter how many initial infectives in this population, the epidemic cannot persist and dies out eventually. The point $E_0(K,0)$ is called a **disease-free equilibrium**.

(2) If $\beta K/(\mu+\gamma) > 1$, in addition to E_0, there is a positive equilibrium E_1 in region D. The Jacobian matrix of (1.10) at the equilibrium E_1 is given by

$$J(E_1) = \begin{pmatrix} -\dfrac{\mu\beta K}{\mu+\gamma} & -(\mu+\gamma) \\ \dfrac{\mu[\beta K-(\mu+\gamma)]}{\mu+\gamma} & 0 \end{pmatrix}.$$

Thus, it follows from $\operatorname{tr} J(E_1) = -\mu\beta K/(\mu+\gamma) < 0$ and $\det J(E_1) = \mu[\beta K-(\mu+\gamma)] > 0$, in this case, the equilibrium E_1 is locally asymptotically stable if it exists. Since region D is a positive invariant set of the system (1.10), to show the global stability of equilibrium E_1, we need only to prove that there is no closed orbit of system (1.10) in the interior of D. Taking the Dulac function $B(S,I) = 1/I$, we obtain

$$\frac{\partial(BP)}{\partial S} + \frac{\partial(BQ)}{\partial I} = -\beta - \frac{\mu}{I} < 0 \quad \text{for } (S,I) \in \operatorname{int} D.$$

By the qualitative theory of planar differential systems, equilibrium E_1 is globally asymptotically stable in region D. This implies that once the disease invades the population, the epidemic persists, and the susceptibles and infectives eventually approach the numbers $(\mu+\gamma)/\beta$ and $\mu[\beta K-(\mu+\gamma)]/[\beta(\mu+\gamma)]$, respectively, so that the disease become **endemic**. The point E_1 is called an **endemic equilibrium**.

Let $R_0 := \beta K/(\mu+\gamma)$. Then $R_0 = 1$ is a threshold that determines whether a disease persists or goes extinct. The epidemic does not persist if $R_0 < 1$, and spreads and eventually forms an endemic if $R_0 > 1$. This can be interpreted from the biological point of view as follows.

From the second equation of system (1.9), we can see that $1/(\mu+\gamma)$ is the mean infective period, or the mean course of infection, K is the number of the individuals in the population, also the number of susceptibles at the disease-free equilibrium E_0. Therefore, $R_0 = \beta K/(\mu+\gamma)$ is actually the average number of secondary infections produced by one infected individual during the mean course of infection in a completely susceptible population, and is called **the basic reproductive number**, or simply the reproductive number. If $R_0 < 1$, then on average, the number of new infections by one infected individual over the mean course of the disease is < 1, which implies that the disease dies out eventually. If $R_0 > 1$, then the number of new infections produced by one infected individual is > 1, which leads to the persistence of the infection.

We have seen from above example that the number of susceptibles, when all the members of the population are susceptible (this usually is assumed at the initial time of the epidemic), and the number of susceptibles at the disease-free equilibrium are the same, both are K. However it is not always the case and we show it in Example 1.2.

Example 1.2. Consider the following SIR model with vaccination:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu K - \beta SI - \mu S - pS,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - (\gamma+\mu)I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R + pS,
\end{aligned} \tag{1.11}$$

where p is the vaccinating rate coefficient for the susceptibles.

System (1.11) has, in addition to the disease-free equilibrium $E_0(\mu K/(\mu+p), 0, pK/(\mu+p))$, a positive equilibrium

$$E_1\left(\frac{\gamma+\mu}{\beta}, \frac{\beta\mu K-(\mu+p)(\mu+\gamma)}{\beta(\mu+\gamma)}, \frac{\beta K\gamma-(\mu+\gamma)(\gamma-p)}{\beta(\mu+\gamma)}\right),$$

if $\beta\mu K/[(\mu+p)(\mu+\gamma)] > 1$.

Let $R_0 = \beta\mu K/[(\mu+p)(\mu+\gamma)]$. Then it is not difficult to prove that if $R_0 < 1$, the disease-free equilibrium E_0 is stable, and that if $R_0 > 1$, E_0 is unstable, and the endemic equilibrium E_1 is stable.

In summary, we have the following conclusions:

(1) The number of susceptibles at the disease-free equilibrium E_0 is $\mu K/(\mu+p)$, but adding the three equations of system (1.11) and denoting $S(t)+I(t)+R(t)=N(t)$, we have

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \mu(K-N).$$

Then the number of all individuals in the population is K, not equal to $\mu K/(\mu+p)$, the number of susceptibles, because of the proportion of vaccination.

(2) The threshold that determines whether the disease dies out ultimately is $R_0 = \beta\mu K/[(\mu+p)(\mu+\gamma)] = 1$ rather than $\beta K/(\mu+\gamma) = 1$. Notice that $\mu K/(\mu+p) = S_0$ is the number of susceptibles at the disease-free equilibrium, so that $R_0 = \beta S_0/(\mu+\gamma)$ is the average number of secondary infections provided by one infected individual during the mean course of infection in the case where the number of susceptibles is counted from the disease-free equilibrium; that is, the total susceptibles of the population when disease is free. It is not the number of susceptibles in the case where all individuals of the population are susceptible. The number $R_0 = \beta S_0/(\mu+\gamma)$ is the reproductive number which we defined above.

(3) Here, the reproductive number $R_0 = \beta S_0/(\mu+\gamma) = 1$ is also a threshold to determine whether the positive equilibrium exists. If $R_0 < 1$ there exists only the disease-free equilibrium E_0. A positive equilibrium E_1 appears, in addition to E_0, if $R_0 > 1$. Furthermore, $R_0 = 1$ also differentiates the stability and instability of the disease-free equilibrium E_0. If $R_0 < 1$, E_0 is stable, whereas E_0 is unstable and E_1 is stable if $R_0 > 1$, all of which are the mathematical representations of the extinction or persistence of the disease.

(4) We need to point out that while conclusion (3) is true, in general, for some other epidemic models, $R_0 = 1$ may not be a threshold as we state above. For some models, when $R_0 > 1$ there is an endemic equilibrium, but when $R_0 < 1$, a positive equilibrium, or even more positive equilibria, may appear. This is called a backward bifurcation, which will be further discussed in Sec. 2.7.1.

There are two methods often used to determine the basic reproductive number of epidemic models. One method is to find conditions for the local stability of the disease-free equilibrium of the model. The other method is to use a next-generation operator [Diekmann *et al.* (1990); Diekman and Heesterbeek (2000); van den Driessche and Watmough (2002)], applications of which are given in Sec. 2.3.2. Moreover, the basic reproductive number can also be determined either by finding the conditions on the existence of an endemic equilibrium or epidemiologic meaning of parameters in the model.

1.3.2.2. *Modified reproductive number*

Before introducing a new concept of modified reproductive numbers in this section, we give an example below.

Example 1.3. Consider the following SIRS model with exponential birth, natural death, disease-induced death rates, standard incidence. The compartmental diagram is shown in Fig. 1.12.

The corresponding differential equations are

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= bN - \mu S - \frac{\beta SI}{N} + \delta R, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{\beta SI}{N} - (\alpha + \mu + \gamma)I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - (\mu + \delta)R, \end{aligned} \tag{1.12}$$

where b and μ are the birth rate and the natural death rate coefficients, respectively, α the disease-induced death rate coefficient, γ is the recovery rate coefficient, δ is the immunity loss rate coefficient, and $N(t) = S(t) + I(t) + R(t)$ is the total population size. From system (1.12), we have

$$\frac{\mathrm{d}N}{\mathrm{d}t} = (b - \mu)N - \alpha I.$$

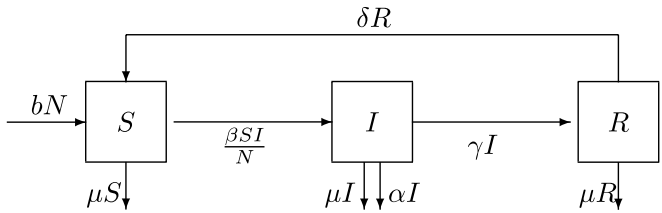


Fig. 1.12. Flow chart of the SIRS model with exponential birth, natural death, disease-induced death, and standard incidence.

Then, the population size $N(t)$ declines exponentially to zero if $b < \mu$, may approach zero, remain finite, or grow exponentially to infinity, depending on the infectives $I(t)$, if $b > \mu$.

System (1.12) has no equilibrium if $b > \mu$. However, we can still determine whether the disease dies out or not by analyzing the changing tendency of the infective fraction $I(t)/N(t)$ in the total population, such that the disease persists if the limit $\lim_{t\to\infty} I(t)/N(t)$ is greater than 0, and dies out if the limit is 0.

Let

$$x = \frac{S}{N}, \quad y = \frac{I}{N}, \quad z = \frac{R}{N}.$$

Then system (1.12) is transformed to

$$\begin{aligned}
\frac{\mathrm{d}x}{\mathrm{d}t} &= b - bx - \beta xy + \delta z + \alpha xy,\\
\frac{\mathrm{d}y}{\mathrm{d}t} &= \beta xy - (b + \alpha + \gamma)y + \alpha y^2,\\
\frac{\mathrm{d}z}{\mathrm{d}t} &= \gamma y - (b + \delta)z + \alpha yz,
\end{aligned}$$

which is equivalent to the following two-dimensional system

$$\begin{aligned}
\frac{\mathrm{d}y}{\mathrm{d}t} &= \beta(1 - y - z)y - (b + \alpha + \gamma)y + \alpha y^2,\\
\frac{\mathrm{d}z}{\mathrm{d}t} &= \gamma y - (b + \delta)z + \alpha yz,
\end{aligned} \tag{1.13}$$

since $x + y + z = 1$. It is easy to see that region $D = \{(y, z) : y \geq 0, z \geq 0, y + z < 1\}$ is invariant for system (1.13).

Define

$$R_1 := \frac{\beta}{b+\alpha+\gamma}.$$

It can be shown (see [Mena-Lorca and Hethcote (1992)]) that system (1.13) has only the disease-free equilibrium $E_0(0,0)$, which is globally asymptotically stable in D, if $R_1 \leq 1$. This disease-free equilibrium, E_0, becomes unstable, and there appears a positive equilibrium $E^*(y^*, z^*)$, which is globally asymptotically stable in the interior of D if $R_1 > 1$.

The fact that the disease-free equilibrium E_0 is globally asymptotically stable implies that $\lim_{t\to\infty} y(t) = \lim_{t\to\infty} I(t)/N(t) = 0$ for any initial values of $I_0 > 0$ and $N_0 > 0$; that is, the infective fraction goes to 0. In this sense, the disease dies out finally no matter whether the total population size keeps finite, goes to 0, or grows infinitely. Similarly, the global asymptotic stability of E^* implies that $\lim_{t\to\infty} I(t)/N(t) = y^* > 0$, which means that the infective fraction in the population goes to a positive constant, so the disease persists and becomes an endemic, no matter whether the total population size keeps finite, or grows infinitely.

For the model in (1.12), the transmission coefficient is β and the mean course of infection is $1/(\alpha+\mu+\gamma)$. Hence, the average number of secondary infections produced by one infected individual during the mean course of infection in a fully susceptible population is $R_0 = \beta/(\alpha+\mu+\gamma)$, not equal to R_1, while the threshold to determine whether the disease dies out is $R_1 = 1$. This number $R_1 = \beta/(b+\alpha+\gamma)$ is then defined as a **modified reproductive number**.

1.3.3. *Average lifespan and average infection age*

Average lift-span. Suppose that $N(a)$ is the number of individuals of a population who have survival until age a, and that μ is the natural death rate coefficient, that is, the proportion of the individuals who die in the population, per unit of time. We notice that time and age have the same scales. Then we have

$$\frac{\mathrm{d}N(a)}{\mathrm{d}a} = -\mu N(a), \tag{1.14}$$

where the minus sign implies the decrease of N with respect to age a due to the natural death. Assume $N(0) = N_0$. Solving differential equation (1.14),

we obtain

$$N(a) = N_0 \mathrm{e}^{-\mu a}, \quad \text{that is, } \mathrm{e}^{-\mu a} = \frac{N(a)}{N_0},$$

so that $\mathrm{e}^{-\mu a}$ expresses the probability of survivals of the population at age a. Hence, the probability of death of the population in the age interval $[0, a]$ is $1 - \mathrm{e}^{-\mu a}$. Thinking of the age at death as a random variable and denoting it by ξ, we have probability $P(0 < \xi \leq a) = 1 - \mathrm{e}^{-\mu a} = \int_0^a \mu \mathrm{e}^{-\mu x} \mathrm{d}x$, so that the probability density function of the random variable ξ is $\mu \mathrm{e}^{-\mu a}$, and thus the mathematical expectation of the random variable ξ is

$$\int_0^{+\infty} a\mu \mathrm{e}^{-\mu a} \mathrm{d}a = -a\mathrm{e}^{-\mu a}|_0^{+\infty} + \int_0^{+\infty} \mathrm{e}^{-\mu a} \mathrm{d}a = \frac{1}{\mu}.$$

From the meaning of mathematical expectation, $1/\mu$ is the average death age of the population, that is, the **average lifespan**.

This can be also seen from the definition of the death rate. It follows from (1.14) that the number of deaths of the population N with age a per unit of time is $\mu N(a)$ because of the same scale for time and age. Hence those individuals of age a die completely after time period $1/\mu$. Therefore, their average life-span is $1/\mu$.

In summary, if μ is the natural death rate coefficient, then $\mathrm{e}^{-\mu a}$ is the probability of the individuals who survive up to age a, $1/\mu$ is the average lifespan of this population, and $1/\mu = \int_0^{+\infty} \mathrm{e}^{-\mu a} \mathrm{d}a$.

Similarly, if γ is a recovery rate coefficient, then $1/\gamma$ is the mean course of infection or the average period of infection in the absence of death, and $\mathrm{e}^{-\gamma t}$ is the probability that those individuals are not recovered until time t. Moreover, if δ is an immunity loss rate coefficient, then $1/\delta$ is the mean immunity period in the absence of death, and $\mathrm{e}^{-\delta t}$ is the probability that those individuals still have the immunity until time t. It should be pointed out, however, that if the death is considered, the mean course of infection or mean immunity period will decrease. For instance, if the natural death rate coefficient μ is incorporated, the mean course of infection is $1/(\gamma + \mu)$.

Average infection age. Let us explain this concept using Example 1.1, where we have seen that if $R_0 > 1$ there exists a positive equilibrium $E_1(S^*, I^*)$ with

$$S^* = \frac{\mu + \gamma}{\beta}, \quad I^* = \frac{\mu[\beta K - (\mu + \gamma)]}{\beta(\mu + \gamma)}. \tag{1.15}$$

It is easy to understand that $\beta I^* S^*$ is the number of infectives per unit of time at the steady state when $R_0 > 1$, so that βI^* is the probability of a susceptible being infected per unit of time at the steady state. It is similar to the average lifespan, from the meaning of mathematical expectation, we know that $e^{-\beta I^* a}$ is the probability that susceptibles are not infected until age a, and $1/\beta I^*$ is the **average infection age** of the susceptibles. It is also called a **waiting time**.

For some diseases in a given area, the average lifespan and average infection age may be obtained by statistic data, so that the reproductive number R_0 can be estimated accordingly.

For instance, the reproductive number is

$$R_0 = \frac{\beta K}{\mu + \gamma} = \frac{K}{S^*}, \tag{1.16}$$

in Example 1.1. It follows from Eq. (1.15) that

$$S^* = \frac{K}{1 + \beta I^*/\mu}.$$

If we denote the average infective age as A and the average lifespan as L, then

$$A = \frac{1}{\beta I^*}, \quad L = \frac{1}{\mu}.$$

Thus (1.16) can be rewritten as

$$R_0 = 1 + \frac{L}{A}. \tag{1.17}$$

Consider the example by Brauer and Castillo-Chavez (2001), in some urban communities in England and Wales between 1956 and 1969. The average age of contracting measles was 4.8 years. If average lifespan in that area is assumed to be 70 years, then the reproductive number can be calculated, by the formula (1.17), as $R_0 = 15.6$.

To control an epidemic, we need to reduce the reproductive number R_0. It follows from formula (1.17), we can see that because the average lifespan in a given area is almost fixed during a short period, reducing R_0 implies increasing the average infection age. However, as it is pointed out by Brauer and Castillo-Chavez (2001), some diseases such as rubella (German measles) have more serious effects on adults than children. Then, as we intend to reduce R_0, a possible negative impact of such an effort needs to be considered.

1.4. Epidemic Models with Various Factors

1.4.1. *Epidemic models with latent period*

In general, SEIR and SEIRS models with latent periods cannot be reduced to planar differential equation systems. The qualitative analysis for such models can be difficult, and, as a result, few complete analytic results have been obtained. Nevertheless, if such a model is a competitive system under certain conditions, then the global stability of its steady states may be investigated by means of study of their orbital stability, the second additive compound matrix, or the method of ruling out the existence of periodic solutions, developed, for example, by Muldowney (1990) and Li and Muldowney (1995b, 1996).

Consider the SEIR model in (1.18) with the saturating contact rate $C(N) = bN/[1 + bN + \sqrt{1 + 2bN}]$. The transfer flow chart is shown in Fig. 1.13.

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \frac{a_0 SI}{h(N)} - \mu S,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \frac{a_0 SI}{h(N)} - \varepsilon_0 E - \mu E,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon_0 E - \gamma_0 I - \mu I - \alpha_0 I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma_0 I - \mu R,
\end{aligned} \tag{1.18}$$

where $a_0 = \beta b, h(N) = 1 + bN + \sqrt{1 + 2bN}$. Let $a = a_0/\mu$, $\varepsilon = \varepsilon_0/\mu$, $\gamma = \gamma_0/\mu$, $\alpha = \alpha_0/\mu$, and $\mu \cdot \mathrm{d}t = \mathrm{d}\tau$. Notice that $N(t) = S(t) + E(t) + I(t) + R(t)$. Then model (1.18) can be rewritten as

$$\begin{aligned}
\frac{\mathrm{d}E}{\mathrm{d}\tau} &= \frac{a(N - E - I - R)I}{h(N)} - (1 + \varepsilon)E,\\
\frac{\mathrm{d}I}{\mathrm{d}\tau} &= \varepsilon E - (1 + \gamma + \alpha)I,\\
\frac{\mathrm{d}R}{\mathrm{d}\tau} &= \gamma I - R,\\
\frac{\mathrm{d}N}{\mathrm{d}\tau} &= \frac{A}{\mu} - N - \alpha I.
\end{aligned} \tag{1.19}$$

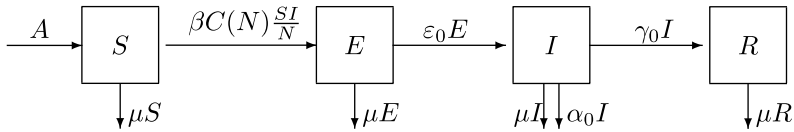


Fig. 1.13. Flow chart of the SEIR model with the saturating contact rate in (1.18).

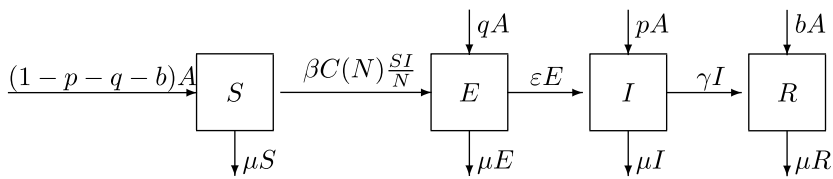


Fig. 1.14. Flow chart of the SEIR model (1.20) with recruitments to all compartments.

We can find the reproductive number for model (1.19) as

$$R_0 = \frac{a\varepsilon A}{\mu\delta\omega h(A/N)} = \beta C\left(\frac{A}{\mu}\right)\frac{\varepsilon_0}{(\mu+\gamma_0+\alpha_0)(\mu+\varepsilon_0)},$$

where $\delta = 1+\gamma+\alpha, \omega = 1+\varepsilon$. We can also prove that the disease-free equilibrium $P_0(0,0,0,A/\mu)$ is globally asymptotically stable in the region $\Gamma = \{(E,I,R,N) \in R_+^4 : 0 \le E+I+R \le N \le A/\mu\}$ if $R_0 \le 1$, and P_0 is unstable and there exists a unique, globally asymptotically stable endemic equilibrium $P^*(E^*,I^*,R^*,N^*)$ in the region Γ if $R_0 > 1$ [Zhang and Ma (2003)].

A more general SEIR model was considered by Zhang *et al.* (2006) with the flow chart shown in Fig. 1.14, where the recruitment enters not only to S but also to compartments E, I and R, and the contact rate $C(N)$ satisfies the conditions (H_1) and (H_2) in Sec. 1.3.1.

The corresponding system is

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= (1-p-q-b)A - \beta C(N)\frac{S}{N}I - \mu S,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= qA + \beta C(N)\frac{S}{N}I - \mu E - qE,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= pA + \varepsilon E - \mu I - \alpha I - \gamma I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= bA + \gamma I - \mu R,\\
N(t) &= S(t) + E(t) + I(t) + R(t).
\end{aligned} \tag{1.20}$$

The reproductive number of system (1.20), R_0, is given by

$$R_0 = \beta C \left(\frac{A}{\mu}\right) \cdot \frac{\varepsilon}{\mu + \varepsilon} \cdot \frac{1}{\mu + \gamma + \alpha},$$

if $p + q + b = 0$. The disease-free equilibrium is globally asymptotically stable in $\Gamma = \{(S, E, I, R) \in R_+^4 : 0 \leq S + E + I + R = N \leq A/\mu\}$ if $R_0 \leq 1$. It is unstable and there exists a unique, globally asymptotically stable endemic equilibrium in Γ, if $R_0 > 1$, for $p + q + b = 0$. In the case of $0 < p + q < 1 - b$, model (1.20) has no disease-free equilibrium (because of the recruitment) and only a globally asymptotically stable endemic equilibrium, $P^*(S^*, E^*, I^*, R^*)$, in Γ [Zhang *et al.* (2006)].

1.4.2. *Epidemic models with time delay*

Inclusion of time delay in epidemic models considers the fact that the transmission dynamic behavior of a disease at time t depends not only on the state of time t but also on the state of previous time. We consider two types of time delays. One of such time delays is a **discrete delay** or **fixed delay**. In models with a discrete or fixed delay, the dynamic behavior of the model at time t depends also on the state at time $t - \tau$, where τ is a fixed constant. For example, the number of newborns at time t depends on the state of population and environment at time $t - \tau$, where τ is the period of pregnancy; the number of infectives at time t for some diseases also depends on the number of infectives at time $t - \tau$, where τ is the latent period. The other type of time delays is a **continuous delay** or **distributed delay**. In a model with a continuous or distributed delay, the dynamic behavior of the model at time t depends also on the states during the whole period prior to time t.

To better understand the biological meaning of time delay in epidemiologic models, we deduce the Kermack–Mckendrick SIS model to its integral form as follows. As we introduced in Sec. 1.2.1, the Kermack–Mckendrick SIS model has the form of

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta SI + \gamma I,$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta SI - \gamma I,$$

where γ is the recovery rate coefficient. Regarding the term βSI in the second equation as a known function and solving this equation formally, we

obtain

$$I(t) = I_0 \mathrm{e}^{-\gamma t} + \int_0^t \beta S(u) I(u) \mathrm{e}^{-\gamma(t-u)} \mathrm{d}u, \tag{1.21}$$

where $I_0 = I(0)$ is the number of infectives at time $t = 0$. It follows from Sec. 1.3.3 that the first term in the right side of the expression (1.21), $I_0 \mathrm{e}^{-\gamma t}$, is the number of the infectives who were infected at $t = 0$ and have not been recovered until time t. Since $\mathrm{e}^{-\gamma(t-u)}$ is the probability that the individuals who were infectives at $t = u$ have not been recovered after the time period $t - u$, that is, at time t, and $\beta S(u) I(u)$ is the number of secondary infections at time u per unit of time, the number of secondary infections during the time period $[u, u + \mathrm{d}u]$ is $\beta S(u) I(u) \mathrm{d}u$, and those who have not been recovered, at time t, is $\beta S(u) I(u) \mathrm{e}^{-\gamma(t-u)} \mathrm{d}u$. Hence, the integral on the right side of expression (1.21) is the number of the individuals who are infected during the time period $(0, t]$ and have not been recovered at time t. Therefore, the number of total infectives at time t, $I(t)$, is given in (1.21).

Let $P(t)$ be a general probability function which is monotone decreasing with respect to time t and $P(0) = 1$. ($P(t) = \mathrm{e}^{-\gamma t}$ in (1.21).) Then we have

$$I(t) = I_0 P(t) + \int_0^t \beta S(u) I(u) P(t-u) \mathrm{d}u. \tag{1.22}$$

By means of mathematical expectation we can prove that the mean course of infection is $\int_0^{+\infty} P(t) \mathrm{d}t$.

1.4.2.1. *Ideas for the modeling*

Models with fixed time delay. There are two types of probability functions often used in epidemic models. One is of the exponential form $P(t) = \mathrm{e}^{-\gamma t}$ used in (1.21), where the recovered rate coefficient is γ. It implies the number of the recovered to be subject to the exponential law. The other form of probability functions is the step function

$$P(t) = \begin{cases} 1 & \text{for } 0 \le t < \tau, \\ 0 & \text{for } t \ge \tau, \end{cases} \tag{1.23}$$

where $\tau = 1/\gamma$ is the mean course of infection. Using this probability function in (1.23) implies that all of the infectives are recovered with no more infectivity after time period τ, but have the same infectivity during the course of infection, $0 < t < \tau$.

Based on $P(t)$ in (1.23), we know

$$P(t-u) = \begin{cases} 1 & \text{for } 0 \le t-u < \tau, \\ 0 & \text{for } t-u \ge \tau, \end{cases}$$

or

$$P(t-u) = \begin{cases} 1 & \text{for } t-\tau < u \le t, \\ 0 & \text{for } 0 \le u \le t-\tau. \end{cases}$$

Notice $I_0 P(t) = 0$ when $t \ge \tau$. Then Eq. (1.22) becomes

$$I(t) = \int_0^t \beta S(u) I(u) P(t-u) \mathrm{d}u = \int_{t-\tau}^t \beta S(u) I(u) \mathrm{d}u, \tag{1.24}$$

for $t \ge \tau$, where $I(0) = \int_{-\tau}^0 \beta S(u) I(u) \mathrm{d}u$ is required to ensure the continuity of $I(0)$. Taking the derivatives of both sides of Eq. (1.24) with respect to t, we obtain

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta S(t) I(t) - \beta S(t-\tau) I(t-\tau). \tag{1.25}$$

Equation (1.25) is an ordinary differential equation with time delay τ, which is also called a differential-difference equation, a special but important form of functional differential equations. The reader is referred to Bellman and Cooke (1963), Hale (1977), and Kuang (1993).

The biological meaning of Eq. (1.25) is clear. $\beta S(t) I(t)$ is the number of secondary infections who were infected at time t per unit of time, $\beta S(t-u) I(t-u)$ is the number of secondary infections who were infected at time $t-u$ per unit of time. Since all the infectives are recovered after time period τ, and there are no birth and death considered, the rate of change of infectives, that is, the recovery rate of the infectives at time t should be the difference between $\beta S(t) I(t)$ and $\beta S(t-u) I(t-u)$. Therefore, Eq. (1.25) can be also formulated directly according to its biological meaning. In this way, if the vital factors of the population are not considered, then the SIS

model with fixed course of infection is

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta S(t)I(t) + \beta S(t-\tau)I(t-\tau),\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - \beta S(t-I)I(t-\tau).\end{aligned} \tag{1.26}$$

If the natural death rate coefficient μ and the disease-induced death rate coefficient α are included in the model, then the recovery rate of the infectives at time t is $\beta S(t-\tau)I(t-\tau)\mathrm{e}^{-(\mu+\alpha)\tau}$, where the factor $\mathrm{e}^{-(\mu+\alpha)\tau}$ is the probability that the infectives survive during the time period τ. Then, in this case, model (1.26) becomes

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta S(t)I(t) - \mu S(t) + \beta S(t-\tau)I(t-\tau)\mathrm{e}^{-(\mu+\alpha)\tau},\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (\mu+\alpha)I(t) - \beta S(t-I)I(t-\tau)\mathrm{e}^{-(\mu+\alpha)\tau}.\end{aligned} \tag{1.27}$$

Models with distributed delay. The case that all the individuals have the same course of infection is special. Usually, the course of infection varies. Assume $P(\tau)$ is the probability that individuals were infected at time $t = 0$ and have not recovered at time $t = \tau$. Then $P(0) = 1$ and $\beta S(t-\tau)I(t-I)P(\tau)\mathrm{d}\tau$ is the number of those individuals who were infected during the time period $[t-(\tau+\mathrm{d}\tau), t-\tau]$ and still remain in the infected compartment at time t. Hence the number of the total infectives at time t is

$$\begin{aligned}I(t) &= \int_0^{+\infty} \beta S(t-\tau)I(t-\tau)P(\tau)\mathrm{d}\tau\\ &= \int_{-\infty}^{t} \beta S(u)I(u)P(t-u)\mathrm{d}u.\end{aligned} \tag{1.28}$$

Assume $P(\tau)$ is differentiable and define $f(\tau) := -P'(\tau)$. Then, by differentiating (1.28), we have

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) + \int_{-\infty}^{t} \beta S(u)I(u)P'(t-u)\mathrm{d}u\\ &= \beta S(t)I(t) - \int_0^{+\infty} \beta S(t-\tau)I(t-\tau)f(\tau)\mathrm{d}\tau,\end{aligned}$$

and we arrive at the corresponding SIS model described by

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta S(t)I(t) + \int_0^{+\infty} \beta S(t-\tau)I(t-\tau)f(\tau)\mathrm{d}\tau,$$
$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta S(t)I(t) - \int_0^{+\infty} \beta S(t-\tau)I(t-\tau)f(\tau)\mathrm{d}\tau.$$

Here we notice that $\int_0^{+\infty} f(\tau)\mathrm{d}\tau = \int_0^{+\infty}[-P'(\tau)]\mathrm{d}\tau = 1$, and $\int_0^{+\infty} \tau P(\tau)\mathrm{d}\tau$ is the course of infections.

Similarly to the case with discrete delays, if the natural death rate coefficient μ and the disease-induced death rate coefficient α are included in the model, then the corresponding SIS model becomes

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\beta S(t)I(t) - \mu S(t) + \int_0^{+\infty} \beta S(t-\tau)I(t-\tau)f(\tau)\mathrm{e}^{-(\mu+\alpha)\tau}\mathrm{d}\tau,$$
$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta S(t)I(t) - (\mu+\alpha)I(t) - \int_0^{+\infty} \beta S(t-I)I(t-\tau)f(\tau)\mathrm{e}^{-(\mu+\alpha)\tau}\mathrm{d}\tau.$$

Epidemic models based on integral equations. Integral equation (1.28) can be used directly to formulate epidemic models. For example, suppose that the input rate of a population is A, the natural and disease-induced death-rate coefficients are μ and α, respectively, the probability that those infectives who were infected at time u, $u \leq t$, and after time period $t-u$ still remain in the infective compartment at time t in the absence of death, is $P(t-u)$, satisfying $P(t-u)|_{u=t} = 1$, and $\int_0^{+\infty} P(t-u)\mathrm{d}u = \tau$, the mean course of infection. Then the number of individuals, who had been infected during the time interval $[0,t]$, remain in the infective compartment, and are still alive at time t, is $\int_0^t \beta S(u)I(u)P(t-u)\mathrm{e}^{-(\mu+\alpha)(t-u)}\mathrm{d}u$. Since the number of individuals who were already infective at $t=0$, remain in the infective compartment, and are still alive at time t, is $I_0P(t)\mathrm{e}^{-(\mu+\alpha)t}$, the total number of infectives who are alive at time t is

$$I(t) = I_0P(t)\mathrm{e}^{-(\mu+\alpha)t} + \int_0^t \beta S(u)I(u)P(t-u)\mathrm{e}^{-(\mu+\alpha)(t-u)}\mathrm{d}u.$$

Let $N(t) = I(t) + S(t)$ be the total number of individuals in the population at time t. Due to recruitment and deaths, the rate of change of

the population size is

$$\frac{\mathrm{d}N}{\mathrm{d}t} = A - \mu N(t) - \alpha I(t).$$

Formally solving this equation, we obtain

$$N(t) = N_0 \mathrm{e}^{-\mu t} + \int_0^t [A - \alpha I(u)] \mathrm{e}^{-\mu(t-u)} \mathrm{d}u.$$

Hence, the SIS model with population dynamics can be expressed in terms of the following integral equations:

$$I(t) = I_0 P(t) \mathrm{e}^{-(\mu+\alpha)t} + \int_0^t \beta [N(u) - I(u)] I(u) P(t-u) \mathrm{e}^{-(\mu+\alpha)(t-u)} \mathrm{d}u,$$

$$N(t) = N_0 \mathrm{e}^{-\mu t} + \int_0^t [A - \alpha I(u)] \mathrm{e}^{-\mu(t-u)} \mathrm{d}u.$$

1.4.2.2. *Examples of models with time delay*

SIS model with birth and death and a constant period of recovery. Suppose that the birth rate of the population is constant, denoted by A, and the natural death rate is μN. For convenience, we let $K := A/\mu$. Then we have

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \mu K - \mu N = \mu(K - N).$$

We can see that $K = A/\mu$ is the carrying capacity of the environment for the population such that the population stops growing when $N = K$ and decays when $N > K$.

An SIS model usually consists of compartments of susceptibles S and infectives I. Since $S(t) + I(t) = N(t)$, it can be convenient, in some cases, if we choose either S or I, in addition to N, as variables.

We consider a case where there is neither disease-induced death nor vertical transmission. Let the course of infection, that is, the period of recovery, be constant, denoted by τ. Then the individuals, who were infected at time $t - \tau$, recover at time t. On the other hand, there are individuals die during the time period $(t - \tau, t]$ due to the natural death such that the number of infectives, who were infected at time $t - \tau$, are alive and recovered at time t is $\beta I(t-\tau) S(t-\tau) \mathrm{e}^{-\mu\tau}$. Then the SIS model, based on

these assumptions, is described by the following system:

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta I(t)[N(t) - I(t)] - \beta I(t-\tau) \\ &\quad \times [N(t-\tau) - I(t-\tau)]\mathrm{e}^{-\mu\tau} - \mu I(t), \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= \mu[K - N(t)].\end{aligned}$$

If the disease-induced death, with coefficient α, is considered in the model, the model equations become

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta I(t)[N(t) - I(t)] - \beta I(t-\tau) \\ &\quad \times [N(t-\tau) - I(t-\tau)]\mathrm{e}^{-(\mu+\alpha)\tau} - (\mu+\alpha) I(t), \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= \mu[K - N(t)] - \alpha I(t),\end{aligned}$$

or, in terms of variables S and I,

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu[K - S(t)] - \beta S(t)I(t) + \beta S(t-\tau)I(t-\tau)\mathrm{e}^{-(\mu+\alpha)\tau}, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - \beta S(t-\tau)I(t-\tau)\mathrm{e}^{-(\mu+\alpha)\tau} - (\mu+\alpha)I(t).\end{aligned} \tag{1.29}$$

The basic reproductive number for model (1.29) is

$$R_0 = \frac{\beta K[1 - \mathrm{e}^{-(\mu+\alpha)\tau}]}{\mu+\alpha}.$$

Instead of a constant input, if the birth rate of the population is proportional to the population size, $bN(t)$, and the standard incidence is chosen, then the SIS model becomes

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= bN(t) - \mu S(t) - \frac{\beta(t)I(t)}{N(t)} + \frac{\beta S(t-\tau)I(t-\tau)}{N(t-\tau)}\mathrm{e}^{-(\mu+\alpha)\tau}, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{\beta S(t)I(t)}{N(t)} - (\mu+\alpha)I(t) - \frac{\beta S(t-\tau)I(t-\tau)}{N(t-\tau)}\mathrm{e}^{-(\mu+\alpha)\tau}.\end{aligned}$$

In case where there exists vertical transmission, then the birth rate $bN(t)$ will be divided into two parts, $bS(t)$ and $bI(t)$, which will be added to the equations of $\mathrm{d}S/\mathrm{d}t$ and $\mathrm{d}I/\mathrm{d}t$, respectively.

SEIR model with constant latent period ω and constant course of infection τ. Notice that the individuals in the compartment I are the infectives with infectivity, whereas the individuals in the compartment E are infectives without infectivity. An individual who enters compartment I at time t should have be infected at time $t-\omega$, and an individual who recovers at time t should enter the compartment I at time $t-\tau$, and been infected at time $t-\omega-\tau$. Hence, if the birth rate of the population is $A := \mu K$, the natural death rate coefficient is μ, the disease-induced death rate coefficient is α, and there is no vertical transmission, then the corresponding SEIR model is

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu[K - S(t)] - \beta S(t)I(t),\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \beta S(t)I(t) - \beta S(t-\omega)I(t-\omega)\mathrm{e}^{-\mu\omega} - \mu E(t),\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t-\omega)I(t-\omega)\mathrm{e}^{-\mu\omega} - \beta S(t-\omega-\tau)\\
&\quad \times I(t-\omega-\tau)\mathrm{e}^{-\mu(\omega+\tau)}\mathrm{e}^{-\alpha\tau} - (\mu+\alpha)I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \beta S(t-\omega-\tau)I(t-\omega-\tau)\mathrm{e}^{-\mu(\omega+\tau)}\mathrm{e}^{-\alpha\tau} - \mu R(t).
\end{aligned}$$

SIRS model with constant period of immunity. Suppose that the recovery and the immunity loss rate coefficients are γ and δ, respectively. Then the corresponding SIRS model is

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu[K - S(t)] - \beta S(t)I(t) + \delta R(t),\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (\mu+\alpha+\gamma)I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - \mu R(t) - \delta R(t),
\end{aligned}$$

where the other parameters are defined the same as before. This is a differential equation system without time delay. It follows from the immunity loss rate δR that the proportion of immunity loss of the recovered individuals is distributed exponentially as $\mathrm{e}^{-\delta t}$, and the mean period of immunity without death is $1/\delta$.

If the period of immunity is a constant $\tau = 1/\delta$, then the corresponding model is described by the following time-delay system:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \mu[K - S(t)] - \beta S(t)I(t) + \gamma I(t-\tau)\mathrm{e}^{-\mu\tau},$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta S(t)I(t) - (\mu + \alpha + \gamma)I(t),$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I(t) - \mu R(t) - \gamma I(t-\tau)\mathrm{e}^{-\mu\tau}.$$

If the recovery period, that is, the course of infection without death, is also a constant, denoted by $\omega = 1/\gamma$, then the corresponding model becomes

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu[K - S(t)] - \beta S(t)I(t) + \beta S(t-\tau-\omega) \\
&\quad \times I(t-\tau-\omega)\mathrm{e}^{-\mu(\tau+\omega)}\mathrm{e}^{-\alpha\omega}, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - \beta S(t-\omega)I(t-\omega)\mathrm{e}^{-(\mu+\alpha)\omega} - (\mu+\alpha)I(t), \qquad (1.30) \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \beta S(t-\omega)I(t-\omega)\mathrm{e}^{-(\mu+\alpha)\omega} - \mu R(t) \\
&\quad - \beta S(t-\tau-\omega)I(t-\tau-\omega)\mathrm{e}^{-\mu(\tau+\omega)}\mathrm{e}^{-\alpha\omega}.
\end{aligned}$$

It is straightforward to show that the basic reproductive number of model (1.30) is

$$R_0 = \frac{\beta K[1 - \mathrm{e}^{-(\mu+\alpha)\omega}]}{\mu + \alpha}.$$

If more factors such as vertical transmission, latent period, density dependence of the population, or some measures of prevention and control for the disease are incorporated, the models become more complicated. Some of the examples will be given later.

1.4.3. *Epidemic models with prevention, control, or treatment*

Two effective methods, quarantine, and vaccination and treatment, are more wildly used in controlling and preventing the spread of diseases. We explain the ideas of their modeling as follows.

1.4.3.1. *Models with quarantine*

Early studies on the effects of quarantine on disease transmissions were carried out by Feng and Thieme (1995), Nuno *et al.* (2005), and Wu and Feng (2000). In those papers, they introduce a quarantined compartment, Q, and assume that all the infectives go to the quarantined compartment before going to the recovery compartment R, or becoming susceptibles again. Hethcote *et al.* (2002) considered a more realistic case where a part of the infectives are quarantined, whereas the others, not quarantined, either enter the recovery compartment or go back to the susceptible compartment after treatment. They analyzed six SIQS and SIQR models with bilinear, standard, or quarantine-adjusted incidence, and found that only the SIQR model with quarantine-adjusted incidence might have a Hopf bifurcation, comparing to the other five models with disease-induced death, each of which has a globally stable disease-free or endemic equilibrium, and their necessary and sufficient stability conditions were obtained.

As an example, we consider an SIQR model with quarantine-adjusted incidence (Fig. 1.15).

In Fig. 1.15, Q is the quarantine compartment. A part of the infectives are quarantined with the rate δI, and the rest of the infectives still remain unquarantined and are recovered with the rate γI. We assume that the mean course of infection without death is $1/\gamma$, the mean period of quarantine without death is $1/\varepsilon$, and the disease-induced death rate coefficient for the individuals in Q is α_1, which is different from α, in I, due to different treatments. Here we use the so-called quarantine-adjusted incidence $\beta SI/(N-Q) \equiv \beta SI/(S+I+R)$, instead of the standard incidence $\beta SI/N$, because the individuals in the quarantine compartment

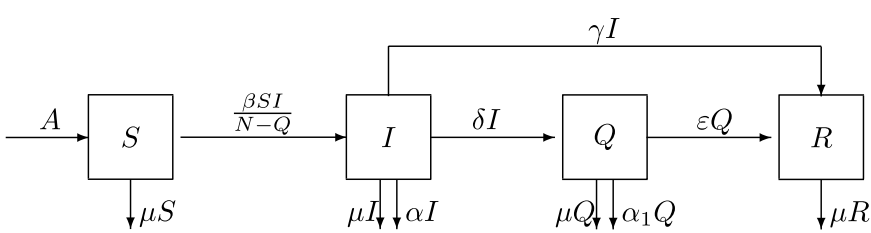


Fig. 1.15. Flow chart of the SIQR model with quarantine-adjusted incidence.

Q cannot contact others. Thus the corresponding model is

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \frac{\beta SI}{S+I+R} - \mu S,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{\beta SI}{S+I+R} - (\mu+\alpha+\gamma+\delta)I,\\
\frac{\mathrm{d}Q}{\mathrm{d}t} &= \delta I - (\mu+\alpha_1+\varepsilon)Q,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I + \varepsilon Q - \mu R.
\end{aligned} \tag{1.31}$$

The quarantine reproductive number R_q for model (1.31) is defined as

$$R_q = \frac{\beta}{\mu+\alpha+\gamma+\delta}.$$

1.4.3.2. *Models with vaccination*

Vaccination is considered to be the most effective and cost-effective method of preventing infectious diseases. To model transmission dynamics of diseases with vaccines, ordinary differential equations, delay differential equations, and pulse differential equations are often used. Here, we introduce ideas for the modeling based on the first two kinds of equations as follows, and consider the pulse differential equations models later. The reader for further details are referred to Li *et al.* (2006) and Li and Ma (2002, 2003, 2004a,b, 2006a).

Ideas for the modeling. In general, we can use SIR models to describe the transmission dynamics of the diseases if the vaccination leads to permanent immunity. For example, we assume that a portion of susceptibles, pS, go to the removed compartment R directly, due to permanent immunity obtained from vaccination. The model flow chart is shown in Fig. 1.16.

In case where the vaccination leads to only temporary immunity — that is, vaccinated individuals lose their immunity and become susceptibles again after a period of time — and if we use SIRS models to describe the transmission dynamics of the diseases, it implies that we assume the same probability for immunity loss for recovered and vaccinated individuals.

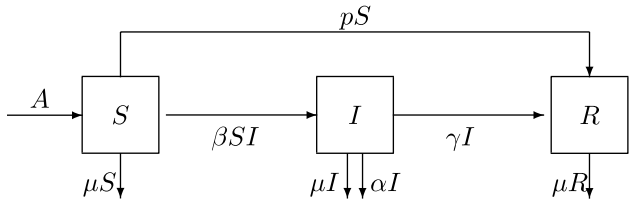


Fig. 1.16. Flow chart for an SIR model with vaccination.

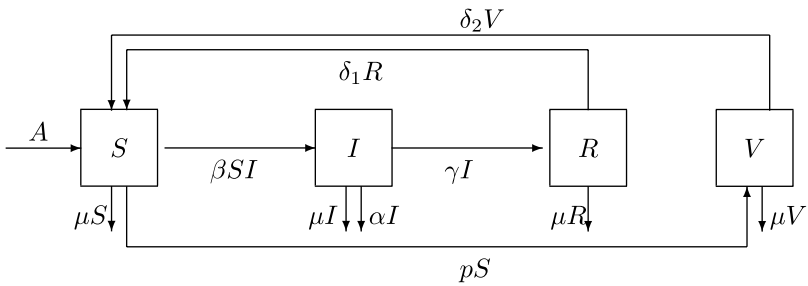


Fig. 1.17. Flow chart of an SIRS model with component V.

However, the two rates are different in most cases. Then, one of the modeling ideas is to introduce another compartment V which consists of the vaccinated susceptibles. A flow chart of a such model is given in Fig. 1.17.

The corresponding model equations are

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mu S - \beta SI - pS + \delta_1 R + \delta_2 V,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - (\mu + \alpha + \gamma)I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R - \delta_1 R,\\
\frac{\mathrm{d}V}{\mathrm{d}t} &= pS - \mu V - \delta_2 V,
\end{aligned} \tag{1.32}$$

where constants $1/\delta_1$ and $1/\delta_2$ are the periods of immunity of the recovereds and vaccinated susceptibles, respectively.

SIS-VS models. Figure 1.18 is the flow chart of an SIS-VS model, where V is the compartment of vaccinated individuals, where we assume that the

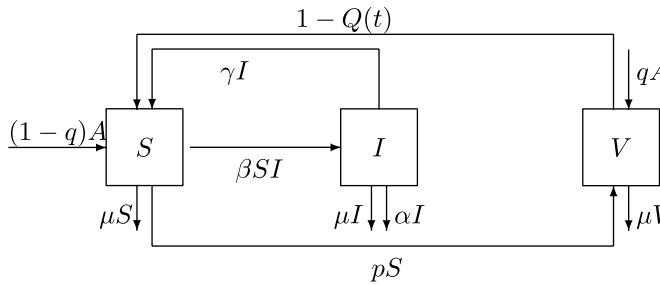


Fig. 1.18. Flow chart of the SIS-VS model.

vaccination is given to both the newborns and the susceptibles. We use A to represent the birth rate, q the fraction of the vaccinated newborns, so that qA enters compartment V, while the rest of newborns $(1-q)A$ enters compartment S, and p the fraction of the vaccinated susceptibles. We assume that the vaccinated individuals have temporary immunity and $Q(t)$ is the probability that a vaccinated individual remains in the compartment V at least t time units before returning to the compartment S, so that $1-Q(t)$ is the probability of those vaccinated individuals who lose immunity within t time units. The corresponding model is then described by the following system:

$$\begin{aligned}
&\frac{\mathrm{d}I}{\mathrm{d}t} = \beta SI - (\mu+\alpha+\gamma)I,\\
&V(t) = V_0(t) + \int_0^t [qA + pS(u)]Q(t-u)\mathrm{e}^{-\mu(t-u)}\mathrm{d}u,\\
&\frac{\mathrm{d}N}{\mathrm{d}t} = A - \mu N - \alpha I,\\
&N = S + I + V,
\end{aligned} \tag{1.33}$$

where $V_0(t)$ is the number of the individuals who were vaccinated before $t=0$ and are still alive and remain immune until time t, and $\int_0^t [qA + pS(u)]Q(t-u)\mathrm{e}^{-\mu(t-u)}\mathrm{d}u$ are the individuals who were vaccinated in the time period $(0,t]$ and are still alive and remain immune until time t.

Suppose we have $Q(t)$ as an exponential distribution with $Q(t) = \mathrm{e}^{-\delta t}$. Then

$$V_0(t) = V_0(0)\mathrm{e}^{-\delta t}\mathrm{e}^{-\mu t} = V_0(0)\mathrm{e}^{-(\mu+\delta)t},$$

and model (1.33) can be written as

$$\begin{aligned}
&\frac{\mathrm{d}I}{\mathrm{d}t} = pSI - (\mu+\alpha+\gamma)I,\\
&V(t) = V_0(0)\mathrm{e}^{-(\delta+\mu)t} + \int_0^t [qA + pS(u)]\mathrm{e}^{-(\mu+\delta)(t-u)}\mu u, \qquad (1.34)\\
&\frac{dN}{dt} = A - \mu N - \alpha I,
\end{aligned}$$

or

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= (1-q)A - \beta SI - (p+\mu)S + \gamma I + \delta V,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - (\mu+\alpha+\gamma)I,\\
\frac{dV}{dt} &= qA + pS - (\delta+\mu)V,\\
\frac{dN}{dt} &= A - \mu N - \alpha I.
\end{aligned} \qquad (1.35)$$

In system (1.35), the third equation is obtained by differentiating both sides of the second equation in system (1.34), and the first equation is derived from the last three equations in (1.35) according to its biological definition. The vaccination reproductive number of the model (1.35) is defined as

$$R_v = \frac{A}{\mu}\cdot\frac{\beta[\varepsilon+\mu(1-q)]}{(\mu+\gamma+\alpha)(\mu+\delta+p)}.$$

If we take $Q(t)$ as a step function

$$Q(t) = \begin{cases} 1 & \text{for } t\in[0,\tau),\\ 0 & \text{for } t\geq\tau, \end{cases}$$

where $[0,\tau)$ is the period of immunity, which means that the period of immunity is uniformly distributed for all the vaccinated individuals, and all the vaccinated individuals lose their immunity and become susceptible

again after time τ. In this case, model (1.33) becomes

$$\begin{aligned}
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - (\mu + \alpha + \gamma)I, \\
V(t) &= \int_{t-\tau}^{t} [qA + pS(u)]\mathrm{e}^{-\mu(t-u)}\mathrm{d}u, \quad \text{for } t \geq \tau, \\
\frac{dN}{dt} &= A - \mu N - \alpha I,
\end{aligned} \tag{1.36}$$

where

$$Q(t-u) = \begin{cases} 1 & \text{for } t - \tau < u \leq t, \\ 0 & \text{for } 0 \leq u \leq t - \tau, \end{cases}$$

and the function $V_0(t)$ in system (1.33) vanishes for $t \geq \tau$, where $V(0) = \int_{-\tau}^{0} [qA + pS(u)]\mathrm{e}^{\mu u}\mathrm{d}u$ is imposed to ensure the continuity of $V(t)$. Similarly to system (1.35), system (1.36) can be written as a differential equations system with time delay:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= (1-q)A - (p+\mu)S(t) - \beta S(t)I(t) \\
&\quad + \gamma I(t) + [qA + pS(t-\tau)]\mathrm{e}^{-\mu\tau}, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (\mu + \alpha + \gamma)I(t), \\
\frac{dV}{dt} &= qA + pS(t) - [qA + pS(t-\tau)]\mathrm{e}^{-\mu\tau} - \mu V(t), \\
\frac{dN}{dt} &= A - \mu N(t) - \alpha I(t).
\end{aligned} \tag{1.37}$$

The vaccination reproductive number of the model (1.37) is defined as

$$R_v = \frac{\beta A\,[1 - q(1 - \mathrm{e}^{-\mu\tau})]}{(\mu + \alpha + \gamma)\,[\mu + p(1 - \mathrm{e}^{-\mu\tau})]}.$$

SIR-VS and SIRS-VS models. Figure 1.19 is the flow chart for an SIR-VS model, where we assume that only the susceptibles are vaccinated with temporary immunity, and that the recovereds have permanent immunity.

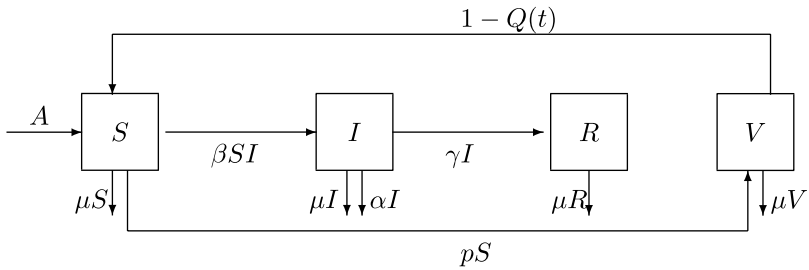


Fig. 1.19. Flow chart for an SIR-VS model.

The corresponding model is described by the system

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta S(t)I(t) - (\mu + \alpha + \gamma)I(t),$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I(t) - \mu R(t),$$

$$V = V_0(t) + \int_0^t pS(u)Q(t-u)\mathrm{e}^{-\mu(t-u)}\mathrm{d}u,$$

$$\frac{dN}{dt} = A - \mu N(t) - \alpha I(t),$$

where $V_0(t)$ is the individuals who were vaccinated before $t = 0$ and stay in the vaccination compartment until time t.

The model shown in Fig. 1.17 can be generalized to the SIRS-VS model as shown in Fig. 1.20.

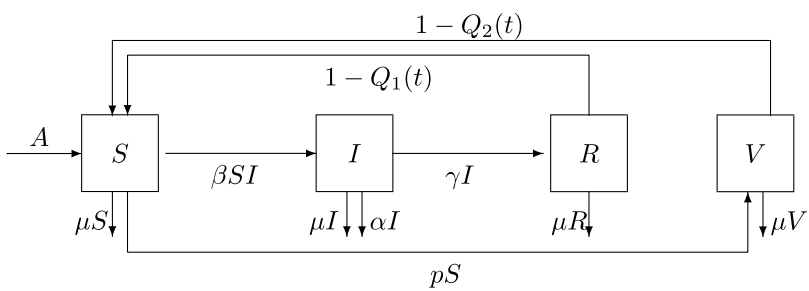


Fig. 1.20. Flow chart for a more general SIRS-VS model.

The corresponding model equations are

$$\begin{aligned}
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (\mu + \alpha + \gamma)I(t), \\
R &= R_0(t) + \int_0^t \gamma I(u)Q_1(t-u)\mathrm{e}^{-\mu(t-u)}\mathrm{d}u, \\
V &= V_0(t) + \int_0^t pS(u)Q_2(t-u)\mathrm{e}^{-\mu(t-u)}\mathrm{d}u, \\
\frac{dN}{dt} &= A - \mu N(t) - \alpha I(t).
\end{aligned} \tag{1.38}$$

If the probability function Q_i has the form of $\mathrm{e}^{-\delta_i t}$, $i = 1, 2$, we have $R_0(t) = R_0(0)\mathrm{e}^{-\delta_1 t}\mathrm{e}^{-\mu t}$ and $V_0(t) = V_0(0)\mathrm{e}^{-\delta_2 t}\mathrm{e}^{-\mu t}$. Then the time-delayed equations in (1.38) are reduced to the ordinary differential equations in (1.32). If the probability function Q_i is a step function

$$Q_i(t) = \begin{cases} 1 & \text{for } t \in [0, \tau_i), \\ 0 & \text{for } t \geq \tau_i, \end{cases} \quad i = 1, 2,$$

then, for $t \geq \tau_i$ the second and third equations in (1.38) become

$$\begin{aligned}
R(t) &= \int_{t-\tau_1}^t \gamma I(u)\mathrm{e}^{-\mu(t-u)}\mathrm{d}u, \\
V(t) &= \int_{t-\tau_2}^t pS(u)\mathrm{e}^{-\mu(t-u)}\mathrm{d}u.
\end{aligned}$$

Similarly as in (1.36), the initial conditions

$$R(0) = \int_{-\tau_1}^0 \gamma I(u)\mathrm{e}^{\mu u}\mathrm{d}u \quad \text{and} \quad V(0) = \int_{-\tau_2}^0 pS(u)\mathrm{e}^{\mu u}\mathrm{d}u$$

are imposed.

Differentiating both sides of the equations for R and V in (1.38), we obtain the following system with time delay:

$$\begin{aligned}
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (\mu+\alpha+\gamma)I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - \mu R(t) - \gamma I(t-\tau_1)\mathrm{e}^{-\mu\tau_1},\\
\frac{\mathrm{d}V}{\mathrm{d}t} &= pS(t) - \mu V(t) - pS(t-\tau_2)\mathrm{e}^{-\mu\tau_2},\\
\frac{\mathrm{d}N}{\mathrm{d}t} &= A - \mu N(t) - \alpha I(t),
\end{aligned}$$

or

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \beta S(t)I(t) - \mu S(t) - pS(t)\\
&\quad + \gamma I(t-\tau_1)\mathrm{e}^{-\mu\tau_1} + pS(t-\tau_2)\mathrm{e}^{-\mu\tau_2},\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (\mu+\alpha+\gamma)I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - \mu R(t) - \gamma I(t-\tau)\mathrm{e}^{-\mu\tau_1},\\
\frac{dV}{dt} &= pS(t) - \mu V(t) - pS(t-\tau_2)\mathrm{e}^{-\mu\tau_2}.
\end{aligned}$$

SIS models with vaccination and vaccine efficacy. In the models discussed above, we assumed that the vaccines have full efficacy, but in reality, the efficacy of a vaccine is usually not 100%. Hence, we need to take this into account when we formulate epidemic models with vaccination. We give an example whose flow chart is shown in Fig. 1.21, where we suppose that the birth rate coefficient is r, the natural death rate coefficient depends on the population size N, denoted by $f(N)$, the vaccination is given to both newborns and susceptibles; standard incidence is chosen, the mean period of immunity without death is $1/\delta$, and the vaccine is not completely efficacious and $\sigma(0 \le \sigma \le 1)$ describes the inefficaciousness of the vaccine such that the infection incidence from the inefficaciously vaccinated individuals is $\sigma\beta VI/N$.

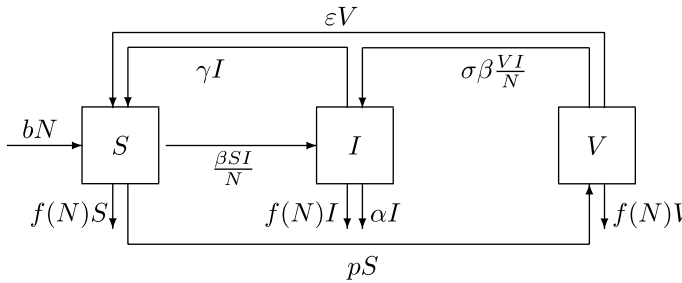


Fig. 1.21. Flow chart of the SIS model with vaccination and efficacy of vaccine.

The model of corresponding to Fig. 1.21 is given by

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= bN - \beta\frac{SI}{N} - [p + f(N)]S + \gamma I + \varepsilon V,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta\frac{SI}{N} + \sigma\beta\frac{VI}{N} - [\gamma + \alpha + f(N)]I,\\
\frac{\mathrm{d}V}{\mathrm{d}t} &= pS - \sigma\beta\frac{VI}{N} - [\varepsilon + f(N)]V,\\
\frac{\mathrm{d}N}{\mathrm{d}t} &= [b - f(N)]N - \alpha I.
\end{aligned} \tag{1.39}$$

The modified reproductive number of model (1.39) is defined as

$$R_v = \frac{\beta[\varepsilon + \sigma p + b]}{(\alpha + b + \gamma)(p + b + \varepsilon)}.$$

1.4.3.3. *Models with treatment*

In classic epidemic models, the treatment rate of the infectives is assumed to be proportional to the number of the infectives. This is based on the assumption of sufficient resource available for treatment when the number of the infectives is large. Nevertheless, this involves the best strategy or optimal available resource for treatment for every community. A community wastes resource for treatment if the resource is prepared for too large, but may have a risk of an outbreak of a disease if the available resource is too small. Thus, it is important to determine optimal resource supplies, or capacity, for the treatment of a disease.

Suppose that the capacity for the treatment of a disease in a community is a constant and the recovery rate coefficient due to the treatment is r. We further assume that the treatment rate is proportional to the number of the infectives when the capacity of the treatment has not been reached, and saturates to a constant when the number of the infectives is so large that the capacity of the treatment is exceeded. With these assumptions, the following SIR model was constructed [Wang (2006b)] as

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mu S - \beta SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - (\mu + \gamma)I - T(I), \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I + T(I) - \mu R, \end{aligned} \tag{1.40}$$

where

$$T(I) = \begin{cases} rI, & \text{if } 0 \le I \le I_0, \\ rI_0, & \text{if } I > I_0, \end{cases} \tag{1.41}$$

is the recovery rate due to the treatment and γI is recovery rate due to other reasons. I_0 reflects the capacity of the treatment. The investigation of the effects of I_0 on the transmission dynamics was investigated [Wang (2006b)], and is shown in Sec. 2.6.3.

1.4.4. *Epidemic models with multiple groups*

If a disease is transmitted among multiple interactive populations or multiple subpopulations of a population, then the number of variables is increased, and the structure of the models becomes more complex. Hence the analysis becomes more difficult and new dynamic features may appear. We introduce some modeling ideas below.

1.4.4.1. *Models with different subgroups*

DS-SIR model with differential susceptibility. Many mechanisms lead to differential susceptibility (DS). For example, genetic variation of susceptible individuals may lead to their differentiation of susceptibility to infection. The efficacy of available vaccinations for many infectious diseases is not perfect. Vaccinated individuals may still contract the disease and

the susceptibility varies from individual to individual. To address the DS in modeling of infectious diseases, DS models are formulated where the susceptible population is partitioned into n subgroups, S_i, $i = 1, \ldots, n$, according to their susceptibilities. It is assumed that the input rate of each subgroup S_i is μS_i^0, and the incidence is $\beta k_i S_i I/N$, where k_i, $i = 1, \ldots, n$, characterizes the susceptibility of individuals in the subgroup S_i [Hyman and Li (2005)]. The flow chart of DS models is given in Fig. 1.22.

The corresponding model equations are

$$\begin{aligned}
\frac{\mathrm{d}S_i}{\mathrm{d}t} &= \mu(S_i^0 - S_i) - \frac{\beta k_i S_i I}{N}, \quad i = 1, 2, \ldots, n, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \sum_{i=1}^{n} \frac{\beta k_i S_i I}{N} - (\mu + \alpha + \gamma) I, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mathrm{d}R.
\end{aligned} \tag{1.42}$$

The basic reproductive number of (1.42) is defined as

$$R_0 = \frac{\beta \sum_{i=1}^{n} k_i S_i^0}{(\mu + \alpha + \gamma) \sum_{i=1}^{n} S_i^0}.$$

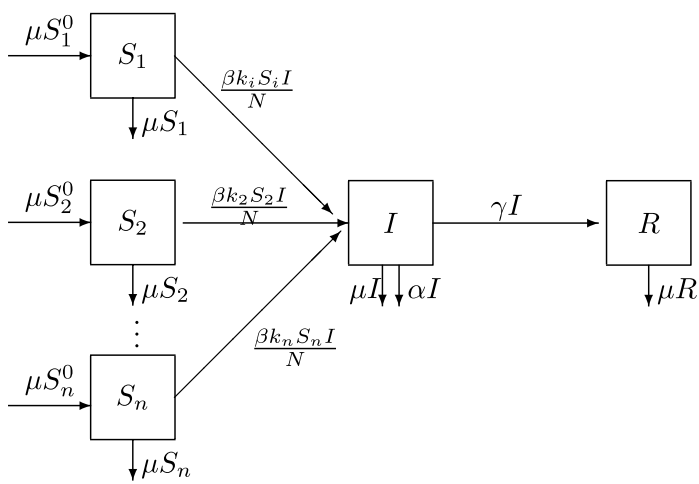


Fig. 1.22. Flow chart of the DS-SIR model.

SIR models with variations in infectiousness. In the studies of the transmission dynamics of HIV, two fundamental hypotheses for variations in infectiousness have been employed. Based on other clinical findings and blood serum level studies, the differential infectivity (DI) hypothesis assumes that the population of infectives is divided into several groups, depending on their infectivity. Infected individuals enter one of the groups and stay in that group until they develop AIDS. Another hypothesis is the staged-progression (SP) hypothesis, in which the infected individuals sequentially pass through a series of stages, being highly infectious in the first few weeks after their own infection, then having low infectivity for many years, and finally becoming gradually more infectious as their immune system breaks down and they progress to AIDS. Both deterministic DI and SP models have been formulated and studied to understand the impact of the DI and the disease progression on the spread of HIV. (See [Hyman *et al.* (1999); Hyman and Li (2000); Ma *et al.* (2003)] and references therein.)

In a DI model, it is assumed that individuals in each infective compartment I_i contact susceptibles with different adequate contact rate. However, the secondary infectives infected by the infectives in I_i are not necessarily belong to the same infective compartment I_i, and the probability that the total secondary infections enter to the compartment I_i is p_i ($\sum_{i=1}^{n} p_i = 1$). The flow chart of a DI model is shown in Fig. 1.23.

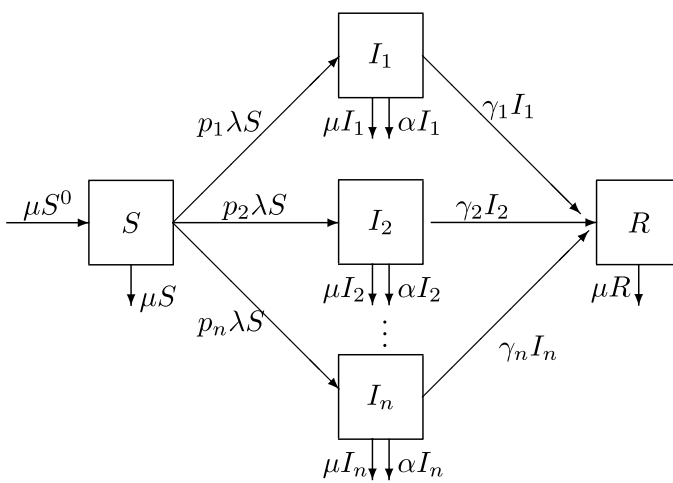


Fig. 1.23. Flow chart of the DI-SIR model.

The corresponding model equations are

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu(S^0 - S) - \lambda S, \\
\frac{\mathrm{d}I_i}{\mathrm{d}t} &= p_i\lambda S - (\mu + \alpha_i + \gamma_i)I_i, \quad i = 1, 2, \ldots, n, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \sum_{i=1}^{n} \gamma_i I_i - \mu R,
\end{aligned} \tag{1.43}$$

where

$$\lambda = \sum_{i=1}^{n} \frac{\beta_i I_i}{N}, \quad N = S + \sum_{k=1}^{n} I_k.$$

The basic reproductive number of infection for the DI model in (1.43) is defined as

$$R_0 = S^0 \sum_{i=1}^{n} \frac{\beta_i p_i}{\mu + \alpha_i + \gamma_i}.$$

In an SP model, infectives sequentially pass through a series of stages, which implies that this model is a Markov chain model, and hence the population of infectives is divided into subgroups, I_i $(i = 1, 2, \ldots, n)$, with different infection stages such that infected susceptible individuals enter the first subgroup I_1 and then gradually progress from subgroup I_1 finally to subgroup I_n. The infectives in stage I_i contact the susceptibles and the incidence of I_i is $\beta_i S I_i$. (See [Hyman *et al.* (1999); Hyman and Li (2000)] for details.) The flow chart of an SP model is shown in Fig. 1.24.

The corresponding model equations are

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu S^0 - \lambda S - \mu S, \\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \lambda S - (\mu + \alpha_1 + \gamma_1)I_1, \\
\frac{\mathrm{d}I_i}{\mathrm{d}t} &= \gamma_{i-1} I_{i-1} - (\mu + \alpha + \gamma_i)I_i, \quad i = 2, \ldots, n, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma_n I_n - \mu R,
\end{aligned}$$

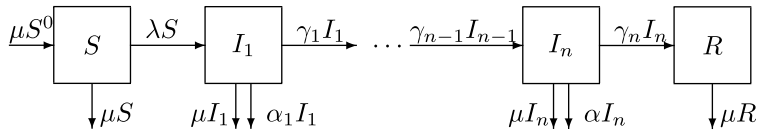


Fig. 1.24. Flow chart of an SP model.

where

$$\lambda = r \sum_{i=1}^{n} \frac{\beta_i I_i}{N}, \quad N = S + \sum_{k=1}^{n} I_k,$$

and r is the number of contacts. The basic reproductive number of infection for the SP model in Sec. 1.4.4.1 is defined as

$$R_0^S = r \sum_{k=1}^{n} \frac{\beta_k q_k}{\gamma_k + \mu},$$

where

$$q_i := \prod_{j=1}^{i-1} \frac{\gamma_j}{\mu + \gamma_j}.$$

SIS models with differential susceptibilities and infectivities. There are also cases in which diseases are transmitted among both different susceptible groups and different infective groups. We briefly describe a DSDI model as follows. The reader is referred to [Hyman and Li (2006)] for further details.

We consider the spread of a disease in a randomly mixing population that approaches a steady state, S^0, if there is no disease infection. We assume that infected individuals become fully immune or are removed from the susceptible population after they recover from the infection. We approximate the transmission dynamics with an SIR model. We assume that susceptibles may have different susceptibility and divide them into n groups, $S_1, S_2, \ldots, S_n$. Here, the individuals in each group have homogeneous susceptibility, but the susceptibilities of individuals from different groups are distinct. The susceptibles are distributed into the n susceptible subgroups, based on their inherent susceptibility, in such a way that the input flow into group S_i is $p_i \mu S^0$ with $\sum_{i=1}^{n} p_i = 1$. The infectives are divided into m groups, $I_1, I_2, \ldots, I_m$, such that a susceptible individual in group S_i can be infected by infectives in all groups, and upon infection, enters group I_j with probability q_{ij} and stays in this group until becoming recovered or removed, where $\sum_{j=1}^{m} q_{ij} = 1$, for $i = 1, 2, \ldots, n$.

We assume full immunity of recovered individuals or complete isolation after individuals are infected and diagnosed, and we group all these individuals to group R. The transmission dynamics of infection are governed by the system of differential equations

$$\begin{aligned}
\frac{\mathrm{d}S_i}{\mathrm{d}t} &= \mu(p_i S^0 - S_i) - \lambda_i S_i, \quad i = 1, \ldots, n, \\
\frac{\mathrm{d}I_j}{\mathrm{d}t} &= \sum_{i=1}^{n} q_{ij}\lambda_i S_i - (\mu + \delta_j + \nu_j) I_j, \quad j = 1, \ldots, m, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \sum_{j=1}^{m} \nu_j I_j - (\mu + \delta_r) R,
\end{aligned} \tag{1.44}$$

where μ is the natural death rate coefficient in the absence of infection, ν_j is the recovery or removal rate coefficient for infectives in group I_j, and δ_j and δ_r are the disease-induced death rate coefficients. The rate of infection for susceptibles in group S_i is given by

$$\lambda_i = c(N) \sum_{j=1}^{m} \alpha_i \beta_j \frac{I_j}{N} = \frac{c(N)}{N} \alpha_i \sum_{j=1}^{m} \beta_j I_j, \tag{1.45}$$

where $c(N)$ is the contacts rate with $N = \sum_{i=1}^{n} S_i + \sum_{j=1}^{m} I_j + R$, α_i is the susceptibility of susceptible individuals in group S_i, and β_j is the infectiousness of infected individuals in group I_j. The choice of the function $c(N)$ depends on the modeled disease or situations investigated.

The reproductive number of infection for model (1.44) is defined as

$$R_0 = \sum_{i=1}^{n} p_i c(S^0) \alpha_i \sum_{j=1}^{m} \frac{q_{ij}\beta_j}{\mu + \delta_j + \nu_j}.$$

1.4.4.2. *Models with multiple populations*

Combining epidemiology with population ecology we may study the transmission of disease among multiple populations in a community.

Models for interacting populations in a community. First, we introduce some basic knowledge of population ecology. A group of individuals of a species in a given environment is called a population. Two or several populations, which interact each other in a given environment, is called a community. Usually, a community consisting of two populations may be

classified as one of the following three types of systems according to the relation between the two populations: predator–prey systems, competitive systems, and cooperative systems. We explain the concepts using the following simple but famous Volterra system:

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= x(r_1 - a_1 x - c_1 y), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= y(r_2 - a_2 x - c_2 y), \end{aligned} \tag{1.46}$$

where x and y are, respectively, the numbers of total individuals in the two populations, $r_i = b_i - \mu_i$, $i = 1, 2$, are the so-called intrinsic growth rate coefficients with b_i and μ_i being the birth and death rate coefficients, a_1 and c_2 are the density dependence coefficients, which are both positive so that the two populations follow the logistic dynamics (see below) in the absence of interaction, and c_1 and a_2 are the interactive coefficients.

(1) If $c_1 > 0$ and $a_2 < 0$, system (1.46) is a predator–prey system with x and y regarded as the numbers of prey and predators, respectively. Then, $c_1 x$ is the number of prey eaten by one predator per unit of time at time t, and is called the functional response of predators to prey, $-a_2 xy$ is the production of predators per unit of time at time t, which comes from the predation $c_1 xy$. Here $-a_2 = kc_1$, with k being the transform rate coefficient from eating the prey to the production of the predator. The functional response $c_1 x$ is proportional to the number of prey population size, which may not be appropriate if x is very large. Hence we sometimes consider the saturation of the predation, and use some other functional responses. The Holling-II functional response $\varphi(x) = ax/(1 + bx)$ is often used, and the ratio functional response

$$\varphi\left(\frac{x}{y}\right) = \frac{ax/y}{1 + bx/y}$$

is also used and even probably more appropriate in some cases.

(2) If $c_1 > 0$ and $a_2 > 0$, system (1.46) is a competitive system. The two populations x and y compete for same limited resource in an environment such that the appearance of population $x(y)$ affects the growth of the other population $y(x)$.

(3) System (1.46) is a cooperative system if $c_1 < 0$ and $a_2 < 0$. The two populations are cooperative with each other. The existence of population $x(y)$ increase the growth of the other population $y(x)$, as the cooperation between bees and flowers.

It should be pointed out that the density dependence affects not only the birth but also the death of the populations. Hence, we need to separate the effects of the density dependence, in some cases. For example, we may have

$$a_1x^2 = a_1[p + (1-p)]x^2, \tag{1.47}$$

where the part p affects the birth rate and the part $(1-p)$ affects the death rate. Thus the first equation in model (1.46) can be rewritten as

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \{(b_1 - a_1px) - [\mu_1 + (1-p)a_1x]\}x - cxy.$$

It also should be pointed out that without predation, the first equation in the system (1.46) can be written as

$$\frac{\mathrm{d}x}{\mathrm{d}t} = x(r_1 - a_1x) = r_1x\left(1 - \frac{x}{K}\right) \tag{1.48}$$

and is called the **logistic equation**, where $K = r_1/a_1$ is the carrying capacity of the environment to the population x, that is the maximum size of the population the environment can support. This can be seen from the logistic equation that the population grows if $x < K$, stops growing at $x = K$, and decays if $x > K$.

It follows from (1.47), logistic equation (1.48) can be rewritten as

$$\frac{\mathrm{d}x}{\mathrm{d}t} = x\left[\left(b_1 - \frac{pr}{K}x\right) - \left(\mu_1 + \frac{(1-p)r}{K}x\right)\right].$$

This decomposition has been introduced by Gao and Hethcote (1992), which implies that population satisfies the logistic equation with the birth rate coefficient $b_1 - prx/K$ and the death rate coefficient $\mu_1 + (1-p)rx/K$, where $r = b_1 - \mu_1 > 0$ and $0 \le p \le 1$. The density dependence affects only the death when $p = 0$, the birth when $p = 1$, and both when $0 < p < 1$.

Disease spreads only in the prey population. Anderson and May incorporated the spread of infectious disease into a predator–prey model in 1986. In that model, they assume that the disease is transmitted only within the prey species, and that the incidence is bilinear. The model is

given by the system

$$\begin{aligned}
\frac{\mathrm{d}H}{\mathrm{d}t} &= rX - (\mu_1 + \alpha)Y - c[(1-f)X + Y]P - \mu_1 X,\\
\frac{\mathrm{d}Y}{\mathrm{d}t} &= \beta XY - (\mu_1 + \alpha)Y - cYP,\\
\frac{\mathrm{d}P}{\mathrm{d}t} &= \delta HP - \mu_2 P,
\end{aligned} \tag{1.49}$$

where H is the prey population size, X and Y are the numbers of the susceptibles and infectives in the prey population, respectively, with $H = X + Y$ and P is the predator population size. The parameters r, μ_1, and α are the birth, natural death, and disease-induced death rate coefficients of the prey population, respectively. The parameter μ_2 is the natural death rate coefficient of the predators, δ is the conversion rate coefficient of the prey to predator, and c the catching rate coefficient of the predators. The parameter f describes the catching difference between the susceptible and infected prey. It is assumed that the infected prey individuals have no fertility and incidence βXY is bilinear.

The results of their study show that the disease dies out when the prey population size H is reduced to a certain level H_T due to predation. Nevertheless. the predator population goes to extinct if the level H_T is too low. Moreover, it is shown that model (1.49) has a stable limit cycle which implies that the presence of the disease may result in a stable periodic oscillation of the two species.

Xiao and Chen (2001a, 2002a) investigated prey–predator models with a disease spreads only in the prey population, where time delays are included which describe the conversion of the prey to predator. The model equations [Xiao and Chen (2001a)] are

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= rS\left(1 - \frac{S+I}{K}\right) - \beta SI - p_1 SY,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - cI - p_2 IY,\\
\frac{\mathrm{d}Y}{\mathrm{d}t} &= -dY + kp_1 S(t-\tau)Y(t-\tau) + kp_2 I(t-\tau)Y(t-\tau),
\end{aligned}$$

where S and I are the numbers of susceptibles and infectives in the prey population and Y is the number of individuals in the predator population. The parameters K and r are the carrying capacity of the environment

and the intrinsic growth rate of the prey population, c is the death rate coefficient of the infected prey, μ is the nature death rate coefficient of the predators, $p_1 S$ and $p_2 I$ are the functional response of the predators to the susceptible and infective prey, respectively, β is the adequate contact rate coefficient for the prey population, and k is the conversion rate coefficient of the prey to predator.

Local stability of the equilibria of the models, stability switch caused by the time delay and Hopf bifurcation are investigated by Xiao and Chen (2001a, 2002a).

They also studied a ratio-dependent predator–prey model with disease in the prey and proved the existence of Hopf bifurcation and local stability for the model.

Disease spreads in both predator and prey populations. Hadeler and Freedman (1989) investigated a predator–prey model with disease spreading in both prey and predator populations, in which it is assumed that the predators are infected when swallowing the infected prey, and that the prey are infected by contacting the excrement of the infected predators. The model equations are given by

$$\begin{aligned}
\frac{\mathrm{d}x_0}{\mathrm{d}t} &= ax - a\frac{x_0 x}{K} - \frac{x_0}{A + x_0 + ex_1} y - \beta x_0 y_1, \\
\frac{\mathrm{d}y_0}{\mathrm{d}t} &= -c\frac{B}{B+A} y_0 + c\frac{x_0 + ex_1}{A + x_0 + ex_1} y - k\frac{ex_1}{A + x_0 + ex_1} y_0, \\
\frac{\mathrm{d}x_1}{\mathrm{d}t} &= \beta y_1 x_0 - \frac{ax_1 x}{K} - \frac{ex_1}{A + x_0 + ex_1} y, \\
\frac{\mathrm{d}y_1}{\mathrm{d}t} &= -c\frac{B}{B+A} y_1 + k\frac{ex_1}{A + x_0 + ex_1} y_0,
\end{aligned} \tag{1.50}$$

where x_0 and x_1 are the numbers of the susceptibles and infectives in prey population, y_0 and y_1 are the numbers of the susceptibles and infectives in predator population, $x = x_0 + x_1$ and $y = y_0 + y_1$ are the total sizes of the prey and predators, respectively, a is the birth rate coefficient of the prey population, K is the carrying capacity of the environment to the prey populations, $cB/(B + A)$ is the natural death rate coefficient of the predator population, $x_0/(A + x_0 + ex_1)$ and $ex_1/(A + x_0 + ex_1)$ are the functional responses of predators to the susceptible and infected prey, respectively, constant $e > 1$ represents the fact that the infected prey are easier to be catched, c is the conversion rate coefficient from the prey to

predator, k is the coefficient of infection of the predators who swallow infected prey, and $\beta x_0 y_1$ is the incidence.

The authors studied the existence and local stability of the equilibria and periodic solutions for model (1.50) in the two cases where the corresponding predator–prey system without disease has a positive equilibrium and a periodic solution, respectively. Their numeric simulation also shows that the positive equilibrium or the positive periodic solution is globally asymptotically stable without analytic proofs.

Han *et al.* (2001) and Han (2002) investigated four types of predator–prey models with disease spreading simultaneously in both populations which are SIS and SIR models with bilinear incidence and standard incidence, respectively. It is assumed that the infection of the prey population is caused by intraspecific contacts, and that of the predator population is caused by, in addition to intraspecific contacts, swallowing infected prey. As an example, we only present an SIS model with standard incidence described by the following system:

$$\begin{aligned}
\frac{\mathrm{d}S_1}{\mathrm{d}t} &= \left(b_1 - \frac{a_1 r_1 N_1}{K_1}\right) N_1 - \left[\mu_1 + (1-a_1)\frac{r_1 N_1}{K_1}\right] S_1 \\
&\quad - aN_2 S_1 - \beta_1 \frac{S_1}{N_1} I_1 + \gamma_1 I_1, \\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta_1 \frac{S_1 I_1}{N_1} - \gamma_1 I_1 - \left[\mu_1 + (1-a_1)\frac{r_1 N_1}{K_1}\right] I_1 - aN_2 I_1, \\
\frac{\mathrm{d}N_1}{\mathrm{d}t} &= \left[r_1\left(1 - \frac{N_1}{K_1}\right) - aN_2\right] N_1, \\
\frac{\mathrm{d}S_2}{\mathrm{d}t} &= kaN_1 N_2 - \alpha \frac{S_2 I_1}{N_2} - \mu_2 S_2 - \beta_2 \frac{S_2 I_2}{N_2} + \gamma_2 I_2, \\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta_2 \frac{S_2 I_2}{N_2} - \mu_2 I_2 + \alpha \frac{S_2 I_1}{N_2} - \gamma_2 I_2, \\
\frac{\mathrm{d}N_2}{\mathrm{d}t} &= (kaN_1 - \mu_2) N_2, \\
N_i &= S_i + I_i, \quad i = 1, 2, \\
r_1 &= b_1 - \mu_1 > 0, \quad 0 \le a_1 \le 1,
\end{aligned} \tag{1.51}$$

where N_1 and N_2 are the population sizes of the prey and predators, respectively, a is the coefficient of predation, β_i, $i = 1, 2$, are the adequate intraspecific contact rate coefficients, α is the adequate interspecific contact rate coefficient, and k is the conversion rate coefficient.

Here the density dependence in the prey population is introduced as follows. The term $(a_1 r_1 N_1/K_1)N_1$ is for the density-dependent birth rate of the prey population. The density-dependent death $[(1-a_1)rN_1/K_1]N_1$ is further divided into two parts: $(1-a_1)rN_1S_1/K_1$ and $(1-a_1)rN_1I_1/K_1$, which represent the natural death rates of the susceptibles and infectives in the prey population, respectively. We note that density dependence is not considered in the predator population.

Since $N_i = S_i + I_i$, model (1.51) can be simplified to

$$\begin{aligned}
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta_1 \frac{(N_1 - I_1)}{N_1} I_1 - \gamma_1 I_1 - \left[\mu_1 + (1-a_1)\frac{r_1 N_1}{K_1}\right] I_1 - aN_2 I_1, \\
\frac{\mathrm{d}N_1}{\mathrm{d}t} &= \left[r_1\left(1 - \frac{N_1}{K_1}\right) - aN_2\right] N_1, \\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta_2 \frac{(N_2 - I_2)}{N_2} I_2 - \mu_2 I_2 - \gamma_2 I_2 + \alpha \frac{(N_2 - I_2)}{N_2} I_1, \\
\frac{\mathrm{d}N_2}{\mathrm{d}t} &= (kaN_1 - \mu_2)N_2, \\
N_i &\geq I_i \geq 0, \quad i = 1, 2, \;\; 0 \leq a_1 \leq 1.
\end{aligned} \tag{1.52}$$

Model (1.52) has five boundary equilibria and one positive equilibrium. Threshold conditions, which determine the global stability of each equilibrium, and other results were obtained [Han *et al.* (2001)].

Disease spread in two competing populations. In 2003, Han and coworkers discussed the spread of a disease in two competitive populations to formulate SIS and SIRS models with bilinear incidence and standard incidence and obtained more completed results [Han *et al.* (2001, 2003)]. We introduce an SIS model with standard incidence as an example. The model is the following

$$\begin{aligned}
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \frac{N_1 - I_1}{N_1}(\beta_{11} I_1 + \beta_{12} I_2) - \gamma_1 I_1 - \left[\mu_1 + (1-a_1)\frac{r_1 N_1}{K_1}\right] I_1 - mN_2 I_1, \\
\frac{\mathrm{d}N_1}{\mathrm{d}t} &= \left[r_1\left(1 - \frac{N_1}{K_1}\right) - mN_2\right] N_1,
\end{aligned}$$

$$\begin{aligned}\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \frac{N_2 - I_2}{N_2}(\beta_{21}I_1 + \beta_{22}I_2) - \gamma_2 I_2 \\ &\quad - \left[\mu_2 + (1-a_2)\frac{r_2 N_2}{K_2}\right] I_2 - nN_1 I_2, \\ \frac{\mathrm{d}N_2}{\mathrm{d}t} &= \left[r_2\left(1 - \frac{N_2}{K_2}\right) - nN_1\right] N_2, \\ N_i &\geq I_i \geq 0, \quad 0 \leq a_i \leq 1, \quad i = 1, 2,\end{aligned} \tag{1.53}$$

where m and n are the coefficients of competition, β_{ii}, $i = 1, 2$, are the adequate contact rate coefficients for the contacts within species and β_{ij}, $i \neq j$, are for those between species.

The model (1.53) exists six boundary equilibria and one positive equilibrium. The existence and global attractivity of each equilibrium have been discussed completely [Han *et al.* (2001)].

1.4.4.3. *Models with vector-host*

There are diseases whose infections are acquired through vectors rather than the direct contacts within the infectives in a population. For instance, the transmission of malaria to human beings is from infected mosquitoes, the transmission of schistosomiasis to human beings is from infected snails. In the following, we introduce the idea for modeling of these vector-borne diseases by a simple malaria model proposed first by Ross (1911).

Let $N_h(t)$ denote the human population size in a given region at time t, $I_h(t)$ the proportion of the infective human beings at time t, $N_m(t)$ the number of female mosquitoes at time t (only female mosquitoes bite human beings because they need blood to produce eggs), and $I_m(t)$ the proportion of infective mosquitoes. Then $k := N_m/N_h$ is the average number of female mosquitoes possessed by a host (human). Suppose that a is the biting rate per female mosquito, that is, the number of bites per female mosquito, per unit of time, β_h and β_m are the probabilities that a bite leads to infection to a susceptible human and to a susceptible mosquito, respectively, γ is the recovery rate coefficient of infective humans, and μ is the death rate coefficient of mosquitoes. Hence, the average number of bites by female mosquitoes per human, per unit of time, is aN_m/N_h, and the probability of infection for one susceptible person per unit of time is $\beta_h aN_m I_m/N_h = \beta_h akI_m$. Noticing that the proportion of the susceptible human beings at

time t is $1 - I_h(t)$, we obtain the following system of equations:

$$\begin{aligned} \frac{\mathrm{d}I_h}{\mathrm{d}t} &= \beta_h a k I_m(1 - I_h) - \gamma I_h, \\ \frac{\mathrm{d}I_m}{\mathrm{d}t} &= \beta_m a I_h(1 - I_m) - \mu I_m. \end{aligned} \tag{1.54}$$

Model (1.54) always has a disease-free equilibrium $(0, 0)$. When the reproductive number $R_0 := a^2\beta_m\beta_h k/(\gamma\mu) > 1$, (1.54) also has a unique endemic equilibrium $E^*(I_h^*, I_m^*)$, where

$$I_h^* = \frac{ak\beta_h(1 - 1/R_0)}{ak\beta_h + \gamma}, \quad I_m^* = \frac{a\beta_m(1 - 1/R_0)}{a\beta_m + \mu}.$$

It can be proved that if the reproductive number $R_0 < 1$, the disease-free equilibrium $E_0(0, 0)$ is asymptotically stable, and if $R_0 > 1$, E_0 becomes unstable, and the endemic equilibrium $E^*(I_h^*, I_m^*)$ is asymptotically stable. It is easy to see that when the biting rate of a mosquito during its whole lifespan, a/μ, increases, the reproductive number R_0, the proportions of the infected humans I_h^* and the infected mosquitoes I_m^* (if $R_0 > 1$) all increase. Unfortunately, this does not always agree with the reality. It follows from the data acquired by experiments that the proportion of the infected mosquitoes is less than 10% even if in highly infected regions. This can be improved by introducing latent periods in the infected mosquitoes. We explain it as follows.

During the life-cycle of malaria transmission, gametocytes are ingested by a mosquito when it ingests human blood. Within the mosquito the gametocytes develop into gametes that fuse to form zygotes. They become motile ookinete form which bore through the gut wall of the vector and form an oocyst from which large numbers of sporozoites are released. These sporozoites then invade the salivary glands of the mosquito from which they are injected into human host when the vector feeds. Hence, there is a latent period, denoted by τ, between a mosquito being infected and becoming infectious. Let $E_m(t)$ be the proportion of the mosquitoes in the exposed (latent) compartment. Model (1.54) can be modified to as the following model with time delay:

$$\begin{aligned} \frac{\mathrm{d}I_h}{\mathrm{d}t} &= \beta_h a k I_m(1 - I_h) - \gamma I_h, \\ \frac{\mathrm{d}E_m}{\mathrm{d}t} &= a\beta_m I_h(t)[1 - I_m(t) - E_m(t)] - \mu E_m(t) \\ &\quad - a\beta_m I_h(t - \tau)[1 - I_m(t - \tau) - E_m(t - \tau)]\mathrm{e}^{-\mu\tau}, \\ \frac{\mathrm{d}I_m}{\mathrm{d}t} &= a\beta_m I_h(t - \tau)[1 - I_m(t - \tau) - E_m(t - \tau)]\mathrm{e}^{-\mu\tau} - \mu I_m(t). \end{aligned} \tag{1.55}$$

It can be shown that the reproductive number of infection for model (1.55) is

$$\bar{R}_0 = R_0 \mathrm{e}^{-\mu\tau} = \frac{a^2\beta_m\beta_h k}{\gamma} \times \frac{\mathrm{e}^{-\mu\tau}}{\mu},$$

and the corresponding components I_h^* and I_m^* are

$$I_h^* = \frac{ak\beta_h \mathrm{e}^{-\mu\tau}(1-1/\bar{R}_0)}{ak\beta_h \mathrm{e}^{-\mu\tau}+\gamma}, \quad I_m^* = \frac{a\beta_m \mathrm{e}^{-\mu\tau}(1-1/\bar{R}_0)}{a\beta_m \mathrm{e}^{-\mu\tau}+\mu}.$$

Another point of view to investigate the epidemic models for vector-borne diseases, such as malaria, is to transform approximately the infected mosquitoes into the infective hosts by means of transformation of time scales. In this way, we need only to investigate the host population in the model. Let us explain it, using an example [Takeuchi *et al.* (2000)], as follows.

Consider an SIR malaria model with vital dynamics included in the human population where the human population size is a constant, N, such that the death rate and birth rate coefficients are the same, denoted by $\tilde{\mu}$, and assume that all human newborns are susceptible. We also assume a constant mosquito population, V_{T}, such that the death rate and birth rate coefficients are the same, denoted by δ, and assume V_{T} is sufficiently larger than N so that $q = N/V_{\mathrm{T}} \ll 1$. We divide the mosquito population into two groups: susceptibles, V_{s}, and infectives, V_{i}, and let τ be the latent period for an infected mosquito to become infectious. Under these assumptions, we have the following equations for the human population

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= -\tilde{\beta}S(t)V_{\mathrm{i}}(t) - \tilde{\mu}S(t) + \bar{\mu}N,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \tilde{\beta}S(t)V_{\mathrm{i}}(t) - \tilde{\lambda}I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \tilde{\lambda}I(t) - \tilde{\mu}R(t),
\end{aligned} \tag{1.56}$$

where $\tilde{\beta}$ is the transmission rate coefficient from mosquitoes to humans, $\tilde{\lambda}$ is the recovery rate, and $N(t) = S(t)+I(t)+R(t) = N(t_0)$; and the following equations for the mosquito population:

$$\begin{aligned}
\frac{\mathrm{d}V_{\mathrm{s}}}{\mathrm{d}t} &= -k\mathrm{e}^{\delta\tau}I(t-\tau)V_{\mathrm{s}}(t-\tau) - \delta V_{\mathrm{s}}(t) + \delta[V_{\mathrm{s}}(t)+V_{\mathrm{i}}(t)],\\
\frac{\mathrm{d}V_{\mathrm{i}}}{\mathrm{d}t} &= k\mathrm{e}^{\delta\tau}I(t-\tau)V_{\mathrm{s}}(t-\tau) - \delta V_{\mathrm{i}}(t),
\end{aligned} \tag{1.57}$$

where k is the the transmission rate coefficient from humans to mosquitoes, δ is the birth and death rate coefficient, and $V_{\rm s}(t)+V_{\rm i}(t)=V_{\rm T}(t)=V_{\rm T}(t_0)$, and the term $k{\rm e}^{\delta\tau}I(t-\tau)V_{\rm s}(t-\tau)$ is the number of mosquitoes who were infected at time $t-\tau$, are still alive after the latent period τ, and become infectious, at time t .

Now we set the two models in dimensionless forms by the transformations

$$s(t)=\frac{S(t)}{N},\quad i(t)=\frac{I(t)}{N},\quad r(t)=\frac{R(t)}{N};$$

and

$$v_{\rm s}(t)=\frac{V_{\rm s}(t)}{V_T},\quad v_{\rm i}(t)=\frac{V_{\rm i}(t)}{V_{\rm T}}.$$

Notice that the time scales for human beings and mosquitoes are quite different, where $\sigma=kNt$ (slow scale) such that $\sigma=1$ at $t_\sigma=1/(kN)$, which is the mean duration of infection for human beings; $\rho=kV_{\rm T}t$ (fast scale) such that $\rho=1$ at $t_\rho=1/(kV_{\rm T})$, which is the mean duration of infection for mosquitoes. Hence, $t_\rho=qt_\sigma$ and $q=N/V_{\rm T}\ll 1$. We uniform the two scales by using the slow scale σ.

Now, we let $t=\rho/(kV_{\rm T})$. It follows from model (1.57) that

$$\begin{aligned}\frac{{\rm d}v_{\rm i}}{{\rm d}\rho}&=q\left[{\rm e}^{-\delta\tau}i(t-\tau)v_{\rm s}(t-\tau)-\frac{\delta}{kN}v_{\rm i}(t)\right],\\ \frac{{\rm d}v_{\rm s}}{{\rm d}\rho}&=-\frac{{\rm d}v_{\rm i}(t)}{{\rm d}\rho}.\end{aligned}\tag{1.58}$$

It can be derived easily from the first expression of (1.58) that

$$-\frac{q\delta}{kN}\le\frac{{\rm d}v_i}{{\rm d}\rho}\le q{\rm e}^{-\delta t},$$

and hence

$$\frac{{\rm d}v_i}{{\rm d}\rho}\to 0\quad\text{if } q\to 0.$$

Thus, when $q=N/V_{\rm T}$ is small enough,

$$\frac{{\rm d}v_{\rm i}}{{\rm d}\rho}=q\left[{\rm e}^{-\delta\tau}i(t-\tau)v_{\rm s}(t-\tau)-\frac{\delta}{kN}v_{\rm i}(t)\right]\approx 0,$$

that is,

$$v_{\rm i}(t)\approx\frac{kN}{\delta}{\rm e}^{-\delta\tau}i(t-\tau)v_{\rm s}(t-\tau).\tag{1.59}$$

Since $v_{\rm s}(t)+v_{\rm i}(t)\equiv 1$, $v_{\rm s}\approx 1$ if the death rate coefficient δ for mosquitoes is sufficiently large such that $kN{\rm e}^{-\delta\tau}/\delta \ll 1$, that is, $\delta{\rm e}^{\delta\tau}\gg kN$. (Note that the assumption of a large death rate for mosquitoes is more realistic.) Hence, it follows from (1.59) that

$$v_{\rm i}(t)\approx \frac{kN}{\delta}{\rm e}^{-\delta\tau}i(t-\tau). \tag{1.60}$$

Next, let $t=\frac{\sigma}{kN}$ and denote

$$s(t):=s\left(\frac{\sigma}{kN}\right)=\bar{s}(\sigma),\quad i(t):=i\left(\frac{\sigma}{kN}\right)=\bar{i}(\sigma),\quad r(t):=r\left(\frac{\sigma}{kN}\right)=\bar{r}(\sigma).$$

By straightforward calculations and using the approximate equality (1.60), models (1.56) and (1.57) can be combined into the following system:

$$\begin{aligned}
\frac{{\rm d}\bar{s}(\sigma)}{{\rm d}\sigma}&=-\beta\bar{s}(\sigma)\bar{i}(\sigma-\tau)-\mu\bar{s}(\sigma)+\mu,\\
\frac{{\rm d}\bar{i}(\sigma)}{{\rm d}\sigma}&=\beta\bar{s}(\sigma)\bar{i}(\sigma-\tau)-\mu\bar{i}(\sigma)+\lambda\bar{i}(\sigma),\\
\frac{{\rm d}\bar{r}(\sigma)}{{\rm d}\sigma}&=\lambda\bar{i}(\sigma)-\mu\bar{r}(\sigma),
\end{aligned}\tag{1.61}$$

where

$$\beta=\frac{\tilde{\beta}V_{\rm T}{\rm e}^{-\delta\tau}}{\delta},\quad \mu=\frac{\tilde{\mu}}{kN},\quad \lambda=\frac{\tilde{\lambda}}{kN}.$$

System (1.61) represents a vector-borne SIR model with an incubation time τ.

Model (1.61) can be further more realistically improved as follows. Assume that the incubation time τ is not the same for whole vector population, but distributed over the interval $[0,h]$, where $h\in R_+$ is the superior limit of incubation time. Then, if we replace the incidence $\beta\bar{s}(\sigma)\bar{i}(\sigma-\tau)$ by $\beta\bar{s}(\sigma)\int_0^h f(\tau)\bar{i}(\sigma-\tau){\rm d}\tau$, system (1.61) becomes

$$\begin{aligned}
\frac{{\rm d}\bar{s}(\sigma)}{{\rm d}\sigma}&=-\beta\bar{s}(\sigma)\int_0^h f(\tau)\bar{i}(\sigma-\tau){\rm d}\tau-\mu\bar{s}(\sigma)+\mu,\\
\frac{{\rm d}\bar{i}(\sigma)}{{\rm d}\sigma}&=\beta\bar{s}(\sigma)\int_0^h f(\tau)\bar{i}(\sigma-\tau){\rm d}\tau-\mu\bar{i}(\sigma)+\lambda\bar{i}(\sigma),\\
\frac{{\rm d}\bar{r}(\sigma)}{{\rm d}\sigma}&=\lambda\bar{i}(\sigma)-\mu\bar{r}(\sigma),
\end{aligned}\tag{1.62}$$

where f is the distribution function of incubation time τ among the vector, $\int_0^h f(\tau){\rm d}\tau=1$.

System (1.62) needs the following appropriate initial conditions: $x_{\sigma_0} = \phi(\theta), \theta \in [-h, 0]$, where $x_{\sigma_0} = (\bar{s}(\sigma_0+\theta), \bar{i}(\sigma_0+\theta), \bar{r}(\sigma_0+\theta))$, for any $\sigma_0 \in R$, $\phi \in C\colon [-h, 0] \to \Omega = \{x \in R^3_{+0} : \bar{s}_\sigma + \bar{i}_\sigma + \bar{r}_\sigma \leq 1, x = (\bar{s}_\sigma, \bar{i}_\sigma, \bar{r}_\sigma)\}$.

Note that model (1.62) neglects a possible latent component for the human population as pointed out by Takeuchi *et al.* (2000). Further improvement of the model is needed.

1.4.5. *Epidemic models with age structure*

Age is one of the most important characteristics in the modeling of populations and infectious diseases. Individuals with different ages may have different reproductive and survival capacities. Diseases may have different infection rates and mortality rates for different age groups. Individuals of different ages may also have different behaviors. Young individuals tend to be more active in interactions within or between populations, and in disease transmissions. STDs are spread through partner interactions with pair formations, and the pair formations are clearly age dependent in most cases. Most AIDS cases occur in the group of young people. Childhood diseases, such as measles, chickenpox, and rubella, are spread mainly by contracts between children of similar ages. More than half of the deaths attributed to malaria are in children under 5 years of age due to their weaker immune systems [Anderson and May (1991)]. All of these suggests that age structure needs to be incorporated into epidemic models in many cases [Gurtin and MacCamy (1985); Webb (1985); Charlesworth (1994); Iannelli (1995); Hethcote (2000); Li and Brauer (2008)].

In this section, we consider three types of age-structured epidemic models: those with discrete age structure, continuous age structure, and age groups or stages, respectively.

To have better understanding of epidemic models with age structure, we first introduce age-structured population models.

1.4.5.1. *Population models with age structure*

Discrete age-structured population growth model. We partition the age interval into n equal subintervals, and discretize the time interval with the step size as same as the length of the age subintervals, starting with t_0. Let N_{ij} $(i = 1, 2, \ldots, n; j = 1, 2, 3, \ldots)$ be the number of individuals whose age is in the ith age subinterval at time j, p_i is the probability that individuals at the ith age subinterval survive to the $(i+1)$th age subinterval,

that is, $N_{i+1,j+1} = p_i N_{ij}$, and B_i is the number of newborns produced by an individual at ith age subinterval. We assume density independence. Then the discrete age-structured population growth model is given by

$$\begin{aligned} N_{1,j+1} &= B_1 N_{1j} + B_2 N_{2j} + \cdots + B_n N_{nj}, \\ N_{2,j+1} &= p_1 N_{1j}, \\ &\vdots \\ N_{n,j+1} &= p_{n-1} N_{n-1,j}, \end{aligned}$$

or in the vector form

$$\mathbf{N}_{j+1} = \mathbf{A}\mathbf{N}_j, \tag{1.63}$$

where

$$\mathbf{N}_j = \begin{bmatrix} N_{1j} \\ N_{2j} \\ \vdots \\ N_{nj} \end{bmatrix}, \quad \mathbf{A} = \begin{bmatrix} B_1 & B_2 & B_3 & \cdots & B_{n-1} & B_n \\ p_1 & 0 & 0 & \cdots & 0 & 0 \\ 0 & p_2 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \cdots & p_{n-1} & 0 \end{bmatrix}.$$

Equation (1.63) is called the **Leslie matrix model** [Leslie (1945, 1948)].

Continuous age-structured population growth model. When population size is sufficiently large or generations overlap, models with a continuous distribution in age are more appropriate for modeling of population growth.

Let $f(a,t)\mathrm{d}a$ be the number of individuals whose age is between a and $a + \mathrm{d}a$, at time t, where $f(a,t)$ is called the age distribution function such that the number of individuals whose age is between $a - \mathrm{d}a$ and a at time t is $f(a - \mathrm{d}a, t)\mathrm{d}a$. Suppose that the probability of death for individuals whose age is between $a - \mathrm{d}a$ and a in unit of time is $\mu(a - \mathrm{d}a)$, such the number of deaths for those individuals growing from age interval $[a - \mathrm{d}a, a]$ to $[a, a + \mathrm{d}a]$ is

$$\mu(a - \mathrm{d}a) f(a - \mathrm{d}a, t)\mathrm{d}a.$$

Thus we have

$$[f(a-\mathrm{d}a,t)-f(a,t+\mathrm{d}t)]\mathrm{d}a=\mu(a-\mathrm{d}a)f(a-\mathrm{d}a,t)\mathrm{d}a\mathrm{d}t. \tag{1.64}$$

Notice that age and time have the same scale so that $\mathrm{d}a = \mathrm{d}t$. Then expanding the both sides of (1.64) in Taylor series, keeping the terms of first degree, and factoring out $\mathrm{d}t$, we obtain

$$\frac{\partial f}{\partial t}+\frac{\partial f}{\partial a}+\mu(a)f=0. \tag{1.65}$$

Equation (1.65) is a hyperbolic partial differential equation with first order. To find the boundary condition, let $B(a)\mathrm{d}a$ express the mean number of offspring produced by an individual with age between a and $a+\mathrm{d}a$. Notice that $f(0,t)\mathrm{d}a$ is the number of all newborns in the population at time t. Thus

$$f(0,t)=\int_0^{+\infty}B(a)f(a,t)\mathrm{d}a.$$

Therefore, the system with definite conditions satisfied by the age distribution function of the population is the following:

$$\begin{aligned} &f_t+f_a+\mu(a)f=0,\\ &f(0,t)=\int_0^{+\infty}B(a)f(a,t)\mathrm{d}a,\\ &f(a,0)=f_0(a), \end{aligned} \tag{1.66}$$

where $f_0(a)$ is an initial age distribution.

Population growth model with age groups or stages. In many circumstances, vital dynamics of individuals are approximately homogeneous in a given age interval, but significantly different compared to those in a different age interval. Then, under certain conditions, the age-structured partial differential equation model (1.66) can be reduced to a system of ordinary differential equations [Hethcote (1997); Li and Hallam (1988); Tudor (1985)].

Partition the age interval into n subintervals $[0,a_1)$, $[a_1,a_2),\ldots,$ $[a_{n-1},a_n)$, where $a_n\le\infty$.

Define the group of individuals with ages in interval $[a_{i-1}, a_i]$, where $a_0 = 0$, by $N_i(t)$ such that $N_i(t) = \int_{a_{i-1}}^{a_i} f(t,a)\mathrm{d}a$, $i = 1, \ldots, n$. Then integrating the partial differential equation in (1.66) from 0 to a_1, we have

$$\frac{\mathrm{d}N_1(t)}{\mathrm{d}t} + f(t,a_1) - f(t,a_0) + \int_0^{a_1} \mu(t,a) f(t,a)\mathrm{d}a = 0. \tag{1.67}$$

Assume that individuals with ages in each interval have the same vital rates such that $B(a) = B_i$, $\mu(t,a) = \mu_i$, for a in $[a_{i-1}, a_i]$, $i = 1, \ldots, n$. Here B_i and μ_i are age independent, but may be density dependent. Then, in age interval $[0, a_1]$, we have

$$f(t,0) = \sum_1^n B_i N_i(t), \quad \int_0^{a_1} \mu f(t,a)\mathrm{d}a = \mu_1 N_1(t),$$

which leads to

$$\frac{\mathrm{d}N_1}{\mathrm{d}t} = \sum_1^n B_i N_i - m_1 N_1 - \mu_1 N_1. \tag{1.68}$$

Here m_1 is the age progression rate from groups 1 to 2, defined by $m_1 = f(t,a_1)/N_1(t)$, and we assume it is time independent.

Integrating (1.66) from a_{i-1} to a_i for $2 \le i \le \infty$, we have

$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = m_{i-1}\ N_{i-1} - (m_i + \mu_i)\, N_i, \quad i = 2, \ldots, n, \tag{1.69}$$

where m_i is the age progression rate from groups i to $i+1$, and we let $m_n = 0$. Then the system (1.66) is reduced into a system of ordinary differential equations.

1.4.5.2. *Epidemic models with age structure*

Epidemic models with continuous age structure. There are many studies on continuous age-structured epidemic models in the literature. See for example, [Busenberg *et al.* (1988, 1991); Capasso (1993); Dietz and Schenzle (1985); Iannelli *et al.* (1992, 1999); Langlais (1995); Li *et al.* (2003); Muller (1998)]. The ideas for modeling are similar as those in the previous sections, but all individuals in every compartment are of continuously age distributed. The following SIS model without disease-induced death is an example [Busenberg *et al.* (1985, 1988)].

Let $s(a,t)$ and $i(a,t)$ be the age distributions of the susceptibles and infectives in a population at time t, and assume that the disease is only transmitted between individuals with the same age. According to the ideas for age-structured population growth models and epidemic compartment SIS models, we have

$$\begin{aligned}
\frac{\partial s(a,t)}{\partial a}+\frac{\partial s(a,t)}{\partial t} &= -\mu(a)s(a,t)-k_0(a)i(a,t)s(a,t)\\
&\quad +\gamma(a)i(a,t),\\
\frac{\partial i(a,t)}{\partial a}+\frac{\partial i(a,t)}{\partial t} &= k_0(a)i(a,t)s(a,t)-(\gamma(a)+\mu(a))i(a,t),\\
s(0,t) &= \int_0^A B(a)[s(a,t)+(1-q)i(a,t)]\mathrm{d}a,\\
i(0,t) &= \int_0^A qB(a)i(a,t)\mathrm{d}a,\\
s(a,0) &= s_0(a),\quad i(a,0)=i_0(a),
\end{aligned} \tag{1.70}$$

where $\mu(a)$ and $B(a)$ are, respectively, the natural death and birth rate coefficients of the individuals with age a, $\gamma(a)$ is the recovery rate coefficient at age a, A is the maximum age of all individuals in the population, and $k_0(a)$ is the infection rate coefficient of the infectives with age a. It also assumed that there exists a vertical transmission with q being the vertical transmission coefficient.

Define $R_0 := q\int_0^A B(a)\mathrm{e}^{\int_0^a[-(\mu(\sigma)+\gamma(\sigma))+p_\infty(\sigma)]\mathrm{d}\sigma}\mathrm{d}a$, where $p_\infty(\sigma) = b_0\mathrm{e}^{-\int_0^a\mu(\sigma)\mathrm{d}\sigma}$ with $b_0\geq 0$, a constant. It is proved in [Busenberg *et al.* (1988)] that the disease-free equilibrium solution is globally asymptotically stable if $R_0<1$, unstable if $R_0>1$, and there exists an endemic equilibrium solution which is globally asymptotically stable if $R_0>1$.

In general, a disease can be transmitted between individuals with different ages. In such a case, the incidence $k_0(a)i(a,t)s(a,t)$ in model (1.70) should be replaced by the term $k_1(a)\int_0^A k_2(a')i(a_1',t)\mathrm{d}a'$, which is the sum of infective forces of all the infectives to the susceptibles with age a.

For some diseases, the course of infection is long and infectives with different infection stages have different infectivities. Then in addition to the chronologic ages, we should also consider infection ages.

Let c denote the infection age, that is the time since infected, and let $f(a,c,t)$ be the distribution function of chronologic age a and infection age c. (We call chronologic age simply age for convenience hereafter.)

We then consider the following epidemic model with age and infection age structures, which was studied by [Zhou *et al.* (2001)]. It is assumed that there is no disease-induced death and all newborns are susceptibles:

$$\begin{cases} \dfrac{\partial s}{\partial a} + \dfrac{\partial s}{\partial t} = -\mu(a)s(a,t) - G(a,t) + \gamma(a)\displaystyle\int_0^a i(a,c,t)\mathrm{d}c, \\ \dfrac{\partial i}{\partial a} + \dfrac{\partial i}{\partial c} + \dfrac{\partial i}{\partial t} = -(\mu(a)+\gamma(a))i(a,c,t), \\ s(0,t) = \displaystyle\int_{A_1}^{A_2} B(a,P(t))p(a,t)\mathrm{d}a, \\ i(a,0,t) = G(a,t) = C(a)S(a,t)\displaystyle\int_0^A \int_0^{a'} \beta(a',c)\frac{i(a',c,t)}{p(a',t)}\rho(a,a',t)\mathrm{d}c\mathrm{d}a', \\ s(a,0) = s_0(a), \quad s(A,t) = 0, \\ i(A,c,t) = 0, \quad i(a,c,0) = i_0(a,c), \end{cases}$$

where $s(a,t)$ and $i(a,c,t)$ are the density functions for susceptibles and infectives, respectively,

$$p(a,t) = s(a,t) + \int_0^a i(a,c,t)\mathrm{d}c$$

is the total population density function such that $P(t) = \int_0^A p(a,t)\mathrm{d}a$ is the total population size at time t, $B(a,P(t))$ is the density-dependent age-specific birth rate, $C(a)$ is the age-specific contact rate, $s_0(a)$ and $i_0(a,c)$ are the initial distributions, $[A_1,A_2]$ is the period of fecundity, $0 < A_1 < A_2 < A$, with A the maximum age, $\beta(a,c)$ is the age-specific probability that a susceptible becomes infected through a contact with an infective with age a and infection-age c, and $\rho(a,a',t)$ is the probability that an individual of age a has contact with an individual of age a', at time t.

We assume proportionate mixing [Busenberg and Castillo-Chavez (1991)] such that

$$\rho(a,a',t) = \rho(a',t) = \frac{C(a')p(a',t)}{\int_0^A C(a)p(a,t)\mathrm{d}a}.$$

Then the reproductive number of infection for model (Sec. 1.4.5.2) is derived as

$$R_0 = \int_0^A \int_0^{a'} C(a'-c)p_\infty(a'-c)\frac{C(a')\beta(a'c)}{\int_0^A C(a')p_\infty(a')\mathrm{d}a'}\pi(a',c)\mathrm{d}c\mathrm{d}a',$$

where

$$p_\infty = P_\infty \frac{\exp(-\int_0^a \mu(\tau))\mathrm{d}\tau}{\exp(-\int_0^a \mu(\tau)d\tau)\mathrm{d}a}$$

is the total population at its demographic steady-state, with P_∞ a positive contact, and

$$\pi(a', c) = \exp\left(-\int_{a'-c}^{a'} [\mu(a) + \gamma(a)]\mathrm{d}a\right)$$

is the survival probability of an infective surviving from $a' - c$ to a'. The global stability of the disease-free steady-state and endemic steady-state are investigated under certain conditions. The reader is refereed to [Zhou *et al.* (2001)] for further details.

Epidemic models with discrete age structure. Since the time unit of collection of data about epidemic transmission is usually days or months, it is more natural and convenient to use models with discrete age structure. Moreover, parameters for discrete age-structure models can be, in general, relatively analyzed and computed easier. In the meantime, many discrete age-structures models exhibit richer dynamics. While continuous age-structured models have been widely used and well developed, taking advantage of the advanced theories of differential equations, integral equations, and dynamic systems, however, theoretic development of discrete systems in epidemic modeling is still in an infant stage, and existing results are relatively fewer. Now we introduce a discrete age-structured SIS model without vertical transmission and disease-induced death in the example below. [See Zhou and Fergola (2004) for further details.]

Let A be the maximum age of the lifespan of individuals, and partition equally the maximum age interval $[0, A]$ into $n + 1$ subintervals. Let $\beta_i\lambda_j$ be the adequate contact rate coefficient for the contact between an infected individual whose age in the interval $[iA/(n+1), (i+1)A/(n+1)]\,(i = 0, 1, \ldots, n)$ and an individual with age in the interval $[jA/(n+1), (j+1)A/(n+1)]$, $j = 0, 1, \ldots, n$, γ_j be the recovery rate coefficient of the infective with age in the interval $[jA/(n+1), (j+1)A/(n+1)]$, μ_j and b_j be the natural death and birth rate coefficients, respectively, and $p_j = 1 - \mu_j$. Then, according to the ideas of constructing population growth models with discrete age structure and

the epidemic compartment models, an SIS model with discrete age structure can be formulated as

$$
\begin{aligned}
&S_0(t+1) = \sum_{k=0}^{n} b_k[S_k(t) + I_k(t)],\\
&I_0(t+1) = 0,\\
&S_{i+1}(t+1) = p_i S_i(t) - \lambda_i \sum_{k=0}^{n} \beta_k I_k(t)\frac{S_i(t)}{N_i(t)} + \gamma_i I_i(t), \quad i = 0, 1, \ldots, n-1,\\
&I_{i+1}(t+1) = p_i I_i(t) + \lambda_i \sum_{k=0}^{n} \beta_k I_k(t)\frac{S_i(t)}{N_i(t)} - \gamma_i I_i(t), \quad i = 0, 1, \ldots, n-1,\\
&S_i(0) = S_{i0} \geq 0, \quad I_i(0) = I_{i0} \geq 0, \quad S_{i0} + I_{i0} = N_i, \quad i = 0, 1, \ldots, n.
\end{aligned}
\tag{1.71}
$$

Consider the function

$$
\begin{aligned}
f(x) = {} & \beta_1\lambda_0 + \beta_2[\lambda_1 + \lambda_0 q_1(x)] + \beta_3[\lambda_2 + \lambda_1 q_2(x) + \lambda_0 q_1(x) q_2(x)] + \cdots\\
& + \beta_n[\lambda_{n-1} + \lambda_{n-2} q_{n-1}(x) + \lambda_{n-3} q_{n-2}(x) q_{n-1}(x) + \cdots\\
& + \lambda_1 q_2(x) q)_3(x) \cdots q_{n-1}(x) + \lambda_0 q_1(x) q_2(x) \cdots q_{n-1}(x),
\end{aligned}
$$

where $q_i(x) = p_i - \gamma_i - \lambda_i x/N_i$, $i = 1, 2, \ldots, n-1$. By defining the basic reproductive number $R_0 = f(0)$, it is proved [Zhou and Fergola (2004)] that the disease-free steady-state is globally asymptotically stable if $R_0 < 1$, unstable if $R_0 > 1$, and that there exists a small endemic steady-state if R_0 is greater and near one. Although sufficient conditions for the uniqueness and global stability of an endemic steady-state have not been obtained for model (1.71), the authors introduced another reproductive number R_{02} and proved that the disease-free steady-state is globally asymptotically stable if $R_{02} < 1$, and the endemic steady-state is globally asymptotically stable if $R_{02} > 1$, for the special case $n = 2$.

Epidemic models with discrete age groups or stages. Epidemic models with age groups or stages have been studied by many authors [Xiao and Chen (2001b, 2002b, 2003); Xiao *et al.* (2002); Lu *et al.* (2003)]. In the following, we introduce an SIS model to show the idea of modeling. The reader is referred to Xiao and Chen (2003) for further details.

Consider a population consisting of only two stages, larva and adult, and assume that a disease is transmitted only among the larvae. Let $x_1(t)$

denote the numbers of the susceptibles in the larvae at time t, $x_2(t)$ the number of adults at time t, $y(t)$ the number of the infected larvae at time t, τ the maturation period, b and μ the birth and natural death rate coefficients, respectively, α the disease-induced death rate coefficient, γ the recovery rate coefficient, and c the coefficient for the density dependence in the adults.

Since the maturation period of the larvae is τ, the number of individuals progressing out of the larva class at time t is just the number of the newborns $bx_2(t-\tau)$ at time $t-\tau$ multiplied by the probability $\mathrm{e}^{-\mu\tau}$ of those newborns who survive to time t. Thus the corresponding model can be described by the following system:

$$\begin{aligned}
\frac{\mathrm{d}x_1(t)}{\mathrm{d}t} &= bx_2(t) - b\mathrm{e}^{-\mu\tau}x_2(t-\tau) - \mu x_1(t) - \beta x_1(t)y(t) + \gamma y(t),\\
\frac{\mathrm{d}y(t)}{\mathrm{d}t} &= \beta x_1(t)y(t) - \mu y(t) - (\gamma+\alpha)y(t),\\
\frac{dx_2(t)}{dt} &= b\mathrm{e}^{-\mu\tau}x_2(t-\tau) - cx_2^2(t).
\end{aligned}$$

Here, it is assumed that the density dependence affects only the death rate of the adults. Results of determining whether the disease dies out or persists have been obtained [Xiao and Chen (2003)].

1.4.6. *Epidemic models with impulses*

Impulse can describe phenomena with sudden, rapid changes in continuous processes, such as changes during seasonal reproductives of some marine animals, and vaccinations given at certain fixed time of a year. In such cases, it is more appropriate to describe their dynamics by means of impulsive differential equations.

1.4.6.1. *Concepts of impulsive differential equations*

Impulsive equations can be classified into two types if the classification is according to the happening time of impulse: equations with fixed times or nonfixed times. If the classification is on the bases of the category of equations, then there are impulsive ordinary differential equations, impulsive delay differential equations, impulsive integral equations, and

so on. In the following, we only introduce impulsive ordinary differential equations with fixed times, which is often used in the population and epidemic models.

In general, differential equations with impulses happening at a fixed times take the following form:

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= f(t,x), \quad t \neq \tau_k, \\ \Delta x_k &= I_k(x(\tau_k)), \quad t = \tau_k, \ k = 1, 2, \ldots, \\ x(t_0) &= x_0, \end{aligned} \tag{1.72}$$

where $f \in C[R \times R^n, R^n]$ satisfies the Lipschitz condition, $t_0 < \tau_1 < \tau_2 < \cdots, I_k \in C[R^n, R^n]$, $\Delta x_k = x(\tau_k+) - x(\tau_k)$, $x_0 \in R^+$, $x(\tau_k^+) = \lim_{n\to 0^+} x(\tau_k + h)$.

Function $x(t)$ is called a **solution** of system (1.72) if it satisfies

(1) $\frac{dx}{dt} = f(t, x(t))$ for $t \in [\tau_k, \tau_{k+1})$;
(2) $\Delta x_k = x(\tau_k^+) - x(\tau_k)$ for $t = \tau_k$, that is, $x(\tau_k^-) = x(\tau_k)$ and $x(\tau_k^+) = x(\tau_k) + \Delta x_k$.

Since impulsive differential equations are nonautonomous, they have no equilibria. When $\Delta\tau_k = \tau_k - \tau_{k-1}$ is a constant, the existence and stability of the periodic solutions are often of interest. For further comprehension with respect to impulsive differential equations, see the related references [Lakshmikantham *et al.* (1989); Bainov and Simeonov (1995)].

1.4.6.2. *Epidemic models consist of impulsive differential equations*

Epidemic models with impulsive birth. We introduce the ideas of the modeling in terms of an SIS model by showing the following example.

Let b and μ denote the birth and natural death rate coefficients, respectively, and k be the carrying capacity of the environment. Assume that there are neither vertical transmission nor disease-induced death, the density dependence only affects the birth, and $\Delta\tau_k = 1$. Notice that the birth happens only at time $t = \tau_k$. Then the impulsive conditions

and the density dependent birth should also only take place at $t = \tau_k$. Thus a corresponding model, investigated by [Han (2002)], is given as follows.

$$\begin{aligned}
\frac{\mathrm{d}N}{\mathrm{d}t} &= -\mu N(t), \quad t \neq k, \\
\frac{\mathrm{d}S}{\mathrm{d}t} &= -\mu S(t) - \beta S(t)I(t) + \gamma I(t), \quad t \neq k, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (\mu + \gamma)I(t), \quad t \neq k, \\
& \qquad\qquad\qquad\qquad\qquad\qquad k = 1, 2, 3, \ldots, \\
N(t^+) &= \left[1 + b - \frac{rN(t)}{K}\right] N(t), \quad t = k, \\
S(t^+) &= S(t) + \left[b - \frac{rN(t)}{K}\right] N(t), \quad t = k, \\
I(t^+) &= I(t), \quad t = k,
\end{aligned}$$

where we write $r = b - \mu$. Since $N = S + I$, we only need to study the following system:

$$\begin{aligned}
\frac{\mathrm{d}N}{\mathrm{d}t} &= -\mu N(t), \quad t \neq k, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta[N(t) - I(t)]I(t) - (\mu + \gamma)I(t), \quad t \neq K, \\
& \qquad\qquad\qquad\qquad\qquad\qquad k = 1, 2, 3, \ldots, \\
N(t^+) &= \left[1 + b - \frac{rN(t)}{K}\right] N(t), \quad t = k, \\
I(t^+) &= I(t), \quad t = k.
\end{aligned}$$

This model always has a disease-free periodic solution $(N_1^*(t), 0)$, and there also exists an endemic periodic solution $(N_2^*(t), I_2^*(t))$, provided $\int_0^1 A(t)\mathrm{d}t > 0$, where $A(t) = \beta N_1^*(t) - (\mu + \gamma)$.

Epidemic models with impulsive vaccinations. Assume, in a population, a fraction, p, of the susceptibles is vaccinated at time $t = k$, $k = 0, 1, 2, \ldots$, and enters into the removed compartment. Then we have an SIR epidemic model with impulsive vaccinations as

follows:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu K - \mu S(t) - \beta S(t)I(t), \quad t \neq k,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (\mu + \alpha + \gamma)I(t), \quad t \neq k,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - \mu R(t), \quad t \neq k, \qquad k = 0, 1, 2, \ldots,\\
S(t^+) &= (1-p)S(t), \quad t = k,\\
I(t^+) &= I(t), \quad t = k,\\
R(t^+) &= R(t) + pS(t), \quad t = k,
\end{aligned} \tag{1.73}$$

where $\mu K = A$ represents recruitment, μ and α are the natural death and disease-induced death rate coefficients, respectively. It is proved in [Jin (2001)] that system (1.73) always has a disease-free periodic solution, $(S^*(t), 0, R^*(t))$, with period 1 and it is globally asymptotically stable if $\sigma < 1$, where

$$\sigma = \frac{\beta K}{\mu + \alpha + \gamma}\left[1 - \frac{p(\mathrm{e}^{\mu} - 1)}{\mu(\mathrm{e}^{\mu} - 1 + p)}\right].$$

1.4.7. *Epidemic models with migration*

The models in the previous sections do not include the diffusion or migration of individuals in space. In fact, with the migration of individuals, the influence of individual diffusions on the spread of a disease should not be neglected. Here, we simply introduce two types of diffusions into the epidemic models.

1.4.7.1. *Epidemic models with migration among different patches*

Although Hethcote (1976) established an epidemic model with migration between two patches, more intensive studies dealing with this aspect only happened in recent years. To explain the ideas of the modeling and the main questions that people are interested in, we introduce the following SIS model as an example.

Wang and Zhao (2004) considered an SIS model with immigration among n patches. It is assumed that in the absence of migration among

patches; that is, the patches are isolated, the dynamic model in the ith patch, $i = 1, 2, \ldots, n$, are given by

$$\frac{\mathrm{d}S_i}{\mathrm{d}t} = B_i(N_i)N_i - \mu_i S_i - \beta_i S_i I_i + \gamma_i I_i,$$

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = \beta_i S_i I_i - (\gamma_i + \mu_i) I_i,$$

where the birth rate coefficient $B_i(N_i)$, for $N_i > 0$, $i = 1, \ldots, n$, satisfies the following common hypothesis:

$$B_i(N_i) > 0, \quad B_i(N_i) \in C^1(0, +\infty), B_i'(N_i) < 0 \quad \text{and} \quad B_i(+\infty) < \mu_i.$$

If the n patches are connected with each other; that is, the individuals between any two patches can migrate, then an SIS epidemic model with migration among the n patches can be formulated as

$$\begin{aligned} \frac{\mathrm{d}S_i}{\mathrm{d}t} &= B_i(N_i)N_i - \mu_i S_i - \beta_i S_i I_i + \gamma_i I_i + \sum_{j=1}^{n} a_{ij} S_j, \\ \frac{\mathrm{d}I_i}{\mathrm{d}t} &= \beta_i S_i I_i - (\mu_i + \gamma_i) I_i + \sum_{j=1}^{n} b_{ij} I_j, \end{aligned} \qquad i = 1, 2, \ldots, n, \tag{1.74}$$

where a_{ii} and b_{ii} ($a_{ii} \leq 0$, $b_{ii} \leq 0$) denote the emigration rates of the susceptibles and the infectives from the ith patch to other patches, respectively; a_{ij} and b_{ij} ($a_{ij} \geq 0$, $b_{ij} \geq 0$) denote the immigration rates of the susceptibles and the infectives from the jth patch to the ith patch, respectively. Model (1.74) assumes that the disease is not fatal, and the death and birth of individuals in the process of migration are neglected. Since the individuals emigrating from the ith patch will move dispersedly to the other $n - 1$ patches, we have

$$-a_{ii} = \sum_{\substack{j=1 \\ j \neq i}}^{n} a_{ji}, \quad -b_{ii} = \sum_{\substack{j=1 \\ j \neq i}}^{n} b_{ji}. \tag{1.75}$$

Under the assumptions that the matrices (a_{ij}) and (b_{ij}) are all irreducible, Wang and Zhao (2004) obtained conditions for the local and global stability of the disease-free equilibrium, and the conditions under which the disease persists in all patches.

For the sake of better understanding, we consider a model with migration only between two patches. In this case, from (1.75) we know

that

$$-a_{11} = a_{21}, \quad -a_{22} = a_{12}, \quad -b_{11} = b_{21}, \quad -b_{22} = b_{12}.$$

Assume that the birth rates satisfy

$$B_i(N_n)N_i = b_i + c_i N_i, \quad c_i < \mu_i, \quad N_i = S_i + I_i, \quad i = 1, 2.$$

Then model (1.75) is simplified as

$$\begin{aligned}
\frac{\mathrm{d}S_1}{\mathrm{d}t} &= b_1 + c_1 I_1 - (\mu_1 - c_1 - a_{11})S_1 - \beta_1 S_1 I_1 + \gamma_1 I_1 - a_{22} S_2, \\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta_1 S_1 I_1 - (\mu_1 + \gamma_1 - b_{11})I_1 - b_{22} I_2, \\
\frac{\mathrm{d}S_2}{\mathrm{d}t} &= b_2 + c_2 I_2 - (\mu_2 - c_2 - a_{22})S_2 - \beta_2 S_2 I_2 + \gamma_2 I_2 - a_{11} S_1, \\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta_2 S_2 I_2 - (\mu_2 + \gamma_2 - b_{22})I_2 - b_{11} I_1,
\end{aligned} \tag{1.76}$$

where $a_{ii} \leq 0$, $b_{ii} \leq 0$, and other parameters are all nonnegative.

In system (1.74), we actually assumed that S_i and I_i are residents in patch i, and that an individual who moves to a new patch will become a resident of the new patch.

Another type of epidemic models with migration describe the transmission from traveling rather than residence. During traveling, susceptibles may get infection when they contact infectives in other patches, and traveling infectives may also transmit a disease to others. We discuss an epidemic model [proposed by Sattenspiel and Dietz (1995)], to describe such situations as follows.

Let S_{ii} be the number of susceptibles, who are the residents in the patch i. They travel to other patches at a rate σ_i per unit of time. These visitors are distributed among the $n-1$ patches with probability v_{ij} to patch j, where $0 \leq v_{ij} \leq 1$, $v_{ii} = 0$, and $\sum_{j=1}^{n} v_{ij} = 1$. Let ρ_{ij} be the rate of the traveling individuals residing in patch i, who return from patch j to patch i, with $\rho_{ii} = 0$. Let I_{jk} be the number of infectives presently in patch k who are residents in patch j, β_{ijk} be the transmission coefficient of an infective from patch j contacting a susceptible from the patch i in patch k. If we omit the death rate, the corresponding SIR epidemic model

with standard incidence can be described as in the following system:

$$\begin{aligned}
\frac{\mathrm{d}S_{ii}}{\mathrm{d}t} &= \sum_{k=1}^{n} \rho_{ik} S_{ik} - \sigma_i S_{ii} - \sum_{j=1}^{n} \beta_{iji} \frac{S_{ii} I_{ji}}{N_i^*}, \\
\frac{\mathrm{d}S_{ik}}{\mathrm{d}t} &= \sigma_i v_{ik} S_{ii} - \rho_{ik} S_{ik} - \sum_{j=1}^{n} \beta_{ijk} \frac{S_{ik} I_{jk}}{N_k^*}, \\
\frac{\mathrm{d}I_{ii}}{\mathrm{d}t} &= \sum_{k=1}^{n} \rho_{ik} I_{ik} - \sigma_i I_{ii} + \sum_{j=1}^{n} \beta_{iji} \frac{S_{ii} I_{ji}}{N_i^*} - \gamma I_{ii}, \\
\frac{\mathrm{d}I_{ik}}{\mathrm{d}t} &= \sigma v_{ik} I_{ii} - \rho_{ik} I_{ik} + \sum_{j=1}^{n} \beta_{ijk} \frac{S_{ik} I_{jk}}{N_k^*} - \gamma I_{ik}, \\
\frac{\mathrm{d}R_{ii}}{\mathrm{d}t} &= \sum_{k=1}^{n} \rho_{ik} R_{ik} - \sigma_i R_{ii} + \gamma I_{ii}, \\
\frac{\mathrm{d}R_{ik}}{\mathrm{d}t} &= \sigma_i v_{ik} R_{ii} - \rho_{ik} R_{ik} + \gamma I_{ik},
\end{aligned} \tag{1.77}$$

where $N_k^* = \sum_{m=1}^{k} (S_{mk} + I_{mk} + R_{mk}), \gamma$ is the recovery rate coefficient. The term $\rho_{ik} S_{ik}$ in the first equation of (1.77) is the number of the residents in patch i who travel back from patch k per unit of time and have not been infected, so that $\sum_{k=1}^{n} \rho_{ik} S_{ik}$ is the number of all susceptibles traveling back from other patches per unit of time, the term $\sigma_i S_{ii}$ represents the number of susceptible residents in patch i who travel out per unit of time, and the term $\sum_{j=1}^{n} \beta_{iji} S_{ii} I_{ji} / N_i^*$ represents the number of newly infected residents in patch i who are infected by the infectives traveling from all other patches to patch i per unit of time.

In the second equation of the system (1.77), S_{ik} is the number of susceptibles presently in patch k who are residents in patch i, the term $\sigma_i v_{ik} s_{ii}$ is the number of susceptibles who presently in patch k but are residents and traveling from patch i per unit of time, $\rho_{ik} S_{ik}$ is the number of susceptibles who traveled to patch k and now return to their home patch i per unit of time, and the term $\sum_{j=1}^{n} \beta_{ijk} S_{ik} I_{jk} / N_k^*$ represents the number of newly infected residents in patch i who traveled to and infected in patch k by infective visitors from all other patches. The meanings of terms in the other equations in (1.77) are similar.

1.4.7.2. *Epidemic models with continuous diffusion in space*

We supposed that individuals in a population and the adequate contacts in a given environment are uniformly distributed in the previous sections.

Nevertheless, it is not always the case in reality. The distribution of individuals and their interactions depend on not only time t, but also location x, in given space Ω. In the following, we explain the idea of modeling by using an SIR model as an example.

Let $S(x,t)$, $I(x,t)$, and $R(x,t)$ be the numbers of susceptibles, infectives, and recovereds at time t and location $x \in \Omega$, respectively, Δ represent the Laplace operator, μ_i, $i = 1, 2, 3$, represent the diffusion rate coefficients, and assume that, at time t and location x, the susceptibles can be infected by infectives at any location $y \in \Omega$ with the adequate contact rate $K(x,y)$. Then an SIR epidemic model with diffusion in space and without death can be described by the system

$$\begin{aligned}
\frac{\partial S}{\partial t} &= \mathrm{d}_1 \Delta S - S(x,t) \int_\Omega I(y,t) K(x,y) \mathrm{d}y, \\
\frac{\partial I}{\partial t} &= \mathrm{d}_2 \Delta I + S(x,t) \int_\Omega I(y,t) K(x,y) \mathrm{d}y - \gamma I(x,t), \\
\frac{\partial R}{\partial t} &= \mathrm{d}_3 \Delta R + \gamma I(x,t),
\end{aligned} \tag{1.78}$$

under the boundary value conditions

$$\frac{\partial S}{\partial n}(x,t) = \frac{\partial I}{\partial n}(x,t) = \frac{\partial R}{\partial n}(x,t) = 0, \quad (x,t) \in \partial\Omega \times (0, +\infty),$$

and initial conditions

$$S(x,0) = S_0(x), \quad I(x,0) = I_0(x), \quad R(x,0) = R_0(x), \ \ x \in \Omega.$$

For some diseases, the infectives at location $x \in \Omega$ at the present time t may be infected at another location $y \in \Omega$ at an earlier time $t - \tau$ with the adequate contact rate $K(x,y,t-\tau)$. In this case, the corresponding SIR model may be described by the system

$$\begin{aligned}
\frac{\partial S}{\partial t} &= \mathrm{d}_1 \Delta S - S(x,t) \int_{-\infty}^{t} \int_\Omega I(y,\tau) K(x,y,t-\tau) \mathrm{d}y \mathrm{d}\tau, \\
\frac{\partial I}{\partial t} &= \mathrm{d}_2 \Delta I + S(x,t) \int_{-\infty}^{t} \int_\Omega I(x,\tau) K(x,y,t-\tau) \mathrm{d}y \mathrm{d}\tau - \gamma I(x,t), \\
\frac{\partial R}{\partial t} &= \mathrm{d}_3 \Delta R + \gamma I(x,t),
\end{aligned} \tag{1.79}$$

under suitable boundary and initial conditions [Takeuchi *et al.* (2007)].

For diffusion models, such as (1.78) and (1.79), the interesting problems to be studied are the stability of the disease-free equilibrium and the existence of traveling waves.

1.4.8. *Epidemic models with time-dependent coefficients*

In many real situation, the growth of a population and the transmission of a disease vary seasonally, which implies that it is more appropriate to assume coefficients of some epidemic models to be time-dependent, and more specifically, to be continuous and bounded periodic functions of time t. In such cases, the corresponding models become nonautonomous differential systems and the model analysis is more difficult. It seems, to our knowledge, that few results appeared in the literature so far for this kind of epidemic models. In the following, we explain some ideas by means of two examples.

1.4.8.1. *SIR model with time-dependent coefficients*

First, we consider the following simple SIR model:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu(t) - \mu(t)S - \beta(t)SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta(t)SI - \gamma(t)I - \mu(t)I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma(t)I - \mu(t)R, \end{aligned} \tag{1.80}$$

where we assume that $\mu(t), \beta(t)$, and $\gamma(t)$ are all continuous functions with upper bounds and positive lower bounds, and that $S(t) + I(t) + R(t) = N(t) \equiv 1$.

To control the spread of an epidemic, we intend to find conditions under which the number of infectives $I(t)$ tends to zero.

We can see, from the second equation of model (1.80), that

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \left[\frac{\beta(t)S(t)}{\gamma(t) + \mu(t)} - 1\right][\gamma(t) + \mu(t)]I(t).$$

Then, if there exists a t_0 such that $\beta(t_0)/[\gamma(t_0) + \mu(t_0)] < 1$ and $S(t_0) \approx 1$, $I(t)$ decreases in a neighborhood of t_0. Hence if we want $I(t)$ to

be decreasing with t for any initial value, then we only need

$$R_{\max} = \max_t \left[\frac{\beta(t)}{\gamma(t) + \mu(t)} \right] < 1.$$

Notice that to make $R_{\max} < 1$ we need to spend more energy and it costs more.

The following results obtained by [Ma and Ma (2006)] gives a threshold to determine whether the disease dies out or not.

Define

$$\bar{R} = \frac{\langle \beta \rangle}{\langle \gamma \rangle + \langle \mu \rangle}.$$

Then the disease-free solution $(1, 0, 0)$ of model (1.80) is unstable if $\bar{R} > 1$, and globally asymptotically stable if $\bar{R} < 1$, where

$$\langle f \rangle = \lim_{t \to \infty} \frac{1}{t} \int_0^t f(u) \mathrm{d}u$$

is defined as the long-term average of function f. We assume that $\langle \beta \rangle$, $\langle \gamma \rangle$, and $\langle \mu \rangle$ all exist.

It is easy to see that if β, γ, and μ are all constants, then $\bar{R} = \beta/(\gamma + \mu)$ is the basic reproductive number. For the nonautonomous system (1.80), the number $\bar{R}$ is actually the basic reproductive number of the following long-term average system:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \langle \mu \rangle - \langle \mu \rangle S - \langle \beta \rangle SI, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \langle \beta \rangle SI - \langle \gamma \rangle I - \langle \mu \rangle I, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \langle \gamma \rangle I - \langle \mu \rangle R.
\end{aligned}$$

For the following SIRS model with disease-induced death, different birth and natural death rate coefficients, and standard incidence,

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= b(t)N - \mu(t)S - \frac{\beta(t)SI}{N} + \delta(t)R, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{\beta(t)SI}{N} - \mu(t)I - \alpha(t)I - \gamma(t)I, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma(t)I - \mu(t)R - \delta(t)R,
\end{aligned} \tag{1.81}$$

it is proved by [Ma and Ma (2006)] that the modified reproductive number for the corresponding long-term average system

$$\bar{R}_1 = \frac{\langle\beta\rangle}{\langle b\rangle + \langle\alpha\rangle + \langle\gamma\rangle} = 1$$

is still the threshold to distinguish between the instability and global stability of the disease-free solution of model (1.81).

Next, we consider the following simple SEIRS model with latent compartment E and no death:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta(t)SI + \delta R,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \beta SI - \sigma E,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \sigma E - \gamma I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \delta R.
\end{aligned} \tag{1.82}$$

We suppose that $S(t) + E(t) + I(t) + R(t) \equiv 1$, and $\langle\beta\rangle = \bar{\beta}$ exists.

The corresponding long-term average system of model (1.82) is

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= -\bar{\beta}SI + \delta R,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \bar{\beta}SI - \sigma E,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \sigma E - \gamma I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \delta R.
\end{aligned} \tag{1.83}$$

It is easy to see that the basic reproductive number of model (1.83) is $\bar{R}_0 = \bar{\beta}/\gamma$ and that the disease-free equilibrium E_0 is globally asymptotically stable if $\bar{R}_0 < 1$, and unstable if $\bar{R}_0 > 1$. However, for model (1.82), is $\bar{R}_0 = \bar{\beta}/\gamma$ still a threshold to determine the stability of the disease-free solution? It is, unfortunately, not necessary! A counterexample was given by [Ma and Ma (2006)]. Nevertheless, the condition of $\bar{R}_0 = \bar{\beta}/\gamma < 1$ is

still sufficient to guarantee the global stability of the disease-free solution of model (1.82), although it is not necessary.

We would like to point out that, actually, for model (1.82), the threshold should be

$$\bar{R}_0 = \frac{\sigma\langle\omega\rangle}{\gamma} = 1,$$

where $\omega(t)$ is a solution of the equation

$$\frac{\mathrm{d}\omega}{\mathrm{d}t} = \beta(t) - (\sigma - \gamma)\omega - \sigma\omega^2.$$

Even though we may not be able to find an explicit formula for the threshold analytically, a numeric approximation can provide useful information to prevent and control the disease.

Chapter 2

Ordinary Differential Equations Epidemic Models

Jianquan Li

Earliest ordinary differential equations epidemic models were proposed by Kermack and Mckendrick (1927). Afterward, especially since 80 years of the 20th century, a mass of ordinary differential equations epidemic models have been playing a significant role in modeling and controlling the spread and the outbreak of infectious diseases, and predicting the developing tendency of infection [Anderson and May (1991); Brauer and Castillo-Chavez (2001); Diekman and Heesterbeek (2000); Capasso (1993)]. In this chapter, we mainly introduce some mathematical methods for ordinary differential equations epidemic models by analyzing some specific models.

For epidemic models in this chapter, we always assume that unique continuous solutions exist in the interval $[0, +\infty)$.

The following results with respect to the limit system theory [Thieme (1992); Castillo-Chavez and Thieme (1995)] are used later in this chapter. Consider the following system:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(t, x) \tag{2.1}$$

and

$$\frac{\mathrm{d}x}{\mathrm{d}t} = g(x), \tag{2.2}$$

where f and g are continuous and locally Lipschitz in x in R^n. Hence solutions of the system exist for all positive time. Equation (2.1) is called asymptotically autonomous with limit equation (2.2) if $f(t, x) \to g(x)$ as $t \to \infty$ uniformly, for $x \in R^n$.

Lemma 2.1. *Let e be a locally asymptotically stable equilibrium of* (2.2) *and ω be the ω-limit set of a forward bounded solution $x(t)$ of* (2.1). *If ω contains a point y_0 such that the solution of* (2.2), *with $y(0) = y_0$ converges to e as $t \to \infty$, then $\omega = \{e\}$, that is, $x(t) \to e$ as $t \to \infty$.*

Corollary 2.1. *If solutions of system* (2.1) *are bounded and the equilibrium e of the limit system* (2.2) *is globally stable, then any solution $x(t)$ of system* (2.1) *satisfies $x(t) \to e$ as $t \to \infty$.*

2.1. Simple SIRS Epidemic Models with Vital Dynamics

When a disease transmits in a population, the vital dynamics (that is, the demographic structure) should be considered if the long-term behavior of a population is to be investigated. In the absence of the disease, the equation with constant immigration and exponential death

$$\frac{\mathrm{d}N}{\mathrm{d}t} = A - \mu N$$

and the logistic equation

$$\frac{\mathrm{d}N}{\mathrm{d}t} = r\left(1 - \frac{N}{K}\right)N$$

are two common types of single population growth models. The generalized logistic equation is

$$\frac{\mathrm{d}N}{\mathrm{d}t} = [B(N) - D(N)]N,$$

where $B(N)$ is the population-size-dependent birth-rate coefficient and $D(N)$ is the population-size-dependent death-rate coefficient. The solutions with $N(0) > 0$ approach the carrying capacity K with appropriate assumptions on $B(N)$ and $D(N)$. Equations with constant immigration and exponential death have been studied in many papers, such as by Mena-Lorca and Hethcote (1992), Lin (1991), Li *et al.* (2008), and Zhou and Hethcote (1994), and the logistic equation or the generalized logistic equation has also been applied widely, such as by Hethcode *et al.* (2005), Gao and Hethcote (1992), and Zhou and Hethcote (1994).

When a disease is not fatal to the infected individuals, and the total population size $N(t)$, with $N(0) > 0$, approaches or keeps at a carrying capacity K, the epidemic model can usually be reduced, by the limit system theory, so that the model analysis becomes simpler. Otherwise, the

reduction for the model may not be easy. In this section, we consider simple SIRS models with disease-induced death and bilinear or standard incidence.

2.1.1. *SIRS models with constant immigration and exponential death*

2.1.1.1. *SIRS models with bilinear incidence*

The model discussed here is given by

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mu S - \beta IS + \delta R, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta IS - (\gamma + \mu + \alpha)I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - (\mu + \delta)R. \end{aligned} \tag{2.3}$$

Let $N = S + I + R$. Then $N' = A - \mu N - \alpha I$. It follows that $\limsup_{t\to\infty} N(t) \le A/\mu$. Thus the region

$$D = \{(S, I, R) \in R_+^3 \colon S + I + R \le A/\mu\}$$

is a positively invariant set for (2.3). It is easy to check that $R_0 = \beta A/(\mu(\mu + \alpha + \gamma))$ is the basic reproductive number for (2.3). In Mena-Lorca and Hethcote (1992), the global stability of the endemic equilibrium was proved only for the case of $\alpha = 0$. Here, we obtain the global stability of the endemic equilibrium for $\alpha \neq 0$ by constructing a Liapunov function.

For the model (2.3), we have

Theorem 2.1. *When $R_0 \le 1$, the disease-free equilibrium $P_0\,(A/\mu, 0, 0)$ is globally stable in D. If $R_0 > 1$, the disease-free equilibrium P_0 is unstable, and there is a unique endemic equilibrium $P^*(S^*, I^*, R^*)$ which is globally stable in* $\operatorname{int} D$, *where*

$$S^* = \frac{A}{\mu R_0}, \quad I^* = \frac{(\delta + \mu)A}{(\alpha + \mu)(\delta + \mu) + \gamma\mu}\left(1 - \frac{1}{R_0}\right),$$

$$R^* = \frac{\gamma A}{(\alpha + \mu)(\delta + \mu) + \gamma\mu}\left(1 - \frac{1}{R_0}\right).$$

Proof. Straightforward calculations can show the existence of the disease-free equilibrium P_0 and the endemic equilibrium P^*.

To prove the global stability of P_0 in D for $R_0 \leq 1$, we define the Liapunov function $L = I$ in D. Then

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t} &= [\beta S - (\gamma + \mu + \alpha)]I \\ &\leq \left[\beta\frac{A}{\mu} - (\gamma + \mu + \alpha)\right] I = (\gamma + \mu + \alpha)(R_0 - 1)I \leq 0.\end{aligned}$$

Notice that $L' = 0$ for $(S, I, R) \in D$ only if $I = 0$, so that $(S, I, R) = P_0$, and that the only positively invariant subset of the plane $I = 0$ is the point P_0. Thus, it follows from the LaSalle–Liapunov theory [Hale (1980)] that the disease-free equilibrium P_0 is globally stable in D for $R_0 \leq 1$.

To prove the global stability of P^* in $\operatorname{int} D$, we consider the following equivalent system of (2.3):

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= I[\beta(N - I - R) - (\gamma + \mu + \alpha)], \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - (\mu + \delta)R, \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= A - \mu N - \alpha I.\end{aligned} \tag{2.4}$$

It is obvious that the positively invariant set of (2.4), corresponding to the positively invariant set D of (2.3), is $D' = \{(I, R, N) \in R^3_+ \colon I + R < N \leq A/\mu\}$, and that, when $R_0 > 1$, (2.4) has a unique endemic equilibrium $\bar{P}^*(I^*, R^*, N^*)$ corresponding to $P^*(S^*, I^*, R^*)$, where

$$N^* = S^* + I^* + R^* = \frac{A}{\mu}\left[1 - \frac{\alpha(\delta + \mu)}{(\alpha + \mu)(\delta + \mu) + \gamma\mu}\left(1 - \frac{1}{R_0}\right)\right].$$

Thus, when $R_0 > 1$, (2.4) can be rewritten as

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta I[(N - N^*) - (I - I^*) - (R - R^*)], \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma(I - I^*) - (\mu + \delta)(R - R^*), \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= -\mu(N - N^*) - \alpha(I - I^*).\end{aligned} \tag{2.5}$$

Consider the Liapunov function

$$V(I, R, N) = \alpha\gamma\left(I - I^* - I^* \ln\frac{I}{I^*}\right) + \frac{\alpha\beta}{2}(R - R^*)^2 + \frac{\beta\gamma}{2}(N - N^*)^2,$$

which is a positive definite function in region D'. The total derivative of $V(I,R,N)$ along the solutions of (2.5) is given by

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\alpha\beta\gamma(I-I^*)^2 - \alpha\beta(\mu+\delta)(R-R^*)^2 - \beta\gamma\mu(N-N^*)^2.$$

Since V' is negative definite, it follows from the Liapunov theorem [Hale (1980)] that the endemic equilibrium $\bar{P}^*$ of (2.4) is globally stable in $\operatorname{int} D'$; that is, the unique endemic equilibrium P^* of (2.3) is globally stable in $\operatorname{int} D$. □

2.1.1.2. *SIRS models with standard incidence*

For the following SIRS epidemic model with disease-induced death and standard incidence

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mu S - \beta\frac{IS}{N} + \delta R,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta\frac{IS}{N} - (\mu+\alpha+\gamma)I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - (\delta+\mu)R,\\
N &= S+I+R,
\end{aligned} \tag{2.6}$$

it is similar to model (2.3) that the region

$$D = \{(S,I,R)\in R_+^3 \colon S+I+R \le A/\mu\}$$

is a positively invariant set for (2.6). It is easy to see that $R_0 = \beta/(\mu+\alpha+\gamma)$ is the basic reproductive number for (2.6). Furthermore, for (2.6), the following result was obtained by Mena-Lorca and Hethcote (1992).

Theorem 2.2. *When $R_0 \le 1$, the disease-free equilibrium $P_0\,(A/\mu, 0, 0)$ is globally stable in D; when $R_0 > 1$, P_0 becomes unstable, and there is a unique endemic equilibrium $P^*(S^*, I^*, R^*)$ which is locally asymptotically stable. Moreover, $P^*(S^*, I^*, R^*)$ is globally stable in* $\operatorname{int} D$ *when $\alpha = 0$, where*

$$S^* = \frac{(\gamma+\delta+\mu)A}{R_0[(\mu+\alpha)(\mu+\delta)+\gamma\mu] - \alpha(\mu+\delta)},$$

$$I^* = \frac{(R_0-1)(\delta+\mu)A}{R_0[(\mu+\alpha)(\mu+\delta)+\gamma\mu] - \alpha(\mu+\delta)},$$

$$R^* = \frac{(R_0 - 1)\gamma A}{R_0[(\mu+\alpha)(\mu+\delta)+\gamma\mu] - \alpha(\mu+\delta)},$$

$$N^* = \frac{R_0(\delta+\gamma+\mu)A}{R_0[(\mu+\alpha)(\mu+\delta)+\gamma\mu] - \alpha(\mu+\delta)}.$$

Proof. Straightforward calculations can show the existence of the disease-free equilibrium P_0 and the endemic equilibrium P^*.

To prove the global stability of P_0 in D for $R_0 \leq 1$, we define the Liapunov function $L = I$ in D, then

$$\begin{aligned}\frac{\mathrm{d}L}{\mathrm{d}t} &= \left[\beta\frac{S}{N} - (\gamma+\mu+\alpha)\right] I \\ &\leq [\beta - (\gamma+\mu+\alpha)]I = \beta\left(1 - \frac{1}{R_0}\right) I \leq 0.\end{aligned}$$

Similarly to the analysis in the proof of Theorem 2.1, we see that P_0 is globally stable in D for $R_0 \leq 1$.

When $R_0 > 1$, the Jacobian matrix of (2.6) at P^* is

$$J(P^*) = \begin{pmatrix} -\mu - \dfrac{\beta I^*}{N^*}\left(1 - \dfrac{S^*}{N^*}\right) & -\dfrac{\beta S^*}{N^*}\left(1 - \dfrac{I^*}{N^*}\right) & \dfrac{\beta I^* S^*}{{N^*}^2} + \delta \\ \dfrac{\beta I^*}{N^*}\left(1 - \dfrac{S^*}{N^*}\right) & -\dfrac{\beta I^* S^*}{{N^*}^2} & -\dfrac{\beta I^* S^*}{{N^*}^2} \\ 0 & \gamma & -(\delta+\mu) \end{pmatrix}.$$

Its characteristic equation is $|\lambda E - J(P^*)| = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$, where

$$\begin{aligned} a_1 &= 2\mu + \delta + pR_0 > 0, \\ a_2 &= p(\delta+\mu+\gamma) + \mu(\mu+\delta+p) + p(R_0-1)(2\mu+\delta+\alpha+\gamma) > 0, \\ a_3 &= p\mu(\delta+\mu+\gamma) + p(R_0-1)[(\mu+\alpha)(\delta+\mu)+\mu\gamma] > 0. \end{aligned}$$

Here we notice that $S^*/N^* = 1/R_0$ and $p = \beta I^*/(R_0 N^*)$. A simple calculation can also show that $a_1 a_2 - a_3 > 0$ for $R_0 > 1$. Then it follows from the Routh–Hurwitz criterion that all characteristic roots have negative real parts, which implies that P^* is locally asymptotically stable when $R_0 > 1$.

For the case $\alpha = 0$, it follows from (2.6) that $N' = A - \mu N$. Then the $\lim_{t\to\infty} N(t) = A/\mu$, and the basic reproductive number for (2.6) is $R_0 = \beta/(\mu+\gamma)$ for $\alpha = 0$. In this case, the dynamic behavior of (2.6) is

equivalent to the limiting system

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mu S - \frac{\mu\beta}{A} SI + \delta\left(\frac{A}{\mu} - S - I\right) := P(S, I),\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \left[\frac{\mu\beta}{A} S - (\mu + \gamma)\right] I := Q(S, I).\end{aligned} \tag{2.7}$$

From the inference above, when $R_0 > 1$, (2.7) has a unique endemic equilibrium $\bar{P}^*(S^*, I^*)$ in the region $D' = \{(S, I) \in R_+^2 \colon S + I \leq A/\mu\}$ which is locally asymptotically stable.

Since

$$\frac{\partial}{\partial S}\left(\frac{P}{I}\right) + \frac{\partial}{\partial I}\left(\frac{Q}{I}\right) = -\frac{\mu + \delta}{I} - \frac{\mu\beta}{A} < 0,$$

there is no periodic solutions of (2.7) in $\operatorname{int} D'$. Thus $\bar{P}^*(S^*, I^*)$ is globally stable in $\operatorname{int} D'$. Therefore, $\bar{P}^*$ is globally stable in $\operatorname{int} D$ when $\alpha = 0$ and $R_0 > 1$. □

While numeric simulations demonstrate that the endemic equilibrium P^* is also globally stable in $\operatorname{int} D$ if $\alpha > 0$, we are unable to prove it analytically.

2.1.2. *SIRS models with logistic growth*

Suppose that, in the absence of disease, the differential equation for the population N is

$$\frac{\mathrm{d}N}{\mathrm{d}t} = r\left(1 - \frac{N}{K}\right) N = \left(b - \frac{arN}{K}\right) N - \left[\mu + \frac{(1-a)rN}{K}\right] N, \tag{2.8}$$

where b and μ are the per capita birth and death rates, respectively. This decomposition of the logistic equation has been shown in Sec. 1.4.4. Here, the intrinsic growth rate coefficient is $r = b - \mu > 0$; that is, $b > \mu$.

We consider an SIRS model with standard incidence as follows:

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= \left(b - \frac{arN}{K}\right) N - \frac{\beta IS}{N} - \left[\mu + \frac{(1-a)rN}{K}\right] S + \delta R,\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{\beta IS}{N} - \left[\gamma + \alpha + \mu + \frac{(1-a)rN}{K}\right] I,\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \left[\delta + \mu + \frac{(1-a)rN}{K}\right] R,\\ N &= S + I + R.\end{aligned} \tag{2.9}$$

For (2.9), we have

$$\frac{\mathrm{d}N}{\mathrm{d}t} = r\left(1 - \frac{N}{K}\right)N - \alpha I.$$

It is convenient to reformulate the model (2.9) in terms $x = S/N$, $y = I/N$, and $z = R/N$, which are the fractions of the susceptibles, infectives, and removeds, respectively. It is easy to verify that x, y, z, and N satisfy the system of differential equations:

$$\begin{aligned}
\frac{\mathrm{d}x}{\mathrm{d}t} &= \left(b - \frac{arN}{K}\right) - (\beta - \alpha)xy - \left(b - \frac{arN}{K}\right)x + \delta z,\\
\frac{\mathrm{d}y}{\mathrm{d}t} &= \left[\beta x + \alpha y - \left(\gamma + \alpha + b - \frac{arN}{K}\right)\right]y,\\
\frac{\mathrm{d}z}{\mathrm{d}t} &= \gamma y - \left(\delta + b - \frac{arN}{K}\right)z + \alpha yz,\\
\frac{\mathrm{d}N}{\mathrm{d}t} &= \left[r\left(1 - \frac{N}{K}\right) - \alpha y\right]N.
\end{aligned} \tag{2.10}$$

Since $x = 1 - y - z$, the last three equations in (2.10) become

$$\begin{aligned}
\frac{\mathrm{d}y}{\mathrm{d}t} &= \left[\beta - (\gamma + \alpha + b) - (\beta - \alpha)y - \beta z + \frac{arN}{K}\right]y,\\
\frac{\mathrm{d}z}{\mathrm{d}t} &= \gamma y - (\delta + b)z + \frac{arNz}{K} + \alpha yz,\\
\frac{\mathrm{d}N}{\mathrm{d}t} &= \left[r\left(1 - \frac{N}{K}\right) - \alpha y\right]N.
\end{aligned} \tag{2.11}$$

It is easy to see that the set $D = \{(y, z, N) \in R_+^3 \colon y + z \le 1,\ N \le K\}$ is a positively invariant set for (2.11). In Gao and Hethcote (1992), the dynamic behaviors of (2.11) in D were discussed.

2.1.2.1. *Equilibrium and threshold*

Set the right sides of (2.11) equal zero, that is,

$$\begin{aligned}
\left[\beta - (\gamma + \alpha + b) - (\beta - \alpha)y - \beta z + \frac{arN}{K}\right]y &= 0,\\
\gamma y - (\delta + b)z + \frac{arNz}{K} + \alpha yz &= 0,\\
\left[r\left(1 - \frac{N}{K}\right) - \alpha y\right]N &= 0.
\end{aligned} \tag{2.12}$$

Then the equilibria of (2.11) are the solutions of Eq. (2.12). It is obvious that (2.12) always has solutions $P_1(0,0,0)$ and $P_2(0,0,K)$, corresponding to the fadeout of the disease with the population size at zero, or at the carrying capacity K, respectively.

Again, for $N = 0$, solution of (2.12) is determined by

$$\begin{aligned} y &= \frac{\beta - (\gamma + \alpha + b) - \beta z}{\beta - \alpha}, \\ y &= \frac{(\delta + b)z}{\gamma + \alpha z}. \end{aligned} \tag{2.13}$$

Analyzing the graphs of Eqs. (2.13), (2.11) has an equilibrium $P_3(y_3, z_3, 0)$ in D, if and only if $R_1 = \beta/(\gamma + \alpha + b) > 1$.

To find the positive (endemic) equilibrium of (2.11), similarly, we consider the system

$$\begin{aligned} y &= \frac{\beta - (\gamma + \alpha + b - ar) - \beta z}{\beta - \alpha(1 - a)}, \\ y &= \frac{(\delta + b - ar)z}{\gamma + \alpha(1 - a)z}, \\ \frac{rN}{K} &= r - \alpha y, \end{aligned} \tag{2.14}$$

which is equivalent to Eq. (2.12) except $y = 0$ and $N = 0$. Then (2.11) has a unique positive equilibrium $P_4(y_4, z_4, N_4)$ in the interior of D if and only if

$$R_0 = \frac{\beta}{\gamma + \alpha + b - ar} > 1$$

and

$$R_2 = \frac{r\beta}{\alpha[\beta - (\gamma + \alpha + \mu)]} \left(1 + \frac{\gamma}{\delta + \mu}\right) > 1.$$

For case $a = 1$, that is, the birth rate is density dependent and the death rate is density independent, we have $R_0 = \beta/(\gamma + \alpha + \mu)$, and the coordinates of the equilibrium P_4 explicitly given as

$$y_4 = \left(1 - \frac{1}{R_0}\right) \frac{\delta + \mu}{\gamma + \delta + \mu}, \quad z_4 = \left(1 - \frac{1}{R_0}\right) \frac{\gamma}{\gamma + \delta + \mu},$$

$$N_4 = K\left(1 - \frac{1}{R_2}\right).$$

In summary, we found three thresholds, R_0, R_1, and R_2, where R_0 is the basic reproductive number, R_1 is the modified reproductive number, and R_2 is the net growth threshold of population, which determines whether the population size approaches zero or a positive constant.

2.1.2.2. *Stability analysis*

It is easy to see that equilibrium $P_1(0,0,0)$ is always unstable. Note that $R_0 \leq 1$ implies that $R_1 \leq 1$ since $R_1 \leq R_0$.

Theorem 2.3. *Equilibrium* $P_2(0,0,K)$ *is globally stable in* $\operatorname{int} D$ *if* $R_0 \leq 1$.

Proof. Since $R_0 \leq 1$ is equivalent to $\beta \leq \gamma+\alpha+b-ar$, then we consider the two cases, $\beta \leq \alpha$ and $\alpha < \beta \leq \gamma + \alpha + b - ar$, separately.

For the case $\beta \leq \alpha$, define the Liapunov function $V = y + z$. Then the derivative of V along the solution of (2.10) is

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -(y+z)\left[b\left(1-\frac{aN}{K}\right)+\frac{a\mu N}{K}\right] - (\alpha-\beta)y(1-y-z) - \delta z \leq 0.$$

Notice that $\{(y,z,N) \in D\colon V' = 0\} = \{(x,y,N) \in D\colon y = 0, z = 0\}$, and that all solutions on the N axis with $N(0) > 0$ approach P_2 as $t \to \infty$. Then it follows from [Hale (1980)] that all solutions in $\operatorname{int} D$ must also approach P_2.

For the case $\alpha < \beta \leq \gamma + \alpha + b - ar$, define the Liapunov function $V = y$. Then the derivative of V along the solution of (2.10) is

$$\frac{\mathrm{d}V}{\mathrm{d}t} = [\beta - (\gamma+\alpha+b-ar)]y - ar\left(1-\frac{N}{K}\right)y - (\beta-\alpha)y^2 - \beta yz \leq 0.$$

Then, it follows from Hale (1980) that all solutions in D approach the largest positively invariant subset of the set $\{(y,z,N) \in D\colon V' = 0\}$, that is, the set $\Gamma = \{(x,y,N) \in D\colon y = 0\}$. When $y = 0$, (2.11) becomes

$$\begin{aligned} \frac{\mathrm{d}z}{\mathrm{d}t} &= \left[-(\delta+b)+\frac{arN}{K}\right]z, \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= r\left(1-\frac{N}{K}\right)N, \\ y &= 0. \end{aligned} \tag{2.15}$$

It is easy to see that all solutions of (2.15) with $N(0) > 0$ approach the equilibrium P_2. It follows from the uniqueness and continuous dependence

on the initial data that all solutions in the set D except the $N = 0$ plane must approach P_2. Hence, $P_2(0, 0, K)$ is globally stable in int D. □

Theorem 2.4. *Suppose $R_1 > 1$. Then the equilibrium $P_3(y_3, z_3, 0)$ in D is locally asymptotically stable if $R_2 < 1$, and unstable if $R_2 > 1$.*

Proof. The Jacobian of system (2.11) at P_3 is

$$J(P_3) = \begin{pmatrix} -(\beta - \alpha)y_3 & -\beta y_3 & ary_3/K \\ \gamma + \alpha z_3 & -\delta - b + \alpha y_3 & arz_3/K \\ 0 & 0 & r - \alpha y_3 \end{pmatrix}.$$

Two of the eigenvalues of $J(P_3)$ are the roots of the quadratic equation

$$\lambda^2 + p\lambda + q = 0, \tag{2.16}$$

where

$$p = (\beta - \alpha)y_3 + (\delta + b - \alpha y_3),$$
$$q = (\beta - \alpha)y_3(\delta + b - \alpha y_3) + \beta y_3(\gamma + \alpha z_3).$$

Notice that $R_1 > 1$ implies $\beta > \alpha$, and, from the last equation of (2.13) we have $\delta + b - \alpha y_3 = \gamma y_3/z_3 > 0$. Then $\delta + b - \alpha y_3 > 0$, and thus p and q are both positive so that both roots of (2.16) have negative real parts. Therefore, the stability of P_3 depends on the sign of the third eigenvalue $r - \alpha y_3$.

From (2.13), y_3 is a root to equation

$$H(y) := \frac{\alpha\,(\beta - \alpha)\,y^2}{\beta} - \left[\frac{(\delta + b)\,(\beta - \alpha)}{\beta} + \gamma + \alpha\left(1 - \frac{1}{R_1}\right)\right] y$$
$$+ (\delta + b)\left(1 - \frac{1}{R_1}\right) = 0$$

in the interval $(0, 1)$ for $R_1 > 1$.

Since

$$H(0) = (\delta + b)(1 - 1/R_1) > 0$$

and

$$H(1) = -[\gamma(\beta - \gamma - b) + (\delta + b)(\gamma + b)]/\beta < 0,$$

then $H(y) > 0$ for $y \in (0, y_3)$ and $H(y) < 0$ for $y \in (y_3, 1)$.

On the other hand,

$$H\left(\frac{r}{\alpha}\right) = \frac{(\delta+\mu)[\beta-(\gamma+\alpha+\mu)]}{\beta} - \frac{(\delta+\mu+\gamma)r}{\alpha}$$
$$= \frac{(\delta+\mu+\gamma)r}{\alpha}\left(\frac{1}{R_2}-1\right),$$

where we write $b = r+\mu$. Hence $H(r/\alpha) > 0$ as $R_2 < 1$ and $H(r/\alpha) < 0$ as $R_2 > 1$. It implies that $r/\alpha < y_3$ as $R_2 < 1$ and that $r/\alpha > y_3$ as $R_2 > 1$. Therefore, the equilibrium $P_3(y_3, z_3, 0)$ in D is locally asymptotically stable if $R_1 > 1 > R_2$, and is unstable if $R_1 > 1$ and $R_2 > 1$. □

Theorem 2.5. *The equilibrium P_4 is locally asymptotically stable if $R_0 > 1$ and $R_2 > 1$.*

Proof. The Jacobian of system (2.11) at P_4 is

$$J(P_4) = \begin{pmatrix} -(\beta-\alpha)y_4 & -\beta y_4 & ary_4/K \\ \gamma+\alpha y_4 & -\gamma y_4/z_4 & arz_4/K \\ -\alpha N_4 & 0 & -rN_4/K \end{pmatrix}.$$

The characteristic equation is

$$\lambda^3 + c_1\lambda^2 + c_2\lambda + c_3 = 0,$$

where

$$c_1 = (\beta-\alpha)y_4 + \frac{\gamma y_4}{z_4} + \frac{rN_4}{K} > 0,$$
$$c_2 = \frac{\gamma(\beta-\alpha)y_4^2}{z_4} + \frac{(\beta-\alpha)y_4 rN_4}{K} + \frac{\gamma r y_4 N_4}{Kz_4} + \frac{\alpha a r y_4 N_4}{K}$$
$$+ \beta y_4(\gamma+\alpha z_4) > 0,$$
$$c_3 = \frac{(\beta-\alpha)r\gamma y_4^2 N_4}{Kz_4} + \frac{\beta r(\gamma+\alpha z_4)y_4 N_4}{K} + \frac{a\alpha r\gamma y_4^2 N_4}{Kz_4} - \frac{\beta\alpha r a y_4 z_4 N_4}{K}$$
$$= \frac{ry_4N_4}{K}\left\{\frac{\gamma[\beta-\alpha(1-a)]y_4}{z_4} + \beta[\gamma+\alpha(1-a)z_4]\right\} > 0.$$

A straightforward calculation yields $c_1c_2 - c_3 > 0$. Then, it follows from the Routh–Hurwitz criteria that all characteristic roots have negative real parts. Thus the equilibrium P_4 is locally asymptotically stable if it exists. □

2.1.2.3. *Global stability of the equilibria for specific case: $\alpha = 0$ or $a = 0$*

In the following, we discuss global stability of the equilibria for two specific cases: $\alpha = 0$ and $a = 0$.

When $\alpha = 0$, (2.11) becomes

$$\begin{aligned}
\frac{\mathrm{d}y}{\mathrm{d}t} &= \left[\beta - (\gamma + b) - \beta y - \beta z + \frac{arN}{K}\right] y, \\
\frac{\mathrm{d}z}{\mathrm{d}t} &= \gamma y - (\delta + b)z + \frac{arNz}{K}, \\
\frac{\mathrm{d}N}{\mathrm{d}t} &= r\left(1 - \frac{N}{K}\right) N.
\end{aligned} \tag{2.17}$$

For (2.17), $R_0 = \beta/(\gamma + b - ar)$, $R_1 = \beta/(\gamma + b)$, and $R_2 = \infty$. Again,

$$P_3(y_3, z_3, 0) = \left(\frac{\delta + b}{\gamma + \delta + b}\left(1 - \frac{1}{R_1}\right), \frac{\gamma}{\gamma + \delta + b}\left(1 - \frac{1}{R_1}\right), 0\right)$$

for $R_1 > 1$, and

$$\begin{aligned}
&P_4(y_4, z_4, N_4) \\
&\quad = \left(\frac{\delta + b - ar}{\gamma + \delta + b - ar}\left(1 - \frac{1}{R_0}\right), \frac{\gamma}{\gamma + \delta + b - ar}\left(1 - \frac{1}{R_0}\right), K\right)
\end{aligned}$$

for $R_0 > 1$. It is easy to see from the last equation in (2.17) that N approaches K as $t \to \infty$ for $N(0) > 0$. Then, P_3 is unstable.

To determine the stability of P_4, we can consider the following limiting system of (2.17):

$$\begin{aligned}
\frac{\mathrm{d}y}{\mathrm{d}t} &= [\beta - (\gamma + b - ar) - \beta y - \beta z]y := F_1(y, z), \\
\frac{\mathrm{d}z}{\mathrm{d}t} &= \gamma y - (\delta + b - ar)z := G_1(y, z), \\
\frac{\mathrm{d}N}{\mathrm{d}t} &= r\left(1 - \frac{N}{K}\right) N.
\end{aligned}$$

Since

$$\frac{\partial}{\partial y}\left(\frac{F_1}{y}\right) + \frac{\partial}{\partial z}\left(\frac{G_1}{y}\right) = -\beta - \frac{\delta + b - ar}{y} < 0,$$

then it follows from Theorem 2.5 that P_4 is globally stable in $\operatorname{int} D$.

In the case of $a = 0$, (2.11) becomes

$$\begin{aligned}
\frac{\mathrm{d}y}{\mathrm{d}t} &= [\beta - (\gamma + \alpha + b) - (\beta - \alpha)y - \beta z]\, y := F_2(y, z), \\
\frac{\mathrm{d}z}{\mathrm{d}t} &= \gamma y - (\delta + b)z + \alpha y z := G_2(y, z), \\
\frac{\mathrm{d}N}{\mathrm{d}t} &= \left[r\left(1 - \frac{N}{K}\right) - \alpha y \right] N.
\end{aligned} \tag{2.18}$$

For (2.18),

$$R_0 = R_1 = \frac{\beta}{\gamma + \alpha + b}, \quad R_2 = \frac{r\beta}{\alpha[\beta - (\gamma + \alpha + \mu)]}\left(1 + \frac{\gamma}{\delta + \mu}\right),$$

and it is obvious that $y_3 = y_4$ and $z_3 = z_4$. From the proofs of Theorems 2.4 and 2.5, P_3 is locally asymptotically stable when $R_1 > 1$ and $R_2 < 1$, and P_4 is locally asymptotically stable when $R_1 > 1$ and $R_2 > 1$.

Moreover, it follows from

$$\frac{\partial}{\partial y}\left(\frac{F_2}{yz}\right) + \frac{\partial}{\partial z}\left(\frac{G_2}{yz}\right) = -\frac{\beta - \alpha}{z} - \frac{\gamma}{z^2} < 0$$

that P_3 is globally stable in D when $R_1 > 1$ and $R_2 < 1$, and P_4 is globally stable in $\operatorname{int} D$ when $R_1 > 1$ and $R_2 > 1$.

In summary, the following conclusions can be obtained.

Theorem 2.6. *For* (2.11), *when* $\alpha = 0$, *the endemic equilibrium* P_4 *is globally stable in* $\operatorname{int} D$ *for* $R_0 > 1$. *When* $a = 0$ *and* $R_1 > 1$, P_3 *is globally stable in* D *as* $R_2 < 1$, *and* P_4 *is globally stable in* $\operatorname{int} D$ *as* $R_2 > 1$.

2.2. Epidemic Models with Latent Period

For epidemic models in the previous sections, we suppose that susceptible individuals become infectious as soon as they are infected. However, in fact, infected individuals may not be infectious at an initial infection period for some diseases, such as tuberculosis and hepatitis B. Thus it is necessary to introduce an exposed compartment, E, into epidemic models for such cases. On the other hand, the exposed compartment is often omitted because the latent period may relatively be too short or it is thought that it is not crucial for the transmission of infection.

When the exposed compartment is introduced, the structure of epidemic models usually is different from that without latent period. Then

the analysis of these models needs more special mathematical methods. In this section, we first introduce some associated mathematical concepts and methods, and then apply them to the analysis of some simple models with latent period.

2.2.1. *Preliminaries*

An $m \times m$ matrix A with all real entries will be identified with the linear operator on R^m that it represents. Let "$\wedge$" denote the exterior product in R^m. With respect to the canonic basis in the exterior product space $\wedge^2 R^m$, the second additive compound matrix $A^{[2]}$ of A represents a linear operator on $\wedge^2 R^m$ whose definition on a decomposable element $u_1 \wedge u_2$ is

$$A^{[2]}(u_1 \wedge u_2) = A(u_1) \wedge u_2 + u_1 \wedge A(u_2).$$

Definition over all $\wedge^2 R^m$ is through linear extension. The entries in $A^{[2]}$ are linear relations of those in A. Let $A = (a_{ij})$. For any integer $i = 1, \ldots, \binom{m}{2}$, let $(i) = (i_1, i_2)$ be the ith member in the lexicographic ordering of integer pairs such that $1 \leq i_1 < i_2 \leq m$. Then, the entry in the ith row and the jth column of $Z = A^{[2]}$ is

$$z_{ij} = \begin{cases} a_{i_1 i_1} + a_{i_2 i_2}, & \text{if } (i) = (j), \\ (-1)^{r+s} a_{i_s j_r}, & \text{if exactly one entry } i_s \text{ of } (i) \text{ does not} \\ & \quad \text{occur in } (j) \text{ and } j_r \text{ does not occur in } (i), \\ 0, & \text{if } (i) \text{ differs from } (j) \text{ in two or more entries.} \end{cases}$$

For any integer $1 \leq k \leq m$, the kth additive compound matrix $A^{[k]}$ of A is defined canonically. For instance, when $n = 3$, the second additive compound matrix of $A = (a_{ij})$ is

$$A^{[2]} = \begin{pmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{pmatrix}.$$

Let $\sigma(A) = \{\lambda_1, \ldots, \lambda_n\}$ be the spectrum of A. Then, $\sigma(A^{[2]}) = \{\lambda_i + \lambda_j : 1 \leq i < j \leq n\}$ is the spectrum of $A^{[2]}$ [Li *et al.* (1999)].

The second additive compound matrix will be used later. The following result gives a criterion for the stability of matrices [Li and Wang (1998)].

Theorem 2.7. *An $n \times n$ real matrix A is stable if and only if $A^{[2]}$ is stable and $(-1)^n \det A > 0$.*

The details of general compound matrices and their properties can be found in Fiedler (1974) and Muldowney (1990). A comprehensive survey on compound matrices and their relations to differential equations is given by Muldowney (1990).

Let $x \mapsto f(x) \in R^n$ be a C^1 function for x in an open set $D \subset R^n$. Consider the differential equation

$$\frac{\mathrm{d}x}{\mathrm{d}t} = f(x). \tag{2.19}$$

Before we give the methods to prove global stability of autonomous system (2.19), some related concepts are introduced first.

An open set $D \subset R^n$ is **simply connected** if each closed curve in D can be continuously deformed to a point within D.

A set K is said to be **absorbing** in D for (2.19) if $x(t, x_0) \in K$ for any $x_0 \in D$ and sufficiently large t, where $x(t, x_0)$ denotes the solution to (2.19) satisfying $x(0, x_0) = x_0$.

System (2.19) is said to **possesses the Poincaré–Bendixson property** if any nonempty compact omega limit set of (2.19) that contains no equilibria is a closed orbit.

System (2.19) is said to be **competitive** in D if, for some diagonal matrix $H = \mathrm{diag}(\varepsilon_1, \ldots, \varepsilon_n)$, where each ε_i is either 1 or -1, $H(\partial f/\partial x)H$ has nonpositive off-diagonal elements for all $x \in D$. If D is convex, the flow of a competitive system preserves, for $t < 0$, the partial ordering in R^n defined by the orthant $\Gamma = \{(x_1, \ldots, x_n) \in R^n \colon \varepsilon_i x_i \geq 0, i = 1, \ldots, n\}$ [Smith (1995)].

A periodic solution $x = p(t)$ to system (2.19) with least period $\omega > 0$ and orbit $\Omega = \{p(t) \colon 0 \leq t < \omega\}$ is said to be **orbitally stable** if, for each $\bar{\varepsilon} > 0$, there exists $\delta > 0$ such that any solution $x(t)$, for which the distance of $x(0)$ from Ω is less than δ, remains at a distance less than ε from Ω for all $t \geq 0$. It is **asymptotically orbitally stable with asymptotic phase** if it is orbitally stable and there exists $\bar{b} > 0$ such that, any solution, for which the distance of $x(0)$ from Ω is less than $\bar{b}$, satisfies $|x(t) - p(t - \tau)| \to 0$ as $t \to \infty$ for some τ which may depend on $x(0)$ [Hale (1980)].

A point $x_0 \in D$ is **wandering** for (2.19) if there exists a neighborhood U of x_0 and $T > 0$ such that $U \bigcap x(t, U)$ is empty for all $t > T$. For example, all equilibria and limit points are nonwandering.

For system (2.19), we make the following two basic assumptions:

(H_1) There exists a compact absorbing set $K \subset D$.
(H_2) Equation (2.19) has a unique equilibrium $\bar{x}$ in D.

The assumptions (H_1) and (H_2) are satisfied if $\bar{x}$ is globally stable in D. For epidemic models and many other biological models where the feasible region is a bounded cone, (H_1) is equivalent to the uniform persistence of (2.19). These two assumptions can be satisfied and verified easily for the systems we discussed.

When $n = 2$, the classic Poincaré–Bendixson theory leads to the following two approaches to solve the global stability problem. Approach I: If we can prove that all periodic orbits Ω of (2.19) in D are locally orbitally asymptotically stable by using Poincaré's stability condition $\int_\Omega \operatorname{div} f \mathrm{d}t < 0$ [Hale (1980)], then the local asymptotic stability of $\bar{x}$ implies its global stability in D. Approach II: If $D \subset R^2$ is simply connected and that the Bendixson's criterion $\operatorname{div} f < 0$ holds in D, then (2.19) has no nontrivial periodic orbits and $\bar{x}$ is globally stable in D. The Bendixson's criterion $\operatorname{div} f < 0$ is later generalized to the Dulac criterion $\operatorname{div}(Bf) < 0$, where $B(x)$ is some scalar-valued differential function.

For higher dimension systems, recent developments [Li and Muldowney (1995b, 1996)] in the qualitative theory make it possible to use similar approaches. We give a brief outline in the following.

2.2.1.1. *Method I: Proving global stability using the Poincaré–Bendixson property.*

Any autonomous system (2.19) in the plane satisfies the Poincaré–Bendixson property due to the classic Poincaré–Bendixson theory [Hale (1980)]. For a three-dimensional competitive system, the Poincaré–Bendixson property is satisfied in a convex region, as shown by Hirsch (1990) and Smith (1995).

Theorem 2.8. *Let $n = 3$, D be convex, and* (2.19) *be competitive in D. Then it satisfies the Poincaré–Bendixson property.*

For higher dimensional systems that satisfy the Poincaré–Bendixson property, there is the following result for the global stability in Li and Wang (2002).

Theorem 2.9. *Assume that*

(1) *assumptions* (H_1) *and* (H_2) *hold*,
(2) *$\bar{x}$ is locally asymptotically stable*,

(3) *system* (2.19) *satisfies the Poincaré–Bendixson property*,
(4) *each periodic orbit of* (2.19) *in* D *is orbitally asymptotically stable.*

Then the unique equilibrium $\bar{x}$ *is globally stable in* D.

The orbital asymptotical stability of periodic solutions in $R^n (n \geq 2)$ can be verified using the following result in Muldowney (1990), which generalizes the Poincaré condition for two-dimensional systems.

Theorem 2.10. *A periodic orbit* $\Omega = \{p(t)\colon 0 \leq t < \omega\}$ *of* (2.19) *is orbitally asymptotically stable with asymptotic phase if the linear system*

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \frac{\partial f^{[2]}}{\partial x}(p(t))z(t) \tag{2.20}$$

is asymptotically stable, where $\partial f^{[2]}/\partial x$ *is the second additive compound matrix of the Jacobian matrix* $\partial f/\partial x$ *of* f.

Using Theorems 2.7, 2.9, and 2.10, the following result was obtained in Li and Wang (2002).

Theorem 2.11. *Assume that*

(1) *assumptions* (H_1) *and* (H_2) *hold*,
(2) *system* (2.19) *satisfies the Poincaré–Bendixson property*,
(3) *for each periodic solution* $x = p(t)$ *to* (2.19) *with* $p(0) \in D$, *system* (2.20) *is asymptotically stable*,
(4) $(-1)^n \det((\partial f/\partial x)(\bar{x})) > 0$, *where* $\bar{x}$ *is the unique equilibrium of* (2.19).

Then the unique equilibrium $\bar{x}$ *is globally stable in* D.

2.2.1.2. *Method II: Proving global stability using autonomous convergence theorems*

If the Poincaré–Bendixson property does not hold for a given system, Theorems 2.9 and 2.11 cannot be applied to prove the global stability of an equilibrium. Then, a certain type of results known as autonomous convergence theorems [Li and Muldowney (1995a); Smith, H. L. (1986a)] may be able to employed.

A condition satisfied by f, which excludes the existence of nonconstant periodic solutions to (2.19), for $n \geq 2$, is called a Bendixson criterion. A Bendixson criterion is said to be robust under C^1 local perturbations of f at $x_1 \in D$ if, for sufficiently small $\varepsilon > 0$ and neighborhood U of x_1, it is also satisfied by $g \in C^1(D \to R^n)$ such that the support $\mathrm{supp}(f - g) \subset U$

and $|f-g|_{C^1} < \varepsilon$, where

$$|f-g|_{C^1} = \sup\left\{|f(x)-g(x)| + \left|\frac{\partial f}{\partial x}(x) - \frac{\partial g}{\partial x}(x)\right| : x \in D\right\}.$$

Such g is called local ε-perturbations of f at x_1. It is easy to see that the classic Bendixson's condition $\operatorname{div} f(x) < 0$ for $n = 2$ is robust under C^1 local perturbations of f at each $x_1 \in R^2$. Bendixson criterion for higher dimensional systems that are C^1 robust are discussed by Li (1996) and Li and Muldowney (1995a, 1996).

The following is a version of the local C^1 Closing Lemma of Pugh (1967) and Pugh and Robinson (1983), as stated by Hirsch (1991).

Lemma 2.2. *Let $f \in C^1(D \to R^n)$. Suppose that x_0 is a nonwandering point of* (2.19) *and that $f(x_0) \neq 0$. Also assume that the positive semiorbit of x_0 has compact closure. Then, for each neighborhood U of x_0 and $\varepsilon > 0$, there exists a C^1 local ε-perturbation g of f at x_0 such that*

(1) $\operatorname{supp}(f-g) \subset U$ *and*
(2) *the perturbed system $x' = g(x)$ has a nonconstant periodic solution whose trajectory passes through x_0.*

For autonomous systems with any finite dimension, the following global stability principle was established [Li and Muldowney (1996)].

Theorem 2.12. *Suppose that assumptions* (H_1) *and* (H_2) *hold, and that* (2.19) *satisfies a Bendixson criterion which is robust under C^1 local perturbations of f at all nonequilibrium nonwandering points for* (2.19). *Then $\bar{x}$ is globally stable in D provided it is locally stable.*

The main idea for the proof of Theorem 2.12 is the following.

Suppose that system (2.19) satisfies a Bendixson criterion. Then it does not have any nonconstant periodic solutions. Moreover, the robustness of the Bendixson criterion implies that all nearby differential equations have no nonconstant periodic solutions. Thus by Lemma 2.2, all nonwandering points of (2.19) in D must be equilibria. In particular, each omega limit point in D must be an equilibrium. Therefore $\omega(x_0) = \{\bar{x}\}$, for all $x_0 \in D$, since $\bar{x}$ is the only equilibrium in D.

The following generalized Bendixson criterion given by Li and Muldowney (1996) shows the robustness required by Theorem 2.12.

Let $x \mapsto P(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 for $x \in D$. Assume that $P^{-1}(x)$ exists and is continuous for $x \in K$, a compact

absorbing set. A quantity $\bar{q}_2$ is defined as

$$\bar{q}_2 = \limsup_{t\to\infty} \sup_{x_0\in K} \frac{1}{t}\int_0^t \mu(B(x(s,x_0)))\mathrm{d}s. \tag{2.21}$$

Here

$$B = P_f P^{-1} + P\frac{\partial f^{[2]}}{\partial x}P^{-1},$$

in which matrix P_f is obtained by replacing each entry p of P by its derivative in the direction of f, p_{ij_f}, and $\mu(B)$ is the Lozinskiĭ measure of B with respect to a vector norm $|\cdot|$ in R^N, where $N = \binom{n}{2}$, defined by Coppel (1995) as

$$\mu(B) = \lim_{h\to 0^+} \frac{|I + hB| - 1}{h}.$$

It is easy to see that $\bar{q}_2$ is well defined and the following global stability result, based on $\bar{q}_2$, was proved by Li and Muldowney (1996).

Theorem 2.13. *Suppose that D is simply connected and that assumptions* (H_1) *and* (H_2) *hold. If $\bar{q}_2 < 0$, then no simple closed rectifiable curve in D can be invariant with respect to* (2.19)*. In particular, the unique equilibrium $\bar{x}$ of* (2.19) *is globally stable in D if $\bar{q}_2 < 0$.*

2.2.2. *Applications*

In the following, we study two simple epidemic models with latent period to demonstrate how the two methods mentioned above can be employed.

2.2.2.1. *Application of method I*

To demonstrate the application of method I, we consider the following SEIR epidemic model with bilinear incidence and no disease-induced death:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu A - \mu S - \beta IS,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \beta IS - (\varepsilon + \mu)E,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma + \mu)I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R.
\end{aligned} \tag{2.22}$$

Since the dynamic behavior of (2.22) can be determined by the system consisting of equations of S, E, and I in (2.22), we consider the system

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu A - \mu S - \beta IS, \\ \frac{\mathrm{d}E}{\mathrm{d}t} &= \beta IS - (\varepsilon + \mu)E, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma + \mu)I. \end{aligned} \tag{2.23}$$

Adding all the equations in (2.23) together, we have

$$\frac{\mathrm{d}(S + E + I)}{\mathrm{d}t} = \mu A - \mu(S + E + I) - \gamma I,$$

which implies that the region $D = \left\{(S, E, I) \in R_+^3 \colon S + E + I \leq A\right\}$ is positively invariant for (2.23). The dynamics of (2.23) in the region D was discussed by Li and Wang (2002).

It is easy to see that

$$R_0 = \frac{\varepsilon \beta A}{(\varepsilon + \mu)(\gamma + \mu)}$$

is the basic reproductive number for (2.23). Then by straightforward calculations, we can show that the disease-free equilibrium $P_0(A, 0, 0)$ is the only equilibrium of (2.23) if $R_0 \leq 1$, and system (2.23) has a unique endemic equilibrium, $P^*(S^*, E^*, I^*)$, in addition to P_0, if $R_0 > 1$, where

$$S^* = \frac{A}{R_0}, \quad E^* = \frac{\mu A}{\varepsilon + \mu}\left(1 - \frac{1}{R_0}\right), \quad I^* = \frac{\varepsilon \mu A}{(\varepsilon + \mu)(\gamma + \mu)}\left(1 - \frac{1}{R_0}\right).$$

The proof of the global stability of the disease-free equilibrium P_0 for (2.23) by LaSalle's invariance principle [LaSalle (1976)] as $R_0 \leq 1$ is straightforward. We omit it. Then we prove the global stability of the endemic equilibrium P^* using Theorem 2.11 as follows.

Theorem 2.14. *If $R_0 > 1$, then the unique endemic equilibrium P^* is globally stable in* $\operatorname{int} D$.

Proof. When $R_0 > 1$, the uniform persistence of (2.23) can be shown by utilizing a similar argument as in the proof of Proposition 3.3 by Li *et al.* (1999); that is, there exists constant $\xi > 0$ such that any solution

$(S(t), E(t), I(t))$ with $(S(0), E(0), I(0)) \in \operatorname{int} D$ satisfies

$$\liminf_{t\to\infty} S(t) > \xi, \quad \liminf_{t\to\infty} E(t) > \xi, \quad \liminf_{t\to\infty} I(t) > \xi. \tag{2.24}$$

The boundedness of D and condition (2.24) imply that (2.23) has a compact absorbing set $K \subset \operatorname{int} D$. Therefore, condition (1) in Theorem 2.11 holds for (2.23) if $R_0 > 1$.

The Jacobian matrix $J(S, E, I)$ of (2.23) is given by

$$J(S, E, I) = \begin{pmatrix} -\mu - \beta I & 0 & -\beta S \\ \beta I & -(\varepsilon + \mu) & \beta S \\ 0 & \varepsilon & -(\gamma + \mu) \end{pmatrix}.$$

Choosing matrix $H = \operatorname{diag}(-1, 1, -1)$, we can see that system (2.23) is competitive in the convex region D, with respect to the partial ordering defined by the orthant $\{(S, E, I) \in R^3 \colon S \le 0, E \ge 0, I \le 0\}$ [Smith (1995)]. Then, it follows from Theorem 2.8 that (2.23) satisfies the Poincaré–Bendixson property. Thus condition (2) of Theorem 2.11 holds.

The second compound system of (2.23) along a solution $(S(t), E(t), I(t))$ is

$$\begin{aligned} \frac{\mathrm{d}X}{\mathrm{d}t} &= -(2\mu + \beta I + \varepsilon)X + \beta SY + \beta SZ, \\ \frac{\mathrm{d}Y}{\mathrm{d}t} &= \varepsilon X - (2\mu + \beta I + \gamma)Y, \\ \frac{\mathrm{d}Z}{\mathrm{d}t} &= \beta IY - (2\mu + \varepsilon + \gamma)Z. \end{aligned} \tag{2.25}$$

To show the asymptotic stability of (2.25), we consider a Liapunov function

$$V(X, Y, Z; S, E, I) = \sup\left\{|X|, \frac{E}{I}(|Y| + |Z|)\right\}. \tag{2.26}$$

Suppose that the solution $(S(t), E(t), I(t))$ is periodic with the least period $\omega > 0$. Then its orbit Ω has a positive distance from the boundary ∂D due to the uniform persistence. Thus there exists a constant $\eta > 0$ such that

$$V(X, Y, Z; S, E, I) \ge \eta \sup\{|X|, |Y|, |Z|\} \tag{2.27}$$

for all $(X, Y, Z) \in R^3$ and $(S, E, I) \in \Omega$. Moreover, the right derivative of V along a solution $(X(t), Y(t), Z(t))$ to (2.25) and $(S(t), E(t), I(t))$ can be

estimated

$$D_+|X(t)| \le -(2\mu + \beta I + \varepsilon)|X(t)| + \frac{\beta IS}{E} \cdot \frac{E}{I}(|Y(t)| + |Z(t)|), \tag{2.28}$$

and

$$D_+|Y(t)| \le \varepsilon|X(t)| - (2\mu + \beta I + \gamma)|Y(t)|,$$
$$D_+|Z(t)| \le \beta I|Y(t)| - (2\mu + \varepsilon + \gamma)|Z(t)|.$$

Hence

$$\begin{aligned} &D_+\frac{E}{I}(|Y(t)| + |Z(t)|) \\ &\quad = \left(\frac{E'}{E} - \frac{I'}{I}\right)\frac{E}{I}(|Y(t)| + |Z(t)|) + \frac{E}{I}D_+(|Y(t)| + |Z(t)|) \\ &\quad \le \frac{\varepsilon E}{I} + \left(\frac{E'}{E} - \frac{I'}{I} - 2\mu - \gamma\right)\frac{E}{I}(|Y(t)| + |Z(t)|), \end{aligned} \tag{2.29}$$

and it follows from (2.28) and (2.29) that

$$D_+V(t) \le \max\{g_1(t), g_2(t)\}V(t), \tag{2.30}$$

where

$$g_1(t) = -2\mu - \beta I - \varepsilon + \frac{\beta IS}{E},$$
$$g_2(t) = \frac{E'}{E} - \frac{I'}{I} - 2\mu - \gamma + \frac{\varepsilon E}{I}.$$

The last two equations in (2.23) gives

$$\frac{\beta IS}{E} = \frac{E'}{E} + \varepsilon + \mu$$

and

$$\frac{\varepsilon E}{I} = \frac{I'}{I} + \gamma + \mu.$$

Then,

$$\max\{g_1(t), g_2(t)\} \le \frac{E'(t)}{E(t)} - \mu,$$

and thus

$$\int_0^\omega \max\{g_1(t), g_2(t)\}\mathrm{d}t \le \log\, E(t)|_0^\omega - \mu\omega = -\mu\omega.$$

It follows from (2.30) that $\lim_{t\to\infty} V(t) = 0$, that is, $\lim_{t\to\infty} X(t) = \lim_{t\to\infty} Y(t) = \lim_{t\to\infty} Z(t) = 0$ by (2.27). Thus, the second compound system (2.25) is asymptotically stable, which implies that condition (3) of Theorem 2.11 holds.

Furthermore, it follows from

$$\det J(P^*) = \begin{vmatrix} -\mu - \beta I^* & 0 & -\beta S^* \\ \beta I^* & -(\varepsilon+\mu) & \beta S^* \\ 0 & \varepsilon & -(\gamma+\mu) \end{vmatrix},$$

$$= -\beta I^*(\varepsilon+\mu)(\gamma+\mu) < 0,$$

where we use that fact of $\beta\varepsilon S^* = (\varepsilon+\mu)(\gamma+\mu)$, that condition (4) of Theorem 2.11 is satisfied. Therefore, P^* is globally stable in $\operatorname{int} D$ by Theorem 2.11. □

2.2.2.2. *Application of method II*

We then consider the following SEIRS epidemic model

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu A - \mu S - \beta IS + \delta R, \\ \frac{\mathrm{d}E}{\mathrm{d}t} &= \beta IS - (\varepsilon+\mu)E, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma+\mu)I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - (\delta+\mu)R, \end{aligned} \tag{2.31}$$

and show the global stability by employing method II.

It is easy to check that the set $\Sigma = \{(S,E,I,R) \in R_+^4 \colon S+E+I+R = A\}$ is positively invariant for (2.31) that is dissipative, and its global attractor is contained in Σ.

Substitute $R = A - S - E - I$ into the first equation in (2.31). System (2.31) can be reduced to the following system:

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu A - \mu S - \beta IS + \delta(A - S - E - I), \\ \frac{\mathrm{d}E}{\mathrm{d}t} &= \beta IS - (\varepsilon+\mu)E, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma+\mu)I. \end{aligned} \tag{2.32}$$

It is easy to see that the basic reproductive number for (2.32) is given by

$$R_0 = \frac{\varepsilon\beta A}{(\varepsilon+\mu)(\gamma+\mu)},$$

and that $D = \{(S,E,I) \in R^3_+ \colon S+E+I \le A\}$ is a positively invariant set of (2.32). Then straightforward calculations show that the disease-free equilibrium $P_0(A,0,0)$ is the only equilibrium of (2.23) if $R_0 \le 1$, and system (2.23) has a unique endemic equilibrium $P^*(S^*,E^*,I^*)$ besides P_0 if $R_0 > 1$, where

$$S^* = \frac{A}{R_0}, \quad E^* = \frac{(\delta+\mu)(\gamma+\mu)A}{(\gamma+\mu)(\varepsilon+\delta+\mu)+\varepsilon\delta}\left(1-\frac{1}{R_0}\right),$$

$$I^* = \frac{\varepsilon(\delta+\mu)A}{(\gamma+\mu)(\varepsilon+\delta+\mu)+\varepsilon\delta}\left(1-\frac{1}{R_0}\right).$$

Similarly as for the previous SEIR model, we first have that the disease-free equilibrium P_0 of (2.32) is globally stable in D if $R_0 \le 1$, and system (2.32) is uniformly persistent if when $R_0 > 1$. We then determine the global stability of P^* for $R_0 > 1$, using Theorem 2.13, as follows.

Theorem 2.15. *Assume that $R_0 > 1$. Then there exists $\bar{\delta} > 0$ such that the unique endemic equilibrium P^* is globally stable in* $\operatorname{int} D$ *when $\delta \le \bar{\delta}$.*

Proof. The uniform persistence of (2.32) implies that assumptions (H_1) and (H_2) hold for $R_0 > 1$. In the following, we will verify that $\bar{q}_2 < 0$, where $\bar{q}_2$ is defined in (2.21).

The Jacobian matrix $J(S,E,I)$ of (2.32) is given by

$$J(S,E,I) = \begin{pmatrix} -\beta I-\mu-\delta & -\delta & \beta S-\delta \\ \beta I & -(\varepsilon+\mu) & \beta S \\ 0 & \varepsilon & -(\gamma+\mu) \end{pmatrix},$$

and the second additive compound matrix, $J^{[2]}(S,E,I)$, of $J(S,E,I)$ is given by

$$J^{[2]}(S,E,I) = \begin{pmatrix} -\beta I-2\mu-\delta-\varepsilon & \beta S & \delta+\beta S \\ \varepsilon & -\beta I-2\mu-\gamma-\delta & -\delta \\ 0 & \beta I & -2\mu-\varepsilon-\gamma \end{pmatrix}.$$

Let $P(S,E,I) = \text{diag}\,(1, E/I, E/I)$. Then the matrix $B = P_f P^{-1} + PJ^{[2]}P^{-1}$ can be written as in the following block form:

$$B = \begin{pmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{pmatrix},$$

where

$$B_{11} = -\beta I - 2\mu - \varepsilon - \delta, \quad B_{12} = \left(\frac{\beta IS}{E}, \frac{I(\beta S + \delta)}{E}\right), \quad B_{21} = \begin{pmatrix} \dfrac{\varepsilon E}{I} \\ 0 \end{pmatrix},$$

$$B_{22} = \begin{pmatrix} \dfrac{E'}{E} - \dfrac{I'}{I} - \beta I - 2\mu - \gamma - \delta & -\delta \\ \beta I & \dfrac{E'}{E} - \dfrac{I'}{I} - 2\mu - \varepsilon - \gamma \end{pmatrix}.$$

Choose the vector norm $|\cdot|$ in $R^3 \cong R^{\binom{3}{2}}$ as

$$|(u,v,w)| = \sup\{|u|, |v| + |w|\}.$$

Then the Lozinskiĭ measure $\mu(B)$ with respect to $|\cdot|$ can be estimated as Martin, Jr. (1974):

$$\mu(B) \leq \sup\{g_1, g_2\}, \tag{2.33}$$

where

$$g_1 = \mu_1(B_{11}) + |B_{12}|, \quad g_2 = |B_{21}| + \mu_1(B_{22}),$$

$|B_{12}|, |B_{21}|$ are matrix norms with respect to the l_1 vector norm, and μ_1 denotes the Lozinskiĭ measure with respect to the l_1 vector norm [Coppel (1965)]. More specifically,

$$\mu_1(B_{11}) = -\beta I - \delta - \varepsilon - 2\mu, \quad |B_{12}| = \frac{(\beta S + \delta)I}{E}, \quad |B_{21}| = \frac{\varepsilon E}{I}.$$

To calculate $\mu_1(B_{22})$, we add the absolute values of the off-diagonal elements to the corresponding diagonal element in each column of B_{22}, and then take the maximum of the two sums [Coppel (1965)] to obtain

$$\begin{aligned} \mu_1(B_{22}) &= \frac{E'}{E} - \frac{I'}{I} - \gamma - 2\mu - \min\{\delta, \varepsilon - \delta\} \\ &\leq \frac{E'}{E} - \frac{I'}{I} - \gamma - 2\mu - \delta, \quad \text{for } \delta \leq \frac{\varepsilon}{2}. \end{aligned}$$

Then, for $\delta \leq \varepsilon/2$,

$$\begin{aligned} g_1 &= -\beta I - \delta - \varepsilon - 2\mu + \frac{(\beta S + \delta)I}{E}, \\ g_2 &\leq \frac{\varepsilon E}{I} + \frac{E'}{E} - \frac{I'}{I} - \gamma - 2\mu - \delta. \end{aligned} \tag{2.34}$$

Hence, it follows from (2.32) that

$$\begin{aligned} \frac{\beta IS}{E} &= \frac{E'}{E} + \varepsilon + \mu, \\ \frac{\varepsilon E}{I} &= \frac{I'}{I} + \gamma + \mu, \end{aligned} \tag{2.35}$$

and from (2.33) to (2.35) that

$$\mu(B) \leq \frac{E'}{E} - \delta - \mu + \sup\left\{\frac{\delta I}{E} - \beta I, 0\right\}.$$

Since (2.32) is uniformly persistent when $R_0 > 1$, there exists $\eta > 0$ and $T > 0$ such that whenever $t > T$,

$$E(t) \geq \eta, \quad I(t) \geq \eta, \quad \text{and} \quad \frac{1}{t}[\log E(t) - \log E(0)] < \frac{\delta + \mu}{2}$$

for all $(S(0), E(0), I(0)) \in K$. Let $\bar{\delta} = \min\{\varepsilon/2, \beta\eta^2\}$. Then if $t > T$ and $\delta < \bar{\delta}$, $\delta I/E - \beta I \leq 0$, and thus

$$\frac{1}{t}\int_0^t \mu(B)\mathrm{d}t \leq \frac{1}{t}[\log E(t) - \log E(0)] - (\delta + \mu) < -\frac{\delta + \mu}{2}$$

for all $(S(0), E(0), I(0)) \in K$, which in turn implies that $\bar{q}_2 < 0$. The proof is complete. □

Li and Wang (2002) investigated an SEIR model with vertical transmission and vaccination

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= b - \beta IS - pbE - qbI - bS - rS, \\ \frac{\mathrm{d}E}{\mathrm{d}t} &= \beta IS + pbE + qbI - (\varepsilon + b)E, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma + b)I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - bR + rS, \end{aligned} \tag{2.36}$$

where $p + q = 1$ and r denotes the vaccinating rate coefficient for susceptibles. Since the first three equations in (2.36) do not contain the variable R, then we need only to consider the following equations:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= b - \beta IS - pbE - qbI - bS - rS, \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \beta IS + pbE + qbI - (\varepsilon + b)E, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma + b)I.
\end{aligned} \tag{2.37}$$

Let matrix

$$P(S, E, I) = \begin{pmatrix} a_1 & 0 & 0 \\ 0 & (1 - a_2)\dfrac{E}{I} & 0 \\ 0 & a_2\dfrac{E}{I} & \dfrac{E}{I} \end{pmatrix}$$

where $1 < a_1 < 1 + \beta c^2/(\beta + b)$, with c a uniform persistence constant of (2.37) for

$$R_0 = \frac{b}{b + r} \cdot \frac{\beta\varepsilon}{[(b + \varepsilon)(b + \gamma) - bp(b + \gamma) - bq\varepsilon]} > 1$$

and

$$a_2 = \begin{cases} 0, & \text{if } \varepsilon \geq pb, \\ 1 - \dfrac{\varepsilon}{pb}, & \text{if } \varepsilon < pb. \end{cases}$$

Similarly as in the proof of Theorem 2.15, we can show that $\bar{q}_2 < 0$. Therefore, the unique endemic equilibrium P^* of (2.36) or (2.37) is globally stable in the interior of $\{(S, E, I) \in R^3_+ \colon S + E + I \leq 1\}$ when $R_0 > 1$. If $r = 0$, (2.36) is reduced to an SEIR model without vaccination, which is discussed by Li *et al.* (2001).

Fan *et al.* (2001) considered an SEIS model

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \beta IS - \mu S + \gamma I, \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \beta IS - (\varepsilon + \mu)E, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma + \alpha + \mu)I.
\end{aligned}$$

Using $P(S,E,I) = \mathrm{diag}(1, E/I, E/I)$, they also show that $\bar{q}_2 < 0$, and hence the unique endemic equilibrium P^* is globally stable in the interior of $\{(S,E,I) \in R^3_+ \colon S+E+I \le A/\mu\}$ for $R_0 = \beta\varepsilon A/[\mu(\mu+\varepsilon)(\mu+\gamma+\alpha)] > 1$.

Using Theorem 2.9, Li and Muldowney (1995b) discussed the global stability of an SEIR model with a nonlinear incidence

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= b - bS - \beta I^p S^q,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \beta I^p S^q - (\varepsilon + b)E,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma + b)I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - bR,
\end{aligned}$$

and obtained that the unique endemic equilibrium is globally stable in the interior of $\{(S,E,I) \in R^3_+ \colon S+E+I \le 1\}$ if $0 < p < 1$ or $p = 1$ and $R_0 = \beta\varepsilon/[(\varepsilon+b)(\gamma+b)] > 1$.

Li *et al.* (1999) considered an SEIR model with the standard incidence

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= bN - \mu S - \beta IS/N,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \beta IS/N - (\varepsilon + \mu)E,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma + \alpha + \mu)I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R,\\
N &= S + E + I + R.
\end{aligned}$$

Let $s = S/N$, $e = E/N$, $i = I/N$, $r = R/N$, then s, e and i satisfy the system

$$\begin{aligned}
\frac{\mathrm{d}s}{\mathrm{d}t} &= b - bs - \beta is + \alpha is,\\
\frac{\mathrm{d}e}{\mathrm{d}t} &= \beta is - (\varepsilon + b)e + \alpha ie,\\
\frac{\mathrm{d}i}{\mathrm{d}t} &= \varepsilon e - (\gamma + \alpha + b)i + \alpha i^2.
\end{aligned} \tag{2.38}$$

If $R_0 = \beta\varepsilon/[(\varepsilon+b)(\gamma+\alpha+b)] > 1$, (2.38) is competitive in the convex region $\{(s,e,i) \in R^3_+ \colon s+e+i \le 1\}$. Thus, it follows from Theorem 2.9 that the unique endemic equilibrium is globally stable in the interior of $\{(s,e,i) \in R^3_+ \colon s+e+i \le 1\}$ provided that $R_0 > 1$ and $\alpha \le \varepsilon$.

Zhang and Ma (2003) considered an SEIR epidemic model with saturating contact rate

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \frac{\beta C(N) IS}{N} - \mu S,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \frac{\beta C(N) IS}{N} - \varepsilon E - \mu E,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \varepsilon E - (\gamma+\mu+\alpha) I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R,\\
N &= S+E+I+R,
\end{aligned}$$

where $C(N) = bN/(1+bN+\sqrt{1+2bN})$, and obtained the global analysis in the region $\{(S,E,I,R) \in R^4_+ \colon S+E+I+R \le A/\mu\}$ by using the limiting system theory and Theorem 2.9.

Zhang *et al.* (2006) formulated an SEIR epidemic model with immigration

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= (1-p-q-b)A - \frac{C(N) IS}{N} - \mu S,\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= qA + \tfrac{C(N) IS}{N} - \varepsilon E - \mu E,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= pA + \varepsilon E - (\gamma+\mu+\alpha) I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= bA + \gamma I - \mu R,\\
N &= S+E+I+R,
\end{aligned}$$

where q, p, and b are fractions of inputs to the compartments E, I, and R, respectively, and $C(N)$ is the adequate contact rate. By reducing the four-dimensional system to a three-dimensional asymptotic autonomous system,

the authors obtained the global stability of the endemic equilibrium by using Theorem 2.13.

2.3. Epidemic Models with Immigration or Dispersal

Spatial structure of population communities plays an important role in modeling of the spread of infectious diseases since communicable diseases can be transmitted easily from one area to another through traveling infectious individuals. Effects of population dispersal on disease transmission dynamics based on patchy space have been studied for SARS [Ruan *et al.* (2006)], influenza [Sattenspiel and Herring (2003)], tuberculosis [Fulford and Roberts (2002)], and malaria [Rodriguez and Torres-Sorando (2001)].

Wang and coauthors [Wang (2004); Wang and Mulone (2003); Wang and Zhao (2004, 2006)] have formulated and analyzed epidemic models without the disease-induced death in given patchy environments. SIS epidemic models with bilinear incidence were considered by Wang and Zhao (2004) and Wang (2004). SIS epidemic models with standard incidence were considered by Wang and Mulone (2003). SIR epidemic models with standard incidence and a constant infectious period were considered by Wang and Zhao (2006). Salmani and van den Driessche (2006) formulated and investigated SEIRS and SIS models with standard incidence and disease-induced death in a patchy environment. Zhang and Zhao (2007) discussed an SIS epidemic model with periodic coefficients in a patchy environment. Formulas for the basic reproductive number which determines if the disease persists in a patchy environment are obtained in all of these papers. Moreover, epidemic models with immigration were also considered, and global dynamics behaviors have been investigated by Brauer and van den Drissche (2001) and Li *et al.* (2004).

In this section, we introduce some results for epidemic models with immigration and analyze the effects of population dispersal on disease transmissions.

2.3.1. *Epidemic models with immigration*

Communicable diseases may be introduced into a population by the arrival (input) of infectives from outside the population. We incorporate the immigration of individuals including the susceptibles, infectives, and

removed into epidemic models, and propose an SIR model with a general incidence as follows:

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= aA - \beta(N)IS - \mu S,\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= bA + \beta(N)IS - (\mu+\gamma+\alpha)I,\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= cA + \gamma I - \mu R,\end{aligned} \tag{2.39}$$

where a, b, and c $(a > 0, b \geq 0, c \geq 0, a + b + c = 1)$ are the fractions of input to the susceptible class, the infective class and the removed class, respectively. It is natural to assume that $\beta(N)$ satisfies the following conditions [Castillo-Chavez *et al.* (1989)]:

$$\beta(N) > 0, \quad \beta'(N) \leq 0, \quad [\beta(N)N]' \geq 0,$$

and

$$[\beta'(N)]^2 + [(\beta(N)N)']^2 > 0.$$

It is easy to see that the standard incidence coefficient $\beta(N) = \lambda/N$ and the mass action incidence coefficient $\beta(N) = \lambda$ are two specific cases.

Since $N = S + I + R$, substituting $S = N - I - R$ into the second equation of (2.39) gives the following system:

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= bA + I[\beta(N)(N - I - R) - (\mu+\gamma+\alpha)],\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= cA + \gamma I - \mu R,\\ \frac{\mathrm{d}N}{\mathrm{d}t} &= A - \mu N - \alpha I.\end{aligned} \tag{2.40}$$

For the cases $b = 0$ and $b > 0$, it implies that there is no input of the infectious individuals, and that there is the constant input, respectively. In the following, we consider dynamics of system (2.40) in these two cases [Li *et al.* (2004)].

2.3.1.1. *SIR model with no immigration of infectives*

For the case $b = 0$, system (2.40) becomes

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= I[\beta(N)(N - I - R) - (\mu + \gamma + \alpha)],\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= cA + \gamma I - \mu R,\\ \frac{\mathrm{d}N}{\mathrm{d}t} &= A - \mu N - \alpha I.\end{aligned} \tag{2.41}$$

It is easy to check that

$$R_0 = \beta\left(\frac{A}{\mu}\right)\frac{(1-c)A}{\mu(\mu+\gamma+\alpha)}$$

is the basic reproductive number of (2.41), and that the region $D = \{(I, R, N) \in R^3_+\colon\ I + R < N \le A/\mu\}$ is positively invariant for (2.41). Straightforward calculations show that the disease-free equilibrium $P_0(0, cA/\mu, A/\mu)$ is the only equilibrium of (2.41) if $R_0 \le 1$, and that, if $R_0 > 1$, system (2.41), in addition to P_0, has a unique endemic equilibrium $P^*(I^*, R^*, N^*)$, where

$$I^* = \frac{A - \mu N^*}{\alpha}, \quad R^* = \frac{(\alpha c + \gamma)A - \gamma\mu N^*}{\alpha\mu},$$

and N^* is the unique root of equation

$$\beta(N)[\mu(\alpha + \mu + \gamma)N - (\mu + \alpha c + \gamma)A] = \alpha\mu(\mu + \gamma + \alpha),$$

in the interval $(0, A/\mu)$.

For the stability of (2.41), we have the following result [Li *et al.* (2004)].

Theorem 2.16. *The disease-free equilibrium P_0 is globally stable in D if $R_0 \le 1$, and the endemic equilibrium P^* is globally stable in* $\operatorname{int} D$ *if $R_0 > 1$.*

Proof. Denote $X = R + \gamma N/\alpha$. Then from the last two equations in (2.41) we have

$$\frac{\mathrm{d}X}{\mathrm{d}t} = A\left(c + \frac{\gamma}{\alpha}\right) - \mu X. \tag{2.42}$$

The solution of (2.42) with the initial value $X(0) = X_0 = R(0) + \gamma N(0)/\alpha$ is

$$X(t) = \mathrm{e}^{-\mu t}X_0 + \bar{X}(1 - \mathrm{e}^{-\mu t}),$$

where $\bar{X} = A(c+\gamma/\alpha)/\mu$. Then

$$R(t) = -\frac{\gamma}{\alpha}N(t) + \mathrm{e}^{-\mu t}X_0 + \bar{X}(1-\mathrm{e}^{-\mu t}). \tag{2.43}$$

Substituting (2.43) into the first equation in (2.41) gives the equivalent system of (2.41):

$$\begin{aligned}
&\frac{\mathrm{d}I}{\mathrm{d}t} = I\left\{\beta(N)\left[\left(1+\frac{\gamma}{\alpha}\right)N - I - \mathrm{e}^{-\mu t}X_0 - \bar{X}(1-\mathrm{e}^{-\mu t})\right] - (\mu+\gamma+\alpha)\right\},\\
&\frac{\mathrm{d}N}{\mathrm{d}t} = A - \mu N - \alpha I.
\end{aligned} \tag{2.44}$$

On the other hand, (2.44) has the following limit system:

$$\begin{aligned}
&\frac{\mathrm{d}I}{\mathrm{d}t} = I\left\{\beta(N)\left[\left(1+\frac{\gamma}{\alpha}\right)N - I - \bar{X}\right] - (\mu+\gamma+\alpha)\right\} := F(I,N),\\
&\frac{\mathrm{d}N}{\mathrm{d}t} = A - \mu N - \alpha I := G(I,N).
\end{aligned} \tag{2.45}$$

System (2.45) has only the equilibrium $\bar{P}_0(0, A/d)$ if $R_0 \le 1$, and a unique positive equilibrium $\bar{P}^*(I^*, N^*)$, in addition to $\bar{P}_0$, if $R_0 > 1$. The region $D' = \left\{(I,N) \in R_+^2 \colon I < N \le A/\mu\right\}$ is a positively invariant set of (2.45).

Linearizing system (2.45) about $\bar{P}_0$ and $\bar{P}^*$, respectively, we obtain that $\bar{P}_0$ is locally asymptotically stable if $R_0 < 1$, and it is unstable and $\bar{P}^*$ is locally asymptotically stable if $R_0 > 1$. We also notice that $\bar{P}_0$ is a higher order equilibrium if $R_0 = 1$.

Since

$$\frac{\partial}{\partial I}\left(\frac{F}{I}\right) + \frac{\partial}{\partial N}\left(\frac{G}{I}\right) = -\beta(N) - \frac{\mu}{I} < 0$$

in int D', then there is no period solution in the set D' for (2.45). Therefore, $\bar{P}_0$ is globally stable on D' if $R_0 < 1$, and $\bar{P}^*$ is globally stable in D' if $R_0 > 1$.

To prove the global stability of $\bar{P}_0$ for $R_0 = 1$, we rewrite (2.45) as

$$\begin{aligned}
&\frac{\mathrm{d}I}{\mathrm{d}t} = I\left\{\beta(N)\left[\left(1+\frac{\gamma}{\alpha}\right)\left(N - \frac{A}{\mu}\right) - I\right] + \frac{aA}{\mu}\left[\beta(N) - \beta\left(\frac{A}{\mu}\right)\right]\right\},\\
&\frac{\mathrm{d}N}{\mathrm{d}t} = -\mu\left(N - \frac{A}{\mu}\right) - \alpha I,
\end{aligned} \tag{2.46}$$

where $\mu+\gamma+\alpha = aA\beta(A/\mu)/\mu$ and $a = 1-c$ are used since $R_0 = 1$ and $a+c = 1$.

Define Liapunov function

$$V(I,N)=\frac{\alpha^2 I}{\alpha+\gamma}+\int_{A/\mu}^{N}\left\{\beta(u)\left(u-\frac{A}{\mu}\right)-\frac{\alpha a A}{\mu(\alpha+\gamma)}\left[\beta\left(\frac{A}{\mu}\right)-\beta(u)\right]\right\}\mathrm{d}u.$$

Then the derivative of $V(I,N)$ along the solutions of (2.46) is given by

$$\begin{aligned}\frac{\mathrm{d}V}{\mathrm{d}t}=&-\frac{\alpha^2 I^2}{\alpha+\gamma}\beta(N)-\mu\left(N-\frac{A}{\mu}\right)\\&\times\left\{\beta(N)\left(N-\frac{A}{\mu}\right)-\frac{\alpha a A}{\mu(\alpha+\gamma)}\left[\beta\left(\frac{A}{\mu}\right)-\beta(N)\right]\right\}.\end{aligned}$$

It is easy to verify that $V(I,N)$ is positive definite, and that $\mathrm{d}V/\mathrm{d}t$ is negative definite. Therefore, equilibrium $\bar{P}_0$ of (14) is globally stable if $R_0=1$.

Since solutions of (2.41) are bounded, solutions of (2.44) are also bounded. Thus, it follows from Corollary 2.1 that the disease-free equilibrium P_0 of (2.41) is globally stable in D if $R_0\le 1$, and the endemic equilibrium P^* of (2.41) is globally stable in $\operatorname{int} D$ for $R_0>1$. □

2.3.1.2. *SIR model with immigration of infectives*

For the case $b>0$, system (2.40) has no disease-free equilibrium for all feasible parameters, but there is always a unique endemic equilibrium $P^*(I^*,R^*,N^*)$, where

$$I^*=\frac{A-\mu N^*}{\alpha},\quad R^*=\frac{(\alpha c+\gamma)A-\gamma\mu N^*}{\alpha\mu},$$

and N^* is the unique positive root of equation

$$\beta(N)[\mu(\alpha+\mu+\gamma)N-(\mu+\alpha c+\gamma)A]=\alpha\mu\left[(\mu+\gamma+\alpha)-\frac{\alpha b A}{A-\mu N}\right]$$

in the interval $(0,A/\mu)$. Using the same method as proving the global stability of (2.41) for $R_0>1$, it can be shown that the unique endemic equilibrium P^* of (2.40) is globally stable as $b>0$ [Li *et al.* (2004)].

For the specific case $\beta(N)=\beta$ and $c=0$ [Brauer and van den Drissche (2001)] proved the global stability of (2.40) using a different approach as shown below.

Let $\beta(N) = \beta$ and $c = 0$. System (2.40) becomes

$$\begin{aligned}
\frac{\mathrm{d}I}{\mathrm{d}t} &= bA + \beta I(N - I - R) - (\mu + \gamma + \alpha)I, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - \mu R, \\
\frac{\mathrm{d}N}{\mathrm{d}t} &= A - \mu N - \alpha I.
\end{aligned} \tag{2.47}$$

Similarly, (2.47) has a unique endemic equilibrium P^* for $b > 0$. It can be shown that P^* is locally asymptotically stable by analyzing the Jacobian matrix of (2.47) at P^*.

Moreover, by solving the second and third equations of (2.47), respectively, in terms of I,

$$\begin{aligned}
R(t) &= R(0)\mathrm{e}^{-\mu t} + \gamma \int_0^t \mathrm{e}^{-\mu(t-s)} I(s)\mathrm{d}s, \\
N(t) &= N(0)\mathrm{e}^{-\mu t} + \frac{A}{\mu}(1 - \mathrm{e}^{-\mu t}) - \alpha \int_0^t \mathrm{e}^{-\mu(t-s)} I(s)\mathrm{d}s
\end{aligned}$$

and then substituting them into the first equation of (2.47). System (2.47) can be reduced to a single integro-differential equation

$$\begin{aligned}
\frac{\mathrm{d}I}{\mathrm{d}t} = bA + \beta I(t) \Bigg\{ &\frac{A}{\mu}(1 - \mathrm{e}^{-\mu t}) + [N(0) - R(0)]\mathrm{e}^{-\mu t} \\
&- I(t) - (\alpha + \gamma) \int_0^t \mathrm{e}^{-\mu(t-s)} I(s)\mathrm{d}s \Bigg\} - (\mu + \gamma + \alpha)I(t).
\end{aligned} \tag{2.48}$$

By further making the change of variable $I(t) = I^*\mathrm{e}^{y(t)}$, we arrive at

$$\begin{aligned}
\frac{\mathrm{d}y}{\mathrm{d}t} = \frac{bA}{I^*}\mathrm{e}^{-y(t)} + \beta \Bigg[&\frac{A}{\mu}(1 - \mathrm{e}^{-\mu t}) + (N(0) - R(0))\mathrm{e}^{-\mu t} - I^*\mathrm{e}^{y(t)} \\
&- (\alpha + \gamma) I^* \int_0^t \mathrm{e}^{-\mu(t-s)} \mathrm{e}^{y(s)} \mathrm{d}s \Bigg] - (\mu + \gamma + \alpha).
\end{aligned} \tag{2.49}$$

Define

$$g(y) = \mathrm{e}^y - 1,$$

$$a(s) = \begin{cases} 0, & \text{for } s \le 0, \\ \beta I^* \left[1 + (\alpha + \gamma) \displaystyle\int_0^s \mathrm{e}^{-\mu u} \mathrm{d}u \right], & \text{for } s > 0, \end{cases}$$

so that $a(s)$ has a jump βI^* at $s = 0$ and $a'(s) = \beta I^*(\alpha+\gamma)\mathrm{e}^{-\mu s}$ for $s > 0$, and then

$$\int_0^t g(y(t-s))\mathrm{d}a(s) = \beta I^*\mathrm{e}^{y(t)} - \beta I^* + \beta I^*(\alpha+\gamma)\int_0^t \mathrm{e}^{y(t-s)}\mathrm{e}^{-\mu s}\mathrm{d}s$$
$$- \frac{\beta I^*(\alpha+\gamma)}{\mu}(1-\mathrm{e}^{-\mu t}).$$

Define

$$h(y) = \frac{bA}{I^*}(1-\mathrm{e}^{-y}),$$
$$f(t) = \beta\mathrm{e}^{-\mu t}\left[(N(0)-R(0)) - \frac{A-(\alpha+\gamma)I^*}{\mu}\right],$$

then the integro-differential equation (2.49) becomes

$$\frac{\mathrm{d}y}{\mathrm{d}t} = -\int_0^t g(y(t-s))\mathrm{d}a(s) - h(y(t)) + f(t), \tag{2.50}$$

where we use the equation $\beta(\mu+\alpha+\gamma)I^{*2} - [\beta A - \mu(\mu+\gamma+\alpha)]I^* - b\mu A = 0$.

Notice that the equilibrium I^* of (2.48) corresponds to the equilibrium $y = 0$ of (2.50). It follows from a theorem by Gipenberg *et al.* (1990) that every bounded solution $y(t)$ of (2.50) has $\lim_{t\to\infty} g(y(t)) = 0$. As $g(y) = 0$ only for $y = 0$, this shows that every solution of (2.50) approaches zero as $t \to \infty$, and therefore the equilibrium I^* of (2.48) is globally stable. Since (2.48) is equivalent to system (2.47), then the unique equilibrium P^* of (2.47) is globally stable.

Li *et al.* (2004) considered an SIRS model with a general incidence and immigration of infectives

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= aA - \beta(N)IS - \mu S + \varepsilon R,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= bA + \beta(N)IS - (\mu+\gamma+\alpha)I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= cA + \gamma I - (\mu+\varepsilon)R,
\end{aligned} \tag{2.51}$$

and obtained the following results.

Theorem 2.17. *When $b > 0$, (2.51) has no disease-free equilibrium, and there is always the unique endemic equilibrium $P^*(I^*, R^*, N^*)$ which is locally asymptotically stable, and globally stable if $\alpha \le \mu + 2\varepsilon$.*

In the case of $b = 0$, *the basic reproductive number of* (2.51) *is*

$$R_0 = \beta \left(\frac{A}{\mu}\right) \frac{A}{\mu} \frac{\varepsilon + (1-c)\mu}{(\mu+\gamma+\alpha)(\mu+\varepsilon)}.$$

The disease-free equilibrium $P_0\,(0, cA/(\mu+\varepsilon), A/\mu)$ *is globally stable, if* $R_0 < 1$, *and unstable if* $R_0 > 1$. *If* $R_0 > 1$, *there is the unique endemic equilibrium* $P^*(I^*, R^*, N^*)$ *which is locally asymptotically stable, where*

$$I^* = \frac{A - \mu N^*}{\alpha}, \quad R^* = \frac{(\alpha c + \gamma)\, A - \gamma \mu N^*}{\alpha\,(\mu+\varepsilon)},$$

and N^* *is the unique root of equation*

$$\beta(N)\{[(\alpha+\mu)(\mu+\varepsilon)+\gamma\mu]N - (\mu+\varepsilon+\alpha c+\gamma)A\} = \alpha(\mu+\varepsilon)(\mu+\gamma+\alpha)$$

in the interval $(0, A/\mu)$. *Furthermore,* P^* *is globally stable if* $\alpha \le \mu + 2\varepsilon$.

2.3.2. *Epidemic models with dispersal*

We now consider an SI type of disease transmission models in an environment of two patches, with bilinear incidence. The population in each patch is divided into two classes: susceptibles and infectives. We denote the number of susceptibles and infectives in patch i, $i = 1, 2$, at time t by $S_i(t)$ and $I_i(t)$, respectively. If there is no population dispersal among patches, that is, the patches are isolated, we suppose that the population dynamics in ith patch is governed by

$$\begin{aligned} \frac{\mathrm{d}S_i}{\mathrm{d}t} &= A_i - \mu_i S_i - \beta_i S_i I_i, \\ \frac{\mathrm{d}I_i}{\mathrm{d}t} &= \beta_i S_i I_i - (\mu_i + \gamma_i) I_i. \end{aligned} \tag{2.52}$$

Then the basic reproductive number of (2.52) is $R_{0i} = \beta_i A_i/(\mu_i(\mu_i+\gamma_i))$. The disease persists if $R_0 > 1$ and dies out if $R_0 > 1$.

If the patches are connected, and there is dispersal among the two patches, the dynamics of the individuals are governed by

$$\begin{aligned}
\frac{\mathrm{d}S_1}{\mathrm{d}t} &= A_1 - \mu_1 S_1 - \beta_1 S_1 I_1 - a_1 S_1 + a_2 S_2,\\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta_1 S_1 I_1 - (\mu_1 + \gamma_1) I_1 - b_1 I_1 + b_2 I_2,\\
\frac{\mathrm{d}S_2}{\mathrm{d}t} &= A_2 - \mu_2 S_2 - \beta_2 S_2 I_2 - a_2 S_2 + a_1 S_1,\\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta_2 S_2 I_2 - (\mu_2 + \gamma_2) I_2 - b_2 I_2 + b_1 I_1,
\end{aligned} \tag{2.53}$$

where a_1 is the coefficient of the rate at which susceptible individuals emigrate from the first patch to the second patch, a_2 the coefficient of the rate at which susceptible individuals emigrate from the second patch to the first patch, b_1 the coefficient of the rate at which infectious individuals emigrate from the first patch to the second patch, b_2 the coefficient of the rate at which infected individuals emigrate from the second patch to the first patch. In this model, we neglect the birth and death of the individuals when they are dispersing. In Wang (2004), the dynamics of (2.53) was considered.

Let $N = S_1 + I_1 + S_2 + I_2$. Then

$$\begin{aligned}
\frac{\mathrm{d}N}{\mathrm{d}t} &= A_1 + A_2 - \mu_1(S_1 + I_1) - \mu_2(S_2 + I_2) - \gamma_1 I_1 - \gamma_2 I_2\\
&\le (A_1 + A_2) - \min\{\mu_1, \mu_2\} N,
\end{aligned}$$

for $I_i \ge 0$, $i = 1, 2$, and hence that $\limsup_{t\to\infty} N(t) \le (A_1 + A_2)/\min\{\mu_1, \mu_2\}$. Therefore, the region

$$\Omega = \left\{ (S_1, I_1, S_2, I_2) \in R_+^4 \colon S_1 + I_1 + S_2 + I_2 \le \frac{A_1 + A_2}{\min\{\mu_1, \mu_2\}} \right\}$$

is a positively invariant set for (2.53).

It is obvious that (2.53) always has the disease-free equilibrium $P_0(S_1^0, 0, S_2^0, 0)$, where

$$S_1^0 = \frac{A_1(\mu_2 + a_2) + a_2 A_2}{(\mu_1 + a_1)(\mu_2 + a_2) - a_1 a_2}, \quad S_2^0 = \frac{A_2(\mu_1 + a_1) + a_1 A_1}{(\mu_1 + a_1)(\mu_2 + a_2) - a_1 a_2}.$$

To derive the basic reproductive number of model (2.53), we first introduce the method of next generation matrix formulated by Diekmann *et al.* (1990) and van den Driessche and Watmough (2002).

Assume that the population is divided into n compartments with m, $m < n$, infected compartments. Let $x = (x_1, x_2, \ldots, x_n)^{\mathrm{T}}$, where $x_i(t)$, $i = 1, 2, \ldots, m < n$, is the number of individuals in the ith infected compartment at time t. For the epidemic model

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \mathcal{F}_i(x) - [\mathcal{V}_i^-(x) - \mathcal{V}_i^+(x)] = \mathcal{F}_i(x) - \mathcal{V}_i(x), \tag{2.54}$$

where $\mathcal{F}_i(x)$ represents the rate of appearance of new infections in compartment i, $\mathcal{V}_i^+(x)$ represents the rate of transfer of individuals into compartment i by all other means, and $\mathcal{V}_i^-(x)$ represents the rate of transfer of individuals out of compartment i.

System (2.54) can be rewritten as follows:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \mathcal{F}(x) - \mathcal{V}(x), \tag{2.55}$$

where

$$\mathcal{F}(x) = (\mathcal{F}_1(x), \mathcal{F}_2(x), \ldots, \mathcal{F}_n(x))^{\mathrm{T}},$$

and

$$\mathcal{V}(x) = (\mathcal{V}_1(x), \mathcal{V}_2(x), \ldots, \mathcal{V}_n(x))^{\mathrm{T}}.$$

The Jacobian matrices of $\mathcal{F}(x)$ and $\mathcal{V}(x)$ at the disease-free equilibrium x_0 of (2.54) are

$$D\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix} \quad \text{and} \quad D\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix},$$

respectively, where F and V are the $m \times m$ matrices defined by

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(x_0)\right] \quad \text{and} \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(x_0)\right].$$

The matrices FV^{-1} is called the next generation matrix for the model (2.54). Further, the spectral radius of FV^{-1}, $\rho(FV^{-1})$, is the basic reproductive number of the model (2.54) [van den Driessche and Watmough (2002)].

For model (2.53), we let $x = (I_1, I_2, S_1, S_2)^{\mathrm{T}}$. Then corresponding to (2.55), the matrices $\mathcal{F}(x)$ and $\mathcal{V}(x)$ are

$$\mathcal{F}(x) = \begin{pmatrix} \beta_1 S_1 I_1 \\ \beta_2 S_2 I_2 \\ 0 \\ 0 \end{pmatrix}, \quad \mathcal{V}(x) = \begin{pmatrix} (\mu_1 + \gamma_1) I_1 + b_1 I_1 - b_2 I_2 \\ (\mu_2 + \gamma_2) I_2 + b_2 I_2 - b_1 I_1 \\ -A_1 + \mu_1 S_1 + \beta_1 S_1 I_1 + a_1 S_1 - a_2 S_2 \\ -A_2 + \mu_2 S_2 + \beta_2 S_2 I_2 + a_2 S_2 - a_1 S_1 \end{pmatrix}.$$

Hence, we have

$$F = \begin{pmatrix} \beta_1 S_1^0 & 0 \\ 0 & \beta_2 S_2^0 \end{pmatrix}, \quad V = \begin{pmatrix} \mu_1 + b_1 + \gamma_1 & -b_2 \\ -b_1 & \mu_2 + b_2 + \gamma_2 \end{pmatrix},$$

and therefore, the basic reproductive number of model (2.53) is

$$R_0 = \rho(FV^{-1}) = \frac{\Delta}{2[(\mu_1 + b_1 + \gamma_1)(\mu_2 + b_2 + \gamma_2) - b_1 b_2]}, \tag{2.56}$$

where

$$\Delta = \beta_1 S_1^0(\mu_2 + b_2 + \gamma_2) + \beta_2 S_2^0(\mu_1 + b_1 + \gamma_1)$$
$$+ \sqrt{[\beta_1 S_1^0(\mu_2 + b_2 + \gamma_2) - \beta_2 S_2^0(\mu_1 + b_1 + \gamma_1)]^2 + 4\beta_1\beta_2 b_1 b_2 S_1^0 S_2^0}.$$

It follows from Theorem 2 [van dem Driessche and Watmough (2002)] that the disease-free equilibrium P_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

We further have

Theorem 2.18. *The disease-free equilibrium P_0 is globally stable, for model* (2.53)*, if $R_0 < 1$ where R_0 is defined in* (2.56)*.*

Proof. It follows from (2.53) that

$$\begin{aligned} \frac{\mathrm{d}S_1}{\mathrm{d}t} &\le A_1 - (\mu_1 + a_1)S_1 + a_2 S_2, \\ \frac{\mathrm{d}S_2}{\mathrm{d}t} &\le A_2 + a_1 S_1 - (\mu_2 + a_2)S_2. \end{aligned} \tag{2.57}$$

For the comparison system

$$\begin{aligned}\frac{\mathrm{d}x_1}{\mathrm{d}t} &= A_1 - (\mu_1 + a_1)x_1 + a_2x_2,\\ \frac{\mathrm{d}x_2}{\mathrm{d}t} &= A_2 + a_1x_1 - (\mu_2 + a_2)x_2,\end{aligned} \tag{2.58}$$

it is easy to see that (S_1^0, S_2^0) is an equilibrium and is globally stable for (2.58). Then, for every $\varepsilon > 0$, there exists constant $T > 0$, large enough, such that

$$S_i(t) < S_i^0 + \varepsilon, \quad i = 1, 2,$$

for $t > T$. Thus, when $t > T$, from (2.53) we have

$$\begin{aligned}\frac{\mathrm{d}I_1}{\mathrm{d}t} &< \beta_1(S_1^0 + \varepsilon)I_1 - (\mu_1 + b_1 + \gamma_1)I_1 + b_2I_2,\\ \frac{\mathrm{d}I_2}{\mathrm{d}t} &< \beta_2(S_2^0 + \varepsilon)I_2 - (\mu_2 + b_2 + \gamma_2)I_2 + b_1I_1.\end{aligned} \tag{2.59}$$

By Lemma 2.1 [Wang and Zhao (2004)], when $R_0 < 1$, we can choose $\varepsilon > 0$ small enough such that positive solutions of the auxiliary system

$$\begin{aligned}\frac{\mathrm{d}y_1}{\mathrm{d}t} &= \beta_1(S_1^0 + \varepsilon) - (\mu_1 + b_1 + \gamma_1)y_1 + b_2y_2,\\ \frac{\mathrm{d}y_2}{\mathrm{d}t} &= \beta_2(S_2^0 + \varepsilon) - (\mu_2 + b_2 + \gamma_2)y_2 + b_1y_1\end{aligned}$$

tend to $(0, 0)$ as $t \to \infty$. Then, by the comparison theorem, it follows from (2.59) that $I_i(t) \to 0$ as $t \to \infty, i = 1, 2$. Furthermore, it easy to see that $S_i(t) \to S_i^0$ as $t \to \infty, i = 1, 2$, by the limit system theory. Therefore, the disease-free equilibrium P_0 is globally stable if $R_0 < 1$. □

Suppose $R_0 > 1$. Wang and Zhao (2004) proved that system (2.53) has at least one positive equilibrium, and that there is a positive constant ε such that every solution $(S_1(t), I_1(t), S_2(t), I_2(t))$ of (2.53) with $(S_1(0), I_1(0), S_2(0), I_2(0)) \in \operatorname{int}\Omega$ satisfies

$$\liminf_{t\to\infty} I_1(t) \geq \varepsilon, \quad \liminf_{t\to\infty} I_2(t) \geq \varepsilon.$$

This implies that the disease is uniformly persistent if $R_0 > 1$.

To investigate the effects of dispersal on disease transmissions, the following analysis is done. The Jacobian matrix of (2.53) at P_0 is

$$J = \begin{pmatrix} -\mu_1 - a_1 & -\beta_1 S_1^0 & a_2 & 0 \\ 0 & \beta_1 S_1^0 - (\mu_1 + \gamma_1 + b_1) & 0 & b_2 \\ a_1 & 0 & -\mu_2 - a_2 & -\beta_2 S_2^0 \\ 0 & b_1 & 0 & \beta_2 S_2^0 - (\mu_2 + \gamma_2 + b_2) \end{pmatrix}.$$

The characteristic equation of matrix J is

$$[(\lambda + \mu_1 + a_1)(\lambda + \mu_2 + a_2) - a_1 a_2] \times [(\lambda + \mu_1 + \gamma_1 + b_1 - \beta_1 S_1^0)(\lambda + \mu_2 + \gamma_2 + b_2 - \beta_2 S_2^0) - b_1 b_2] = 0.$$

It is easy to see that all the roots of equation $(\lambda + \mu_1 + a_1)(\lambda + \mu_2 + a_2) - a_1 a_2 = 0$ have negative real parts. Thus, according to the stability of P_0, $R_0 > 1$ is equivalent to the fact that, for the equation $(\lambda + \mu_1 + \gamma_1 + b_1 - \beta_1 S_1^0)(\lambda + \mu_2 + \gamma_2 + b_2 - \beta_2 S_2^0) - b_1 b_2 = 0$ of λ, there is a root with positive real part.

Let

$$R_1 = \frac{\beta_1 S_1^0}{\mu_1 + \gamma_1 + b_1}, \quad R_2 = \frac{\beta_2 S_2^0}{\mu_2 + \gamma_2 + b_2},$$

and

$$R_{12} = \frac{\beta_1 S_1^0 + \beta_2 S_2^0}{\mu_1 + \gamma_1 + b_1 + \mu_1 + \gamma_1 + b_1}.$$

Then it is easy to verify that equation $(\lambda + \mu_1 + \gamma_1 + b_1 - \beta_1 S_1^0)(\lambda + \mu_2 + \gamma_2 + b_2 - \beta_2 S_2^0) - b_1 b_2 = 0$ has a root with positive real part if and only if one of the following two conditions holds:

(1) $R_{12} > 1$;
(2) $R_{12} < 1$ and

$$(1 - R_1)(1 - R_2) < \frac{b_1}{\mu_1 + \gamma_1 + b_1} \cdot \frac{b_2}{\mu_2 + \gamma_2 + b_2}. \tag{2.60}$$

Here, R_i, $i = 1, 2$, is the basic reproductive number of i-patch when there exists the dispersal between the two patches and that the two patches are all in the disease-free steady-state, and R_{12} is the basic reproductive number if we consider the two patches as one patch. In this case, the instability of P_0 is clear if $R_{12} > 1$. However, the condition $R_{12} < 1$ does not necessarily lead to the extinction of the disease in both patches, and, even if both $R_1 < 1$ and $R_2 < 1$ hold, the disease may also spread in

both two patches provided (2.60) holds. Thus, if $R_{12} < 1$, the additional condition $(1 - R_1)(1 - R_2) > b_1/(\mu_1 + \gamma_1 + b_1) \cdot b_2/(\mu_2 + \gamma_2 + b_2)$ leads to the extinction of the disease.

We now consider the following three cases to illustrate the effects of population dispersal on the spread of disease.

Case 1. Choose $\mu_1 = \mu_2 = \gamma_1 = \gamma_2 = a_1 = b_1 = A_1 = A_2 = 1$, $a_2 = b_2 = 0.4, \beta_1 = 3$, and $\beta_2 = 1$. Then $R_{01} = 1.5$, $R_{02} = 0.5$, and $R_0 = 0.87$. While the disease persists in the first patch but goes to extinct in the second patch in the absence of population dispersal, the disease dies out in both patches if the population dispersals among the two patches.

Case 2. Choose $\mu_1 = \mu_2 = \gamma_1 = \gamma_2 = a_1 = b_1 = A_1 = 1, A_2 = 1.8a_2 = b_2 = 1.5, \beta_1 = 1.8$, and $\beta_2 = 19/18$. Then $R_{01} = 0.9$, $R_{02} = 0.95$, and $R_0 = 1.4$. The disease can persist in both patches if the population dispersals among two patches, whereas the disease dies out in both patches in the absence of population dispersal.

Case 3. Choose $\mu_1 = \mu_2 = \gamma_1 = \gamma_2 = a_1 = b_1 = A_1 = A_2 = 1, a_1 = a_2, b_1 = b_2 = 2, \beta_1 = 3$, and $\beta_2 = 1.5$. Then $R_{01} = 1.5$, $R_{02} = 0.75$, and $R_0 = 1.18$. The disease persists in the first patch but dies out in the second patch in the absence of population dispersal. However, with the population dispersal among two patches, the disease can persist in both patches.

From the three cases above, we see that the population dispersal can intensify the disease spread under certain conditions and can also reduce the disease spread under some other conditions.

2.4. Epidemic Models with Multiple Groups

Genetic variation of susceptible individuals may lead to their differential susceptibility. Infectivity of infectives for some diseases, such as AIDS/HIV, usually depends on the viral loads in infected hosts, which also leads to differential infectivities. SIR epidemic models with differential susceptibilities or infectivities were studied by Hyman and Li (2000, 2005a, 2005b), Hyman *et al.* (1999) and Ma *et al.* (2003), respectively, and SIR epidemic models with differential susceptibilities and infectivities were investigated by Hyman and Li (2006, 2008).

In this section, we mainly consider global analysis of some epidemic models with differential susceptibility or infectivity, which were studied by Li and coworkers.

We consider the spread of a disease in a randomly mixing population. We assume that susceptibles have differential susceptibilities and divide them into n groups, $S_1, S_2, \ldots, S_n$. The individuals in each group have homogeneous susceptibility, but the susceptibilities of individuals from different groups are distinct. The newborn susceptibles are distributed into the n susceptible groups based on their inherent susceptibility, in such a way that the input flow into group S_i is $p_i\mu A$ with $\sum_{i=1}^{n} p_i = 1$. The infectives are divided into m groups, $I_1, I_2, \ldots, I_m$, such that upon infection, an infected individual from group S_i enters group I_j with probability q_{ij} and stays in this group until becoming recovered or removed, where $\sum_{j=1}^{m} q_{ij} = 1$, for $i = 1, 2, \ldots, n$.

We assume that population approaches a steady state, A, in the absence of infection. Then an SIR model with differential susceptibility and infectivity, bilinear incidence, and disease-induced death is given by

$$\begin{aligned}
\frac{\mathrm{d}S_i}{\mathrm{d}t} &= \mu(p_i A - S_i) - \lambda_i S_i, \quad i = 1, 2, \ldots, n, \\
\frac{\mathrm{d}I_j}{\mathrm{d}t} &= \sum_{i=1}^{n} q_{ij}\lambda_i S_i - (\mu + \alpha_j + \gamma_j) I_j, \quad j = 1, 2, \ldots, m, \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \sum_{j=1}^{m} \gamma_j I_j - \mu R,
\end{aligned} \tag{2.61}$$

where $\lambda_i = \omega_i \sum_{j=1}^{m} \beta_j I_j$, and ω_i is the susceptibility of susceptible individuals in group S_i.

Because equations of S_i and I_j in (2.61) are independent of variable R, we need only to consider the following system consisting of equations of S_i and I_j in (2.61):

$$\begin{aligned}
\frac{\mathrm{d}S_i}{\mathrm{d}t} &= \mu(p_i A - S_i) - \lambda_i S_i, \quad i = 1, 2, \ldots, n, \\
\frac{\mathrm{d}I_j}{\mathrm{d}t} &= \sum_{i=1}^{n} q_{ij}\lambda_i S_i - \sigma_j I_j, \quad j = 1, 2, \ldots, m,
\end{aligned} \tag{2.62}$$

where $\sigma_j = \mu + \alpha_j + \gamma_j$.

Let $N = \sum_{i=1}^{n} S_i + \sum_{j=1}^{m} I_j$. Then

$$\frac{\mathrm{d}N}{\mathrm{d}t} = \mu A - \mu N - \sum_{j=1}^{m} (\alpha_j + \gamma_j) I_j,$$

and hence $\limsup_{t\to\infty} N(t) \le A$. Again, it follows from (2.61) that

$$\frac{\mathrm{d}S_i}{\mathrm{d}t} \le \mu(p_i A - S_i), \quad i = 1, 2, \ldots, n,$$

and then $\limsup_{t\to\infty} S_i(t) \le p_i A$. Therefore, the region

$$G = \left\{ (S, I) \in R_+^{n+m} \colon \sum_{i=1}^{n} S_i + \sum_{j=1}^{m} I_j \le A, S_i \le p_i A \right\}$$

is a positively invariant set for system (2.62), where $S = (S_1, S_2, \ldots, S_n)^{\mathrm{T}}$, $I = (I_1, I_2, \ldots, I_m)^{\mathrm{T}}$.

It is obvious that (2.62) always has the disease-free equilibrium $E_0(p_1 A, p_2 A, \ldots, p_n A, 0, 0, \ldots, 0)$ for all feasible parameters.

To find the basic reproductive number R_0 of (2.61) or (2.62), we first investigate the local asymptotic stability of the disease-free equilibrium. The Jacobian matrix of model (2.62) at the disease-free equilibrium E_0 has the form

$$D = \begin{pmatrix} D_{11} & \cdot \\ 0 & D_{22} \end{pmatrix},$$

where

$$D_{11} = \mathrm{diag}(-\mu, -\mu, \ldots, -\mu)$$

and

$$D_{22} = \begin{pmatrix} -\sigma_1 + L_1\beta_1 & L_1\beta_2 & \cdots & L_1\beta_m \\ L_2\beta_1 & -\sigma_2 + L_2\beta_2 & \cdots & L_2\beta_m \\ \vdots & \vdots & \vdots & \vdots \\ L_m\beta_1 & L_m\beta_2 & \cdots & -\sigma_m + L_m\beta_m \end{pmatrix},$$

with $L_j = A\sum_{i=1}^{n} q_{ij}\omega_i p_i, j = 1, 2, \ldots, m$. Then the local stability of the disease-free equilibrium E_0 is determined by matrix D_{22}.

Consider matrix $-D_{22}$. It has all off-diagonal elements negative. Let $V = (L_1/\sigma_1, \ldots, L_m/\sigma_m)^{\mathrm{T}}$, then

$$-D_{22}V = \left(1 - \sum_{j=1}^{m} \frac{L_j \beta_j}{\sigma_j}\right)(L_1, L_2, \ldots, L_m)^{\mathrm{T}}.$$

Since $L_j > 0, j = 1, \ldots, m$, if we define $R_0 = \sum_{j=1}^{m} L_j \beta_j / \sigma_j$, then it follows from the M-matrix theory that each eigenvalue of D_{22} has negative real part if $R_0 < 1$. Hence the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$.

By mathematical induction, it can be shown that

$$\det D_{22} = (-1)^{m+1} \prod_{j=1}^{m} \sigma_j (R_0 - 1).$$

Then, if $R_0 > 1$, D_{22} has at least one positive eigenvalue. It implies that the disease-free equilibrium E_0 is unstable. Hence, the basic reproductive number for model (2.61) or (2.62) can be defined by R_0, which is expressed as

$$R_0 = A \sum_{i=1}^{n} \sum_{j=1}^{m} \frac{p_i \omega_i q_{ij} \beta_j}{\sigma_i}. \tag{2.63}$$

For (2.62), the global stability of the disease-free equilibrium and the existence of the endemic equilibrium were obtained by Hyman and Li (2006).

Theorem 2.19. *For model* (2.62), *the disease-free equilibrium* E_0 *is globally stable in* G *if* $R_0 < 1$.

Proof. Define vectors $P = (p_1, p_2, \ldots, p_n)^{\mathrm{T}}$ and $B = (\beta_1, \beta_2, \ldots, \beta_m)^{\mathrm{T}}$, and define matrices $A = \mathrm{diag}(\omega_1, \omega_2, \ldots, \omega_n)$, $D = \mathrm{diag}(\sigma_1, \sigma_2, \ldots, \sigma_m)$, and

$$Q = \begin{pmatrix} q_{11} & q_{12} & \cdots & q_{1m} \\ q_{21} & q_{22} & \cdots & q_{2m} \\ \vdots & \vdots & \vdots & \vdots \\ q_{n1} & q_{n2} & \cdots & q_{nm} \end{pmatrix}.$$

Then system (2.62) can be written as

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu(AP - S) - ASB^{\mathrm{T}}I, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= Q^{\mathrm{T}}ASB^{\mathrm{T}}I - DI, \end{aligned} \tag{2.64}$$

where $S = (S_1, S_2, \ldots, S_n)^{\mathrm{T}}$, $I = (I_1, I_2, \ldots, I_m)^{\mathrm{T}}$, and the basic reproductive number in (2.63) can be expressed as

$$R_0 = AB^{\mathrm{T}}D^{-1}Q^{\mathrm{T}}AP.$$

Define function $V = B^{\mathrm{T}}D^{-1}I$. Then V is positive definite for $I_j \geq 0$. It follows from (2.64) that

$$\begin{aligned} \frac{\mathrm{d}V}{\mathrm{d}t} &= B^{\mathrm{T}}D^{-1}(Q^{\mathrm{T}}ASB^{\mathrm{T}}I - DI) = (B^{\mathrm{T}}D^{-1}Q^{\mathrm{T}}AS - 1)B^{\mathrm{T}}I \\ &\leq (AB^{\mathrm{T}}D^{-1}Q^{\mathrm{T}}AP - 1)B^{\mathrm{T}}I = (R_0 - 1)B^{\mathrm{T}}I. \end{aligned} \tag{2.65}$$

Then $\mathrm{d}V/\mathrm{d}t \leq 0$ in G if $R_0 < 1$. Notice that $\mathrm{d}V/\mathrm{d}t = 0$ only if $I = 0$. Hence the disease-free equilibrium E_0 is the only positively invariant set in the set $\{(S, I) \in G\colon \mathrm{d}V/\mathrm{d}t = 0\}$. Therefore, It follows from the Liapunov stability theory [Hale (1980)] that the disease-free equilibrium E_0 is globally stable in G. □

Theorem 2.20. *System* (2.62) *has a unique endemic equilibrium in* G *if and only if* $R_0 > 1$.

Proof. For system (2.62), an endemic equilibrium needs to satisfy the equations

$$\begin{aligned} &\mu(p_iA - S_i) - \lambda_i S_i = 0, \quad i = 1, 2, \ldots, n, \\ &\sum_{i=1}^{n} q_{ij}\lambda_i S_i - \sigma_j I_j = 0, \quad j = 1, 2, \ldots, m. \end{aligned} \tag{2.66}$$

Let $W = \sum_{j=1}^{m} \beta_j I_j$. Then $\lambda_i = W\omega_i$. It follows from (2.66) that

$$\begin{aligned} S_i &= \frac{\mu p_i A}{\mu + \omega_i W}, \quad i = 1, 2, \ldots, n, \\ I_j &= \frac{\mu W A}{\sigma_j} \sum_{i=1}^{n} \frac{q_{ij}\omega_i p_i}{\mu + \omega_i W}, \quad j = 1, 2, \ldots, m. \end{aligned} \tag{2.67}$$

Hence

$$W = \sum_{j=1}^{m} \beta_j I_j = \mu W A \sum_{j=1}^{m} \sum_{i=1}^{n} \frac{\beta_j q_{ij} \omega_i p_i}{\sigma_j(\mu + \omega_i W)}.$$

Define

$$H(W) = \mu A \sum_{j=1}^{m} \sum_{i=1}^{n} \frac{\beta_j q_{ij} \omega_i p_i}{\sigma_j(\mu + \omega_i W)} - 1.$$

Then there exists an endemic equilibrium for system (2.62) if and only if there exists a positive root for $H(W) = 0$.

Note that

$$H'(W) = -\mu A \sum_{j=1}^{m} \sum_{i=1}^{n} \frac{\beta_j q_{ij} \omega_i^2 p_i}{\sigma_j(\mu + \omega_i W)^2} < 0,$$

$\lim_{W \to \infty} H(W) = -1$, and $H(0) = R_0 - 1$. It follows that equation $H(W) = 0$ has a unique positive root if and only if $R_0 > 1$. Hence, from equations of I_j in (2.67), there exists a unique endemic equilibrium of (2.62) if and only if $R_0 > 1$. □

Since the differential susceptibility and the differential infectivity are both contained in system (2.62), it is difficult to investigate the global stability of the endemic equilibrium. Then we will consider the global stability of the endemic equilibrium for two specific cases: the models with only differential susceptibility and those only differential infectivity, respectively.

2.4.1. *The global stability of epidemic model only with differential susceptibility*

For model with only differential susceptibility, (2.62) becomes

$$\begin{aligned} \frac{\mathrm{d}S_i}{\mathrm{d}t} &= \mu(p_i A - S_i) - \omega_i \beta I S_i, \quad i = 1, 2, \ldots, n, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \sum_{i=1}^{n} \omega_i \beta I S_i - (\mu + \alpha + \gamma) I. \end{aligned} \tag{2.68}$$

From (2.63), the basic reproductive number for (2.68) is

$$R_0 = \frac{\beta A}{\mu + \alpha + \gamma} \sum_{i=1}^{n} p_i \omega_i.$$

And the global stability of the endemic equilibrium for (2.68) was proved by Hyman and Li (2005).

Theorem 2.21. *Assume $R_0 > 1$. The unique endemic equilibrium of system* (2.68) *is globally asymptotically stable.*

Proof. Let $(S_1^*, S_2^*, \ldots, S_n^*, I^*)$ be the unique endemic equilibrium and we make the following transformation

$$I = I^*(1+y), \quad S_i = S_i^*(1+x_i), \quad i = 1, 2, \ldots, n,$$

where $y > -1, x_i > -1, i = 1, 2, \ldots, n$. By substituting this transformation into (2.68), x_i and y satisfy the system

$$\begin{aligned} \frac{\mathrm{d}x_i}{\mathrm{d}t} &= -[(\mu + \beta\omega_i I^*)x_i + (1+x_i)\beta\omega_i I^* y], \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \beta \sum_{i=1}^{n} \omega_i S_i^* x_i (1+y), \end{aligned} \tag{2.69}$$

and the stability of the endemic equilibrium of system (2.68) is equivalent to the stability of the trivial solution of system (2.69).

Define Liapunov function

$$V = \sum_{i=1}^{n} \frac{S_i^* x_i^2}{2I^*} + y - \ln(1+y).$$

Then V is positive definite for $x_i > -1$ and $y > -1$, and $V = 0$ if and only if $(x_1, x_2, \ldots, x_n, y) = (0, 0, \ldots, 0)$. Along trajectories of system (2.69), we have

$$\begin{aligned} \frac{\mathrm{d}V}{\mathrm{d}t} &= -\sum_{i=1}^{n} \frac{S_i^* x_i}{I^*}[(\mu + \beta\omega_i I^*)x_i + (1+x_i)\beta\omega_i I^* y] \\ &\quad + \frac{y}{1+y}\beta \sum_{i=1}^{n} \omega_i S_i^* x_i (1+y) \\ &= -\sum_{i=1}^{n} \frac{S_i^* \mu}{I^*} x_i^2 - \beta \sum_{i=1}^{n} \omega_i S_i^* x_i^2 (1+y) \le 0. \end{aligned}$$

Moreover, the maximum invariant subset of set

$$\left\{ (x_1, x_2, \ldots, x_n, y) \colon \frac{\mathrm{d}V}{\mathrm{d}t} = 0 \right\},$$

for $x_i > -1$ and $y > -1$, consists of only the origin $(0, 0, \ldots, 0)$. Then, it follows from the Liapunov stability theory that the origin of system (2.69), and hence the endemic equilibrium of (2.68), is globally asymptotically stable. □

2.4.2. *The global stability of epidemic model only with differential infectivity*

For the model with only differential infectivity, (2.62) becomes

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu(A - S) - \sum_{j=1}^{m} \beta_j I_j S, \\ \frac{\mathrm{d}I_j}{\mathrm{d}t} &= q_j \sum_{j=1}^{m} \beta_j I_j S - (\mu + \alpha_j + \gamma_j) I_j, \quad j = 1, 2, \ldots, m, \end{aligned} \tag{2.70}$$

where $\sum_{j=1}^{m} q_j = 1$. From (2.63), the basic reproductive number of (2.70) is

$$R_0 = A \sum_{j=1}^{m} \frac{\beta_j q_j}{\mu + \alpha_j + \gamma_j}.$$

If $R_0 > 1$, (2.70) has a unique endemic equilibrium $E^*(S^*, I_1^*, \ldots, I_m^*)$, where

$$S^* = \frac{A}{R_0}, \quad I_j^* = \frac{A\mu(R_0 - 1)q_j}{R_0(\mu + \alpha_j + \gamma_j)}, \ \ j = 1, 2, \ldots, m.$$

And the global stability of the endemic equilibrium E^* for (2.70) was proved by Ma *et al.* (2003).

Theorem 2.22. *If $R_0 > 1$, the endemic equilibrium E^* of system* (2.70) *is globally asymptotically stable.*

Proof. From the definition of I_j^*, we have

$$\frac{q_j I_k^*}{I_j^*(\mu + \alpha_j + \gamma_j)} = \frac{q_k}{\mu + \alpha_k + \gamma_k}.$$

Then, by transformation $S = S^*(1 + x), I_j = I_j^*(1 + y_j)$, $j = 1, 2, \ldots, m$, system (2.70) becomes

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\left[\mu + \sum_{j=1}^{m} \beta_j I_j^*(1 + y_j)\right] x - \sum_{j=1}^{m} \beta_j I_j^* y_j,$$

$$\begin{aligned}\frac{\mathrm{d}y_j}{\mathrm{d}t} &= (\mu+\alpha_j+\gamma_j)x(1+y_j)\\ &\quad+(\mu+\alpha_j+\gamma_j)\sum_{k=1}^{m}\frac{q_k\beta_k}{\mu+\alpha_k+\gamma_k}\\ &\quad\times S^*(1+x)(y_k-y_j),\quad j=1,2,\ldots,m,\end{aligned}\tag{2.71}$$

and the endemic equilibrium of (2.70) corresponds to the trivial equilibrium of (2.71).

Now, we prove the global stability of the trivial solution of (2.71). Define Liapunov function V as

$$V=\frac{x^2}{2}+\sum_{j=1}^{m}\frac{\beta_j I_j^*}{\mu+\alpha_j+\gamma_j}\left[y_j-\ln(1+y_j)\right],$$

then V is positive definite for $x>-1$ and $y_j>-1$, and $V=0$ if and only if $(x,y_1,y_2,\ldots,y_m)=(0,0,\ldots,0)$. Along trajectories of system (2.71), we have

$$\frac{\mathrm{d}V}{\mathrm{d}t}=-\left[\mu+\sum_{j=1}^{m}\beta_j I_j^*(1+y_j)\right]x^2+S^*(1+x)\sum_{j=1}^{m}\sum_{k=1}^{m}h_{jk},$$

where

$$h_{jk}=\frac{\beta_j I_j^* q_k\beta_k}{\mu+\alpha_k+\gamma_k}\frac{y_k-y_j}{1+y_j}y_j.$$

Notice that

$$\frac{I_j^* q_k}{\mu+\alpha_k+\gamma_k}=\frac{I_k^* q_j}{\mu+\alpha_j+\gamma_j}.$$

Then

$$h_{jk}+h_{kj}=-\frac{\beta_j\beta_k q_k I_j^*}{(\mu+\alpha_k+\gamma_k)(1+y_j)(1+y_k)}(y_k-y_j)^2.$$

Hence,

$$\begin{aligned}\frac{\mathrm{d}V}{\mathrm{d}t} &= -\left[\mu+\sum_{j=1}^{m}\beta_j I_j^*(1+y_j)\right]x^2\\ &\quad-S^*(1+x)\sum_{1\le j<k\le m}\frac{\beta_j\beta_k q_k I_j^*}{(\mu+\alpha_k+\gamma_k)(1+y_j)(1+y_k)}(y_k-y_j)^2\le 0.\end{aligned}$$

The maximum invariant set of the set

$$\left\{(x, y_1, y_2, \ldots, y_n)\colon \frac{\mathrm{d}V}{\mathrm{d}t} = 0\right\}$$

is the origin $(0, 0, \ldots, 0)$. By the Liapunov stability theory, the origin of system (2.71), and hence the endemic equilibrium of (2.70), is globally asymptotically stable. □

2.5. Epidemic Models with Different Populations

In the real world, species do not exist alone, but always interact with one another. Therefore, to study the transmission of diseases among the interactive populations, combining epidemiology with population ecology is important. For ecologic systems, predatory and competitive systems have been studied by many researchers. In recent years, incorporating epidemic models into predatory or competitive system is one tendency in studying of disease spreads in different populations.

There have been some works on disease spread in prey–predator systems [Hadeler and Freedman (1989); Venturino (1994); Packer *et al.* (2003); Hudson *et al.* (1992); Chattopadhyay and Arion (1999); Xiao and Chen (2001a,c); Han *et al.* (2001); Hethcote *et al.* (2004); Chattopadhyay *et al.* (2002); Mukherjee (1998)]. In particular, the case where the infected prey is more vulnerable to predation was considered by Hudson *et al.* (1992) and Hethcote *et al.* (2004), and the case that disease spreads in competing system was considered by Han *et al.* (2003), Saenz and Hethcote (2006), Anderson and May (1986), Bowers and Turner (1997), Begon *et al.* (1999) and Venturino (2001). Anderson and May (1986) described that how a disease could affect the competition. Bowers and Turner (1997) considered an SIS competition model with bilinear incidence, density-independent death rates, and disease-induced deaths, and developed criteria to show how the forces of competition and infection combine. Begon *et al.* (1999) studied the cowpox virus in coexisting populations of bank voles and wood mice, and found that frequency-dependent incidence was clearly superior. Venturino (2001) formulated competing models with a disease in one species and bilinear and standard incidences, and found periodic solutions numerically in one model with bilinear incidence. Han *et al.* (2001, 2003) considered an SIRS epidemic model with two competitive species, standard incidence, and logistic growth. Saenz and Hethcote (2006) investigated SIS

and SIRS epidemic models with standard incidence, disease-induced deaths and logistic growth.

In this section, we consider epidemic models that describe diseases spread in prey–predator systems and competitive systems. For the case that disease spreads in prey–predator systems, we mainly introduce some results by Hethcote *et al.* (2004) and Han *et al.* (2001). An SIS model with standard incidence and logistic growth, and the disease spread only in the prey species was considered by Hethcote *et al.* (2004). Four prey–predator systems with infectious diseases were studied by Han *et al.* (2001), all of which describe disease spread in both prey and predator species. For the case that disease spreads in competitive systems, we mainly introduce some results by Han *et al.* (2001), which describes disease spreads in both competing species.

2.5.1. *Disease spread in prey–predator system*

Before considering disease spread in a prey–predator system, we first give an outline with respect to the results of prey–predator systems and SIS models with the standard incidence.

Let $H(t)$ and $P(t)$ be the sizes of prey and predator population at time t, respectively. The prey–predator model used here takes the form

$$\begin{aligned} \frac{\mathrm{d}H}{\mathrm{d}t} &= r\left(1-\frac{H}{K}\right)H - aHP = \left[r\left(1-\frac{H}{K}\right) - aP\right]H, \\ \frac{\mathrm{d}P}{\mathrm{d}t} &= kaHP - cP = (kaH - c)P, \end{aligned} \tag{2.72}$$

which is a modification of the classic Lotka–Volterra model with the density-dependent logistic growth in the prey. The meaning of all the parameters in system (2.72) was introduced in Sec. 1.4.4. Here, the density dependence of population P is not considered. It is easy to see that the region $D = \{(H,P) \in R_+^2 \colon H \le K\}$ is a positively invariant set of (2.72). This model was also formulated and explained by Pielou (1969). The following lemma is from the Kolmogorov–Brauer theorem.

Lemma 2.3 [Nisbet and Gurney (1982)]. *For system* (2.72) *in* D, $\lim_{t\to\infty}(H,P) = (K,0)$ *if* $H(0) > 0$ *and* $kaK/c \le 1$, *or* $H(0) > 0$ *and* $P(0) = 0$; $\lim_{t\to\infty}(H,P) = (H_{\mathrm{E}}, P_{\mathrm{E}})$ *if* $H(0) > 0, P(0) > 0$ *and* $kaK/c > 1$, *where* $H_{\mathrm{E}} = c/(ka)$ *and* $P_{\mathrm{E}} = r[1 - c/(kaK)]/a$.

Consider an SIS model with the standard incidence in the absence of predator population

$$\begin{aligned}
\frac{\mathrm{d}H}{\mathrm{d}t} &= r\left(1-\frac{H}{K}\right)H,\\
\frac{\mathrm{d}X}{\mathrm{d}t} &= \left(b-\frac{\theta rH}{K}\right)H-\left[\mu+\frac{(1-\theta)rH}{K}\right]X-\frac{\beta XY}{H}+\gamma Y,\\
\frac{\mathrm{d}Y}{\mathrm{d}t} &= \frac{\beta XY}{H}-\gamma Y-\left[\mu+\frac{(1-\theta)rH}{K}\right]Y,
\end{aligned} \tag{2.73}$$

where $X = X(t)$ and $Y = Y(t)$ are the numbers of the susceptible and infected individuals in prey population at time t, respectively, $H = X + Y$, b and μ are the natural birth and death rate coefficients, respectively, and r is the intrinsic growth rate coefficient.

The population satisfies the logistic differential equation with birth rate coefficient $b - \theta rH/K$ and death rate coefficient $r = b - \mu > 0$. Using $I = Y/H$, and $S = X/H = 1 - I$, the three differential equations above can be reduced to the following two dimensional system:

$$\begin{aligned}
\frac{\mathrm{d}H}{\mathrm{d}t} &= r\left(1-\frac{H}{K}\right)H,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \left[\beta(1-I)-\left(\gamma+b-\frac{\theta rH}{K}\right)\right]I.
\end{aligned} \tag{2.74}$$

This model is mathematicalally well posed and all solutions stay or enter the positively invariant region $D = \{(H, I)\colon 0 \le I \le 1,\ 0 \le H \le K\}$. Dynamic behavior of system (2.74) can be determined by two epidemiologic threshold quantities: the basic reproductive number R_0 and the modified basic reproductive number R_2, which are given by

$$R_0 = \frac{\beta}{\gamma + b - \theta r}, \quad R_2 = \frac{\beta}{\gamma + b}.$$

System (2.74) has at most four equilibria on the boundary of D. Equilibria $E_0(0, 0)$ and $E_1(K, 0)$ always exist. At E_0, both the population and the disease vanish. At E_1, the disease dies out, and the size of the population is at the carrying capacity of the environment. If $R_2 > 1$, there exists an equilibrium $E_3 = (0, 1 - 1/R_2)$, which shows that the disease always persists in the population until the population goes to extinct. If $R_0 > 1$, there is an equilibrium $E_4 = (K, 1 - 1/R_0)$, which implies that the

disease always persists in the population while the population approaches to the carrying capacity of the environment.

The lemma below on the global asymptotic behavior is for a special case [Gao and Hethcote (1992)], where the disease-induced death is not considered.

Lemma 2.4. *For solution orbits of system* (2.74) *in* D, $\lim_{t\to\infty}(H, I) = E_0$ *if* $I(0) > 0$, $H(0) = 0$ *and* $R_2 \le 1$, *and* $\lim_{t\to\infty}(H, I) = E_3$ *if* $I(0) > 0$, $H(0) = 0$ *and* $R_2 > 1$; $\lim_{t\to\infty}(H, I) = E_1$ *if* $I(0) = 0$, *and* $H(0) > 0$; $\lim_{t\to\infty}(H, I) = E_1$ *if* $I(0) > 0$, $H(0) > 0$ *and* $R_0 \le 1$; $\lim_{t\to\infty}(H, I) = E_4$ *if* $I(0) > 0$, $H(0) > 0$ *and* $R_0 > 1$.

2.5.1.1. *Disease spread only in the prey population*

Suppose that a disease spreads only in a prey population, and that the infected prey are more vulnerable to predation. Combining the predator–prey and SIS models in the previous part, a predator–prey model with infected prey [Hethcote *et al.* (2004)] is given by

$$\begin{aligned}
\frac{\mathrm{d}H}{\mathrm{d}t} &= r\left(1-\frac{H}{K}\right)H - a(X+qY)P,\\
\frac{\mathrm{d}X}{\mathrm{d}t} &= \left(b-\frac{\theta rH}{K}\right)H - \left[\mu+\frac{(1-\theta)rH}{K}\right]X - \frac{\beta XY}{H} + \gamma Y - aXP,\\
\frac{\mathrm{d}Y}{\mathrm{d}t} &= \frac{\beta XY}{H} - \gamma Y - \left[\mu+\frac{(1-\theta)rH}{K}\right]Y - aqYP,\\
\frac{\mathrm{d}P}{\mathrm{d}t} &= ka(X+qY)P - cP,
\end{aligned} \tag{2.75}$$

where the factor $q \ge 1$ reflects that infected prey are more vulnerable to predation. Let $I = Y/H$ and $X/H = 1 - I$ denote the fractions of the infected and susceptible individuals in the prey population, respectively. Then system (2.75) of four differential equations can be reduced to the following three-dimensional system:

$$\begin{aligned}
\frac{\mathrm{d}H}{\mathrm{d}t} &= \left[r\left(1-\frac{H}{K}\right) - a(1+(q-1)I)P\right]H,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \left[\beta(1-I) - \left(\gamma+b-\frac{\theta rH}{K}\right) - a(q-1)(1-I)P\right]I,\\
\frac{\mathrm{d}P}{\mathrm{d}t} &= [kaH(1+(q-1)I) - c]P.
\end{aligned} \tag{2.76}$$

It is easy to see that the region $D = \{(H, I, P) \in R^3_+ \colon H \leq K, I \leq 1\}$ is positively invariant for (2.76). The dynamics of (2.76) was analyzed by [Hethcote *et al.* (2004)].

System (2.76) has at most five equilibria on the boundary of D. The first two are $E_0 = (0, 0, 0)$ and $E_1 = (K, 0, 0)$. When $kaK/c > 1$, there is an equilibrium $E_2 = (H_{\rm E}, 0, P_{\rm E})$, where $H_{\rm E}$ and $P_{\rm E}$ are given in Lemma 2.3. When $R_2 > 1$, there is an equilibrium $E_3 = (0, 1 - 1/R_2, 0)$. When $R_0 > 1$, there is an equilibrium $E_4 = (K, 1 - 1/R_0, 0)$.

First, we look at the dynamic behavior of (2.76) on the boundary of D.

The orbits of model (2.76) on the H axis with $H(0) > 0$ go to the equilibrium $E_1 = (K, 0, 0)$, since without any predators, the prey population goes to the carrying capacity. The orbits on the P axis go to the equilibrium $E_0 = (0, 0, 0)$, since without any prey, the predator population goes to extinction. The orbits on the I axis go to the equilibrium $E_0 = (0, 0, 0)$, when $R_2 \leq 1$, and go to the equilibrium $E_3 = (0, 1-1/R_2, 0)$, when $R_2 > 1$.

It follows from Lemmas 2.3 and 2.4, the dynamic behavior of the orbits on the $I = 0$ or the $P = 0$ plane of region D can be determined, respectively. On the $H = 0$ surface of D, $P \to 0$. Hence the orbits on this surface with $I(0) > 0$ go to $E_0 = (0, 0, 0)$ when $R_2 \leq 1$, and go to the equilibrium $E_3 = (0, 1 - 1/R_2, 0)$ when $R_2 > 1$. Orbits (except the equilibrium $E_1 = (K, 0, 0)$) starting on the $H = K$ surface of D enter the interior of D. All orbits starting on the $I = 1$ surface of D enter the interior of D.

Next, analyzing the linearized system of (2.76) at equilibria, the following results can be obtained.

Theorem 2.23. *Denote*

$$R_1 = \frac{\beta}{(\gamma + b - \theta rc/(kaK)) + (q-1)r(1 - c/(kaK))},$$

and

$$\psi = (q-1)\left(1 - \frac{1}{R_0}\right) - \left(\frac{c}{kaK} - 1\right).$$

Then both equilibria E_0 and E_3 of system (2.76) *are unstable for all feasible parameter values. Equilibrium E_1 is locally asymptotically stable if $R_0 < 1$ and $kaK/c < 1$, and unstable if $R_0 > 1$ or $kaK/c > 1$; E_2 is locally asymptotically stable if $R_1 < 1$ and $kaK/c > 1$, and unstable if $R_1 > 1$ and $kaK/c > 1$; and equilibrium E_4 is locally asymptotically stable if $R_0 > 1$ and $\psi < 0$, and unstable if $R_0 > 1$ and $\psi > 0$.*

With respect to the global stability, we have

Theorem 2.24. *For the orbits of system* (2.76) *starting in the interior of* D,

(1) $\lim_{t\to\infty}(H, I, P) = E_1$ *if* $kaK/c \le 1$ *and* $R_0 \le 1$; $\lim_{t\to\infty}(H, I, P) = E_2$ *if* $kaK/c > 1$ *and* $R_0 \le 1$.
(2) $\lim_{t\to\infty}(H, I, P) = E_4$ *if* $R_0 > 1$ *and* $\psi < 0$.
(3) *For the case* $q = 1$, *when* $kaK/c > 1$ *and* $R_1 > 1$, (2.76) *has a unique positive equilibrium* $E_5 = (H_{\rm E}, I_5, P_{\rm E})$ (*here* $I_5 = 1 - 1/R_1$) *which is globally stable*; *when* $kaK/c > 1$ *and* $R_1 \le 1$, $\lim_{t\to\infty}(H, I, P) = E_2$. *When* $kaK/c \le 1$, $\lim_{t\to\infty}(H, I, P) = E_1$ *for* $R_0 \le 1$, *and* $\lim_{t\to\infty}(H, I, P) = E_4$ *for* $R_0 > 1$.

Proof.

(1) The differential equation for I in (2.76) satisfies

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= \left[\beta(1-I) - (\gamma + b - \theta r) - \theta r\left(1 - \frac{H}{K}\right) - a(q-1)(1-I)P\right] I,\\ &\le (\gamma + b - \theta r)[R_0(1-I) - 1]I < 0 \quad \text{for } I(0) > 0.\end{aligned}$$

It is easy to obtain that $\lim_{t\to\infty} I(t) = 0$ as $R_0 \le 1$.

Let system (2.76) be the system $x' = f(t, x)$ in Corollary 2.1 in which the variable $I(t)$ is considered to be a function of t. Then the limiting system, as $t \to \infty$, is system (2.72) with the added equation $I' = 0$. By Corollary 2.1 the solutions of the original system (2.76) approach the asymptotically stable equilibrium of system (2.72). Thus, it follows from Lemma 2.3 that condition (1) in Theorem 2.24 holds.

(2) When $R_0 > 1$ and $\psi < 0$, the solutions H and I in system (2.76) satisfy the differential inequalities

$$\begin{aligned}\frac{\mathrm{d}H}{\mathrm{d}t} &\le r\left(1 - \frac{H}{K}\right) H,\\ \frac{\mathrm{d}I}{\mathrm{d}t} &\le \left[\beta(1-I) - (\gamma + b) + \frac{\theta r H}{K}\right] I.\end{aligned}$$

Then, for $R_0 > 1$, it follows from Lemma 2.4 and the comparison principle that the solutions to the inequalities above satisfy

$$\limsup_{t\to\infty} H(t) \le K, \quad \limsup_{t\to\infty} I(t) \le 1 - \frac{1}{R_0}. \tag{2.77}$$

Take $\varepsilon > 0$ small enough such that

$$ka(K+\varepsilon)\left[1+(q-1)\left(1-\frac{1}{R_0+\varepsilon}\right)\right]-c<0,$$

for $\psi < 0$. It follows from (2.77) that there exists $T > 0$, large enough, such that $H(t) < K+\varepsilon$ and $I(t) < 1-1/(R_0+\varepsilon)$ for $t > T$. Hence, when $t > T$, P satisfies

$$\frac{\mathrm{d}P}{\mathrm{d}t} \le \left[ka(K+\varepsilon)\left(1+(q-1)\left(1-\frac{1}{R_0+\varepsilon}\right)\right)-c\right]P,$$

and then $\lim_{t\to\infty} P = 0$ as $R_0 > 1$ and $\psi < 0$. Similar to the part (1), (condition (2)) of Corollary 2.1 implies condition (2) of Theorem 2.24.

(3) When $q = 1$, $R_1 = \beta/(\gamma + b - \theta rc/(kaK))$ and $\psi = 1 - c/(kaK)$, the equations for H and P in system (2.76) do not involve I. Then the asymptotic behaviors of H and P are given in Lemma 2.3.

When $kaK/c > 1$, $\lim_{t\to\infty} H = H_{\mathrm{E}}$ and $\lim_{t\to\infty} P = P_{\mathrm{E}}$ by Lemma 2.3. Hence, the second equation in system (2.76) becomes

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta\left[1-\frac{1}{R_1}-I+\frac{F(t)}{\beta}\right]I, \tag{2.78}$$

where $F(t) = \theta r(H - H_{\mathrm{E}})/K \to 0$ as $t \to \infty$. Then Eq. (2.78) has the limiting equation $I' = \beta(1 - 1/R_1 - I)I$. By Corollary 2.1, solutions I approach the globally stable equilibrium of this logistic differential equation, that is, $\lim_{t\to\infty}(H, I, P) = E_2$, if $kaK/c > 1$ and $R_1 \le 1$, and $\lim_{t\to\infty}(H, I, P) = E_5$, if $kaK/c > 1$ and $R_1 > 1$.

When $kaK/c \le 1$, $\lim_{t\to\infty}(H, P) = (K, 0)$. Then

$$I' = \beta\left[1-\frac{1}{R_0}-I+\frac{F(t)}{\beta}\right]I,$$

where $F(t) = \theta r(H/K-1) \to 0$ as $t \to \infty$. Similarly, $\lim_{t\to\infty}(H, I, P) = E_1$ if $kaK/c \le 1$ and $R_0 \le 1$, and $\lim_{t\to\infty}(H, I, P) = E_4$, if $kaK/c \le 1$ and $R_0 > 1$. □

When $q > 1$, we have the following results on the existence of interior equilibria of (2.76).

Theorem 2.25. *For case $q > 1$, system (2.76) has at least an interior equilibrium when $kaK/c > 1$ and $R_1 > 1$, or $1/q < kaK/c \le 1$ and $\psi > 0$.*

Proof. A positive equilibrium $E^*(H^*, I^*, P^*)$ of (2.76) satisfies the equations

$$r\left(1-\frac{H}{K}\right) = a(1+(q-1)I)P, \tag{2.79}$$

$$\beta(1-I) - \gamma - b + \frac{\theta r H}{K} = a(q-1)P(1-I), \tag{2.80}$$

$$kaH(1+(q-1)I) = c. \tag{2.81}$$

Combining (2.79) and (2.81), we obtain

$$P = \frac{rk}{c}H\left(1-\frac{H}{K}\right) := f_1(H), \tag{2.82}$$

which is a parabola that is zero at $H = 0$ and $H = K$. From (2.81) we have $1 - I = (qH - H_{\rm E})/((q-1)H)$ where $H_{\rm E} = c/(ka)$. Substituting this into (2.80) yields

$$P = \frac{\beta}{a(q-1)} - \frac{(\gamma + b - \theta r H/K)H}{a(qH - H_{\rm E})} := f_2(H). \tag{2.83}$$

From $0 < 1 - I^* < 1$, we have $H_{\rm E}/q < H^* < H_{\rm E}$. Then $H_{\rm E}/q < H^* < \min\{H_{\rm E}, K\} := \bar{H}$. It is easy to show that the function $f_2(H)$ is increasing and concave downward on the interval $[H_{\rm E}/q, \bar{H}]$ and approaches $-\infty$ as H decreases to $H_{\rm E}/q$ for $1/q < kaK/c$.

It follows from $kaK/c > 1$ that $H_{\rm E} < K$, and then $\bar{H} = H_{\rm E}$ for $kaK/c > 1$. A straightforward calculation shows that $f_2(H_{\rm E}) - f_1(H_{\rm E}) = \beta(1 - 1/R_1)/(a(q-1)) > 0$ for $R_1 > 1$.

It follows from $1/q < kaK/c \le 1$ that $H_{\rm E} \ge K$, and then $\bar{H} = K$ for $1/q < kaK/c \le 1$. A straightforward calculation again shows that

$$f_2(K) - f_1(K) = \frac{\beta}{a(q-1)} - \frac{(\gamma + b - \theta r)K}{a(qK - H_{\rm E})} > 0 \quad \text{for } \psi > 0.$$

If follows from $kaK/c \le 1/q$ that $H_{\rm E}/q \ge K$, and then Eqs. (2.79)–(2.81) has no positive solutions.

From the inference above, Theorem 2.25 holds. □

For $q > 1$, while Theorem 2.25 shows the existence of interior equilibria of (2.76), it does not seem analytically tractable to find explicit formulas for the equilibria and their stability. Some results on the uniform persistence of the predator population P and the endemicity of the disease were obtained by Hethcote *et al.* (2004).

2.5.1.2. *Disease spread in prey–predator populations*

The following prey–predator SIS models with the standard incidence

$$\begin{aligned}
\frac{\mathrm{d}H}{\mathrm{d}t} &= r\left(1-\frac{H}{K}\right)H - aHP = \left[r\left(1-\frac{H}{K}\right) - aP\right]H,\\
\frac{\mathrm{d}S_1}{\mathrm{d}t} &= \left(b-\frac{\theta rH}{K}\right)H - \left[\mu+(1-\theta)\frac{rH}{K}\right]S_1 - aPS_1 - \frac{\beta_1 S_1 I_1}{H} + \gamma_1 I_1,\\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \frac{\beta_1 S_1 I_1}{H} - \gamma_1 I_1 - \left[\mu+(1-\theta)\frac{rH}{K}\right]I_1 - aPI_1,\\
\frac{\mathrm{d}P}{\mathrm{d}t} &= kaHP - cP = (kaH-c)P,\\
\frac{\mathrm{d}S_2}{\mathrm{d}t} &= kaHP - \frac{\alpha S_2 I_1}{P} - cS_2 - \frac{\beta_2 S_2 I_2}{P} + \gamma_2 I_2,\\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \frac{\beta_2 S_2 I_2}{P} - cI_2 + \frac{\alpha S_2 I_1}{P} - \gamma_2 I_2,
\end{aligned} \tag{2.84}$$

have been given in Sec. 1.4.4. Because $H = S_1 + I_1$ and $P = S_2 + I_2$, system (2.84) can be reduced to the following system:

$$\begin{aligned}
\frac{\mathrm{d}H}{\mathrm{d}t} &= r\left(1-\frac{H}{K}\right)H - aHP = \left[r\left(1-\frac{H}{K}\right) - aP\right]H,\\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \frac{\beta_1 (H-I_1) I_1}{H} - \gamma_1 I_1 - \left[\mu+(1-\theta)\frac{rH}{K}\right]I_1 - aPI_1,\\
\frac{\mathrm{d}P}{\mathrm{d}t} &= kaHP - cP = (kaH-c)P,\\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \frac{\beta_2 (P-I_2) I_2}{P} - cI_2 + \frac{\alpha (P-I_2) I_1}{P} - \gamma_2 I_2.
\end{aligned} \tag{2.85}$$

It is easy to see that the region $D = \{(H, I_1, P, I_2)\colon 0 \le I_1 \le H \le K, 0 \le I_2 \le P\}$ is a positively invariant set of (2.85). For system (2.85), there are three epidemiologic threshold quantities

$$R_0 = \frac{\beta_1}{\gamma_1 + b - \theta r}, \quad R_1 = \frac{\beta_1}{\gamma_1 + \mu + (1-\theta)rc/(kaK) + aP_{\mathrm{E}}},$$

$$R_2 = \frac{\beta_2}{c+\gamma_2},$$

where $P_{\mathrm{E}} = r(1 - c/(kaK))/a$. It is not difficult to see that R_0 and R_2 are the basic reproductive numbers for the isolated prey population and predator population, respectively; and R_1 is the basic reproductive number for the prey population in the case where the two populations reach the coexistent equilibrium.

System (2.85) has at most six equilibria in D. The first two are $P_0 = (0, 0, 0, 0)$ and $P_1 = (K, 0, 0, 0)$. When $R_0 > 1$, there is an equilibrium $P_2 = (K, K(1 - 1/R_0), 0, 0)$. When $kaK/c > 1$, there is an equilibrium $P_3 = (H_{\mathrm{E}}, 0, P_{\mathrm{E}}, 0)$, where H_{E} and P_{E} are given in Lemma 2.3. When $kaK/c > 1$ and $R_2 > 1$, there is an equilibrium $P_4 = (H_{\mathrm{E}}, 0, P_{\mathrm{E}}, I_{2\mathrm{E}})$, where $I_{2\mathrm{E}} = P_{\mathrm{E}}(1 - 1/R_2)$. When $kaK/c > 1$ and $R_1 > 1$, there is an equilibrium $P_5 = (H_{\mathrm{E}}, I_{1\mathrm{EE}}, P_{\mathrm{E}}, I_{2\mathrm{EE}})$, where $I_{1\mathrm{EE}} = H_{\mathrm{E}}(1 - 1/R_1)$, and $I_{2\mathrm{EE}}$ is the positive root of

$$x^2 + \left[\frac{(c+\gamma_2)P_{\mathrm{E}}}{\beta_2} - P_{\mathrm{E}} + \frac{\alpha I_{1\mathrm{EE}}}{\beta_2}\right] x - \frac{\alpha P_{\mathrm{E}} I_{1\mathrm{EE}}}{\beta_2} = 0.$$

By using Lemma 2.3 and Corollary 2.1, the following results were obtained by Han *et al.* (2001).

Theorem 2.26. *For system* (2.85), *the orbits with* $H(0) = 0$ *go to* P_0; *when* $kaK/c \leq 1$ *and* $R_0 \leq 1$, *the orbits with* $H(0) > 0$ *go to* P_1; *when* $kaK/c \leq 1$ *and* $R_0 > 1$, *the orbits with* $H(0) > 0$ *go to* P_2; *when* $kaK/c > 1$, $R_1 \leq 1$ *and* $R_2 \leq 1$, *the orbits with* $H(0) > 0$ *and* $P(0) > 0$ *go to* P_3; *when* $kaK/c > 1$, $R_1 \leq 1$ *and* $R_2 > 1$, *the orbits with* $H(0) > 0$ *and* $I_2(0) > 0$ *go to* P_4; *and when* $kaK/c > 1$ *and* $R_1 > 1$, *the orbits with* $I_1(0) > 0$ *and* $P(0) > (0)$ *go to* P_5.

2.5.2. *Disease spread in competitive population systems*

Competitive population systems were introduction in Sec. 1.4.4. For the simple two-species ($N1$ and $N2$) competitive system:

$$\begin{aligned} \frac{\mathrm{d}N_1}{\mathrm{d}t} &= \left[r_1\left(1 - \frac{N_1}{K_1}\right) - \sigma_1 N_2\right] N_1, \\ \frac{\mathrm{d}N_2}{\mathrm{d}t} &= \left[r_2\left(1 - \frac{N_2}{K_2}\right) - \sigma_2 N_1\right] N_2, \end{aligned} \tag{2.86}$$

where r_i, K_i, and σ_i $(i = 1, 2)$ are all positive constants, r_i is the intrinsic growth rates of species i, K_i is the carrying capacities of the environment,

and σ_i measures the competitive effect, it is easy to see that the region $\Omega = \{(N_1, N_2) \,|\, 0 < N_i \leq K_i, i = 1, 2\}$ is a positively invariant set of (2.86).

Let

$$\Phi = \frac{r_1}{r_2}, \quad \Psi_1 = \frac{r_1}{\sigma_2 K_1}, \quad \Psi_2 = \frac{\sigma_1 K_2}{r_2}.$$

The following results were given by Murray (1998).

Lemma 2.5. *For system* (2.86), *the following results hold*:

(1) *When* $\Psi_2 < \Phi < \Psi_1$, *there exist four equilibria* O, P, Q, *and* M, *where* M *is an interior equilibrium which is globally stable in* Ω.

(2) *When* $\Psi_2 > \Phi > \Psi_1$, *there exist four equilibria* O, P, Q, *and* M, *where* M *is an interior equilibrium which is a saddle point. Region* Ω *is divided into two parts* Ω_1 *and* Ω_2, *by a separatrix* $\widehat{OMS}$ *which passes through* $M(N_{1\mathrm{E}}, N_{2\mathrm{E}})$. *Any orbit starting on the separatrix tends to* $M(N_{1\mathrm{E}}, N_{2\mathrm{E}})$; Q *is globally stable in* Ω_1; *and* P *is globally stable in* Ω_2 (*see Fig.* 2.1).

(3) *When* $\Phi > \max\{\Psi_1, \Psi_2\}$, *there exist three equilibria* O, P, *and* Q, *where* P *is globally stable in* Ω.

(4) *When* $\Phi < \min\{\Psi_1, \Psi_2\}$, *there exist three equilibria* O, P, *and* Q, *where* Q *is globally stable in* Ω.

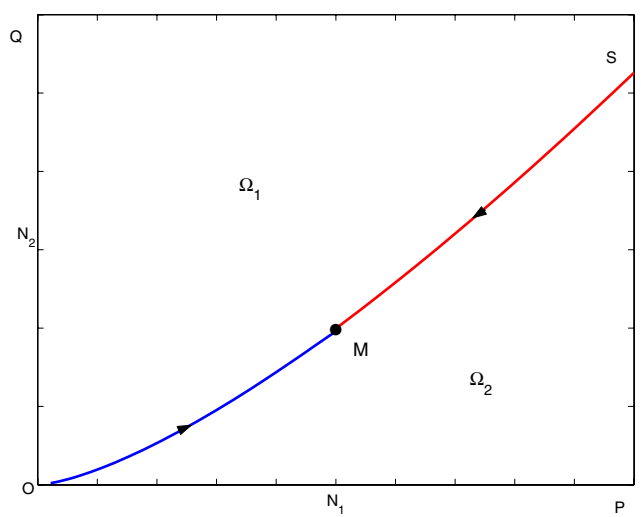


Fig. 2.1. Phase plane of system (2.86) in case 2.

Here $O = (0,0)$, $P = (K_1, 0)$, $Q = (0, K_2)$, $M = (N_{1\mathrm{E}}, N_{2\mathrm{E}})$, *and* $(N_{1\mathrm{E}}, N_{2\mathrm{E}})$ *is the positive solution of the following equations*:

$$r_1\left(1 - \frac{N_1}{K_1}\right) - \sigma_1 N_2 = 0,$$
$$r_2\left(1 - \frac{N_2}{K_2}\right) - \sigma_2 N_1 = 0.$$

The following SIS model with the bilinear incidence for two competitive species is investigated [Han *et al.* (2001a,b)]:

$$\begin{aligned}
\frac{\mathrm{d}S_1}{\mathrm{d}t} &= \left(b_1 - \frac{\theta_1 r_1 N_1}{K_1}\right) N_1 - \left[\mu_1 + (1-\theta_1)\frac{r_1 N_1}{K_1}\right] S_1 \\
&\quad - \sigma_1 N_2 S_1 - S_1(\beta_{11} I_1 + \beta_{12} I_2) + \gamma_1 I_1, \\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= S_1(\beta_{11} I_1 + \beta_{12} I_2) - \gamma_1 I_1 - \left[\mu_1 + (1-\theta_1)\frac{r_1 N_1}{K_1}\right] I_1 - \sigma_1 N_2 I_1, \\
\frac{\mathrm{d}N_1}{\mathrm{d}t} &= \left[r_1\left(1 - \frac{N_1}{K_1}\right) - \sigma_1 N_2\right] N_1, \\
\frac{\mathrm{d}S_2}{\mathrm{d}t} &= \left(b_2 - \frac{\theta_2 r_2 N_2}{K_2}\right) N_2 - \left[\mu_2 + (1-\theta_2)\frac{r_2 N_2}{K_2}\right] S_2 \\
&\quad - \sigma_2 N_1 S_2 - S_2(\beta_{21} I_1 + \beta_{22} I_2) + \gamma_2 I_2, \qquad (2.87) \\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= S_2(\beta_{21} I_1 + \beta_{22} I_2) - \gamma_2 I_2 - \left[\mu_2 + (1-\theta_2)\frac{r_2 N_2}{K_2}\right] I_2 - \sigma_2 N_1 I_2, \\
\frac{\mathrm{d}N_2}{\mathrm{d}t} &= \left[r_2\left(1 - \frac{N_2}{K_2}\right) - \sigma_2 N_1\right] N_2,
\end{aligned}$$

$$\begin{aligned}
N_i &= S_i + I_i, \quad i = 1, 2, \\
r_i &= b_i - \mu_i > 0, \quad i = 1, 2, \\
0 &\le \theta_i \le 1, \quad i = 1, 2.
\end{aligned}$$

Since $S_i = N_i - I_i$, then the six differential equations above can be reduced to the following four-dimensional system:

$$\begin{aligned}
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= (N_1 - I_1)(\beta_{11} I_1 + \beta_{12} I_2) - \gamma_1 I_1 \\
&\quad - \left[\mu_1 + (1-\theta_1)\frac{r_1 N_1}{K_1}\right] I_1 - \sigma_1 N_2 I_1,
\end{aligned}$$

$$\begin{aligned}
\frac{\mathrm{d}N_1}{\mathrm{d}t} &= \left[r_1\left(1-\frac{N_1}{K_1}\right)-\sigma_1 N_2\right]N_1,\\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= (N_2-I_2)(\beta_{21}I_1+\beta_{22}I_2)-\gamma_2 I_2\\
&\quad -\left[\mu_2+(1-\theta_2)\frac{r_2 N_2}{K_2}\right]I_2-\sigma_2 N_1 I_2,\\
\frac{\mathrm{d}N_2}{\mathrm{d}t} &= \left[r_2\left(1-\frac{N_2}{K_2}\right)-\sigma_2 N_1\right]N_2.
\end{aligned} \tag{2.88}$$

It is easy to see that the region $D=\{(I_1,N_1,I_2,N_2)\colon 0\le I_i\le N_i\le K_i, i=1,2\}$ is a positively invariant set of (2.88).

For (2.88), there are at most five equilibria on the boundary of D. Three equilibria $P_0=(0,0,0,0), P_1=(0,0,0,K_2)$, and $P_3=(0,K_1,0,0)$ exist for all parameter value. When

$$R_2=\frac{\beta_{22}K_2}{\gamma_2+b_2-\theta_2 r_2}>1,$$

there is an equilibrium $P_2=(0,0,I_{2\mathrm{E}},K_2)$, where $I_{2\mathrm{E}}=K_2(1-1/R_2)$. When

$$R_1=\frac{\beta_{11}K_1}{\gamma_1+b_1-\theta_1 r_1}>1,$$

there is an equilibrium $P_4=(I_{1\mathrm{E}},K_1,0,0)$, where $I_{1\mathrm{E}}=K_1(1-1/R_1)$. When $\Psi_2<\Phi<\Psi_1$ or $\Psi_2>\Phi>\Psi_1$, there is an equilibrium $P_5=(0,N_{1\mathrm{E}},0,N_{2\mathrm{E}})$.

To find a positive equilibrium, we need that point $(N_{1\mathrm{E}},N_{2\mathrm{E}})$ is an equilibrium of (2.86), which implies that $\Psi_2<\Phi<\Psi_1$ or $\Psi_2>\Phi>\Psi_1$. Then substituting $N_1=N_{1\mathrm{E}}$ and $N_2=N_{2\mathrm{E}}$ into the right-hand side of the first and third equations in (2.88) yields

$$\begin{aligned}
I_2 &= \frac{I_1[(\Lambda_1-\beta_{11}N_{1\mathrm{E}})+\beta_{11}I_1]}{\beta_{12}(N_{1\mathrm{E}}-I_1)}:=f_1(I_1),\\
I_1 &= \frac{I_2[(\Lambda_2-\beta_{22}N_{2\mathrm{E}})+\beta_{22}I_2]}{\beta_{21}(N_{2\mathrm{E}}-I_2)}:=f_2(I_2),
\end{aligned} \tag{2.89}$$

where

$$\Lambda_1=\gamma_1+\left[\mu_1+(1-\theta_1)\frac{r_1 N_{1\mathrm{E}}}{K_1}\right]+\sigma_1 N_{2\mathrm{E}},$$

and

$$\Lambda_2 = \gamma_2 + \left[\mu_2 + (1-\theta_2)\frac{r_2 N_{2\mathrm{E}}}{K_2}\right] + \sigma_2 N_{1\mathrm{E}}.$$

The existence of positive equilibrium implies that the curves l_1 and l_2, which are determined by equations $I_2 = f_1(I_1)$ and $I_1 = f_2(I_2)$ respectively, can intersect in the region $D' = \{(I_1, I_2)\colon 0 < I_1 < N_{1\mathrm{E}}, 0 < I_2 < N_{2\mathrm{E}}\}$. Straightforward calculations show $f_1'(I_1) > 0, f_1''(I_1) > 0, f_2'(I_2) > 0$, and $f_2''(I_2) > 0$ for $(I_1, I_2) \in D'$. Notice that curve l_1 passes through the original and point $(N_{1\mathrm{E}} - \Lambda_1/\beta_{11}, 0)$, and has the asymptotic line $I_1 = N_{1\mathrm{E}}$ and that curve l_2 passes through the original and point $(0, N_{2\mathrm{E}} - \Lambda_2/\beta_{22})$, and has the asymptotic line $I_2 = N_{2\mathrm{E}}$. Thus, curves l_1 and l_2 has no intersection points in D' when $\Lambda_2 - \beta_{22}N_{2\mathrm{E}} < 0$ or $\Lambda_1 - \beta_{11}N_{1\mathrm{E}} < 0$. Furthermore, since $f_1'(0) = (\Lambda_1 - \beta_{11}N_{1\mathrm{E}})/(\beta_{12}N_{1\mathrm{E}})$ and $f_2'(0) = (\Lambda_2 - \beta_{22}N_{2\mathrm{E}})/(\beta_{21}N_{2\mathrm{E}})$, then in the case where $\Lambda_2 - \beta_{22}N_{2\mathrm{E}} > 0$ and $\Lambda_1 - \beta_{11}N_{1\mathrm{E}} > 0$, curves l_1 and l_2 have a unique intersection point in D' if $f_1'(0) < 1/f_2'(0)$, namely

$$R_3 = \frac{\beta_{12}\beta_{21}N_{1\mathrm{E}}N_{2\mathrm{E}}}{(\Lambda_1 - \beta_{11}N_{1\mathrm{E}})(\Lambda_2 - \beta_{22}N_{2\mathrm{E}})} > 1,$$

and there is no intersection points in D' if $R_3 \le 1$.

In summary, the following results were obtained [Han *et al.* (2001)].

Theorem 2.27. *When* $\Lambda_2 - \beta_{22}N_{2\mathrm{E}} > 0, \Lambda_1 - \beta_{11}N_{1\mathrm{E}} > 0$, *and* $R_3 > 1$, *there is a unique interior equilibrium* $P_6 = (I_{1\mathrm{EE}}, N_{1\mathrm{E}}, I_{2\mathrm{EE}}, N_{2\mathrm{E}})$, *if* $\Psi_2 < \Phi < \Psi_1$ *or* $\Psi_2 > \Phi > \Psi_1$, *where* $(I_{1\mathrm{EE}}, I_{2\mathrm{EE}})$ *is the positive unique solution of Eqs.* (2.89).

Similarly as to the analysis for system (2.85), concerning the dynamic behaviors of (2.88), we have

Theorem 2.28. *For orbits of* (2.88) *in* D, *when*

(1) $\Psi_1 < \Phi < \Psi_2, R_2 < 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_1$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_1$;
(2) $\Psi_1 < \Phi < \Psi_2, R_2 > 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_2$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_2$;
(3) $\Phi < \min\{\Psi_1, \Psi_2\}, R_2 < 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_1$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_3$;

(4) $\Phi < \min\{\Psi_1, \Psi_2\}, R_2 > 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_2$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_4$;

(5) $\Psi_1 < \Phi < \Psi_2, R_1 < 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_3$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_5$;

(6) $\Psi_1 < \Phi < \Psi_2, R_1 > 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_4$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_6$;

(7) $\Phi > \max\{\Psi_1, \Psi_2\}, R_1 < 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_3$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_7$;

(8) $\Phi > \max\{\Psi_1, \Psi_2\}, R_1 > 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_4$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_8$;

(9) $\Psi_2 < \Phi < \Psi_1$, $\Lambda_1 - \beta_{11}N_{1\mathrm{E}} > 0, \Lambda_2 - \beta_{22}N_{2\mathrm{E}} > 0$, *and* $R_3 < 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_5$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_9$;

(10) $\Psi_2 < \Phi < \Psi_1$, $\Lambda_1 - \beta_{11}N_{1\mathrm{E}} > 0, \Lambda_2 - \beta_{22}N_{2\mathrm{E}} > 0$, *and* $R_3 > 1$ $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_6$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_{10}$;

(11) $\Psi_2 > \Phi > \Psi_1$, $\Lambda_1 - \beta_{11}N_{1\mathrm{E}} > 0, \Lambda_2 - \beta_{22}N_{2\mathrm{E}} > 0$, *and* $R_3 < 1$ $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_5$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_{11}$;

(12) $\Psi_2 > \Phi > \Psi_1$, $\Lambda_1 - \beta_{11}N_{1\mathrm{E}} > 0, \Lambda_2 - \beta_{22}N_{2\mathrm{E}} > 0$, *and* $R_3 > 1$, $\lim_{t\to\infty}(I_1, N_1, I_2, N_2) = P_6$ *for* $(I_1(0), N_1(0), I_2(0), N_2(0)) \in \Omega_{12}$,

where $\Phi, \Psi_1, \Psi_2, \Omega_1, \Omega_2$, *and* $\widehat{OMS}$ *are defined in Lemma* 2.5.

$$
\begin{aligned}
\Omega_1 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, (N_1, N_2) \in \Omega_1\};\\
\Omega_2 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, (N_1, N_2) \in \\
&\qquad \Omega_1, I_2 \ne 0\};\\
\Omega_3 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, N_2 \ne 0\};\\
\Omega_4 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, N_2 \ne 0, I_2 \ne 0\};\\
\Omega_5 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, (N_1, N_2) \in \Omega_2\};\\
\Omega_6 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, (N_1, N_2) \in \\
&\qquad \Omega_2, I_1 \ne 0\};\\
\Omega_7 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, N_1 \ne 0\};\\
\Omega_8 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, N_1 \ne 0, I_1 \ne 0\};\\
\Omega_9 &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, N_1 \ne 0, N_2 \ne 0\};\\
\Omega_{10} &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, N_i \ne 0, I_i \ne 0, i = 1, 2, \};\\
\Omega_{11} &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, i = 1, 2, (N_1, N_2) \in \widehat{OMS}\};\\
\Omega_{12} &= \{(I_1, N_1, I_2, N_2)^{\mathrm{T}} \,|\, 0 \le I_i \le N_i \le K_i, I_i \ne 0, i = 1, 2, (N_1, N_2) \in \\
&\qquad \widehat{OMS}\}.
\end{aligned}
$$

In fact, similarly as to a disease spreading in both prey and predator populations, $R_i\,(i = 1, 2)$ are the basic reproductive numbers for the

isolated population N_i; R_3 is the basic reproductive number for the two competing populations in the case where the two populations reach the coexistent equilibrium.

2.6. Epidemic Models with Control and Prevention

In this section, we introduce some methods and results on epidemic models with control and prevention, which include quarantine, vaccination, and treatment.

2.6.1. *Epidemic models with quarantine*

Quarantine is one of the common measures to control or to reduce transmissions of diseases.

Feng and Thieme (1995) considered an SIQR model with a quarantine class and found periodic solutions through a Hopf bifurcation, which is a special case of the SIQR model with the quarantine-adjusted incidence [Hethcote *et al.* (2002)]. Wu and Feng (2000) showed that, for the SIQR endemic model formulated by Feng and Thieme (1995), an epidemic approximation near $R_0 = 1$ can have a homoclinic bifurcation. Feng and Thieme (2000a,b) considered SEIQR models with arbitrarily distributed periods of infection, including quarantine, and a general incidence, assumed that all infected individuals go through the quarantine stage, and investigated the model dynamics. Nuno *et al.* (2005) studied the dynamics of two-strain influenza models with isolation and partial cross-immunity and showed the coexistence of both strains in an oscillatory way. Hethcote *et al.* (2002) considered SIQS and SIQR epidemic models with three forms of incidence, which include the bilinear, standard and quarantine-adjusted incidences. The quarantine-adjusted incidence is given by $\beta SI/(N - Q)$, where the average number of adequate contacts is β, and these contacts occur within the population with the size $N - Q$, where N and Q denote the size of total population and the number of the quarantined individuals, respectively. This incidence is suitable for the case that the quarantined individuals do not participate in transmission of infection.

In this subsection, based on the results by Hethcote *et al.* (2002), we show the analysis of two epidemic models with quarantine: the SIQS model with bilinear incidence and the SIQR model with quarantine-adjusted incidence.

2.6.1.1. *SIQS model with bilinear incidence*

The SIQS model discussed here is

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \beta SI - \mu S + \gamma I + \varepsilon Q,\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= [\beta S - (\gamma + \delta + \mu + \alpha_1)]I,\\ \frac{\mathrm{d}Q}{\mathrm{d}t} &= \delta I - (\varepsilon + \mu + \alpha_2)Q,\end{aligned} \tag{2.90}$$

where $S = S(t), I = I(t)$, and $Q = Q(t)$ are the numbers of the susceptible, infected, and isolated individuals at time t. It is easy to see that the region $D = \left\{(S, I, Q) \in R_+^3 \colon S + I + Q \le A/\mu\right\}$ is a positively invariant set of (2.90), and that the quarantine reproductive number is $R_q = \beta(A/\mu)/(\gamma + \delta + \mu + \alpha_1)$. The basic reproductive number for the SIS model without quarantine ($\delta = 0$) in (2.90) is $R_0 = \beta(A/\mu)/(\gamma + \mu + \alpha_1)$. Straightforward calculations show that (2.90) always has the disease-free equilibrium $P_0 = (A/\mu, 0, 0)$ and that, when $R_q > 1$, (2.90) also has a unique endemic equilibrium $P^* = (S^*, I^*, Q^*)$ in D where

$$S^* = \frac{A}{\mu R_q}, \quad I^* = \frac{A(1 - 1/R_q)}{(\mu + \alpha_1) + \delta(\mu + \alpha_2)/(\varepsilon + \mu + \alpha_2)}, \quad Q^* = \frac{\delta I^*}{\varepsilon + \mu + \alpha_2}.$$

Note that

$$N^* = S^* + I^* + Q^* = \frac{A}{\mu} - \frac{A(1 - 1/R_q)[(\varepsilon + \mu + \alpha_2)\alpha_1 + \delta\alpha_2]}{\mu[(\varepsilon + \mu + \alpha_2)(\mu + \alpha_1) + \delta(\mu + \alpha_2)]}.$$

Theorem 2.29. *For system* (2.90), *when* $R_q \le 1$, *the disease-free equilibrium* P_0 *is globally stable in* D; *when* $R_q > 1$, *the disease-free equilibrium* P_0 *is unstable, and the endemic equilibrium* P^* *is globally stable in* $\operatorname{int} D$.

Proof. Analyzing the Jacobian matrix of system (2.90) at equilibrium P_0 shows that it is locally asymptotically stable if $R_q < 1$, and is unstable if $R_q > 1$. To prove the global stability when $R_q \le 1$, we consider the Liapunov function $V = I$ with the Liapunov derivative

$$\frac{\mathrm{d}V}{\mathrm{d}t} = [\beta S - (\gamma + \delta + \mu + \alpha_1)]I \le [\beta A/\mu - (\gamma + \delta + \mu + \alpha_1)]I \le 0,$$

as $S \leq A/\mu$. By the Liapunov–Lasalle theorem [Hale (1980)], solutions in D approach the largest positively invariant subset of the set where $V' = 0$, which is the set with $I = 0$. In this set, $Q' = -(\varepsilon + \mu + \alpha_2)Q$, and then $Q \to 0$ as $t \to \infty$. Thus $S' = A - \mu S + \varepsilon Q$ is asymptotically equivalent to $S' = A - \mu S$, which implies $S \to A/\mu$. Hence all solutions in the set with $I = 0$ go to the disease-free equilibrium P_0. By Lemma 2.1, all solutions in D must also approach P_0.

When $R_q > 1$, the analysis of the local stability of the endemic equilibrium P^* shows that it is locally asymptotically stable by the Routh–Hurwitz criteria. To prove the global stability of P^*, when $R_q > 1$, first we note that system (2.90) is equivalent to the following system, involving N, I, and Q, and the endemic equilibrium values N^*, I^*, and Q^*:

$$\begin{aligned}
\frac{\mathrm{d}N}{\mathrm{d}t} &= -\mu(N - N^*) - \alpha_1(I - I^*) - \alpha_2(Q - Q^*), \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta[(N - N^*) - (I - I^*) - (Q - Q^*)]I, \\
\frac{\mathrm{d}Q}{\mathrm{d}t} &= \delta(I - I^*) - (\varepsilon + \mu + \alpha_2)(Q - Q^*).
\end{aligned} \tag{2.91}$$

Consider the Liapunov function

$$V = \frac{\alpha_1(\varepsilon + 2\mu) + \alpha_2(\alpha_1 + \delta)}{\beta\alpha_2}\left(I - I^* - I^* \ln \frac{I}{I^*}\right) + \frac{1}{2}\left\{\frac{\varepsilon + 2\mu}{\alpha_2}(N - N^*)^2 + [(N - N^*) - (Q - Q^*)]^2 + \frac{\alpha_1(\varepsilon + 2\mu)}{\delta\alpha_2}(Q - Q^*)^2\right\}$$

which is positive definite in $\operatorname{int} D$. The derivative of V along the solutions to (2.91) is

$$\frac{\mathrm{d}V}{\mathrm{d}t} = -\frac{\alpha_1(\varepsilon + 2\mu) + \alpha_2(\alpha_1 + \delta)}{\alpha_2}(I - I^*)^2 - \frac{\mu(\varepsilon + 2\mu + \alpha_2)}{\alpha_2}(N - N^*)^2 - \left[-\frac{\alpha_1(\varepsilon + 2\mu)(\varepsilon + \mu + \alpha_2)}{\delta\alpha_2} + (\varepsilon + \mu)\right](Q - Q^*)^2 < 0.$$

Then, it follows from the Liapunov theorem [Hale (1980)] that the endemic equilibrium is globally stable in $\operatorname{int} D$. □

2.6.1.2. *SIQR model with quarantine-adjusted incidence*

The following SIQR model with quarantine-adjusted incidence

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \frac{\beta SI}{S+I+R} - \mu S,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \left[\frac{\beta S}{S+I+R} - (\gamma+\delta+\mu+\alpha_1)\right] I,\\
\frac{\mathrm{d}Q}{\mathrm{d}t} &= \delta I - (\varepsilon+\mu+\alpha_2)Q,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I + \varepsilon Q - \mu R,
\end{aligned} \tag{2.92}$$

was introduced in Sec. 1.4.3. It is easy to see that the region $D = \{(S,I,Q,R) \in R_+^4 \colon S+I+Q+R \le A/\mu\}$ is a positively invariant set of (2.92), and that the quarantine reproductive number is $R_q = \beta/(\gamma+\delta+\mu+\alpha_1)$. Straightforward calculations show that (2.92) always has the disease-free equilibrium $P_0 = (A/\mu, 0, 0)$ and that, when $R_q > 1$, (2.92) also has a unique endemic equilibrium $P^* = (S^*, I^*, Q^*, R^*)$ in D where

$$S^* = \frac{(A/\mu)[(\gamma+\mu)(\varepsilon+\mu+\alpha_2)+\varepsilon\delta]}{(\varepsilon+\mu+\alpha_2)[R_q(\gamma+\delta+\mu+\alpha_1)-(\delta+\alpha_1)]+\varepsilon\delta},$$

$$I^* = \frac{A(R_q-1)(\varepsilon+\mu+\alpha_2)}{(\varepsilon+\mu+\alpha_2)[R_q(\gamma+\delta+\mu+\alpha_1)-(\delta+\alpha_1)]+\varepsilon\delta},$$

$$Q^* = \frac{\delta A(R_q-1)}{(\varepsilon+\mu+\alpha_2)[R_q(\gamma+\delta+\mu+\alpha_1)-(\delta+\alpha_1)]+\varepsilon\delta},$$

$$R^* = \frac{(A/\mu)(R_q-1)[\gamma(\varepsilon+\mu+\alpha_2)+\varepsilon\delta]}{(\varepsilon+\mu+\alpha_2)[R_q(\gamma+\delta+\mu+\alpha_1)-(\delta+\alpha_1)]+\varepsilon\delta},$$

$$\begin{aligned}
N^* &= S^* + I^* + Q^* + R^*\\
&= \frac{(A/\mu)\{R_q[(\gamma+\mu)(\varepsilon+\mu+\alpha_2)+\delta(\varepsilon+\mu)]-\mu\delta\}}{(\varepsilon+\mu+\alpha_2)[R_q(\gamma+\delta+\mu+\alpha_1)-(\delta+\alpha_1)]+\varepsilon\delta}.
\end{aligned}$$

The following theorem [Hethcote *et al.* (2002)] describes the dynamic behavior of solutions of (2.92) in the region D. An interesting aspect of this SIQR model is that Hopf bifurcation can occur for $R_q > 1$.

Theorem 2.30. *For system* (2.92), *the disease-free equilibrium* P_0 *is globally stable in* D *if* $R_q \le 1$ *and unstable if* $R_q > 1$. *When* $R_q > 1$,

Hopf bifurcation can occur for (2.92) *so that periodic solutions around* P^* *can appear.*

Proof. Analyzing the linearized system (2.92) at equilibrium P_0 shows that it is locally asymptotically stable if $R_q < 1$ and is unstable if $R_q > 1$. The proof of global stability when $R_q \leq 1$ uses the Liapunov function $V = I$ and is analogous with the proof in the previous part. It follows from Theorem 4.5 [Thieme (1993)] that the disease is uniformly persistent.

The Jacobian matrix of (2.92) at the endemic equilibrium P^* is

$$J(P^*) = \begin{pmatrix} C - B - \mu & C - K & 0 & C \\ B - C & -C & 0 & -C \\ 0 & \delta & -D & 0 \\ 0 & \gamma & \varepsilon & -\mu \end{pmatrix},$$

where

$$K = \gamma + \delta + \mu + \alpha_1, \quad D = \varepsilon + \mu + \alpha_2, \quad B = \frac{KI^*}{S^*} = \frac{K\mu(R_q - 1)D}{(\gamma + \mu)D + \varepsilon\delta},$$

and

$$C = \frac{KI^*}{S^* + I^* + R^*} = \frac{K\mu(R_q - 1)D}{R_q[(\gamma + \mu)D + \varepsilon\delta]} = \frac{B}{R_q}.$$

The characteristic equation of $J(P^*)$ is a fourth degree polynomial given by $P_4(z) = z^4 + c_1 z^3 + c_2 z^2 + c_3 z + c_4 = 0$, where the coefficients are

$$\begin{aligned} c_1 &= 2\mu + B + D, \\ c_2 &= (B - C)(\mu + D + K) + C(2\mu + \gamma + D) + 2\mu D + \mu^2, \\ c_3 &= \mu^2 D + (B - C)(\mu D + \mu K + KD) + C(\mu^2 + \mu\gamma + 2\mu D + \gamma D + \varepsilon\delta), \\ c_4 &= \mu[(B - C)KD + C(\mu D + \gamma D + \varepsilon\delta)]. \end{aligned}$$

Since $B > C > 0$, all of the coefficients c_i $(i = 1, 2, 3, 4)$ are positive. By the Routh–Hurwitz criteria, the necessary and sufficient conditions for the local asymptotic stability of P^* are that the coefficients are $H_1 = c_1 > 0$, $H_2 = c_1 c_2 - c_3 > 0$, $H_3 = c_1 c_2 c_3 - c_1^2 c_4 - c_3^2 > 0$, and $H_4 = c_4 H_3 > 0$.

Using a Maple computer algebra program, we find that

$$\begin{aligned}
H_2 &= -\delta\varepsilon C + 2\mu(\mu + D)^2 + CD^2 + 4\mu C(\mu + D) \\
&\quad + C(2\mu C + CD + \gamma\mu + \gamma C) + (B - C) \\
&\quad \times [CK + 3C\mu + 2CD + \gamma C + 4D\mu + K\mu + D^2 + 3\mu^2] \\
&\quad + (B - C)^2(K + \mu + D), \\
H_3 &= [\delta\varepsilon C + 2\mu(\mu C + \mu D + CD) + 2\mu^3 + (B - C)(\mu + D)(\mu + K) \\
&\quad + \gamma C(\mu + D)][H_2 - \mu(D + 2\mu + B)(D + \mu + B)].
\end{aligned}$$

Since $c_i > 0$ $(i = 1, 2, 3, 4)$, when $H_2 > 0$ and $H_3 = 0$, equation $P_4(z) = 0$ has a pair of pure imaginary roots, and the real parts of the remaining roots are negative. Hence, the endemic equilibrium P^* is locally asymptotically stable if $H_2 > \mu(D + 2\mu + B)(D + \mu + B)$, and unstable if $0 < H_2 < \mu(D + 2\mu + B)(D + \mu + B)$.

It is obvious that the Hopf bifurcation surface given by $H_3 = 0$, that is, $H_2 = \mu(D + 2\mu + B)(D + \mu + B)$, depends on the seven parameters μ, α_1, α_2, ε, γ, δ, and R_q, and its determination, therefore, is analytically intractable. However, we can examine this surface numerically. A contour plot of $H_2 = \mu(D + 2\mu + B)(D + \mu + B)$ with $A = \mu = 0.00027473, \alpha_1 = 0, \alpha_2 = 0, \gamma = 0.5$, and $\delta = 1$, 2, and 4, respectively, is shown in Fig. 2.2, where the contours are functions of R_q and ε. Note that the curves in Fig. 2.2 are cross-sections of the Hopf bifurcation surface in the hyperplane when the five parameters $\mu, \alpha_1, \alpha_2, \gamma$, and δ are fixed. Hence, we have verified transversality by showing that $\mu(H_2 - \mu(D+2\mu+B)(D+\mu+B))/\mu\varepsilon \neq 0$ on these cross-sections of the Hopf surface; that is, the real parts of the complex conjugate pair of eigenvalues do change sign as the Hopf bifurcation surface is crossed. □

2.6.2. *Epidemic models with vaccination*

Vaccinating susceptibles against disease infections is an effective measure to control and prevent the spread of the infection. An SIS model with vaccination, standard incidence, and no disease-induced deaths was investigated [Kribs-Zaleta and Velasco-Hernadez (2000)]; an SIRS model with vaccination, standard incidence and no disease-induced deaths was formulated [Arino *et al.* (2003)]; an SIS model with vaccination, standard incidence, and the disease-induced deaths was studied [Li *et al.* (2006)]; and an SIS model with vaccination, general incidence and no disease-induced

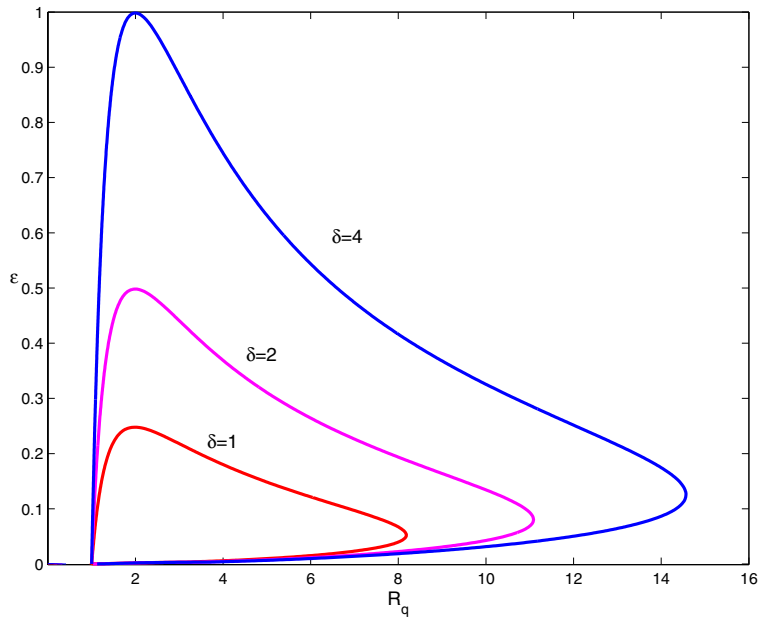


Fig. 2.2. The cross-sections of the Hopf bifurcation surface are shown in the $R_q\varepsilon$ plane when the parameters are $A = \mu = 0.00027473, \alpha_1 = 0, \alpha_2 = 0, \gamma = 0.5$, and $\delta = 1, 2$, and 4, respectively. Note that these curves change only imperceptibly when γ ranges from 0.1 to 2.

deaths was investigated [Brauer (2004)]. All models [Kribs-Zaleta and Velasco-Hernadez (2000); Arino *et al.* (2003); Li *et al.* (2006); Brauer (2004); Hui and Zhu (2005)] incorporated vaccine efficacy and showed backward bifurcations. Li amd Ma (2002, 2004b) also analyzed global behavior of simple SIS vaccination epidemic models under the condition that the vaccine is perfectly efficient.

Now we consider again the following SIS model with vaccination and efficacy of vaccine, introduced in Sec. 1.4.3

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= bN - \beta\frac{SI}{N} - [p + f(N)]S + \gamma I + \varepsilon V,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta(S + \sigma V)\frac{I}{N} - [\gamma + \alpha + f(N)]I,\\
\frac{\mathrm{d}V}{\mathrm{d}t} &= pS - \sigma\beta\frac{IV}{N} - [\varepsilon + f(N)]V,\\
N &= S + I + V.
\end{aligned} \tag{2.93}$$

Here, the fraction σ $(0 \leq \sigma \leq 1)$, reflects the reduction of infection due to vaccination such that, in the extreme cases, $\sigma = 0$ means completely effective vaccination, while $\sigma = 1$ means completely ineffective vaccination, that is, the vaccination fails if $\sigma = 1$. These two extreme cases were discussed by Li and Ma (2002) and Lajmanovich and Yorke (1976), respectively. In the following, we consider only the case where $0 < \sigma < 1$.

It follows from (2.93) that

$$\frac{\mathrm{d}N}{\mathrm{d}t} = [b - f(N)]N - \alpha I. \tag{2.94}$$

Let $x = S/N$, $y = I/N$, and $z = V/N$ denote the fractions of the classes S, I, and V in the population, respectively. It is easy to verify that x, y, z, and N satisfy the system of differential equations:

$$\begin{aligned}
\frac{\mathrm{d}x}{\mathrm{d}t} &= b - (\beta - \alpha)xy - (p + b)x + \gamma y + \varepsilon z,\\
\frac{\mathrm{d}y}{\mathrm{d}t} &= y[\beta x + \alpha y + \beta\sigma z - (\gamma + \alpha + b)],\\
\frac{\mathrm{d}z}{\mathrm{d}t} &= px - (\varepsilon + b)z + (\alpha - \sigma\beta)yz,\\
x + y + z &= 1,
\end{aligned} \tag{2.95}$$

and

$$N' = N\left[r\left(1 - \frac{N}{K}\right) - \alpha y\right]. \tag{2.96}$$

2.6.2.1. *The existence and local stability of equilibria*

Substituting $x = 1 - y - z$ into the middle two equations of (2.95) gives

$$\begin{aligned}
\frac{\mathrm{d}y}{\mathrm{d}t} &= y[\beta - (\gamma + \alpha + b - (\beta - \alpha)y - \beta(1 - \sigma)z] := yF(y, z),\\
\frac{\mathrm{d}z}{\mathrm{d}t} &= p - py - (p + b + \varepsilon)z + (\alpha - \sigma\beta)yz := G(y, z).
\end{aligned} \tag{2.97}$$

Thus, it is easy to see that $D = \{(y, z)\colon\ y \geq 0, z > 0, y + z < 1\}$ is a positively invariant set of (2.97), and that there exits a disease-free equilibrium $P_0(0, p/(p + b + \varepsilon))$.

A positive equilibrium (endemic equilibrium) of (2.97) satisfies the equations

$$\begin{aligned}(\beta-\alpha)y+\beta(1-\sigma)z&=\beta-(\gamma+\alpha+b),\\ py+(p+b+\varepsilon)z-(\alpha-\sigma\beta)yz&=p,\end{aligned}\tag{2.98}$$

in the interior of D. That is, a positive equilibrium of (2.97) is the intersection point of the straight line l_1:

$$z=h_1(y):=\frac{\beta-(\gamma+b+\alpha)-(\beta-\alpha)y}{\beta(1-\sigma)}$$

and the curve l_2:

$$z=h_2(y):=\frac{p-py}{(p+b+\varepsilon)-(\alpha-\sigma\beta)y},$$

in the interior of D.

Analyzing the intersection points of l_1 and l_2, we obtain the following results on the existence of the endemic equilibrium of (2.97):

Theorem 2.31. *Let* $R_0=\frac{\beta(b+\varepsilon+\sigma p)}{(\alpha+b+\gamma)(p+\varepsilon+b)}$. *Then for* (2.97), *the following are true*:

(1) *If* $R_0>1$, *there exists a unique endemic equilibrium* $P^*(y^*,z^*)$.
(2) *If* $R_0<1$, $\beta>b+\alpha+\gamma$, $\alpha<\sigma\beta$, *and* $B>2\sqrt{AC}$, *there exist two endemic equilibria* $P_1^*(y_1^*,z_1^*)$ *and* $P_2^*(y_2^*,z_2^*)$, *with* $y_1^*<y_2^*$ *and* $z_1^*>z_2^*$.
(3) *If* $R_0<1$, $\beta>b+\alpha+\gamma$, $\alpha<\sigma\beta$, *and* $B=2\sqrt{AC}$, *there exists a unique endemic equilibrium* $P_3^*(y^*,z^*)$.
(4) *If* $R_0=1$, $\alpha<\sigma\beta$, *and* $B>0$, *there exists a unique endemic equilibrium* $P_4^*(y^*,z^*)$, *where*

$$\begin{aligned}A&=(\alpha-\sigma\beta)(\beta-\alpha),\\ B&=\alpha(p+\varepsilon+\gamma+\alpha+2b)-\beta[(\alpha+b+\varepsilon)-\sigma(\beta-b-\alpha-\gamma-p)],\\ C&=\beta(b+\varepsilon+\sigma p)-(p+b+\varepsilon)(b+\alpha+\gamma)\\ &=(p+b+\varepsilon)(b+\alpha+\gamma)(R_0-1),\end{aligned}$$

and y^*, z^*, y_1^*, y_2^*, z_1^*, *and* z_2^* *satisfy Eqs.* (2.98).

To better understand the effects of vaccination efficiency upon the dynamic behavior of the model, we show that Theorem 2.31 is equivalent to the following theorem.

Theorem 2.32. *Let*

$$\sigma_1 = \frac{(p+\varepsilon+b)(b+\alpha+\gamma)-\beta(\varepsilon+b)}{\beta p}.$$

Denote σ_2 *the root of* $B=0$ *with respect to* σ (*if it exists*), *and* σ_c, ($\sigma_2 < \sigma_c < \sigma_1 < 1$), *the root of* $B = 2\sqrt{AC}$ *with respect to* σ (*if it exists*). *For* (2.97), *there always exists the disease-free equilibrium* $P_0(0, z_0)$, *and the following conclusions hold*:

(1) *If* $\sigma > \sigma_1$, *there exists a unique endemic equilibrium* $P^*(y^*, z^*)$.
(2) *If* $\sigma_c < \sigma < \sigma_1 < 1$, *then there exist two endemic equilibria* $P_1^*(y_1^*, z_1^*)$ *and* $P_2^*(y_2^*, z_2^*)$, *with* $y_1^* < y_2^*$ *and* $z_1^* > z_2^*$.
(3) *If* $\sigma = \sigma_c < \sigma_1 < 1$, *then there exists a unique endemic equilibrium* $P_3^*(y^*, z^*)$.
(4) *If* $\sigma_c < \sigma = \sigma_1 < 1$, *then there exists a unique endemic equilibrium* $P_4^*(y^*, z^*)$, *where* R_0, A, B, C, y^*, z^*, y_1^*, y_2^*, z_1^*, *and* z_2^* *are the same as those in Theorem* 2.31.

Remark 2.1.

(a) Denote

$$R_c := \frac{\beta[\varepsilon + \sigma_c p + b(1-(1-\sigma_c)q)]}{(\alpha+b+\gamma)(p+\varepsilon+b)}.$$

Then, $\sigma_c < \sigma < \sigma_1 < 1$ is equivalent to $R_c < R_0 < 1$, $\sigma = \sigma_c < \sigma_1 < 1$ is equivalent to $R_c = R_0 < 1$, and $\sigma_c < \sigma = \sigma_1 < 1$ is equivalent to $R_c < R_0 = 1$.

(b) From the proof of Theorem 2.31, we have the following:
When $R_0 > 1$, $h_1'(y^*) < h_2'(y^*) < 0$, as $\alpha \le \sigma\beta$, or $\alpha > \sigma\beta$ and $(p+b+\varepsilon)/(\alpha-\sigma\beta) > 1$, $h_2'(y^*) > 0 > h_1'(y^*)$, as $\alpha > \sigma\beta$ and $(p+b+\varepsilon)/(\alpha-\sigma\beta) < 1$, $h_2'(y^*) = 0 > h_1'(y^*)$, as $\alpha > \sigma\beta$ and $(p+b+\varepsilon)/(\alpha-\sigma\beta) = 1$.
When $R_0 < 1$, $\beta > b+\alpha+\gamma$, $\alpha < \sigma\beta$, and $B > 2\sqrt{AC}$, $h_2'(y_1^*) < h_1'(y_1^*) < 0$, and $h_1'(y_2^*) < h_2'(y_2^*) < 0$.
When $R_0 = 1$, $\alpha < \sigma\beta$, and $B > 0$, $h_1'(y_4^*) < h_2'(y_4^*) < 0$.

Remark 2.1(b) will be used in the proof of the local stability of equilibria.

In the following, we prove the local stability of equilibria of (2.97). Here, the following lemma is used.

Lemma 2.6 [Zhang *et al.* (1992)]. *For system*

$$\frac{\mathrm{d}x}{\mathrm{d}t} = P_2(x,y), \quad \frac{\mathrm{d}y}{\mathrm{d}t} = y + Q_2(x,y), \tag{2.99}$$

suppose that $O(0,0)$ *is an isolated critical point of* (2.99) *and* P_2, Q_2 *are analytic functions with orders no less than* 2, *in a sufficiently small neighborhood* $S_\delta(O)$ *of* $O(0,0)$. *Then, for* δ *sufficiently small, there exists an analytic function* $\phi(x)$ *satisfying*

$$\phi(x) + Q_2(x, \phi(x)) \equiv 0, \quad |x| < \delta.$$

Let

$$\psi(x) = P_2(x, \phi(x)) = a_m x^m + [x]_{m+1},$$

where $[x]_{m+1}$ *represents the sum of those terms in* $\psi(x)$ *with orders no less than* $m+1$, *and* $a_m \neq 0, m \geq 2$. *Then the following properties hold.*

(i) *If* m *is odd and* $a_m > 0$, *then* $O(0,0)$ *is an unstable node.*
(ii) *If* m *is odd and* $a_m < 0$, *then* $O(0,0)$ *is a saddle point with its four separatrices connecting to* $O(0,0)$ *along the directions* $\theta = 0$, $\pi/2$, π, $3\pi/2$, *respectively.*
(iii) *If* m *is even, then* $O(0,0)$ *is a saddle node.*

Theorem 2.33. *For system* (2.97), *the following conclusions hold*:

(1) *The disease-free equilibrium* P_0 *is locally asymptotically stable if* $R_0 < 1$, *and unstable if* $R_0 > 1$.
(2) *The endemic equilibrium* P^* *is locally asymptotically stable if* $R_0 > 1$.
(3) *The endemic equilibrium* P_1^* *is a saddle point, and* P_2^* *is locally asymptotically stable, respectively, when they exist.*
(4) *If* $R_0 = 1$, $\alpha < \sigma\beta$, *and* $B > 0$, *then the disease-free equilibrium* P_0 *is unstable in the interior of* D, *and the endemic equilibrium* P_4^* *is locally asymptotically stable.*
(5) *The endemic equilibrium* P_3^* *is a saddle node when it exists.*

Proof. (i) By a straightforward calculation, the Jacobian matrix of system (2.97) at the disease-free equilibrium P_0 is

$$J(P_0) = \begin{pmatrix} (\gamma + b + \alpha)(R_0 - 1) & 0 \\ -p + (\alpha - \sigma\beta)z_0 & -(p + b + \varepsilon) \end{pmatrix}.$$

Then, it is easy to verify that P_0 is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$.

(ii) The Jacobian matrix of system (2.97) at the endemic equilibrium $\bar{P}(\bar{y},\bar{z})$ is

$$J(\bar{P}) = \begin{pmatrix} \bar{y}F_y(\bar{y},\bar{z}) & \bar{y}F_z(\bar{y},\bar{z}) \\ \\ G_y(\bar{y},\bar{z}) & G_z(\bar{y},\bar{z}) \end{pmatrix},$$

where

$$F_y(\bar{y},\bar{z}) = -(\beta-\alpha), \quad F_z(\bar{y},\bar{z}) = -\beta(1-\sigma) < 0,$$

$$G_y(\bar{y},\bar{z}) = -p + (\alpha-\sigma\beta)\bar{z}, \quad G_z(\bar{y},\bar{z}) = -(p+b+\varepsilon) + (\alpha-\sigma\beta)\bar{y}.$$

It follows from Theorem 2.31 that $\beta > \alpha$ is the necessary condition for the existence of the endemic equilibrium. Hence $F_y(\bar{y},\bar{z}) < 0$. It follows from the expression of $h_2(y)$ that $G_z(\bar{y},\bar{z}) = -(p+b+\varepsilon) + (\alpha-\sigma\beta)\bar{y} < 0$. Therefore, $\operatorname{Tr} J(\bar{p}) < 0$.

Notice that

$$h_1'(\bar{y}) = -\frac{F_y(\bar{y},\bar{z})}{F_z(\bar{y},\bar{z})} \quad \text{and} \quad h_2'(\bar{y}) = -\frac{G_y(\bar{y},\bar{z})}{G_z(\bar{y},\bar{z})}.$$

Then

$$\begin{aligned} \det J(\bar{P}) &= \bar{y}F_z(\bar{y},\bar{z})G_z(\bar{y},\bar{z})\left(\frac{F_y(\bar{y},\bar{z})}{F_z(\bar{y},\bar{z})} - \frac{G_y(\bar{y},\bar{z})}{G_z(\bar{y},\bar{z})}\right) \\ &= \bar{y}F_z(\bar{y},\bar{z})G_z(\bar{y},\bar{z})(h_2'(\bar{y}) - h_1'(\bar{y})). \end{aligned}$$

According to Remark 2.1(b), we have that $\det J(P^*) > 0$, $\det J(P_2^*) > 0$, $\det J(P_4^*) > 0$, and $\det J(P_1^*) < 0$ since $F_z(\bar{y},\bar{z}) < 0$ and $G_z(\bar{y},\bar{z}) < 0$. Thus P_1^* is a saddle point, and P^*, P_2^*, and P_4^* are locally asymptotically stable.

(iii) When $R_0 = 1$, $\alpha < \sigma\beta$, and $B > 0$, using the transformations

$$u = y, \quad v = [p - (\alpha-\sigma\beta)z_0]y + (p+b+\varepsilon)(z-z_0), \quad t = -s,$$

(2.97) becomes

$$\begin{aligned} \frac{\mathrm{d}u}{\mathrm{d}s} &= u\left\{\left[(\beta-\alpha) - \frac{\beta(1-\sigma)(p-(\alpha-\sigma\beta)z_0)}{p+b+\varepsilon}\right]u + \frac{\beta(1-\sigma)}{p+b+\varepsilon}v\right\}, \\ \frac{\mathrm{d}v}{\mathrm{d}s} &= (p+b+\varepsilon)v - u\left\{v\left[(\alpha-\sigma\beta) - (p-(\alpha-\sigma\beta)z_0)\frac{\beta(1-\sigma)}{p+b+\varepsilon}\right]\right. \\ &\quad \left. - u\beta(1-\sigma)[p-(\alpha-\sigma\beta)z_0]\frac{b+\varepsilon+(\alpha-\sigma\beta)z_0}{p+b+\varepsilon}\right\}. \end{aligned} \tag{2.100}$$

Set the right-hand side of the second equation of (2.100) equal to zero. Then we have

$$v = \frac{\beta(1-\sigma)[p-(\alpha-\sigma\beta)z_0][b+\varepsilon+(\alpha-\sigma\beta)z_0]}{(p+b+\varepsilon)^2}u^2 + [u]_2, \qquad (2.101)$$

where $[u]_2$ represents the higher-order terms.

Substituting (2.101) into the first equation of (2.100), we have

$$\frac{\mathrm{d}u}{\mathrm{d}s} = \left\{(\beta-\alpha) - \frac{\beta(1-\sigma)[p-(\alpha-\sigma\beta)z_0]}{p+b+\varepsilon}\right\}u^2 + [u]_2. \qquad (2.102)$$

Since $R_0 = 1$ is equivalent to $\beta(1-\sigma)z_0 = \beta-(\alpha+b+\gamma)$, Eq. (2.102) is equivalent to

$$\frac{\mathrm{d}u}{\mathrm{d}s} = -\frac{B}{p+b+\varepsilon}u^2 + [u]_2.$$

Since $B > 0$, it follows from Lemma 2.6 that P_0 is a saddle node, and that the orbits of (2.97) approach P_0 along the z-axis and are away from P_0 in the interior of D. Hence, the disease-free equilibrium P_0 is unstable in the interior of D.

Similarly, P_3^* is also a saddle node.

The proof of Theorem 2.33 is completed. □

2.6.2.2. *Global analysis of* (2.97)

To rule out the existence of periodic solutions of (2.97), we utilize the method used by Busenberg and van den Driessche (1990).

Theorem 2.34. *There is no periodic solution for system* (2.97).

Proof. Obviously, system (2.97) has the same dynamic behavior as system (2.95) since $x + y + z = 1$. Thus we prove that there is no periodic solution for system (2.95) in the following manner. Since the region $\Omega = \{(x, y, z)\colon x > 0,\ y \geq 0,\ z > 0,\ x + y + z = 1\}$ is an invariant set of (2.95), we consider the existence of periodic solution of (2.95) in Ω.

It is easy to see that the boundary of the domain Ω cannot form a periodic solution of system (2.95). Then we only consider the interior of Ω.

Assume that system (2.95) has a periodic solution $\phi(t) = \{x(t), y(t), z(t)\}$, and that the orbit Γ of $\phi(t)$ is the boundary of a plane domain Π in the interior of Ω.

Let f_1, f_2, and f_3 denote the right-hand sides of the first three equations in system (2.95), respectively, $f = (f_1, f_2, f_3)^{\mathrm{T}}$, where T denotes transpose, and $g(x, y, z) = (r \times f)/(xyz)$, where $r = (x, y, z)^{\mathrm{T}}$. Then, clearly,

$$g \cdot f = 0.$$

Let $g = (g_1, g_2, g_3)$, then

$$\mathrm{rot}\ g = \left(\frac{\partial g_3}{\partial y} - \frac{\partial g_2}{\partial z}, \frac{\partial g_1}{\partial z} - \frac{\partial g_3}{\partial x}, \frac{\partial g_2}{\partial x} - \frac{\partial g_1}{\partial y} \right).$$

Then, by calculating straightforwardly, we have

$$\begin{aligned} \mathrm{rot}\ g \cdot (1,1,1)^{\mathrm{T}} = &- \frac{px + \gamma y + \varepsilon z}{xyz} - \frac{bq + px}{z^2} \left(\frac{1}{x} + \frac{1}{y} \right) \\ &- \frac{b(1-q) + \sigma y + \varepsilon z}{x^2} \left(\frac{1}{y} + \frac{1}{z} \right) < 0, \end{aligned}$$

in the interior of domain Ω.

Suppose that the normal vector of plane domain Π is upward, and that the direction of the orbit Γ conforms to the right-hand rule with the normal vector of plane domain Π. Since the vector $(1, 1, 1)$ is the normal vector of plane domain Π, we obtain, by Stokers's theorem,

$$\frac{1}{\sqrt{3}} \int\int_{\Pi} \mathrm{rot}\ g \cdot (1,1,1)^{\mathrm{T}} \mathrm{d}S = \oint_{\Gamma} \frac{g \cdot f}{|f|} \mathrm{d}s = 0.$$

This is a contradiction to the calculation above. Theorem 2.34 is proved. □

From Theorems 2.31, 2.32, and 2.34, the following theorem is easy to obtain.

Theorem 2.35. *For system* (2.97), *the following results hold*:

(i) *Equilibrium* P^* *is globally asymptotically stable if* $R_0 > 1$.

(ii) *If* $R_0 < 1$, $\alpha < \sigma\beta$, $\beta > b + \gamma + \alpha$, *and* $B > 2\sqrt{AC}$, *then there exist stable manifolds of equilibrium* P_1^*, *which divide the region* D *into two parts. Positive orbits in the lower part approach to the endemic equilibrium* P_2^*, *and positive orbits in the upper part approach to the disease-free equilibrium* P_0.

(iii) *If* $R_0 < 1$, $\alpha < \sigma\beta$, $\beta > b + \gamma + \alpha$, *and* $B = 2\sqrt{AC}$, *then there exist stable manifolds of equilibrium* P_1^*, *which divide the region* D *into two parts. Positive orbits in the lower part approach to the endemic*

equilibrium P_1^* *and positive orbits in the upper part approach to the disease-free equilibrium* P_0.

(iv) *Equilibrium* P_4^* *is globally asymptotical stable if* $R_0 = 1$, $\alpha < \sigma\beta$, *and* $B > 0$.

(v) *If the parameters of* (2.97) *do not satisfy any of the assumptions in cases* (i)–(iv), *then* P_0 *is globally asymptotical stable.*

2.6.3. *Epidemic models with treatment*

In this part, we introduce some results of epidemic models with treatment obtained by Wang. The model constructed by Wang has been presented in Sec. 1.4.3. The model is

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mu S - \beta SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - (\mu + \gamma)I - T(I), \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I + T(I) - \mu R, \end{aligned} \tag{2.103}$$

where

$$T(I) = \begin{cases} rI, & \text{if } 0 \le I \le I_0, \\ rI_0, & \text{if } I > I_0. \end{cases} \tag{2.104}$$

Since the first two equations in (2.103) are independent of the variable R, it suffices to consider the following reduced model with (2.104):

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mu S - \beta SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - (\mu + \gamma)I - T(I). \end{aligned} \tag{2.105}$$

For (2.105), straightforward calculations gives the following results with respect to the existence of an endemic equilibrium [Wang (2006b)].

Theorem 2.36. *Point* $E^* = (S^*, I^*)$ *is an endemic equilibrium of* (2.105) *if and only if* $1 < R_0 \le p_2$. *Furthermore,* E^* *is the unique endemic equilibrium of* (2.105) *if* $1 < R_0 \le p_2$ *and one of the following conditions is satisfied*:

(i) $R_0 < p_0$,

(ii) $p_0 \le R_0 < p_1$,

where

$$R_0 = \frac{\beta A}{\mu(\mu+\gamma+r)}, \quad S^* = \frac{A}{\mu R_0}, \quad I^* = \frac{\mu(R_0-1)}{\beta} < I_0,$$

$$p_0 = 1 + \frac{rI_0\beta - \mu r}{\mu(\mu+\gamma+r)} + 2\frac{\sqrt{\beta(\mu+\gamma)rI_0\mu}}{(\mu+\gamma++r)\mu},$$

$$p_1 = 1 + \frac{rI_0\beta - \mu r}{\mu(\mu+\gamma+r)} + 2\frac{\beta(\mu+\gamma)I_0}{(\mu+\gamma+r)\mu}, \quad p_2 = 1 + \frac{\beta I_0}{\mu}.$$

Let

$$b = \mu^2 + \mu\gamma + rI_0\beta - A\beta, \quad \Delta = b^2 - 4\beta(\mu+\gamma)\mu r I_0,$$

$$S_1 = \frac{A}{\mu+\beta I_1}, \quad I_1 = -\frac{b+\sqrt{\Delta}}{2\beta(\mu+\gamma)} > I_0,$$

$$S_2 = \frac{A}{\mu+\beta I_2}, \quad I_2 = \frac{-b+\sqrt{\Delta}}{2\beta(\mu+\gamma)} > I_0.$$

Theorem 2.37. *Neither $E_1(S_1, I_1)$ nor $E_2(S_2, I_2)$ of* (2.105) *exist if $R_0 < p_0$. Furthermore, if $R_0 \geq p_0$, the following conclusions hold.*

(i) *Suppose $\mu r > \beta(\mu+\gamma)I_0$. Then both $E_1 = (S_1, I_1)$ and $E_2 = (S_2, I_2)$ exist when $p_1 < R_0 < p_2$.*
(ii) *Suppose $\mu r > \beta(\mu+\gamma)I_0$. Then E_1 does not exist but E_2 exists if $R_0 \geq p_2$.*
(iii) *Let $\mu r \leq \beta(\mu+\gamma)I_0$. Then E_1 does not exist. Furthermore, E_2 exists when $p_2 < R_0$, and does not exist when $R_0 \leq p_2$.*

For the case $p_0 > 1$, if $\mu r \geq \beta(\mu+\gamma)I_0$, a typical bifurcation diagram is given in Fig. 2.3, where the bifurcation from the disease-free equilibrium at $R_0 = 1$ is forward and there is a backward bifurcation from an endemic equilibrium at $R_0 = 1.5$, which gives rise to the existence of multiple endemic equilibria. Further, if $\mu r < \beta(\mu+\gamma)I_0$, a typical bifurcation diagram is given in Fig. 2.4, where the bifurcation at $R_0 = 1$ is forward and (2.105) has one unique endemic equilibrium for all $R_0 > 1$.

As I_0 increases, p_0 increases. When I_0 is sufficiently large such that $p_0 > 1$, it follows from Theorem 2.37 that there is no backward bifurcation when $R_0 < 1$. If we increase I_0 to $R_0 < p_0$, (2.105) does not have a backward bifurcation because endemic equilibria E_1 and E_2 do not exist. So the backward

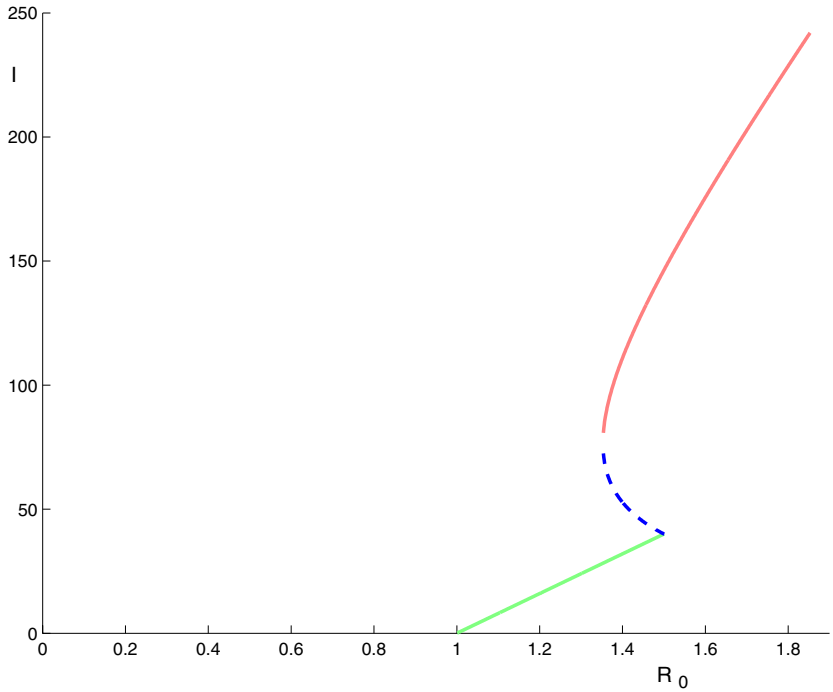


Fig. 2.3. The size of infectives at equilibria versus R_0 when $I_0 = 40, \beta = 0.01, \gamma = 0.02, \mu = 0.8$, and $r = 1.5$, where assumption (i) of Theorem 2.37 holds. The bifurcation from the disease-free equilibrium at $\mathcal{R}_0 = 1$ is forward and there is a backward bifurcation from an endemic equilibrium at $\mathcal{R}_0 = 1.5$, which leads to the existence of multiple endemic equilibria.

bifurcation may appear only if $p_0 < R_0 < 1$. This means that an insufficient capacity for treatment is a source of the backward bifurcation. By analyzing the eigenvalues of the Jacobian matrices of (2.105) at the equilibria, which is similar to the discussions of Theorem 2.1 [Wang and Ruan (2004a,b)], the following results for the stability of the endemic equilibria were obtained [Wang (2006a,b)].

Theorem 2.38. *The disease-free equilibrium E_0 is asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$. E^* is asymptotically stable if $I^* < I_0$. E_1 is a saddle whenever it exists. For E_2, we have*

(i) *E_2 is stable if either*

$$\beta A - 3\mu^2 - \mu\gamma - \frac{2\mu^3}{\gamma} \leq \beta r I_0$$

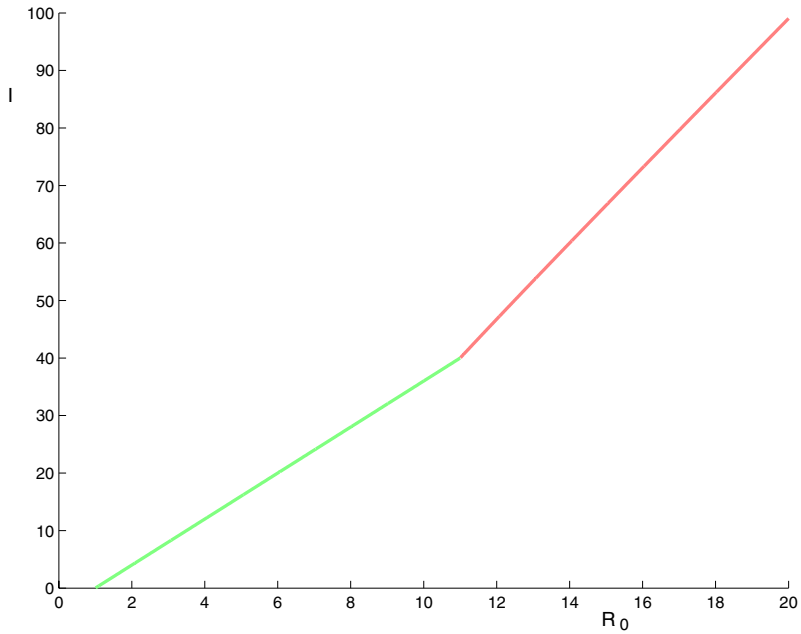


Fig. 2.4. The diagram of I^*, I_2 versus R_0 when $I_0 = 40, \beta = 0.2, \gamma = 0.2, \mu = 0.8$, and $r = 0.6$, where (iii) of Theorem 2.37 holds. The bifurcation at $\mathcal{R}_0 = 1$ is forward and (2.105) has a unique endemic equilibrium for $\mathcal{R}_0 > 1$.

or

$$\beta r I_0 < \beta A - 3\mu^2 - \mu\gamma - \frac{2\mu^3}{\gamma},$$

$$\beta r I_0 < \frac{1}{2}\left[2\beta A + (2\mu+\gamma)(\mu+\gamma)\left(1 - \sqrt{1 + \frac{4\beta A}{(\gamma+\mu)^2}}\right)\right].$$

(ii) *E_2 is unstable if*

$$\beta r I_0 < \beta A - 3\mu^2 - \mu\gamma - \frac{2\mu^3}{\gamma},$$

$$\beta r I_0 > \frac{1}{2}\left[2\beta A + (2\mu+\gamma)(\mu+\gamma)\left(1 - \sqrt{1 + \frac{4\beta A}{(\gamma+\mu)^2}}\right)\right].$$

Theorem 2.38 shows that there exist bistable endemic equilibria as the capacity of treatment is low (see Fig. 2.5).

With respect to the global stability of the disease-free equilibrium E_0, the following result was obtained [Wang (2006b)].

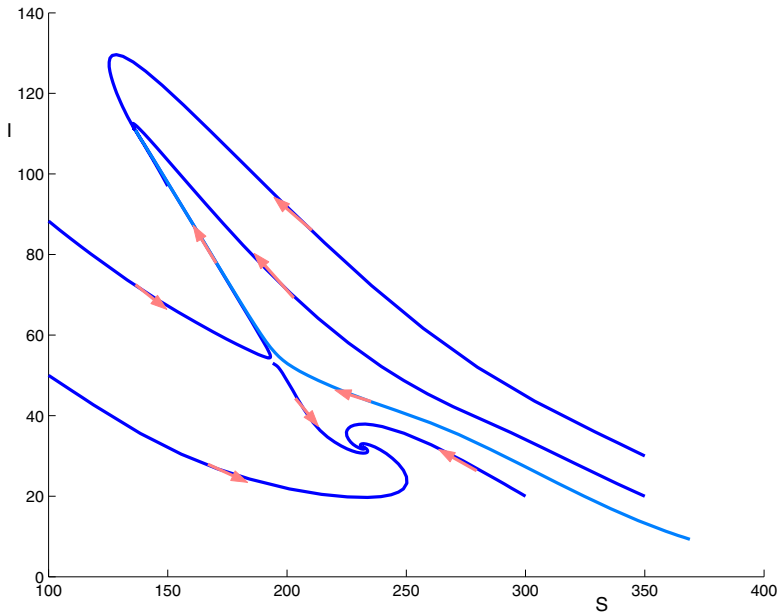


Fig. 2.5. A bistable case where endemic equilibria E^* and E_2 are stable when $A = 260$, $I_0 = 40$, $\beta = 0.01$, $\gamma = 0.02$, $\mu = 0.8$, and $r = 1.5$, where (i) of Theorem 2.38 holds.

Theorem 2.39. *The disease-free equilibrium E_0 is globally stable, if one of the following conditions is satisfied:*

(i) $R_0 < 1$ *and* $p_0 > 1$.
(ii) $R_0 < 1, p_0 < 1$ *and* $p_1 \geq 1$.

Proof. If $R_0 < 1$, then E^* does not exist. Suppose $p_0 \geq 1$. It follows from the discussions for Theorem 2.37 that E_1 or E_2 exists only if $R_0 > p_0$, which is impossible since we have $R_0 < 1$. Suppose $p_0 < 1$ and $p_1 \geq 1$. If $\mu r > \beta(\mu+\gamma)I_0$, since $p_1 < p_2$, it follows from the discussions for (i) and (ii) of Theorem 2.37 that E_1 or E_2 exists only if $R_0 > p_1$, which is impossible since we have $R_0 < 1$. If $\mu r \leq \beta(\mu + \gamma)I_0$, since $1 < p_2$, it follows from (iii) of Theorem 2.37 that E_1 and E_2 do not exist. In summary, endemic equilibria do not exist under the assumptions.

It is easy to verify that positive solutions of (2.105) are ultimately bounded. Note that the nonnegative S-axis is positively invariant and that the nonnegative I-axis repels positive solutions of (2.105). Since E_0 is asymptotically stable, it follows from the Bendixson Theorem that every positive solution of (2.105) approaches E_0 as t goes to infinity. □

Theorem 2.39 shows that, when $R_0 < 1$, the disease eventually dies out as long as the capacity of treatment resource is sufficiently large.

2.7. Bifurcation

Many classic epidemic models have thresholds, determined by the basic reproductive number R_0. If $R_0 \leq 1$, the corresponding model only has the disease-free equilibrium, which is globally stable in the feasible region. If the basic reproductive number $R_0 > 1$, in addition to the unstable disease-free equilibrium, the model also has a unique endemic equilibrium which is globally stable. This means that the disease dies out if $R_0 \leq 1$ and persists in the population if $R_0 > 1$. However, there are increasing evidences indicating that the basic reproductive number R_0 alone cannot fully determine the global dynamics of the disease transmission. Indeed, even for some simple epidemiologic models, backward bifurcation with multiple endemic equilibria and/or Hopf bifurcation yielding periodic solutions can happen [Alexander and Moghadas (2004, 2005); Berezovsky *et al.* (2005); Dushoff (1996); Dushoff *et al.* (1998); Greenhalgh *et al.* (2000); Hadeler and Castillo-Chavez (1995); Hadeler and van den Driessche (1997); Hethcote and van den Driessche (1991); Hui and Zhu (2005); Kribs-Zaleta (1999); Kribs-Zaleta and Velasco-Hernadez (2000); Li *et al.* (2004, 2006); Liu *et al.* (1986, 1987); Safan *et al.* (2006); van den Driessche and Watmough (2000), Wang (2006a,b)], and the Bogdanov–Takens singularity may also occur [Ruan and Wang (2003); Wang and Ruan (2004a,b); Li *et al.* (2007); Zhou *et al.* (2007); Wu and Feng (2000)].

In a model with only forward bifurcation, the level (number or fraction) of the infective individuals is low when R_0 is greater than but closed to one, but in a system with backward bifurcation, when R_0 is less than but closed to one, the model has two endemic equilibria, one of which is a saddle, and one of which is locally asymptotically stable. When $R_0 > 1$, while there exists a unique endemic equilibrium as the model with forward bifurcation, the level (number or fraction) of the infective individuals is higher when R_0 is greater than but closed to one, compared to the model with forward bifurcation.

For systems with backward bifurcation, there are usually two thresholds: $R_0 = R_c (0 < R_c < 1)$ and $R_0 = 1$. At $R_0 = R_c$ there is a saddle-node bifurcation, and at $R_0 = 1$ it has a backward bifurcation. The model has a unique endemic equilibrium if $R_0 \geq 1$ or $R_c = R_0 < 1$; two endemic equilibria if $R_c < R_0 < 1$, and no endemic equilibrium if $R_0 < R_c$. The bistability

phenomenon happens as $R_c < R_0 < 1$, and, in such a case, the eradication or persistence of disease depends on not only the reproductive number, but also other factors such as the initial conditions of the subpopulations.

When Hopf bifurcation occurs, the stability of an endemic equilibrium can change and the model can have a family of periodic solutions as R_0 (or the other parameter) passes through the bifurcation point. For systems with more complicated dynamics, the bifurcation of cusp type of codimension 2 (that is, Bogdanov–Takens bifurcation) may happen at the degenerate equilibrium, which includes a saddle-node bifurcation, a Hopf bifurcation, or a homoclinic bifurcation.

In this section, we show bifurcations and corresponding analysis methods by analyzing some specific epidemic models.

2.7.1. *Backward bifurcation*

We divide population into three classes: the susceptible class (S), the infected class (I), in which individuals are infected and infectious as well; and the recovered class (J). After recovery, individuals in J have no immunity to the infection, but their susceptibility is different from that in the class S. Then, we consider the following epidemic model:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu A - \mu S - \beta_1 SI, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta_1 SI - (\mu+\gamma)I + \beta_2 JI, \\
\frac{\mathrm{d}J}{\mathrm{d}t} &= \gamma I - \mu J - \beta_2 JI,
\end{aligned} \tag{2.106}$$

where β_2 denotes the transmission rate coefficient of infection for the recovered individuals with susceptibility.

Let $N(t) = S(t)+I(t)+J(t)$, then $N' = \mu(A-N)$, and $\lim_{t\to\infty} N(t) = A$. It implies that the plane $S+I+J=A$ is an omega limit set of (2.106). It is easy to see that the basic reproductive number of (2.106) is $R_0 = \beta_1 A/(\mu+\gamma)$.

Substituting $J = A-S-I$ into the second equation in (2.106), we have

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu A - \mu S - \beta_1 SI := P(S,I), \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= I[(\beta_1-\beta_2)S - (\mu+\gamma) + \beta_2 A - \beta_2 I] := Q(S,I).
\end{aligned} \tag{2.107}$$

It is obvious that the region $D = \{(S, I)\colon S > 0, I \geq 0, S + I \leq A\}$ is a positive invariant set of (2.107). Thus, we only need to consider (2.107) in D.

It is clear that $E_0(A, 0)$ is always the disease-free equilibrium of (2.107), and its endemic equilibrium $\bar{E}(\bar{S}, \bar{I})$ is determined by equations

$$\begin{aligned} \mu A - \mu S - \beta_1 SI = 0, \\ (\beta_1 - \beta_2)S - (\mu + \gamma) + \beta_2 A - \beta_2 I = 0. \end{aligned} \tag{2.108}$$

Then, it follows that $\bar{I}$ satisfies equation

$$H(I) := \beta_1\beta_2 I^2 + b(\beta_2)I + c = 0,$$

where $b(\beta_2) = \beta_1(\mu + \gamma) - \beta_2(\beta_1 A - \mu)$, $c = \mu[(\mu + \gamma) - \beta_1 A] = \mu(\mu + \gamma)\ (1 - R_0)$.

Since $H(A) = \beta_1\gamma A + \mu(\mu + \gamma + \beta_2 A) > 0$ and $H'(A) = \beta_1(\mu + \gamma + \beta_2 A) + \beta_2\mu > 0$, then $H(I) > 0$ for $I \geq A$, which implies that equation $H(I) = 0$ has no roots in $[A, \infty)$. Thus, we only consider the existence of root of $H(I) = 0$ in $(0, A)$.

For the sake of simplicity, we denote

$$\begin{aligned} \Delta(\beta_2) &= b^2(\beta_2) - 4\beta_1\beta_2 c \\ &= (\beta_1 A - \mu)^2\beta_2^2 - 2\beta_1\beta_2[\beta_1 A(\gamma - \mu) + \mu(\mu + \gamma)] + \beta_1^2(\mu + \gamma)^2. \end{aligned}$$

When $R_0 > 1$, $H(0) = c = \mu(\mu + \gamma)(1 - R_0) < 0$. Then $H(I) = 0$ has a uniquely positive root I^*: $-b(\beta_2)/(2\beta_1\beta_2) < I^* = [-b(\beta_2) + \sqrt{\Delta(\beta_2)}]/(2\beta_1\beta_2)$.

When $R_0 = 1$, that is, $\beta_1 A = \mu + \gamma$, then $H(0) = c = 0$. If $\beta_2 \leq \beta_1(\mu + \gamma)/(\beta_1 A - \mu) = \beta_1^2 A/\gamma$, then $b(\beta_2) \geq 0$ and hence $H(I) = 0$ has no positive roots. If $\beta_2 > \beta_1^2 A/\gamma$, then $b(\beta_2) < 0$ and hence $H(I) = 0$ has a uniquely positive root $I_1^* = -b(\beta_2)/(\beta_1\beta_2) = (\beta_2\gamma - \beta_1^2 A)/(\beta_1\beta_2)$.

When $R_0 < 1$, we consider three cases:

(1) If $R_0 \leq \mu/(\mu + \gamma)$, that is, $\beta_1 A \leq \mu$, then $b(\beta_2) > 0$ and $c > 0$, so that $H(I) = 0$ had no positive roots.
(2) If $\mu/(\mu + \gamma) < R_0 < 1$ and $\beta_2 \leq \beta_1(\mu + \gamma)/(\beta_1 A - \mu)$, similarly, we have $b(\beta_2) \geq 0$ and $c > 0$, so that $H(I) = 0$ had no positive roots.

(3) If $\mu/(\mu+\gamma) < R_0 < 1$ and $\beta_2 > \beta_1(\mu+\gamma)/(\beta_1 A - \mu)$ which implies that $b(\beta_2) < 0$, since

$$\Delta\left(\frac{\beta_1(\mu+\gamma)}{\beta_1 A-\mu}\right) = \frac{4\beta_1^2\mu(\mu+\gamma)[\beta_1 A-(\mu+\gamma)]}{\beta_1 A-\mu} < 0$$

and $\Delta(+\infty) = +\infty$, then the equation $\Delta(\beta_2) = 0$ of β_2 has a unique root in the interval $(\beta_1(\mu+\gamma)/(\beta_1 A-\mu), \infty)$

$$\bar{\beta}_2 = \frac{\beta_1}{(\beta_1 A-\mu)^2}\left\{\beta_1 A(\gamma-\mu)+\mu(\mu+\gamma)+2\sqrt{\beta_1 A\mu\gamma[(\mu+\gamma)-\beta_1 A]}\right\}$$

such that $\Delta(\beta_2) > 0$ for $\beta_2 > \bar{\beta}_2$, and $\Delta(\beta_2) < 0$ for $\beta_1(\mu+\gamma)/(\beta_1 A-\mu) < \beta_2 < \bar{\beta}_2$. Therefore, when $\mu/(\mu+\gamma) < R_0 < 1$ and $\beta_2 = \bar{\beta}_2$, $H(I) = 0$ has a repeated root $I_*^* = -b(\beta_2)/(2\beta_1\beta_2)$; when $\mu/(\mu+\gamma) < R_0 < 1$ and $\beta_2 > \bar{\beta}_2$, $H(I) = 0$ has two distinct positive roots:

$$I^* = \frac{-b(\beta_2)+\sqrt{\Delta(\beta_2)}}{2\beta_1\beta_2} > -\frac{b(\beta_2)}{2\beta_1\beta_2}$$

and

$$I_* = \frac{-b(\beta_2)-\sqrt{\Delta(\beta_2)}}{2\beta_1\beta_2} < -\frac{b(\beta_2)}{2\beta_1\beta_2}.$$

Substituting the root $\bar{I}$ of $H(I) = 0$ into the first equation in (2.108), we have $\bar{S} = \mu A/(\mu+\beta_1\bar{I})$. Summarizing the above about the existence of the endemic equilibrium, we have

Theorem 2.40.

(1) *When* $R_0 > 1$, (2.107) *has a unique endemic equilibrium* $E^*(S^*, I^*)$.
(2) *When* $R_0 = 1$ *and* $\beta_2 > \beta_1^2 A/\gamma$, (2.107) *has a unique endemic equilibrium* $E_1^*(S_1^*, I_1^*)$.
(3) *When* $\mu/(\mu+\gamma) < R_0 < 1$ *and* $\beta_2 = \bar{\beta}_2$, (2.107) *has a unique endemic equilibrium* $E_*^*(S_*^*, I_*^*)$.
(4) *When* $\mu/(\mu+\gamma) < R_0 < 1$ *and* $\beta_2 > \bar{\beta}_2$, (2.107) *has two endemic equilibria* $E^*(S^*, I^*)$ *and* $E_*(S_*, I_*)$ *where*

$$S^* = \frac{2\beta_2\mu A}{2\beta_2\mu - b(\beta_2)+\sqrt{\Delta(\beta_2)}}, \quad I^* = \frac{-b(\beta_2)+\sqrt{\Delta(\beta_2)}}{2\beta_1\beta_2},$$

$$S_1^* = \frac{\beta_2\mu}{\beta_1(\beta_2-\beta_1)}, \qquad I_1^* = \frac{\beta_2\gamma-\beta_1^2 A}{\beta_2\beta_1},$$

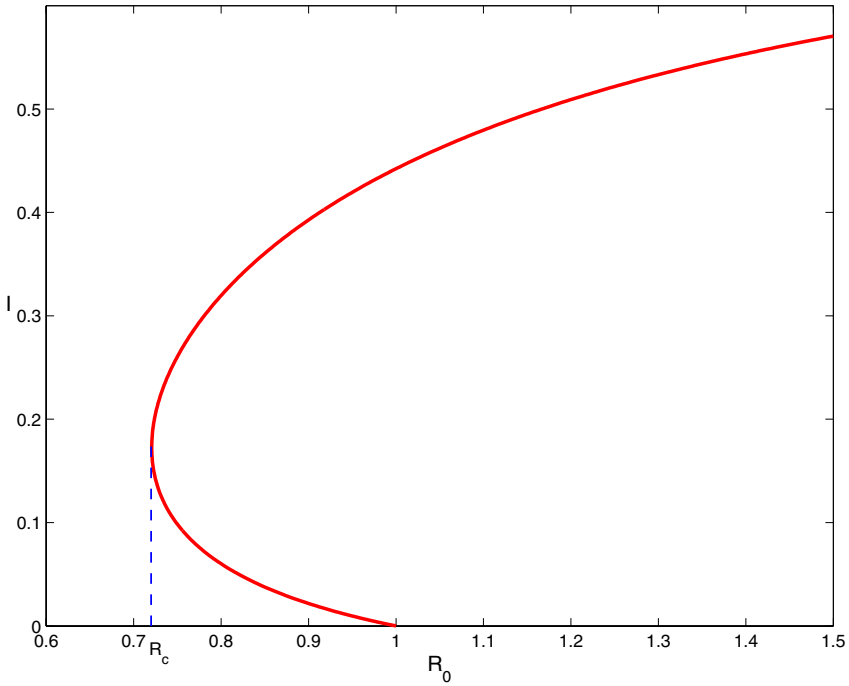


Fig. 2.6. The level of the infective individuals versus R_0 as a backward bifurcation occurs, where $A = 1, \mu = 0.5, \gamma = 1.5, \beta_2 = 6.5$, and $R_c = 0.72063$.

$$S_*^* = \frac{2\beta_2\mu A}{2\beta_2\mu - b(\beta_2)}, \qquad I_*^* = -\frac{b(\beta_2)}{2\beta_1\beta_2},$$

$$S_* = \frac{2\beta_2\mu A}{2\beta_2\mu - b(\beta_2) - \sqrt{\Delta(\beta_2)}}, \quad I_* = \frac{-b(\beta_2) - \sqrt{\Delta(\beta_2)}}{2\beta_1\beta_2}.$$

Figure 2.6 shows the relation between the level of the infective individuals and R_0 as a backward bifurcation occurs.

Analyzing the linearized system of (2.107) at equilibrium shows that the disease-free equilibrium E_0 is locally asymptotically stable as $R_0 < 1$ and unstable as $R_0 > 1$, that the endemic equilibria E^* and E_1^* are locally asymptotically stable if they exist, and that the endemic equilibrium E_* is a saddle point if it exists.

In the following, we discuss the stability of E_0 as $R_0 = 1$, and the stability of E_*^*.

When $R_0 = 1$, making a transformation $u = \mu(S - A) + \beta_1 AI$, $v = I$ for (2.107) to translate E_0 to the origin, we have

$$\begin{aligned}\frac{\mathrm{d}u}{\mathrm{d}t} &= -\mu u - \beta_1 v\left[\frac{\mu - (\beta_1 - \beta_2)A}{\mu}u + (\beta_2 - \beta_1)\left(1 - \frac{\beta_1 A}{\mu}\right)Av\right],\\ \frac{\mathrm{d}v}{\mathrm{d}t} &= -\frac{v}{\mu}\left[\left(\beta_1^2 A - \gamma\beta_2\right)v + (\beta_2 - \beta_1)u\right].\end{aligned} \tag{2.109}$$

Let the right-hand side of the first equation in (2.109) be zero, namely,

$$\mu u + \beta_1 v\left\{\frac{\mu - (\beta_1 - \beta_2)A}{\mu}u + (\beta_2 - \beta_1)\left(1 - \frac{\beta_1 A}{\mu}\right)Av\right\} = 0.$$

It follows that

$$u = -\frac{\beta_1 A(\beta_2 - \beta_1)}{\mu}\left(1 - \frac{\beta_1 A}{\mu}\right)v^2 + o(v^2).$$

Substituting it into the second equation in (2.109) gives

$$\frac{\mathrm{d}v}{\mathrm{d}t} = -\frac{\beta_1^2 A - \gamma\beta_2}{\mu}v^2 + \frac{\beta_1 A(\beta_2 - \beta_1)^2}{\mu^2}\left(1 - \frac{\beta_1 A}{\mu}\right)v^3 + o(v^3).$$

It follows from Lemma 2.6 that $E_0(A, 0)$ is locally asymptotically stable in D as $R_0 = 1$ and $\beta_2 \le \beta_1^2 A/\gamma$, and unstable in D as $R_0 = 1$ and $\beta_2 > \beta_1^2 A/\gamma$.

For the endemic equilibrium E_*^*, the Jacobian matrix of (2.107) is

$$J(E^*) = \begin{pmatrix} -\mu - \beta_1 I_*^* & -\beta_1 S_*^* \\ (\beta_1 - \beta_2)I_*^* & -\beta_2 I_*^* \end{pmatrix} = \begin{pmatrix} -k\beta_1 S_*^* & -\beta_1 S_*^* \\ -k\beta_2 I_*^* & -\beta_2 I_*^* \end{pmatrix},$$

where $k = (\beta_2 - \beta_1)/\beta_2 > 0$ since $\beta_2 = \bar{\beta}_2 > \beta_1(\mu + \gamma)/(\beta_1 A - \mu) > \beta_1(\mu + \gamma)/\gamma > \beta_1$.

By making a transformation $u = \beta_2 I_*^*(S - S_*^*) - \beta_1 S_*^*(I - I_*^*), v = k(S - S_*^*) + (I - I_*^*)$, for (2.107) to translate E_0 to the origin, we have

$$\begin{aligned}u' = &-\beta_1 \frac{u + \beta_1 S_*^* v}{(\beta_2 I_*^* + k\beta_1 S_*^*)^2}\\ &\times\left\{-(\beta_2 - \beta_1)I_*^* u + [\beta_2^2 I_*^*(I_*^* - S_*^*) + \beta_1 S_*^{*2}(\beta_1 - \beta_2)]v\right\},\end{aligned}$$

$$v' = -(\beta_2 I_*^* + k\beta_1 S_*^*)v - \frac{u + \beta_1 S_*^* v}{(\beta_2 I_*^* + k\beta_1 S_*^*)^2}$$
$$\times \left\{-k^2\beta_1 u + [\beta_2 I_*^*(k\beta_1 + \beta_2) - \beta_1 S_*^*(\beta_1 - \beta_2)]v\right\}. \tag{2.110}$$

Similarly as to the inference for the case $R_0 = 1$, we have

$$v' = \frac{\beta_1(\beta_2 - \beta_1)I_*^*}{(\beta_2 I_*^* + k\beta_1 S_*^*)^2}u^2 + o(u^2).$$

It follows from Lemma 2.6 that E_*^* is a saddle-node point as $\beta_2 > \beta_1$.

Since

$$\frac{\partial}{\partial S}\left(\frac{P}{I}\right) + \frac{\partial}{\partial I}\left(\frac{Q}{I}\right) = -\left(\beta_1 + \beta_2 + \frac{\mu}{I}\right) < 0$$

in the region D, there is no periodic solutions of (2.107) in D. Incorporating the local analysis above leads to the following results:

Theorem 2.41.

(1) *The disease-free equilibrium E_0 is globally stable in D when any of the following conditions holds*:

(i) $R_0 \le \mu/(\mu + \gamma)$;
(ii) $\mu/(\mu + \gamma) < R_0 < 1$ *and* $\beta_2 < \bar{\beta}_2$;
(iii) $R_0 = 1$ *and* $\beta_2 \le \beta_1^2 A/\gamma$.

(2) *The endemic equilibrium E^* is globally stable in D when any of the following conditions holds*:

(i) $R_0 > 1$;
(ii) $R_0 = 1$ *and* $\beta_2 > \beta_1^2 A/\gamma$.

(3) *When $\mu/(\mu + \gamma) < R_0 < 1$ and $\beta_2 > \bar{\beta}_2$, there exist stable manifolds of equilibrium E_*, which divide the region D into two parts*: *positive orbits in the lower part approach to the disease-free equilibrium E_0 and positive orbits in the upper part approach to the endemic equilibrium E^** (*see Fig.* 2.7).

(4) *When $\mu/(\mu + \gamma) < R_0 < 1$ and $\beta_2 = \bar{\beta}_2$, there exist stable manifolds of equilibrium E_*^*, which divide the region D into two parts*: *positive orbits in the lower part approach to the disease-free equilibrium E_0 and positive orbits in the upper part approach to the endemic equilibrium E_*^** (*see Fig.* 2.8).

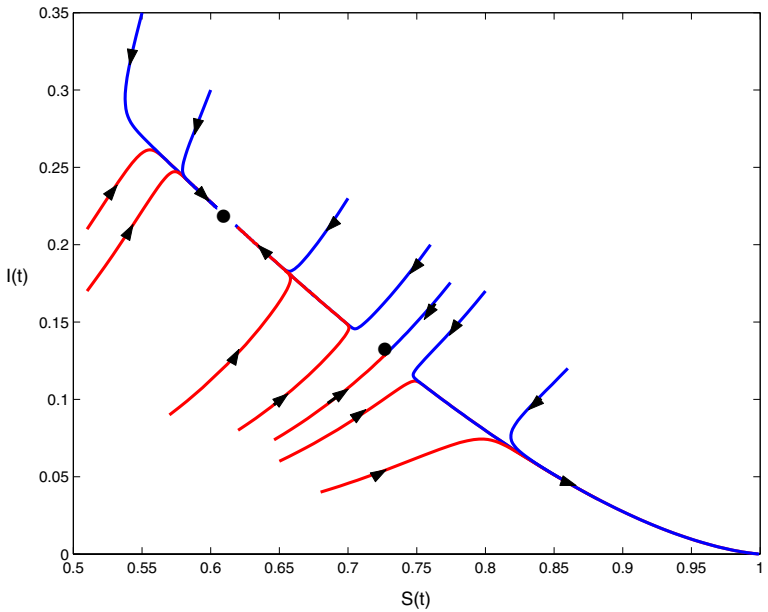


Fig. 2.7. The case that a saddle and a node coexist, where $A = 1, \mu = 0.5, \gamma = 1.5$, $\beta_2 = 6.5$, and $R_0 = 0.73 > R_c$.

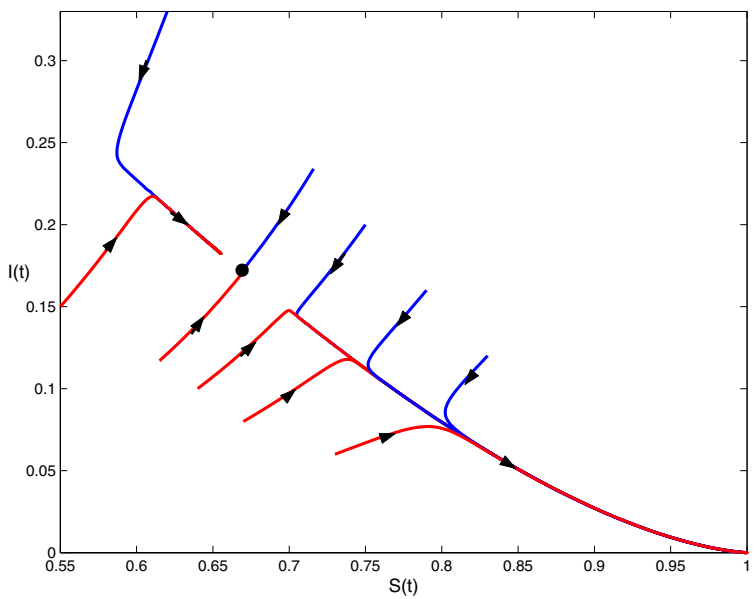


Fig. 2.8. The case that a saddle node appears, where $A = 1, \mu = 0.5, \gamma = 1.5, \beta_2 = 6.5$, and $R_0 = R_c = 0.72063$.

2.7.2. *Hopf and Bogdanov–Takens bifurcations*

In this section, to show Hopf and Bogdanov–Takens bifurcations, we investigate the following SIRS model with nonlinear incidence:

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= B - \mu S - \frac{kI^2S}{1+\alpha I^2} + \nu R,\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{kI^2S}{1+\alpha I^2} - (\mu+\gamma)I,\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - (\mu+\nu)R,\end{aligned} \tag{2.111}$$

which was investigated by Ruan and Wang (2003). The normal forms and bifurcation curves of Hopf and Bogdanov–Takens bifurcations were obtained by a series of nontrivial transformations as follows.

Summing up the three equations in (2.111) and denoting the size of the total population by $N(t)$, we obtain

$$\frac{\mathrm{d}N}{\mathrm{d}t} = B - \mu N.$$

Since $N(t)$ tends to constant, B/μ, as t goes to infinity, then we assume that the population is at equilibrium and investigate the behavior of system (2.111) on the plane $S + I + R = B/\mu$, and consider the reduced system

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{kI^2}{1+\alpha I^2}\left(\frac{B}{\mu} - I - R\right) - (\mu+\gamma)I,\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - (\mu+\nu)R.\end{aligned} \tag{2.112}$$

To be concise in notations, rescale (2.112) by $X = I\sqrt{k/(\mu+\nu)}, Y = R\sqrt{k/(\mu+\nu)}$, and $\theta = (\mu+\nu)t$. For simplicity, we still use variables I, R, t instead of X, Y, θ. Then we obtain

$$\begin{aligned}\frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{I^2}{1+pI^2}(A - I - R) - mI,\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= qI - R,\end{aligned} \tag{2.113}$$

where

$$p = \frac{\alpha(\mu+\nu)}{k}, \quad A = \frac{B}{\mu}\sqrt{\frac{k}{\mu+\nu}}, \quad m = \frac{\mu+\gamma}{\mu+\nu}, \quad q = \frac{\gamma}{\mu+\nu}.$$

To find positive equilibria of (2.113), set

$$\frac{I}{1+pI^2}(A-I-R)-m=0,$$
$$qI-R=0,$$

which yields

$$(mp+q+1)I^2-AI+m=0. \tag{2.114}$$

Then we have the following results:

(i) There exists no positive equilibrium if $A^2<4m(mp+q+1)$.
(ii) There exists one positive equilibrium if $A^2=4m(mp+q+1)$.
(iii) There exist two positive equilibria if $A^2>4m(mp+q+1)$.

Suppose that $A^2>4m(mp+q+1)$. Then (2.113) has two positive equilibria (I_1,R_1) and (I_2,R_2), where

$$I_1=\frac{A-\sqrt{A^2-4m(mp+q+1)}}{2(mp+q+1)},\quad R_1=qI_1,$$
$$I_2=\frac{A+\sqrt{A^2-4m(mp+q+1)}}{2(mp+q+1)},\quad R_2=qI_2.$$

Ruan and Wang (2003) have shown that the equilibrium (I_1,R_1) is a saddle point, and that (I_2,R_2) is a node, a focus, or a center.

Furthermore, they have shown that (I_2,R_2) is locally asymptotically stable if either of the following conditions holds:

(1) $m\le 1$,
(2) $m>1$ and $q\le(2mp+1)/(m-1)$.

In the following, we consider Hopf bifurcation and Bogdanov–Takens bifurcation for (2.113).

2.7.2.1. *Hopf bifurcation*

In this section, we discuss Hopf bifurcation for equilibrium (I_2,R_2) under the assumption:

(H1) $m>1$ and $q>(2mp+1)/(m-1)$.

The Jacobian matrix of (2.113) at (I_2, R_2) is

$$M_2 = \begin{pmatrix} \dfrac{I_2(A - ApI_2^2 - 2I_2 - qI_2 + qI_2^3p)}{(1+pI_2^2)^2} & \dfrac{-I_2^2}{1+pI_2^2} \\ q & -1 \end{pmatrix}.$$

The inference by Ruan and Wang (2003) shows that $\det(M_2) > 0$, and that $\mathrm{Tr}(M_2)$ has the same sign as

$$r_3 = -[(m-1)(mp+p+1)A^2 - (mq+2m-1-q+2m^2p)^2]. \quad (2.115)$$

Notice that (H1) implies that $4m(mp+q+1) < A_c^2 (A_c > 0)$, where

$$A_c^2 = \frac{(mq+2m-1-q+2m^2p)^2}{(m-1)(mp+p+1)}.$$

Thus, under condition (H1), we can choose A as a bifurcation parameter, and Hopf bifurcation occurs at $A = A_c$. Moreover, (I_2, R_2) is stable when $A^2 > A_c^2$, and unstable when $4m(mp+q+1) < A^2 < A_c^2$.

To investigate how periodic solutions appear, we consider the following system which is equivalent to (2.113):

$$\begin{aligned} \frac{\mathrm{d}I}{\mathrm{d}t} &= I^2(A - I - R) - mI(1+pI^2), \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= (qI - R)(1+pI^2). \end{aligned} \quad (2.116)$$

Making a transformation, $x = I - I_2$, $y = R - R_2$, to translate (I_2, R_2) to the origin, we have

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= a_{11}x + a_{12}y + f_1(x,y), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= a_{21}x + a_{22}y + f_2(x,y), \end{aligned} \quad (2.117)$$

where $f_i(x,y)$, $i = 1, 2$, represents the higher-order terms in x and y, and

$$\begin{aligned} &a_{11} = 2I_2(A - I_2 - R_2) - I_2^2 - m(1+pI_2^2) - 2mI_2^2p, \quad a_{12} = -I_2^2, \\ &a_{21} = q(1+pI_2^2) + 2(qI_2 - R_2)pI_2, \quad a_{22} = -(1+pI_2^2). \end{aligned}$$

In the case (H1), when $A = A_c$, we can simplify a_{ij} and obtain

$$a_{11} = \frac{2mp+1}{mp+p+1}, \quad a_{12} = -\frac{m-1}{mp+p+1},$$
$$a_{21} = \frac{(2mp+1)q}{mp+p+1}, \quad a_{22} = -\frac{2mp+1}{mp+p+1}.$$

Now, using transformation $X = x$, $Y = a_{11}x + a_{12}y$ to (2.117), we obtain

$$\begin{aligned} \frac{\mathrm{d}X}{\mathrm{d}t} &= Y + f_1\left(X, \frac{Y - a_{11}X}{a_{12}}\right), \\ \frac{\mathrm{d}Y}{\mathrm{d}t} &= -k_1 X + a_{11} f_1\left(X, \frac{Y - a_{11}X}{a_{12}}\right) + a_{12} f_2\left(X, \frac{Y - a_{11}X}{a_{12}}\right), \end{aligned} \tag{2.118}$$

where

$$k_1 = \frac{(-2mp + mq - q - 1)(2mp+1)}{(mp+p+1)^2} > 0.$$

Set $u = -X$, $v = Y/\sqrt{k_1}$. Then (2.118) becomes

$$\begin{aligned} \frac{\mathrm{d}u}{\mathrm{d}t} &= -\sqrt{k_1}v + F_1(u,v), \\ \frac{\mathrm{d}v}{\mathrm{d}t} &= \sqrt{k_1}u + F_2(u,v), \end{aligned} \tag{2.119}$$

where

$$F_1(u,v) = -f_1(-u, (v\sqrt{k_1} + a_{11}u)/a_{12}),$$
$$F_2(u,v) = \frac{a_{11} f_1(-u, (v\sqrt{k_1} + a_{11}u)/a_{12}) + a_{12} f_2(-u, (v\sqrt{k_1} + a_{11}u)/a_{12})}{\sqrt{k_1}}.$$

Set

$$\begin{aligned} \sigma = {} & \frac{1}{16}\left[\frac{\partial^3 F_1}{\partial u^3} + \frac{\partial^3 F_1}{\partial^3 u \partial v^2} + \frac{\partial^3 F_2}{\partial u^2 \partial v} + \frac{\partial^3 F_2}{\partial v^3}\right] \\ & + \frac{1}{16\sqrt{k_1}}\left[\frac{\partial^2 F_1}{\partial u \partial v}\left(\frac{\partial^2 F_1}{\partial u^2} + \frac{\partial^2 F_1}{\partial v^2}\right) - \frac{\partial^2 F_2}{\partial u \partial v}\left(\frac{\partial^2 F_2}{\partial u^2} + \frac{\partial^2 F_2}{\partial v^2}\right)\right. \\ & \left. - \frac{\partial^2 F_1}{\partial u^2}\frac{\partial^2 F_2}{\partial u^2} + \frac{\partial^2 F_1}{\partial v^2}\frac{\partial^2 F_2}{\partial v^2}\right]. \end{aligned}$$

Using the fact that $A = A_c$, with the aid of Maple, we can see that the sign of σ is determined by δ,

$$\delta = q(m-1)(2mp-4p-1) + (2m^2p + 2\,m + 4p + 1)(2mp+1). \quad (2.120)$$

Therefore, by the results [Guckenheimer and Holmes (1996)], we have

Theorem 2.42. *In the case* (H1), *if* $\delta < 0$, *then there is a family of stable periodic orbits in* (2.113) *as* A^2 *decreases from* $(mq + 2m - 1 - q + 2m^2p)^2/((m-1)(mp+p+1))$, *and if* $\delta > 0$, *there is a family of unstable periodic orbits in* (2.113) *as* A^2 *increases from* $(mq+2m-1-q+2m^2p)^2/((m-1)(mp+p+1))$.

Choose $m = 4.0$, $q = 3.6$, and $p = 0.2$. Condition $q > (2mp+1)/(m-1)$ is satisfied. Then choose $A = A_c = 9.879608628$. By (2.120), we have $\delta = 39.96$. Thus, there is an unstable periodic orbit when A increase from 9.879608628 (see Fig. 2.9).

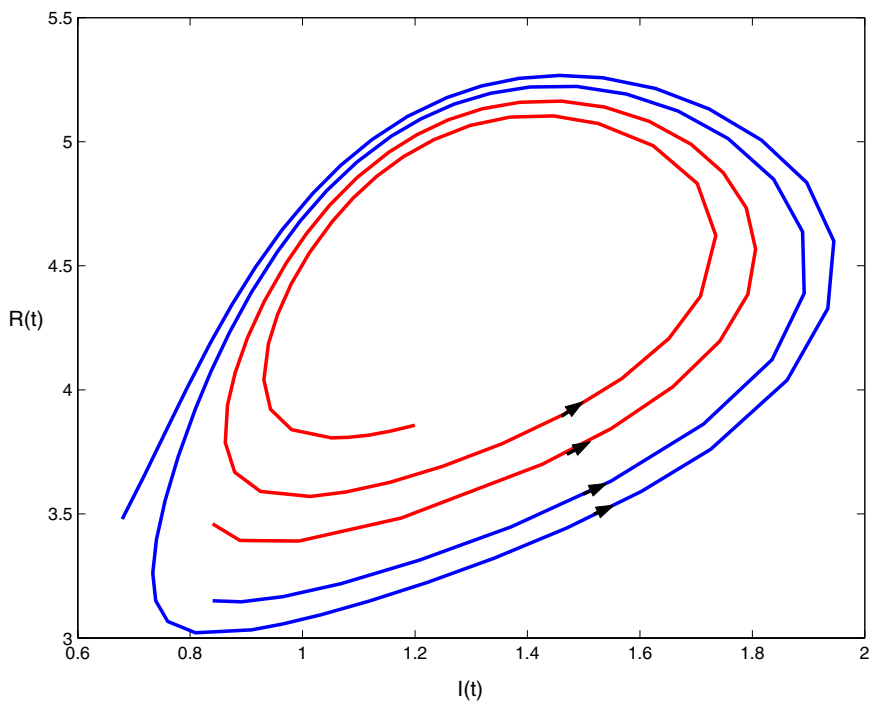


Fig. 2.9. An unstable limit cycle when $A = 10.02, m = 4.0, q = 3.6$, and $p = 0.2$.

2.7.2.2. *Bogdanov–Takens bifurcations*

The purpose of this section is to study the Bogdanov–Takens bifurcations of (2.113). When $A^2 = 4m(mp+q+1)$, (2.113) admits a unique positive equilibrium (I^*, R^*) where

$$I^* = \frac{A}{2(mp+q+1)}, \quad R^* = qI^*.$$

To translate the interior equilibrium (I^*, R^*) to the origin, we set $x = I - I^*$ and $y = R - R^*$. Then (2.113) becomes

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= a_{11}x + a_{12}y + f_1(x,y), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= qx - y, \end{aligned} \tag{2.121}$$

where $f_1(x,y)$ is higher terms and

$$\begin{aligned} a_{11} &= \frac{I^*(A - 2I^* - R^* - Ap(I^*)^2 + R^*p(I^*)^2)}{(1+p(I^*)^2)^2}, \\ a_{12} &= -\frac{(I^*)^2}{1+p(I^*)^2}. \end{aligned}$$

Since we are interested in codimension 2 bifurcations, we further assume $a_{11} = 1$, which is equivalent to $q = (2mp+1)/(m-1)$ under the condition $A^2 = 4m(mp+q+1)$. Thus, we choose a point (A_0, p_0, m_0, q_0) satisfying the following assumption:

(H2) $A^2 = 4m(mp+q+1), \quad q = (2mp+1)/(m-1), \quad m > 1.$

Under assumption (H2), a straightforward calculation shows that $a_{12} = -1/q_0$, and (2.121) becomes

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= x - \frac{1}{q_0}y + a_{21}x^2 + a_{22}xy + P(x,y), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= q_0 x - y, \end{aligned} \tag{2.122}$$

where P is a smooth function in (x,y) of order at least three, and

$$\begin{aligned} a_{22} &= -\frac{(m_0-1)(m_0p_0+p_0+1)A_0}{m_0(2m_0p_0+1)^2}, \\ a_{21} &= -\frac{A_0(m_0p_0+p_0+1)(-2+m_0)}{2m_0(2m_0p_0+1)}. \end{aligned} \tag{2.123}$$

Set $X = x$ and $Y = x - y/q_0$, then (2.122) is transformed into

$$\begin{aligned} \frac{\mathrm{d}X}{\mathrm{d}t} &= Y + (a_{21} + q_0 a_{22})X^2 - a_{22} q_0 XY + \bar{P}(X, Y), \\ \frac{\mathrm{d}Y}{\mathrm{d}t} &= (a_{21} + q_0 a_{22})X^2 - a_{22} q_0 XY + \bar{P}(X, Y), \end{aligned} \tag{2.124}$$

where $\bar{P}$ is a smooth function in (X, Y) of order at least three.

To obtain the canonic normal forms, we perform the transformation of variables by

$$u = X + \frac{a_{22} q_0}{2} X^2, \quad v = Y + (a_{21} + q_0 a_{22})X^2.$$

Then, we obtain

$$\begin{aligned} \frac{\mathrm{d}u}{\mathrm{d}t} &= v + R_1(u, v), \\ \frac{\mathrm{d}v}{\mathrm{d}t} &= (a_{21} + q_0 a_{22})u^2 + (2a_{21} + q_0 a_{22})uv + R_2(u, v), \end{aligned} \tag{2.125}$$

where R_i $(i = 1, 2)$ are smooth functions in (u, v) of order at least three. It follows from (2.123) that

$$\begin{aligned} a_{21} + q_0 a_{22} &= -\frac{A_0 \, (m_0 p_0 + p_0 + 1)}{2(2m_0 p_0 + 1)} < 0, \\ 2a_{21} + q_0 a_{22} &= -\frac{(m_0 - 1)(m_0 p_0 + p_0 + 1) A_0}{m_0 (2m_0 p_0 + 1)} < 0. \end{aligned}$$

Therefore, we can state the following theorem [Ruan and Wang (2003)].

Theorem 2.43. *Suppose that* (H2) *holds. Then the equilibrium* (I^*, R^*) *of* (2.113) *is a cusp of codimension* 2; *that is, it is a Bogdanov–Takens singularity.*

In the following, we find the versal unfolding depending on the original parameters in (2.113). In this way, we know the approximate bifurcation curves. Choose A and m as bifurcation parameters. Suppose A_0, p, m_0, q satisfy (H2). Let

$$\begin{aligned} A &= A_0 + \lambda_1, \quad m = m_0 + \lambda_2, \\ I^* &= \frac{A_0}{2(m_0 p + q + 1)}, \quad R^* = q I^*. \end{aligned}$$

If $\lambda_1 = \lambda_2 = 0$, (I^*, R^*) is a degenerate equilibrium of (2.113). Substituting $x = I - I^*, y = R - R^*$ into (2.113) and using the Taylor expansion, we

obtain

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= a_0 + a_1 x - \frac{1}{q}y + a_2 x^2 + a_3 xy + W_1(x, y, \lambda),\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= qx - y,\end{aligned} \tag{2.126}$$

where $\lambda = (\lambda_1, \lambda_2)$, W_1 is a smooth function of x, y, λ of order at least three in x and y, and

$$\begin{aligned}a_0 &= -\frac{A_0(m_0-1)(2m_0(2m_0p+1)\lambda_2 - A_0(m_0-1)\lambda_1)}{4(2m_0p+1)(m_0p+p+1)m_0^2},\\ a_1 &= 1 + \frac{A_0(m_0-1)(m_0p+p+1)\lambda_1 - m_0(2\,m_0p+1)^2\lambda_2}{m_0(2m_0p+1)^2},\\ a_2 &= -\frac{\begin{array}{c}(m_0p+q+1)[2\lambda_1(-q-1+2m_0p)(m_0p+q+1)\\ +A_0(2m_0p+q+1)(q+1+2p)]\end{array}}{2(2m_0p+q+1)^3},\\ a_3 &= -\frac{A_0(m_0-1)(m_0p+p+1)}{m_0(2m_0p+1)^2}.\end{aligned}$$

Making the change of variables $X = x$ and $Y = a_0 + a_1x - y/q + a_2x^2 + a_3xy + W_1(x, y)$, and rewriting X and Y as x and y, respectively. We have

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= y,\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= a_0 + (a_1-1)x + a_4y + (a_3q+a_2)x^2\\ &\quad + a_5xy - a_3qy^2 + W_2(x, y, \lambda),\end{aligned} \tag{2.127}$$

where

$$a_4 = a_1 - 1 + qa_3a_0, \quad a_5 = 2a_2 + a_3qa_1 + a_0a_3^2q^2.$$

It is easy to see that

$$a_5 \to -\frac{A_0(m_0-1)(m_0p+p+1)}{(2m_0p+1)m_0} < 0,$$

if $\lambda_i \to 0$, $i = 1, 2$. By setting $X = x + a_4/a_5$ and rewriting X as x, we have

$$\begin{aligned}\frac{\mathrm{d}x}{\mathrm{d}t} &= y,\\ \frac{\mathrm{d}y}{\mathrm{d}t} &= b_0 + b_1x + (a_3q+a_2)x^2 + a_5xy - qa_3y^2 + W_3(x, y, \lambda),\end{aligned} \tag{2.128}$$

where $W_3(x, y, \lambda)$ is a smooth function of x, y and λ of order at least three and

$$b_0 = \frac{a_0 a_5^2 + a_5 a_4 - a_5 a_1 a_4 + q a_3 a_4^2 + a_2 a_4^2}{a_5^2},$$
$$b_1 = -\frac{a_5 - a_1 a_5 + 2 q a_3 a_4 + 2 a_2 a_4}{a_5}.$$

Now, introducing the new time τ by $\mathrm{d}t = (1 + q a_3 x)\mathrm{d}\tau$ and rewrite τ as t, we obtain

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= y(1 + q a_3 x), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= (1 + q a_3 x)(b_0 + b_1 x + (a_3 q + a_2)x^2 \\ &\quad + a_5 x y - q a_3 y^2 + W_3(x, y, \lambda)). \end{aligned} \tag{2.129}$$

Set $X = x$, $Y = y(1 + q a_3 x)$ and rename X, Y as x, y. We have

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= y, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= b_0 + c_1 x + c_2 x^2 + a_5 x y + W_4(x, y, \lambda), \end{aligned} \tag{2.130}$$

where $W_4(x, y, \lambda)$ is a smooth function of x, y and λ of order at least three, and

$$c_1 = 2 b_0 a_3 q + b_1,$$
$$c_2 = a_3^2 q^2 b_0 + 2 b_1 a_3 q + a_3 q + a_2.$$

Notice that

$$b_i \to 0, \quad (i = 0, 1)$$
$$a_5 \to -\frac{A_0(m_0 - 1)(m_0 p + p + 1)}{(2 m_0 p + 1) m_0} < 0,$$
$$c_2 \to -\frac{(m_0 p + p + 1) A_0}{2(2 m_0 p + 1)} < 0,$$

as $\lambda_i \to 0$, $i = 1, 2$.

Making the final change of variables by

$$X = a_5^2 x / c_2, \quad Y = a_5^3 y / c_2^2, \quad \tau = c_2 t / a_5$$

and denoting them again by x, y, t, respectively, we obtain

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= y, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \tau_1 + \tau_2 x + x^2 + xy + W_5(x, y, \lambda), \end{aligned} \tag{2.131}$$

where $W_5(x, y, \lambda)$ is a smooth function of x, y, and λ of order at least three, and

$$\tau_1 = \frac{b_0 a_5^4}{c_2^3}, \quad \tau_2 = \frac{c_1 a_5^2}{c_2^2}. \tag{2.132}$$

By the theorems [Bogdanov (1981a,b); Takens (1974)], the following local representations of the bifurcation curves in a small neighborhood of the origin were obtained [Ruan and Wang (2003)]:

Theorem 2.44. *Let* (H2) *hold. Then* (2.113) *has the following bifurcation properties:*

(1) *There is a saddle-node bifurcation curve* $SN = \{(\lambda_1, \lambda_2)\colon 4c_2b_0 = c_1^2\}$.
(2) *There is a Hopf bifurcation curve* $H = \{(\lambda_1, \lambda_2)\colon b_0 = 0, c_1 < 0\}$.
(3) *There is a homoclinic bifurcation curve* $HL = \{(\lambda_1, \lambda_2)\colon 25b_0c_2 + 6c_1^2 = 0 + o(\|\lambda\|)^2\}$.

Suppose $p_0 = 0.1$ and $m_0 = 2$. Then it follows from (H2) that $q_0 = 1.4$ and $A_0 = 4.5607017$. By the formulas above, the homoclinic curve is given by

$$\begin{aligned} &0.9841399516\lambda_2^2 - 2.424322230\lambda_2\lambda_1 + 1.395121027\lambda_1^2 \\ &\quad + 1.166710988\lambda_2 - 0.9501822832\lambda_1 + o(\|\lambda\|^2) = 0. \end{aligned}$$

2.8. Persistence of Epidemic Models

In the previous sections, most of results showed the global behavior of epidemic models or the ultimate states of systems. However, for some complicated epidemic models, these results, especially with respect to the endemic equilibrium, are hard to be obtained. It becomes even more difficult when parameters in models depend on time: that is, when the models are nonautonomous. For those models, some different methods are needed to analyze the properties of disease transmissions. We focus on the cases where the disease may persist in population forever in the epidemiologic sense.

Usually, we call a disease to be persistent or endemic in the population with two meanings. One is that if the fraction of infective individuals in the population is bounded away from zero. With this meaning, even

if the population goes extinct, the disease persistence means that the disease persists in the population before the population completely vanishes. Another meaning is that the number of infective individuals is bounded away from zero, which means that the size of infective individuals ultimately keeps above a certain level.

To obtain persistence for systems in ecology, epidemics, etc., some results have been obtained based on the analysis of the dynamic behavior of the system near a boundary [Thieme (1993, 2000); Freedman and Moson (1990)]. An approach in persistence theory was presented for autonomous differential systems, and the approach was illustrated for a model with the disease-induced death and exponent growth in the absence of the disease to derive conditions for both host and disease persistence [Thieme (1993)]. On the other hand, Liapunov-like functions were used to prove persistence [Fonda (1988); Margheri and Rebelo (2003); Wang and Li (2006)]. For nonautonomous systems, Thieme (2000) presented conditions for uniformly strong persistence, applied these conditions to an nonautonomous SIRS epidemic model, and obtained uniform persistence of the disease. Approaches based on analysis of the long-term average were used to investigate persistence of epidemic model [Xamxinur and Teng (2006); Teng *et al.* (2008); Ma and Ma (2006); Wang and Ma (2004); Zhang *et al.* (2008); Zhang and Teng (2007)]. Some nonautonomous epidemic models with seasonal variation were studied [Ireland *et al.* (2007); Greenhalgh and Moneim (2003); Roberts and Kao (1998); White *et al.* (1996); Williams and Dye (1997)] to obtain persistence or periodicity of the disease.

In this section, we introduce the persistence of epidemic models of autonomous and nonautonomous ordinary differential equations based on the results of Thieme (1993) and Xamxinur and Teng (2006).

2.8.1. *Persistence of epidemic models of autonomous ordinary differential equations*

Before discussing persistence of epidemic models of autonomous ordinary differential equations, we first introduce some preliminaries from Thieme (1993) which consist of persistence theory, fluctuation methods, and acyclicity methods of the boundary flow.

2.8.1.1. *Preliminaries*

Persistence theory and fluctuation methods. We consider a metric space X with metric d. Let X be the union of two disjoint subsets X_1 and

X_2, and Φ a continuous semiflow on X_1, that is, a continuous mapping $\Phi\colon [0,\infty)\times X_1 \to X_1$ with the following properties:

$$\Phi_t \circ \Phi_s = \Phi_{t+s}, \quad t,s \geq 0; \qquad \Phi_0(x) = x, \quad x \in X_1.$$

Here Φ_t denotes the mapping from X_1 to X_1 given by $\Phi_t(x) = \Phi(t,x)$. The distance $d(x,Y)$ of a point $x \in X$ from a subset Y of X is defined by

$$d(x,Y) = \inf_{y\in Y} d(x,y).$$

Let Y_2 be a subset of X_2.

Y_2 is called **a weak repeller** for X_1 if

$$\limsup_{t\to\infty} d(\Phi_t(x_1), Y_2) > 0 \quad \text{for all } x_1 \in X_1.$$

Y_2 is called **a strong repeller** for X_1 if

$$\liminf_{t\to\infty} d(\Phi_t(x_1), Y_2) > 0 \quad \text{for all } x_1 \in X_1.$$

Y_2 is called **a uniformly weak repeller** for X_1 if there exists $\varepsilon > 0$ such that

$$\limsup_{t\to\infty} d(\Phi_t(x_1), Y_2) > \varepsilon \quad \text{for all } x_1 \in X_1.$$

Y_2 is called **a uniformly strong repeller** for X_1 if there exists $\varepsilon > 0$ such that

$$\liminf_{t\to\infty} d(\Phi_t(x_1), Y_2) > \varepsilon \quad \text{for all } x_1 \in X_1.$$

In our applications, we usually choose X_1 open in X, and X_2 as the "boundary" of X. A dynamic system Φ is called (uniformly) weakly or (uniformly) strongly persistent if X_2 is a (uniformly) weak or (uniformly) strong repeller for X_1.

An approach to obtain uniformly strong persistence from persistence theory was provided by Thieme (1993).

Theorem 2.45. *Let X be a locally compact metric space with metric d. Let X be the disjoint union of two sets X_1 and X_2 such that X_2 is compact. Let Φ be a continuous semiflow on X_1. Then X_2 is a uniformly strong repeller for X_1, whenever it is a uniformly weak repeller for X_1.*

To apply Theorem 2.45, the condition that X_2 is a uniformly weak repeller for X_1 usually is proved by fluctuation methods. For a real-valued function f on $[t_0, \infty)$ we denote

$$f_\infty = \liminf_{t\to\infty} f(t), \quad f^\infty = \limsup_{t\to\infty} f(t).$$

The following fluctuation lemma can be found [Hirsch *et al.* (1985)].

Lemma 2.7. *Let f: $[t_0, \infty) \to R$ be a differentiable function that has no limit for $t \to \infty$. Then there are sequences s_n, $t_n \to \infty$ with the following properties*:

$$f(s_n) \to f_\infty, \quad f'(s_n) = 0,$$
$$f(t_n) \to f^\infty, \quad f'(t_n) = 0$$

for $n \to \infty$. If f is twice continuously differentiable, we have, in addition, that

$$f''(s_n) \geq 0, \quad f''(t_n) \leq 0, \ n \in N.$$

This statement is quite intuitive. If f has no limit for $t \to \infty$, it has to oscillate between f_∞ and f^∞. So we can choose appropriate sequences of local minima $f(s_n)$ and local maxima $f(t_n)$ that have the desired properties. Furthermore, the following lemma can be obtained [Thieme (1993)].

Lemma 2.8. *Let f: $(t_0, \infty) \to R$ be bounded and continuously differentiable. Then there are sequences s_n, $t_n \to \infty$ with the following properties*:

$$f(s_n) \to f_\infty, \quad f'(s_n) \to 0,$$
$$f(t_n) \to f^\infty, \quad f'(t_n) \to 0$$

as $n \to \infty$.

The following theorem can be obtained based on Lemma 2.8 [Thieme (1993)].

Theorem 2.46. *Let D be a bounded interval in R and g: $(t_0, \infty) \times D \to R$ be bounded and uniformly continuous. Further, let x: $(t_0, \infty) \to D$ be a solution of*

$$x' = g(t, x),$$

which is defined on the whole interval (t_0, ∞). *Then there exist sequences* $s_n, t_n \to \infty$ *such that*

$$\lim_{n\to\infty} g(s_n, x_\infty) = 0 = \lim_{n\to\infty} g(t_n, x^\infty).$$

To establish the uniformly weak repeller relation we will mainly use the following version [Thieme (1993)].

Corollary 2.2. *Let the assumptions of Theorem* 2.46 *hold. Then*

(a) $\liminf_{t\to\infty} g(t, x_\infty) \le 0 \le \limsup_{t\to\infty} g(t, x_\infty)$,
(b) $\liminf_{t\to\infty} g(t, x^\infty) \le 0 \le \limsup_{t\to\infty} g(t, x^\infty)$.

Acyclicity methods of the boundary flow. Since we cannot always obtain sharp conditions for uniformly weak persistence by the fluctuation method, then we adapt another approach given by Butler and Waltman (1986), Butler *et al.* (1986), and Hale and Waltman (1989) for showing (uniformly) strong persistence.

Again we consider a continuous semiflow Φ on a metric space X, with X being the disjoint union of two sets X_1 and X_2, where X_1 is open.

We define

$$\Omega = \bigcup_{y\in Y} \omega(y), \quad Y = \{x \in X_2 \colon \Phi_t(x) \in X_2, \forall\, t > 0\},$$

where $\omega(y)$ represents the ω-limit set of a point y is given by

$$\omega(y) = \bigcap_{t\ge 0} \overline{\Phi([t, \infty) \times \{y\})}.$$

It is easy to see that Ω has compact closure and is invariant. A finite covering $M = \bigcup_{k=1}^m M_k$ in X_2 is called isolated if the sets M_k are pairwise disjoint subsets of X_2, which are isolated compact invariant sets in X [Hale and Waltman (1989)].

A set $M \subset X_2$ is said to be **chained** (in X_2) to another (not necessarily different) set $N \subset X_2$, denoted by $M \mapsto N$, if there is $y \in X_2$, $y \notin M \cup N$, and a full orbit through y in X_2 whose α-limit set is contained in M, and ω-limit set is contained in N.

A finite covering $M = \bigcup_{k=1}^m M_k$ is called **cyclic** if, after possible renumbering, $M_1 \mapsto M_1$ or $M_1 \mapsto M_2 \mapsto M_3 \mapsto \cdots \mapsto M_k \mapsto M_1$, for some $k \in \{2, 3, \ldots, m\}$. M is called an acyclic covering otherwise.

Notice that Y and hence Ω may be empty if all orbits starting from X_2 leave X_2 and never return. Then Ω has an acyclic covering. In many applications, however, X_2 is forward invariant such that $Y = X_2$.

The following theorem by Thieme (1993) provides an approach to obtain uniformly strong persistence from an acyclicity consideration.

Theorem 2.47. *Let X be locally compact, and let X_2 be compact in X, and X_1 be forward invariant under the continuous semiflow Φ on X. Assume that Ω has an acyclic isolated covering $M = \bigcup_{k=1}^{m} M_k$. If each part M_k of M is a weak repeller for X_1, then X_2 is a uniformly strong repeller for X_1.*

2.8.1.2. *Applications*

The SIRS epidemic model with general contact rate

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= bN - \mu S - C(N)\frac{IS}{N} + \rho R, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= C(N)\frac{IS}{N} - (\mu + \gamma + \alpha)I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I - (\mu + \rho)R, \\ N &= S + I + R, \end{aligned} \tag{2.133}$$

was discussed by Thieme (1993). Here, $b > \mu$ is assumed, which implies that the population size increases exponentially in the absence of the disease. The general effective contact rate $C(N)$ satisfies the following conditions: (a) $C(N)$ is positive and continuously differentiable in $N > 0$; (b) $C(N)$ is monotone nondecreasing in N.

Let

$$x = \frac{S}{N}, \quad y = \frac{I}{N}, \quad z = \frac{R}{N}. \tag{2.134}$$

Then x, y, and z denote the fractions of the susceptible, infective, and recovered individuals in the population, respectively, and $x + y + z = 1$. Then, model (2.133) becomes

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= b(1 - x) - (C(N) - \alpha)xy + \rho z, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= C(N)xy - (\gamma + \alpha + b)y + \alpha y^2, \end{aligned}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = \gamma y - (b+\rho)z + \alpha yz,$$
$$\frac{\mathrm{d}N}{\mathrm{d}t} = (b-\mu-\alpha y)N. \tag{2.135}$$

Applications of persistence theory and fluctuation methods. The uniformly weak persistence of the disease in model (2.135) can be obtained by applying fluctuation methods as follows [Thieme (1993)]:

Theorem 2.48. *Let $\alpha + b + \gamma < C(\infty)$. Then the disease is uniformly weakly persistent.*

Proof. Suppose that the disease is not uniformly weakly persistent. Then the inequality

$$y^\infty < \frac{b-\mu}{\alpha}$$

holds. It follows from the equation for N in (2.135) that

$$\liminf_{t\to\infty} \frac{1}{N}\frac{\mathrm{d}N}{\mathrm{d}t} > 0.$$

This implies that $N(t) \to \infty$ as $t \to \infty$, so that $\lim_{t\to\infty} C(N(t)) = C(\infty)$. Applying Corollary 2.2(b) to the z equation in (2.135) yields

$$0 \le \gamma y^\infty - (b+\rho)z^\infty + \alpha y^\infty,$$

where $z \le 1$ is used, so that

$$z^\infty \le \frac{\gamma+\alpha}{b+\rho} y^\infty.$$

Substituting $x = 1 - y - z$ into the y equation in (2.135) gives

$$\frac{\mathrm{d}y}{\mathrm{d}t} = C(N)(1-y-z)y - (\gamma+\alpha+b)y + \alpha y^2.$$

Thus

$$\liminf_{t\to\infty} \frac{1}{y}\frac{\mathrm{d}y}{\mathrm{d}t} \ge C(\infty)\left(1 - \frac{b+\rho+\gamma+\alpha}{b+\rho} y^\infty\right) - (b+\alpha+\gamma).$$

If

$$y^\infty < \frac{b+\rho}{b+\rho+\gamma+\alpha}\left(1 - \frac{b+\alpha+\gamma}{C(\infty)}\right),$$

we have

$$\liminf_{t\to\infty} \frac{1}{y}\frac{\mathrm{d}y}{\mathrm{d}t} > 0,$$

which implies that $y(t) \to \infty$ as $t \to \infty$. It contradicts $y \leq 1$. Hence, the disease is uniformly weakly persistent. □

Theorem 2.48 does not implies that the disease is uniformly strongly persistent since compactness of the repeller in Theorem 2.45 is not satisfied. In the following, the condition $C(\infty) < \infty$ is needed to obtain the uniformly strong persistence of the disease [Thieme (1993)].

Theorem 2.49. *Let* $\alpha + b + \gamma < C(\infty) < \infty$ *and* $y(0) > 0$. *Then the disease is uniformly strongly persistent*; *this is*, *there is* $\varepsilon > 0$, *independent of the initial data*, *such that*

$$\liminf_{t\to\infty} y(t) \geq \varepsilon > 0.$$

Proof. Since we cannot exclude that $N(t)$ is unbounded for the set $X = \{(x, y, z, N)\colon 0 \leq N \leq \infty, x, y, z \geq 0, x + y + z = 1\}$, we make X a metric space with

$$\begin{aligned} &d((x_1, y_1, z_1, N_1), (x_2, y_2, z_2, N_2)) \\ &\quad = |x_1 - x_2| + |y_1 - y_2| + |z_1 - z_2| + |\varphi(N_1) - \varphi(N_2)|, \end{aligned}$$

where

$$\varphi(N) = \begin{cases} \dfrac{N}{1+N}, & 0 \leq N < \infty, \\ 1, & N = \infty. \end{cases}$$

If $N_0 < \infty$, the semiflow $\Phi_t(x_0, y_0, z_0, N_0)$ is defined to be the solution of (2.135) at time t, for initial data (x_0, y_0, z_0, N_0). If $N_0 = \infty$, then $\Phi_t(x_0, y_0, z_0, \infty) = (x(t), y(t), z(t), \infty)$ with x, y, z being the solutions of the x, y, z equations in (2.135), and $C(N)$ replaced by $C(\infty)$. It is easy to see that Φ is a continuous semiflow. Our metric makes X a compact space.

We first show that y is bounded away from zero; that is, $X_2 = \{(x, 0, z, N)\colon 0 \leq N \leq \infty, x, z \geq 0, y = 0, x + z = 1\}$ is a uniformly strong repeller for $X_1 = \{(x, y, z, N)\colon 0 \leq N \leq \infty, x, z \geq 0, y > 0, x + y + z = 1\}$. Notice that both X_1 and X_2 are forward invariant.

Since Theorem 2.48 implies that X_2 is a uniformly weak repeller for X_1, then X_2 is a uniformly strong repeller for X_1 by Theorem 2.45.

Notice that $d((x,y,z,N),X_2) = y$. Hence y is bounded away from zero, with the bound being independent of the initial data. This completes the proof. □

Application of the acyclicity method. We first define the metric space X in the same way as in Theorem 2.49. We then apply Theorem 2.47 to show that the set $X_2 = \{(x,y,z,N)\colon x,y,z,N \geq 0, x+y+z=1, N=\infty, \text{or } y=0\}$ is a uniformly strong repeller for the set $X_1 = \{(x,y,z,N)\colon 0 \leq N < \infty, x,z \geq 0, y > 0, x+y+z=1\}$. To this end, we analyze the flow on the forward invariant set X_2, that is, $N=\infty$, and

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= b(1-x) - (C(\infty)-\alpha)xy + \rho z, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= C(\infty)xy - (\gamma+\alpha+b)y + \alpha y^2, \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= \gamma y - (b+\rho)z + \alpha yz, \\ x+y+z &= 1. \end{aligned} \tag{2.136}$$

This is a special case of the model studied by Busenberg and van den Driessche (1990) and Busenberg and Hadeler (1990), and the following results have been obtained [Thieme (1993)].

Theorem 2.50. *For* (2.136), *the following conclusions hold*:

(a) *When* $C(\infty) \leq b+\alpha+\gamma$, $\lim_{t\to\infty} y(t) = \lim_{t\to\infty} z(t) = 0$ *and* $\lim_{t\to\infty} x(t) = 1$.

(b) *When* $C(\infty) > b+\alpha+\gamma$, *there exists a unique endemic equilibrium* $E^*(x^*,y^*,z^*)$ *with* $x^*,y^*,z^* > 0$. *Furthermore, for any solution to* (2.136), *satisfying* $x(0) \geq 0, y(0) > 0, z(0) \geq 0$, *and* $x(0)+y(0)+z(0) = 1$, *it holds that* $\lim_{t\to\infty} x(t) = x^*$, $\lim_{t\to\infty} y(t) = y^*$ *and* $\lim_{t\to\infty} z(t) = z^*$. *However, for any solution to* (2.136), *satisfying* $x(0) \geq 0$, $y(0) = 0$, $z(0) \geq 0$, *and* $x(0)+z(0) = 1$, *it holds that* $\lim_{t\to\infty} x(t) = 1$, $\lim_{t\to\infty} y(t) = 0$ *and* $\lim_{t\to\infty} z(t) = 0$.

Since the disease can limit the host population only if it becomes endemic by the N equation in (2.135), then we assume $C(\infty) > b+\alpha+\gamma$. The following theorem [Thieme (1993)] shows the limits of host and persistence of disease.

Theorem 2.51. *Let* $N(0) > 0$, $y(0) > 0$ *and*

$$\frac{\gamma + \alpha + \mu}{C(\infty)} < 1 - \frac{b - \mu}{\alpha}\left(1 + \frac{\gamma}{\mu + \rho}\right).$$

Then

$$\limsup_{t\to\infty} N(t) \le c < \infty, \quad \liminf_{t\to\infty} y(t) \ge \varepsilon > 0,$$

where c *and* ε *are independent of the initial data.*

Proof. Notice that the condition

$$\frac{\gamma + \alpha + \mu}{C(\infty)} < 1 - \frac{b - \mu}{\alpha}\left(1 + \frac{\gamma}{\mu + \rho}\right)$$

implies that $C(\infty) > b + \gamma + \alpha$ as $b > \mu$. Hence, Theorem 2.50(b) holds under this condition.

For this case, $\Omega = \bigcup_{\bar{y}\in X_2} \omega(\bar{y})$ consists of two equilibria, the disease-free equilibrium, $N = \infty$, $x = 1$, $y = z = 0$, and the endemic equilibrium, $N = \infty$, $x = x^*$, $y = y^*$, $z = z^*$. Apparently the disease-free and the endemic equilibria cannot be chained to themselves or to each other in X_2. So we only need to show that each of these two equilibria are isolated for the semiflow in X and that the two equilibria do not attract orbits that start in X_1.

For the disease-free equilibrium, it follows from Theorem 2.50 and from Theorem 2.49, which shows that y remains bounded away from zero if $y(0) > 0$ with the bound being independent of $y(0)$.

When the endemic equilibrium exists, that the disease can limit the host population needs for the endemic equilibrium to satisfy $y^* > (b - \mu)/\alpha$ from the last equation in (2.135). Again, y^* and z^* need to satisfy equations:

$$C(\infty)(1 - y - z) - (\gamma + \alpha + b) + \alpha y = 0$$

and

$$\gamma y - (\beta + \rho)z + \alpha y z = 0.$$

These requirements can be satisfied under the condition of Theorem 2.51. This implies that the endemic equilibrium cannot attract orbits starting in X_2. Therefore, Theorem 2.51 holds. □

2.8.2. *Persistence of epidemic models of nonautonomous ordinary differential system*

A total population with size N is divided into three subpopulations: the susceptible (S), the infective (I), and the recovered (R) [Thieme (2000)], and proposed the following nonautonomous SIRS epidemic model:

$$\begin{aligned} N &= S + I + R, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta(t)IS - \mu(t)I - \gamma(t)I, \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma(t)I - \mu(t)R - \xi(t)R, \end{aligned} \tag{2.137}$$

where the population size $N(t)$ is a given function of time t, $\beta(t)$ is the instantaneous transmission rate coefficient of infection, $\mu(t)$ is the instantaneous natural mortality rate per capita, and $\gamma(t)$ and $\xi(t)$ are the instantaneous rates of leaving the infective stage and removed stage per capita, respectively.

Substituting $S = N - I - R$ into the first equation in model (2.137) gives

$$\begin{aligned} \frac{\mathrm{d}I}{\mathrm{d}t} &= I[b(t) - \beta(t)I - \beta(t)R], \\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma(t)I - \delta(t)R, \end{aligned} \tag{2.138}$$

where $b(t) = \beta(t)N(t) - \mu(t) - \gamma(t)$ and $\delta(t) = \mu(t) + \xi(t)$.

Under assumptions that N, μ, β, γ, and ξ are arbitrary nonnegative, continuous, bounded functions on $[0, \infty)$ and that μ is bounded away from 0, Thieme (2000) derived conditions for extinction and persistence of the disease by applying persistence theory for nonautonomous theory, and an almost sharp threshold result was obtained in the case where N, μ, α, and γ are almost periodic.

Xamxinur and Teng (2006) analyzed the persistence and extinction for (2.138) by using a different method. Teng *et al.* (2008) added the disease-induced death into (2.138) and obtained conditions on the persistence and the extinction of the disease. Ma and Ma (2006) considered seasonally forced SEIR epidemic models and obtained threshold conditions for eradication of diseases.

The persistence of the disease for (2.138) is studied [Teng *et al.* (2008)] based on the results by Xamxinur and Teng (2006).

Theorem 2.52. *The disease is uniformly strongly persistent if* $I(0) > 0$ *and there is a constant* $\omega > 0$ *such that*

$$\begin{aligned} &\liminf_{t\to\infty} \int_t^{t+\omega} b(s)\mathrm{d}s > 0, \\ &\liminf_{t\to\infty} \int_t^{t+\omega} \beta(s)\mathrm{d}s > 0, \\ &\liminf_{t\to\infty} \int_t^{t+\omega} \delta(s)\mathrm{d}s > 0. \end{aligned} \tag{2.139}$$

Proof. For (2.138), it is easy to see that a solution $(I(t), R(t))$ with the initial value $(I(0), R(0)) \in R_+^2$ is nonnegative and ultimately bounded on $[0, \infty)$; that is, there is a positive constant M such that $0 \le I(t) \le M$ and $0 \le R(t) \le M$.

Notice the boundedness of the coefficients in (2.137). For (2.139) we can choose a set of positive constants $\varepsilon, \varepsilon_0$ and $\varepsilon_1 (\varepsilon_0 > \varepsilon_1)$ small enough and a constant $T_0 > 0$ large enough such that

$$\int_t^{t+\omega} \{b(s) - \beta(s)\varepsilon_1 - \beta(s)\varepsilon_0[1 + (\bar{\gamma} + \bar{\delta})\omega]\}\mathrm{d}s > \varepsilon, \tag{2.140}$$

and

$$\int_t^{t+\omega} [\gamma(s)\varepsilon_1 - \delta(s)\varepsilon_0]\mathrm{d}s < -\varepsilon, \tag{2.141}$$

for all $t \ge T_0$, where $\bar{\gamma} = \sup_{t\ge 0} \gamma(t)$ and $\bar{\delta} = \sup_{t\ge 0} \delta(t)$.

Let $(I(t), R(t))$ be any nonnegative solution of system (2.138) with initial value $I(0) > 0$ and $R(0) \ge 0$. Firstly, we prove that

$$\limsup_{t\to\infty} I(t) \ge \varepsilon_1. \tag{2.142}$$

Suppose that (2.142) is not true. Then there exists $T_1 \ge T_0$ such that $I(t) < \varepsilon_1$ for all $t > T_1$. If $R(t) \ge \varepsilon_0$ for all $t \ge T_1$, then from the second equation of system (2.138), we have, for all $t \ge T_1$

$$\begin{aligned} R(t) - R(T_1) &= \int_{T_1}^t [\gamma(s)I(s) - \delta(s)R(s)]\mathrm{d}s \\ &\le \int_{T_1}^t [\gamma(s)\varepsilon_1 - \delta(s)\varepsilon_0]\mathrm{d}s. \end{aligned}$$

From (2.141), it follows that $\lim_{t\to\infty} R(t) = -\infty$, a contradiction. Hence, there is a $t_1 > T_1$ such that $R(t_1) < \varepsilon_0$. We claim that, for all $t > t_1$

$$R(t) \le \varepsilon_0[1 + (\bar{\gamma} + \bar{\delta})\omega]. \tag{2.143}$$

In fact, if (2.143) is not true, then there is $t_2 > t_1$ such that $R(t_2) > \varepsilon_0[1 + (\bar{\gamma} + \bar{\delta})\omega]$. Hence, there must be $t_3 \in (t_1, t_2)$ such that $R(t_3) = \varepsilon_0$ and $R(t) > \varepsilon_0$, for all $t \in (t_3, t_2)$. Choose an integer $p \ge 0$ such that $t_2 \in (t_3 + p\omega, t_3 + (p+1)\omega]$. Integrating the second equation of system (2.138) from t_3 to t_2, from (2.141) we obtain

$$\begin{aligned}
\varepsilon_0[1 + (\bar{\gamma} + \bar{\delta})\omega] &< R(t_2) \\
&= R(t_3) + \int_{t_3}^{t_2} [\gamma(s)I(s) - \delta(s)R(s)]\mathrm{d}s \\
&\le \varepsilon_0 + \int_{t_3+p\omega}^{t_2} [\gamma(s)\varepsilon_1 - \delta(s)\varepsilon_0]\mathrm{d}s \\
&\le \varepsilon_0[1 + (\bar{\gamma} + \bar{\delta})\omega],
\end{aligned}$$

where $\varepsilon_0 > \varepsilon_1$ is used. This is a contradiction. Hence, inequality (2.143) holds. Since we have

$$I(t) \ge I(t_1) \exp \int_{t_1}^{t} \{b(s) - \beta(s)\varepsilon_1 - \beta(s)\varepsilon_0[1 + (\bar{\gamma} + \bar{\delta})\omega]\}\mathrm{d}s,$$

for all $t \ge t_1$, it follows from (2.140) that $\lim_{t\to\infty} I(t) = \infty$. This is a contradiction to $I(t) < \varepsilon_1$ for all $t \ge T_1$. Hence the conclusion $\limsup_{t\to\infty} I(t) \ge \varepsilon_1$ holds.

Second, we prove that there is a constant $\eta > 0$, independent of any nonnegative solution $(I(t), R(t))$ of system (2.138), such that

$$\liminf_{t\to\infty} I(t) > \eta. \tag{2.144}$$

In fact, from (2.140) and (2.141) we obtain that there is a positive constant τ such that

$$\int_{t}^{t+\nu} \{b(s) - \beta(s)\varepsilon_1 - \beta(s)\varepsilon_0[1 + (\bar{\gamma} + \bar{\delta})\omega]\}\mathrm{d}s > \varepsilon, \tag{2.145}$$

and

$$\int_{t}^{t+\nu} [\gamma(s)\varepsilon_1 - \delta(s)\varepsilon_0]\mathrm{d}s < -M, \tag{2.146}$$

for all $t \geq T_0$ and $\nu > \tau$. If (2.144) is not true, then there is a sequence of initial values $X_n = (I_n, R_n)$ with $I_n > 0$ and $R_n \geq 0$ $(n = 1, 2, \ldots)$ such that

$$\liminf_{t\to\infty} I(t, X_n) < \frac{\varepsilon_1}{n^2}, \quad n = 1, 2, \ldots.$$

From inequality (2.142), for every n there are two time sequences $\{t_k^{(n)}\}$ and $\{s_k^{(n)}\}$, satisfying

$$T_0 < s_1^{(n)} < t_1^{(n)} < s_2^{(n)} < t_2^{(n)} \cdots < s_k^{(n)} < t_k^{(n)} < \cdots$$

and $\lim_{k\to\infty} s_k^{(n)} = \lim_{k\to\infty} t_k^{(n)} = \infty$, such that

$$I(s_k^{(n)}, X_n) = \frac{\varepsilon_1}{n}, \quad I(t_k^{(n)}, X_n) = \frac{\varepsilon_1}{n^2} \tag{2.147}$$

and

$$\frac{\varepsilon_1}{n^2} < I(t, X_n) < \frac{\varepsilon_1}{n} \quad \text{for all } t \in (s_k^{(n)}, t_k^{(n)}). \tag{2.148}$$

From the ultimate boundedness of solutions of system (2.138), we can choose a positive integer $K^{(n)}$ for each n such that

$$I(t, X_n) < M, \quad R(t, X_n) < M, \ \ n = 1, 2, \ldots$$

for all $k > K^{(n)}$ and $t \in (s_k^{(n)}, t_k^{(n)})$. Let $k > K^{(n)}$, then for any $t \in (s_k^{(n)}, t_k^{(n)})$ we have

$$\begin{aligned}\frac{\mathrm{d}I(t, X_n)}{\mathrm{d}t} &= I(t, X_n)[b(t) - \beta(t)I(t, X_n) - \beta(t)R(t, X_n)] \\ &\geq I(t, X_n)[b(t) - \beta(t)M - \beta(t)M] \\ &\geq -\eta_0 I(t, X_n),\end{aligned}$$

where $\eta_0 = \sup_{t\geq 0}\{|b(t)| + \beta(t)M + \beta(t)M\} > 0$. Integrating the above inequality from $s_k^{(n)}$ to $t_k^{(n)}$ yields

$$I(t_k^{(n)}, X_n) \geq I(s_k^{(n)}, X_n) \exp[-\eta_0(t_k^{(n)} - s_k^{(n)})].$$

Consequently, it follows from (2.147) that

$$\frac{\varepsilon_1}{n^2} \geq \frac{\varepsilon_1}{n} \exp[-\eta_0(t_k^{(n)} - s_k^{(n)})],$$

and then

$$t_k^{(n)} - s_k^{(n)} \geq \frac{\ln n}{\eta_0} \to \infty \quad \text{as } n \to \infty,\ k > K^{(n)}.$$

Thus, we can choose a sufficiently large positive integer N such that $t_k^{(n)} - s_k^{(n)} > 2\tau$ for all $n \geq N$ and $k > K^{(n)}$.

If $R(t, X_n) \geq \varepsilon_0$ for all $t \in (s_k^{(n)}, s_k^{(n)} + \tau)$, then integrating the second equation of system (2.138) yields, from (2.146),

$$\begin{aligned} R(s_k^{(n)} + \tau, X_n) &= R(s_k^{(n)}, X_n) + \int_{s_k^{(n)}}^{s_k^{(n)}+p} [\gamma(t) I(t, X_n) - \delta(t) R(t, X_n)] \mathrm{d}t \\ &\leq M + \int_{s_k^{(n)}}^{s_k^{(n)}+\tau} [\gamma(t)\varepsilon_1 - \delta(t)\varepsilon_0] \mathrm{d}t < 0. \end{aligned}$$

This is a contradiction. Hence, there must be $t_1 \in (s_k^{(n)}, s_k^{(n)} + p)$ such that $R(t_1, X_n) < \varepsilon_0$. Using a similar argument for (2.143), we obtain

$$R(t, X_n) \leq \varepsilon_0 [1 + (\bar{\gamma} + \bar{\delta})\omega] \tag{2.149}$$

for all $t \geq t_1$. Integrating the first equation of system (2.138) from t_1 to $t_k^{(n)}$, from (2.145), (2.147), (2.148), and (2.149), we have

$$\begin{aligned} \frac{\varepsilon_1}{n^2} &= I(t_k^{(n)}, X_n) \\ &= I(t_1, X_n) \exp \int_{t_1}^{t_k^{(n)}} [b(t) - \beta(t) I(t, X_n) - \beta(t) R(t, X_n)] \mathrm{d}t \\ &\geq \frac{\varepsilon_1}{n^2} \exp \int_{t_1}^{t_k^{(n)}} [b(t) - \beta(t)\varepsilon_1 - \beta(t)\varepsilon_0(1 + (\bar{\gamma} + \bar{\delta})\omega)] \mathrm{d}t > \frac{\varepsilon_1}{n^2}. \end{aligned}$$

This is again a contradiction. Therefore, inequality (2.144) holds. □

Chapter 3

Modeling of Epidemics with Delays and Spatial Heterogeneity

Wendi Wang

In this chapter we shall present methodology to simulate the evolution of epidemics that incorporate the ingredients of delays or spatial heterogeneity, and introduce basic techniques to analyze the mathematical models.

3.1. Model Formulations

In this section, we will illustrate approaches to establish mathematical models incorporating delays or spatial heterogeneity. We always adopt the following nomenclature in this chapter:

t: time;
N: population density or population size;
S: the number or density of susceptible individuals;
E: the number or density of exposed individuals;
I: the number or density of infectious individuals;
R: the number or density of recovered individuals.

3.1.1. *Models incorporating delays*

For many infectious diseases, it is important to consider influences of delays that represent incubation period, infection period, or immune-keeping period. This is because not only the lengthes of delays may be long, for example, the incubation time for HIV could reach 10 years, but also quite different dynamic behaviors of mathematical models can be induced by time

delays. Here, we will give several typical examples to show how to introduce time delays into epidemic models.

We begin from the model proposed by Kermack and McKendrick (1927) for an SIR type of disease:

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta S(t)I(t),\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - \gamma I(t),\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t),\end{aligned} \tag{3.1}$$

where β is the valid contact coefficient and γ is the recovery rate. In (3.1), it is assumed that there is neither birth nor death in the process of epidemic development. If an incubation period of the disease, denoted by τ, is to be considered, since there is no mortality, the new infection rate at time t is $\beta S(t-\tau)I(t-\tau)$. Thus, we can modify (3.1) into

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta S(t)I(t),\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t-\tau)I(t-\tau) - \gamma I(t),\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t).\end{aligned} \tag{3.2}$$

Similarly, the following model proposed by Cooke and Yorke (1973) for gonorrhea epidemics incorporates the fixed infection period τ of the disease:

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta S(t)I(t) + \beta S(t-\tau)I(t-\tau),\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - \beta S(t-\tau)I(t-\tau).\end{aligned} \tag{3.3}$$

It was proposed by Hethcote *et al.* (1981) that an $SIRS$ model includes a constant period τ of temporary immunity:

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta S(t)I(t) + \gamma I(t-\tau),\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - \gamma I(t),\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - \gamma I(t-\tau).\end{aligned} \tag{3.4}$$

In the introduction of delays in above examples, since there is no death, the coefficients of the models are constants, independent of delays. If mortality of individuals must be considered, which is the case when an epidemic disease persists in a long time or disease-induced death is significant, we will have delay-dependent coefficients. For illustration purpose, let us assume that the demographic structure of a population in the absence of disease takes the form:

$$\frac{\mathrm{d}N}{\mathrm{d}t} = A - \mu N, \tag{3.5}$$

where A is the recruitment rate of the population and μ is the per capita death rate. If disease transmissions are horizontal, with the introduction of the above vital dynamics, (3.2) can be modified into

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mu S(t) - \beta S(t)I(t),\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta \mathrm{e}^{-\mu\tau} S(t-\tau)I(t-\tau) - \mu I(t) - \gamma I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - \mu R(t).
\end{aligned} \tag{3.6}$$

Here, $\mathrm{e}^{-\mu\tau}$ gives the survival probability of individuals that pass through the incubation stage. Similarly, with the demographic structure (3.5) and the disease-induced death-rate ϵ, (3.3) and (3.4) can be modified, respectively, into

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mathrm{d}S(t) - \beta S(t)I(t) + \beta \mathrm{e}^{-(d+\epsilon)\tau} S(t-\tau)I(t-\tau),\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - \beta \mathrm{e}^{-(d+\epsilon)\tau} S(t-\tau)I(t-\tau) - (d+\epsilon)I(t),
\end{aligned} \tag{3.7}$$

and

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - \mathrm{d}S(t) - \beta S(t)I(t) + \gamma \mathrm{e}^{-\mathrm{d}\tau} I(t-\tau),\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - (d+\epsilon+\gamma)I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - \gamma \mathrm{e}^{-\mathrm{d}\tau} I(t-\tau) - \mathrm{d}R(t).
\end{aligned} \tag{3.8}$$

Note that (3.6)–(3.8) exhibit delay-dependent coefficients. The stability analysis of such models is different from those with delay-independent coefficients.

Delays appeared in the above models are discrete, which are suitable when the periods they represent are around fixed values. In many cases, it seems more appropriate to use distributed delays. We present an SIS model, proposed by Hethcote and van den Driessche (2000), to show basic approaches to introduce distributed delays. We consider only influences of infection period. Let $P(t)$ be the fraction of infectives remaining in the infective class t time units after becoming infected. Generally, $P(t)$ is assumed to be nonnegative, nonincreasing, and piecewise continuous with $P(0) = 1$. With the transfer diagram given in Fig. 3.1, we have

$$\begin{aligned} I(t) &= I_0(t) + \int_0^t \lambda \left[(N(u) - I(u)) \frac{I(u)}{N(u)} \right] P(t-u) \mathrm{e}^{-(d+\epsilon)(t-u)} \mathrm{d}u, \\ \frac{\mathrm{d}N}{\mathrm{d}t} &= A - \mathrm{d}N(t) - \epsilon I(t), \end{aligned} \tag{3.9}$$

where $I_0(t)$ is the number of infectives who were in the infectious class at time 0 and are still infectious at time t, the integral is the summation up to time t of those who became infected at time u and have neither recovered back to the susceptible class nor died from natural or disease-related causes in the time interval $[u, t]$. The function $I_0(t)$ is a nonnegative, nonincreasing, piecewise continuous function. Here $S = N - I$ is used.

For vector-borne diseases Beretta and Takeuchi (1995) introduced distributed delays to describe infection forces from infectious vectors. It is assumed that when a susceptible vector is infected by a person, there is a time τ during which the infectious agents develop in the vector and it is only after that time that the infected vector itself becomes infectious. It is also assumed that the vector population is very large and at any time t the infectious vector population is simply proportional to the infectious human

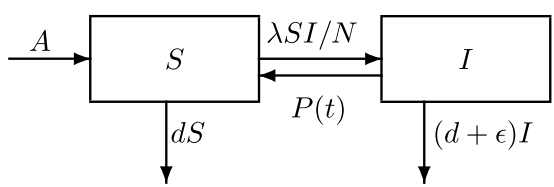


Fig. 3.1. Transfer diagram.

population at time $t-\tau$. Let $f(\tau)$ be the fraction of vector population that takes time τ to become infectious. Then the incidence is

$$\beta S(t)\int_0^{+\infty} f(\tau)I(t-\tau)\mathrm{d}\tau$$

and the model is:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu - \mu S(t) - \beta S(t)\int_0^{\infty} f(s)I(t-s)\mathrm{d}s,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)\int_0^{\infty} f(s)I(t-s)\mathrm{d}s - (\mu+\lambda)I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \lambda I(t) - \mu R(t),
\end{aligned} \tag{3.10}$$

where μ is the birth rate and death rate of human population, and λ is the recovery rate.

3.1.2. *Patchy models*

Population mobility and spatial structure play important roles in the spread of a disease. Some epidemic diseases have occurred in some regions frequently and were transmitted to other regions due to population dispersal. This has been demonstrated by many communicable diseases. SARS was first reported in Guangdong Province of China in November 2002. The emerging disease spread very quickly, due to the traveling of infectious persons by airplanes, trains, or buses, to some other regions in the mainland of China, as well as Hong Kong, Singapore, Vietnam, and Canada. By late June 2003, it had spread to 32 countries and regions causing about 800 deaths and more than 8000 infections (see, for example [Ruan *et al.* (2006); Wang and Ruan (2004a); Zhang *et al.* (2005); Zhou *et al.* (2004)]. For measles, Bartlett (1957) discovered that population size was a crucial determinant of disease persistence. In large towns, measles was endemic with periodic eruptions. In cities below a population size threshold, measles displayed an epidemic pattern with complete disappearance of the disease between epidemics. These show that spatial structures and population movements, which give rise to spatio-temporal variations of population dynamics, may be of crucial importance for the prevalence of diseases. Thus, it is important to study how population movement, spatial structure, and disease transmission interact to determine the evolution of diseases. Basically, there are two ways for this purpose. First, we can introduce space

variables and use reaction diffusion equations (see [Murray (1998); Britton (2003)], and the references cited therein). One of the major limitations of diffusion models is the assumption of the movements of individuals among direct neighborhoods. In nature, many populations live in the form of communities and can move or can be transferred over large distances. For example, the human population lives in cities, and can move into other countries in a short time due to modern transportation tools. Thus, it is reasonable to adopt, as an alternative, patch models, in epidemiology. Here, one patch may represent a city or a biological habitat, and population movements in space are simulated by population dispersals among patches.

Now, we illustrate the basic procedures to simulate epidemic propagations with spatial heterogeneity [Wang and Zhao (2004)]. We consider n patches. To accommodate more epidemic diseases that have longer time scales, we consider the demography of populations and suppose that the demographic structure of the population in patch i is described by

$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = B_i(N_i(t))N_i(t) - \mu_i N_i(t),$$

where B_i is the per capita birth rate, μ_i the per capita death rate. We assume that $B_i(N_i)$ satisfy the following basic assumptions for $N_i \in (0, \infty)$:

(A1) $B_i(N_i) > 0$, $i = 1, 2, \ldots, n$.
(A2) $B_i'(N_i)$ is continuous and $B_i'(N_i) < 0, i = 1, 2, \ldots, n$.
(A3) $\mu_i > B_i(\infty)$, $i = 1, 2, \ldots, n$.

Assumption (A1) means that the per capita birth rate is positive, (A2) indicates that it is a decreasing function of population density, and (A3) implies that the net growth rate of the population is negative when population density is large, which prevents an unbounded population size. From Cooke *et al.* (1999), the following birth functions B_i can be chosen:

(B1) $B_i(N_i) = b_i \mathrm{e}^{-a_i N_i}$ with $a_i > 0, b_i > 0$.
(B2) $B_i(N_i) = p_i/(q_i + N_i^m)$ with $p_i, q_i, m > 0$.
(B3) $B_i(N_i) = A_i/N_i + c_i$ with $A_i > 0, c_i > 0$.

Assumption (B1) means that the birth process obeys Ricker's law, (B2) indicates that the birth process is of Beverton–Holt type, and in the type

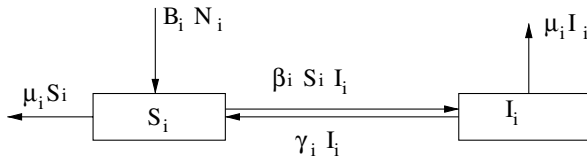


Fig. 3.2. Scheme of population demography and disease transmission in patch i.

of (B3), the population dynamics is given by

$$\frac{\mathrm{d}N_i}{\mathrm{d}t} = A_i - (\mu_i - c_i)N_i.$$

This type of demographic structure has been adopted by many studies in the literature.

Let us consider an SIS type of disease transmission models. If there is no population dispersal among patches, that is, the patches are isolated, with the transfer diagram given in Fig. 3.2, the dynamics of disease transmissions in ith patch are governed by

$$\begin{aligned} \frac{\mathrm{d}S_i}{\mathrm{d}t} &= B_i(N_i)N_i - \mu_i S_i - \beta_i S_i I_i + \gamma_i I_i, \\ \frac{\mathrm{d}I_i}{\mathrm{d}t} &= \beta_i S_i I_i - (\mu_i + \gamma_i)I_i, \end{aligned} \tag{3.11}$$

where μ_i is the per capita death rate of the population, β_i is the disease transmission coefficient, and γ_i is the recovery rate.

We now consider population dispersal among the patches. Let $-a_{ii}$ represent the emigration rate of susceptible individuals in the ith patch and $-b_{ii}$ represent the emigration rate of infective individuals in the ith patch, where $a_{ii},\ b_{ii},\ 1 \le i \le n$, are nonpositive constants. We further let $a_{ij}, j \ne i$, represent the immigration rate of susceptible individuals from the jth patch to the ith patch, and $b_{ij}, j \ne i$, the immigration rate of infective individuals from the jth patch to the ith patch. Hence, when the patches are connected, we have the following epidemic model with population dispersal:

$$\begin{aligned} \frac{\mathrm{d}S_i}{\mathrm{d}t} &= B_i(N_i)N_i - \mu_i S_i - \beta_i S_i I_i + \gamma_i I_i + \sum_{j=1}^{n} a_{ij} S_j, \\ \frac{\mathrm{d}I_i}{\mathrm{d}t} &= \beta_i S_i I_i - (\mu_i + \gamma_i)I_i + \sum_{j=1}^{n} b_{ij} I_j, \\ 1 &\le i \le n. \end{aligned} \tag{3.12}$$

Wang and Zhao (2005) introduced an age structure in (3.12). We consider an epidemic disease that spreads only in an adult population, such as sexually-transmitted diseases. For simplicity, we assume that

(C1) Disease transmission only occurs in adult individuals, and juvenile individuals are immune to the disease.
(C2) Juvenile individuals do not have ability to reproduce, and adults are responsible to the reproduction of the population.

Let J_i be the number of juvenile individuals in patch i and A_i be the number of adult individuals in patch i. When the patches are isolated, we assume that J_i satisfies the following equation:

$$\frac{\mathrm{d}J_i}{\mathrm{d}t} = B_i(A_i)A_i - \mu_i J_i, \tag{3.13}$$

where $B_i(A_i)$ is the per capita birth rate of adult individuals in patch i, and μ_i is the per capita death rate of juveniles in patch i.

With the disease of SIS type, the adult population is divided into two classes: susceptible individuals and infectious individuals. We denote the number of susceptible individuals by S_i and the number of infective individuals by I_i, in patch i, such that $A_i = S_i + I_i$. When the patches are isolated, we assume that S_i and I_i obey the following system:

$$\begin{aligned} \frac{\mathrm{d}S_i}{\mathrm{d}t} &= R_i(t) - d_i S_i - \beta_i S_i I_i + \gamma_i I_i, \\ \frac{\mathrm{d}I_i}{\mathrm{d}t} &= \beta_i S_i I_i - (d_i + \gamma_i) I_i, \end{aligned} \tag{3.14}$$

where $R_i(t)$ is the transition rate of juvenile individuals from juvenile stage to adult stage, d_i is the death rate of adults, β_i is the contact rate of susceptible individuals with infectious individuals, and γ_i is the recovery rate of infectives, all in patch i.

When the patches are connected, we suppose that the immigration rate of susceptible individuals from jth patch to ith patch is a_{ij}, the immigration rate of infective individuals from jth patch to ith patch is b_{ij}, $-a_{ii} > 0$ is the emigration rate of susceptible individuals in the ith patch, $-b_{ii} > 0$ is the emigration rate of infective individuals in the ith patch, c_{ij} is the immigration rate of juvenile individuals from jth patch to ith patch, and $-c_{ii} > 0$ is the emigration rate of juvenile individuals in the ith patch.

Under these assumptions, we have the following model:

$$\begin{aligned}
\frac{\mathrm{d}J_i}{\mathrm{d}t} &= B_i(A_i(t))A_i(t) - \mu_i J_i(t) - R_i(t) + \sum_{j=1}^{n} c_{ij} J_j(t),\\
\frac{\mathrm{d}S_i}{\mathrm{d}t} &= R_i(t) - d_i S_i - \beta_i S_i I_i + \gamma_i I_i + \sum_{j=1}^{n} a_{ij} S_j, \qquad i = 1, \ldots, n.\\
\frac{\mathrm{d}I_i}{\mathrm{d}t} &= \beta_i S_i I_i - (d_i + \gamma_i) I_i + \sum_{j=1}^{n} b_{ij} I_j,
\end{aligned} \tag{3.15}$$

We now derive a formula for $R_i(t)$ in terms of the parameters and the variables in the model. For simplicity, we define r as the age at which a juvenile in each patch becomes an adult host. Let $J(t,a) := (J_1(t,a), \ldots, J_n(t,a))^{\mathrm{T}}$, where $J_i(t,a)$ is the number of juveniles in patch i at time t with age a. Clearly, $R(t) := (R_1(t), \ldots, R_n(t))^{\mathrm{T}} = J(t,r)$. For simplicity, we neglect the death and birth of individuals when they disperse so that we have

$$\sum_{j=1}^{n} a_{ji} = 0, \quad \sum_{j=1}^{n} b_{ji} = 0, \quad \sum_{j=1}^{n} c_{ji} = 0, \quad i = 1, \ldots, n.$$

To determine the distribution of juveniles at age r, we consider the following age-structured system:

$$\begin{aligned}
(\partial_t + \partial_a) J_i(t,a) &= \sum_{j=1}^{n} c_{ij} J_j(t,a) - \left(\sum_{j=1}^{n} c_{ji} + \mu_i \right) J_i(t,a)\\
&= \sum_{j=1}^{n} c_{ij} J_j(t,a) - \mu_i J_i(t,a)
\end{aligned} \tag{3.16}$$

with the birth law given by

$$J(t,0) = G(A(t)) := (B_1(A_1(t))A_1(t), \ldots, B_n(A_n(t))A_n(t))^{\mathrm{T}}.$$

Define $V(t,a) := J(t, t-a)$, $\forall t \geq a \geq 0$. Then $V(t,a)$ satisfies

$$\frac{\partial V(t,a)}{\partial t} = C_J V(t,a), \quad t \geq a, \tag{3.17}$$

where

$$C_J := \begin{bmatrix} -\mu_1 + c_{11} & c_{12} & \cdots & c_{1n} \\ c_{21} & -\mu_2 + c_{22} & \cdots & c_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ c_{n1} & c_{n2} & \cdots & -\mu_n + c_{nn} \end{bmatrix}.$$

Integrating (3.17) from a to t, we have

$$V(t,a) = \exp(C_J(t-a))V(a,a) = \exp(C_J(t-a))G(A(a)), \quad \forall t \geq a,$$

and hence

$$J(t,s) = V(t,t-s) = \exp(C_J s)G(A(t-s)), \quad \forall t \geq s \geq 0.$$

It then follows that

$$R(t) = J(t,r) = \exp(C_J r)G(A(t-r)). \tag{3.18}$$

Note that $R(t)$ does not depend on the variables of juveniles. The S_i and I_i equations can be decoupled from the J_i equations in (3.15) to obtain the following reduced model:

$$\begin{aligned} \frac{\mathrm{d}S_i}{\mathrm{d}t} &= R_i(t) - d_i S_i - \beta_i S_i I_i + \gamma_i I_i + \sum_{j=1}^{n} a_{ij} S_j, \\ \frac{\mathrm{d}I_i}{\mathrm{d}t} &= \beta_i S_i I_i - (d_i + \gamma_i) I_i + \sum_{j=1}^{n} b_{ij} I_j, \\ (R_1(t), \ldots, R_n(t))^{\mathrm{T}} &= \exp(C_J r)G(A(t-r)), \qquad i = 1, \ldots, n. \end{aligned} \tag{3.19}$$

Wang and Zhao (2006) introduced a delay that represents an infection period into an epidemic model with population dispersals. We consider an SIR type of disease that may spread in a geography of two patches. It is assumed that all infectious individuals have a constant length of infection τ. Let a be the infection-age, that is, the time since infection, and let $I_i(a,t)$ be the density of infected individuals at time t with respect to infection-age a in the ith patch. We assume that the number of recovered individuals due to treatment per unit time is proportional to that of infectious individuals. This means that we neglect the time delay for treatment to take effect, which is reasonable when treatment takes effect in a short time. As a consequence, infected individuals in patch i are treated at a constant rate $r_i \geq 0$ up to infection-age τ when any remaining infected individuals of

infection-age τ immediately transfer to the recovered class. For simplicity, we assume that the death rates, the disease transmission coefficients, the treatment rates and the migration rates are all independent of infection-ages. Then the force of infection in patch i at time t is $k_i \int_0^\tau I_i(a,t)\mathrm{d}a$. By similar arguments as above, we obtain

$$\begin{aligned}
&\frac{\mathrm{d}S_1}{\mathrm{d}t} = B_1(N_1(t))N_1(t) - (\mu_1 + d_1)S_1(t) - \lambda_1(t)S_1(t) + d_2S_2(t),\\
&\frac{\mathrm{d}S_2}{\mathrm{d}t} = B_2(N_2(t))N_2(t) - (\mu_2 + d_2)S_2(t) - \lambda_2(t)S_2(t) + d_1S_1(t),\\
&\frac{\partial I_1}{\partial t} + \frac{\partial I_1}{\partial a} = -(\mu_1 + r_1 + b_1)I_1(a,t) + b_2I_2(a,t), \quad 0 < a \le \tau,\\
&\frac{\partial I_2}{\partial t} + \frac{\partial I_2}{\partial a} = -(\mu_2 + r_2 + b_2)I_2(a,t) + b_1I_1(a,t), \quad 0 < a \le \tau,\\
&\frac{\mathrm{d}R_1}{\mathrm{d}t} = r_1\int_0^\tau I_1(a,t)\mathrm{d}a + I_1(\tau,t) - (\mu_1 + c_1)R_1(t) + c_2R_2(t),\\
&\frac{\mathrm{d}R_2}{\mathrm{d}t} = r_2\int_0^\tau I_2(a,t)\mathrm{d}a + I_2(\tau,t) - (\mu_2 + c_2)R_2(t) + c_1R_1(t),\\
&\lambda_i(t) = k_i\int_0^\tau I_i(a,t)\mathrm{d}a,\ N_i(t) = S_i(t) + R_i(t) + \int_0^\tau I_i(a,t)\mathrm{d}a,\\
&I_i(0,t) = \lambda_i(t)S_i(t), \quad i = 1,2
\end{aligned} \tag{3.20}$$

with the initial conditions given by

$$\begin{aligned}
&S_i(0) = S_i^0 > 0, \quad R_i(0) = R_i^0 \ge 0,\ \ i = 1,2,\\
&I_i(a,0) = f_i(a) \ge 0, \quad \text{for } 0 \le a \le \tau,\ \ i = 1,2.
\end{aligned} \tag{3.21}$$

Here, d_i, b_i, and c_i are dispersal coefficients of susceptible, infectious, and recovered individuals, respectively.

Because of our assumptions, we can reduce (3.20) to a system of delay-differential equations. Let $P_i(t) = \int_0^\tau I_i(a,t)\mathrm{d}a$ be the total density of infected members at time t in the ith patch. We derive the equations for $P_1(t)$ and $P_2(t)$ for $t \ge \tau$. Set $V_i(a,t) = I_i(t-a,t)$ for $0 \le t-a \le \tau$ and $\mathbf{V}(a,t) = (V_1(a,t), V_2(a,t))^{\mathrm{T}}$, where T denotes a transpose of a vector. Then $\mathbf{V}$ satisfies

$$\frac{\partial \mathbf{V}(a,t)}{\partial t} = \mathbf{B}\mathbf{V}(a,t), \quad a \le t \le a + \tau, \tag{3.22}$$

where

$$\mathbf{B} = \begin{bmatrix} -\mu_1 - r_1 - b_1 & b_2 \\ b_1 & -\mu_2 - r_2 - b_2 \end{bmatrix}.$$

Integrating (3.22) from a to t, we have

$$\mathbf{V}(a,t) = \exp(\mathbf{B}(t-a))(I_1(0,a), I_2(0,a))^{\mathrm{T}}, \quad a \le t \le a+\tau,$$

and hence

$$\begin{aligned} \mathbf{I}(a,t) &= \mathbf{V}(t-a,t) \\ &= \exp(\mathbf{B}a)(I_1(0,t-a), I_2(0,t-a))^{\mathrm{T}}, \quad a \le \tau. \end{aligned} \tag{3.23}$$

Set

$$(b_{ij}(a)) := \exp(\mathbf{B}a), \quad Q_i(t) := k_i S_i(t) P_i(t).$$

It then follows from (3.20) that

$$\begin{aligned} I_1(a,t) &= b_{11}(a)Q_1(t-a) + b_{12}(a)Q_2(t-a), \\ I_2(a,t) &= b_{21}(a)Q_1(t-a) + b_{22}(a)Q_2(t-a), \end{aligned} \tag{3.24}$$

for $t \ge \tau \ge a$.

Integrating (3.24) from 0 to τ, we have

$$\begin{aligned} P_1(t) &= \int_0^\tau b_{11}(a)Q_1(t-a)\mathrm{d}a + \int_0^\tau b_{12}(a)Q_2(t-a)\mathrm{d}a, \quad t \ge \tau, \\ P_2(t) &= \int_0^\tau b_{21}(a)Q_1(t-a)\mathrm{d}a + \int_0^\tau b_{22}(a)Q_2(t-a)\mathrm{d}a, \quad t \ge \tau, \end{aligned} \tag{3.25}$$

which is equivalent to

$$\mathbf{P}(t) = \int_0^\tau \exp(\mathbf{B}a)\mathbf{Q}(t-a)\mathrm{d}a = \int_{t-\tau}^t \exp(\mathbf{B}(t-s))\mathbf{Q}(s)\mathrm{d}s, \quad t \ge \tau, \tag{3.26}$$

where $\mathbf{P}(t) = (P_1(t), P_2(t))^T$ and $\mathbf{Q}(t) = (Q_1(t), Q_2(t))^{\mathrm{T}}$. It then follows that

$$\frac{\mathrm{d}\mathbf{P}}{\mathrm{d}t} = \mathbf{Q}(t) - \exp(\mathbf{B}\tau)\mathbf{Q}(t-\tau) + \mathbf{B}\mathbf{P}(t), \quad t \ge \tau. \tag{3.27}$$

Define

$$\gamma_i(t) := r_i P_i(t) + b_{i1}(\tau)Q_1(t-\tau) + b_{i2}(\tau)Q_2(t-\tau), \quad i = 1, 2. \tag{3.28}$$

Consequently, we obtain the following time-delayed model:

$$\begin{aligned}
\frac{\mathrm{d}S_1}{\mathrm{d}t} &= B_1(N_1(t))N_1(t) - (\mu_1 + d_1)S_1(t) - Q_1(t) + d_2 S_2(t),\\
\frac{\mathrm{d}S_2}{\mathrm{d}t} &= B_2(N_2(t))N_2(t) - (\mu_2 + d_2)S_2(t) - Q_2(t) + d_1 S_1(t),\\
\frac{\mathrm{d}\mathbf{P}}{\mathrm{d}t} &= \mathbf{Q}(t) - \exp(\mathbf{B}\tau)\mathbf{Q}(t-\tau) + \mathbf{B}\mathbf{P}(t),\\
\frac{\mathrm{d}R_1}{\mathrm{d}t} &= \gamma_1(t) - (\mu_1 + c_1)R_1(t) + c_2 R_2(t),\\
\frac{\mathrm{d}R_2}{\mathrm{d}t} &= \gamma_2(t) - (\mu_2 + c_2)R_2(t) + c_1 R_1(t),\\
N_i(t) &= S_i(t) + R_i(t) + P_i(t), \quad i = 1, 2,
\end{aligned} \tag{3.29}$$

for $t \geq \tau$. In view of (3.26), we need to impose the following condition on initial functions:

$$\mathbf{P}(\tau) = \int_0^\tau \exp(\mathbf{B}(\tau - s))\mathbf{Q}(s)\mathrm{d}s. \tag{3.30}$$

3.2. Basic Techniques for Stability of Delayed Models

For readers' convenience, we present some basic methods to analyze stability of delayed epidemic models. The basic approach for the local stability analysis of a delayed system is to linearize the system at an equilibrium and then consider the characteristic equation of the linearized system. Let $C([-\tau, 0], R^n)$ denote the Banach space of continuous functions mapping $[-\tau, 0]$ into R^n with the maximum norm, which is the working space for models of finite delays. Let $x_t \in C([-\tau, 0], R^n)$ be defined by $x_t(\theta) = x(t + \theta), -\tau \leq \theta \leq 0$. Note that autonomous models with finite delays can be written into an abstract form:

$$\dot{x} = f(x_t), \tag{3.31}$$

where f is a functional from $C([-\tau, 0], R^n)$ into R^n. If f be continuously differentiable, for any initial function $\phi \in C([-\tau, 0], R^n)$, (3.31) has a unique solution $x(t, \phi)$ through ϕ.

For a linear system

$$\dot{x} = L(x_t), \tag{3.32}$$

where L is a linear operator from $C := C([-\tau, 0], R^n)$ into R^n, if we write

$$L(\phi) = \int_{-\tau}^{0} [d\eta(\theta)]\phi(\theta), \quad \phi \in C, \tag{3.33}$$

where $\eta(\theta)$ is an $n \times n$ matrix whose elements are of bounded variation on $[-\tau, 0]$, then the characteristic equation of (3.32) is

$$D(\lambda) := \det \Delta(\lambda) = 0 \tag{3.34}$$

with

$$\Delta(\lambda) = \lambda I_n - \int_{-\tau}^{0} \mathrm{e}^{\lambda\theta} \mathrm{d}\eta(\theta),$$

where I_n is an identity matrix. If there is only one discrete delay, the characteristic equation takes the form:

$$D(\lambda) := P(\lambda) + Q(\lambda)\mathrm{e}^{-\lambda\tau} = 0, \tag{3.35}$$

where

$$P(\lambda) = \sum_{k=0}^{n} a_k \lambda^k, \quad Q(\lambda) = \sum_{k=0}^{m} b_k \lambda^k, \tag{3.36}$$

with a_k and b_k constants.

By the stability theory of delayed differential equations [Hale and Lunel (1993); Kuang (1993); Wu (1996)], we have

Theorem 3.1. *The equilibrium is stable if all characteristic roots of* (3.34) *have negative real parts, and is unstable if there is one characteristic root which has the positive real part.*

A basic approach of stability analysis for such equations is the D-subdivision method [Brauer and Ma(1987); Ma (1996)]. The idea is as follows. For a fixed delay τ, we consider the equation $D(iy) = 0$, which gives information that pure imaginary characteristic roots occur. As y varies in $(-\infty, \infty)$, the graphs of the equation split the parameter space of a_i and b_j into a number of domains in each of which the stability is unchanged. The exact stability information can be drawn with the aid of the direction

of the real parts of characteristic roots as a point crosses the curves. We illustrate this by considering the following model:

$$\begin{aligned}\frac{\mathrm{d}S}{\mathrm{d}t} &= -\beta S(t)I(t) + \gamma I(t-\tau),\\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - \gamma I(t),\\ \frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - \gamma I(t-\tau),\end{aligned} \tag{3.37}$$

which is described in Sec. 3.1.1.

The third equation of (3.37) can be written as

$$R(t) = \gamma \int_{t-\tau}^{t} I(\theta)\mathrm{d}\theta.$$

Since the population size in (3.37) is constant, we may assume $S(t)+I(t)+R(t)=1$ without loss of generality. It follows from (3.37) that

$$\frac{\mathrm{d}I}{\mathrm{d}t} = -\gamma I(t) + \beta I(t)\left[1 - I(t) - \gamma\int_{t-\tau}^{t} I(\theta)\mathrm{d}\theta\right]. \tag{3.38}$$

Let $\sigma = \beta/\gamma$. If $\sigma > 1$, (3.38) has an endemic equilibrium $I_e = (1-1/\sigma)/(1+\gamma\tau)$. If we translate I_e to the origin by using $I = I_e(1+X)$ and change the time scale by letting $t = \tau\xi$, then (3.38) becomes

$$X'(\xi) = -\frac{\tau\gamma(\sigma-1)}{1+\tau\gamma}(X+1)\left[X + \tau\gamma\int_{-1}^{0} X(\xi+\theta)\mathrm{d}\theta\right]. \tag{3.39}$$

The linearization of (3.39) about $X=0$ has the characteristic equation:

$$D(\lambda) = \lambda + \frac{\tau\gamma(\sigma-1)}{1+\tau\gamma}\left[1 + \tau\gamma\int_{-1}^{0} \mathrm{e}^{\lambda\theta}\mathrm{d}\theta\right] = 0. \tag{3.40}$$

To know the trace that pure imaginary roots of (3.40) occur, we substitute $\lambda = iy$ into (3.40) to obtain

$$\begin{aligned} p &= -\frac{y}{\sin\, y},\\ \sigma - 1 &= \left(1 - \frac{y}{\sin\, y}\right)\frac{\sin^2 y}{1-\cos\, y},\end{aligned} \tag{3.41}$$

where $p = \tau\gamma$. When $y \in ((2k-1)\pi, 2k\pi), k = 1, 2, \ldots$, we obtain a family of curves in $(\sigma-1)-p$ plane (see Fig. 3.3).

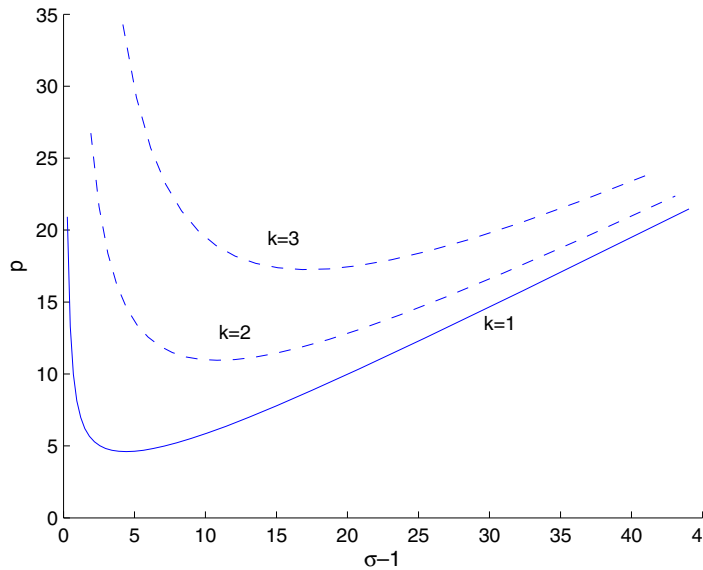


Fig. 3.3. Curves where imaginary roots occur.

Note that I_e is asymptotically stable when $\tau = 0$. It follows that the region below curve $k = 1$ is a stable region. To determine the stability above the curve, we substitute $\lambda = x + iy$ into (3.40) and then separate its real part and imaginary part to obtain

$$P(x, y, \sigma) := x + \frac{p(\sigma - 1)}{1 + p}\left(1 - \frac{p(-x + \mathrm{e}^{-x}x\cos(y) - \mathrm{e}^{-x}y\sin(y))}{x^2 + y^2}\right) = 0,$$

$$Q(x, y, \sigma) := y + \frac{p^2(\sigma - 1)(-y + \mathrm{e}^{-x}y\cos(y) + \mathrm{e}^{-x}x\sin(y))}{(1 + p)(x^2 + y^2)} = 0.$$

Based on this system, we can determine the direction of the real part of a characteristic root when p crosses the curves with imaginary roots. First, note that

$$\frac{\partial x}{\partial p} = -\begin{vmatrix} \dfrac{\partial P}{\partial p} & \dfrac{\partial P}{\partial y} \\ \dfrac{\partial Q}{\partial p} & \dfrac{\partial Q}{\partial y} \end{vmatrix} \Bigg/ \begin{vmatrix} \dfrac{\partial P}{\partial x} & \dfrac{\partial P}{\partial y} \\ \dfrac{\partial Q}{\partial x} & \dfrac{\partial Q}{\partial y} \end{vmatrix}. \tag{3.42}$$

Then, by direct calculations, we see that the sign of $\partial x/\partial\sigma$ on the curves is determined by

$$c_0 := -(y^2 + p^4 + p^2\sigma + 2p^3 - p^2 + py^2 - 2p^3\sigma - p^4\sigma) - p^2(p^2 + 2p - 1)(\sigma - 1)\cos(y) + yp(-p^2 + p\sigma - 4p - 2)\sin(y).$$

Since the stability is not altered in a region with boundary of two consecutive curves with imaginary roots, it is sufficient to consider the direction of real part of the characteristic root when p crosses some special points on the curves. Fix $y = (2k-1)\pi + \pi/2$. By (3.41) we have $p = (2k-1)\pi + \pi/2$ and $\sigma = 2 + (2k-1)\pi + \pi/2$. Then it is easy to see that $c_0 > 0$ for all positive integers. This means that a characteristic root with positive real part occurs in any region which lies above the curve $k = 1$. Hence, the equilibrium is stable if $(\sigma - 1, p)$ is below the curve $k = 1$, and is unstable if it is above the curve $k = 1$.

The advantage of analyzing characteristic roots is that sharp conditions may be found in some cases. However, it is difficult to apply when the number of equations of a model is more than two or when there are several delays. In these cases, the Liapunov direct method can be very helpful (see, for example, [Chen *et al.* (2003); Lu (1995); Mulone *et al.* (2007)]. Let $R^+ = [0, \infty)$. Suppose that $x = 0$ is an equilibrium of (3.31). Then we have the following fundamental stability theorems [Hale and Lunel (1993); Kuang (1993)].

Theorem 3.2. *Suppose $f\colon C \to R^n$ takes bounded sets of C into bounded sets of R^n, and $\omega_1, \omega_2\colon R^+ \to R^+$ are continuous nondecreasing functions, satisfying $\omega_1(0) = \omega_2(0) = 0, \lim_{r\to\infty}\omega_1(r) = +\infty$ and $\omega_1(r) > 0$ for $r > 0$. If there is a continuous functional $V\colon C \to R$ such that*

$$V(\phi) \geq \omega_1(|\phi(0)|), \quad V'(\phi)|_{(3.31)} \leq -\omega_2(|\phi(0)|),$$

then $x = 0$ is stable, and every solution is bounded. If we also have $\omega_2(r) > 0$ for $r > 0$, then $x = 0$ is globally asymptotically stable.

We say $V\colon C \to R$ is a Liapunov function on a set G in C if V is continuous on $\bar{G}$, the closure of G, and $\dot{V} \leq 0$. Let

$$S = \{\phi \in \bar{G}\colon \dot{V}(\phi) = 0\},$$

$M = \{$largest invariant set in S which is invariant with respect to (3.31)$\}$.

Theorem 3.3. *If V is a Liapunov function on G and $x_t(\phi)$ is a bounded solution that remains in G, then $x_t(\phi)$ tends to M as $t \to \infty$.*

We will use Theorems 3.2 and 3.3 to analyze stability of some epidemic models in subsequent sections.

3.3. An *SIS* Epidemic Model with Vaccination

Vaccination is one of the most important strategies to prevent and control communicable diseases. Thus, it is important to analyze influences of vaccinations to perform optimal vaccination policy. Li and Ma (2004a) introduced a vaccination compartment into an SIS model. It is assumed that a vaccine takes effect in a duration of length τ. After that the vaccinated individuals lose immunity and return to susceptible class.

Let $S(t)$ denote the number of susceptible individuals, $I(t)$ the infective individuals, and $V(t)$ the immune individuals due to vaccination, in a population at time t, respectively. The total population size at time t is denoted by $N(t)$, $N = S + I + V$.

The basic demographic assumptions are:

(i) The size of the population is a constant with the birth rate and death rate μ.
(ii) A fraction q $(0 \le q \le 1)$ of newborns is vaccinated per unit time.
(iii) A nonnegative constant p is the rate that susceptible individuals are vaccinated per unit time.

With the standard incidence and the natural recovery rate γ, we have

$$\begin{aligned} S' = {} & \mu(1-q)N - \frac{\beta IS}{N} - (\mu+p)S + \gamma I \\ & + [\mu q N(t-\tau) + pS(t-\tau)]\mathrm{e}^{-\mu\tau}, \\ I' = {} & \frac{\beta IS}{N} - (\mu+\gamma)I, \\ V' = {} & (\mu q N + pS) - [\mu q N(t-\tau) + pS(t-\tau)]\mathrm{e}^{-\mu\tau} - \mu V. \end{aligned} \tag{3.43}$$

Since the population size N is a constant, if s, i and v denote the fraction of susceptible, infectious, and vaccinated individuals in the population, respectively, then (3.43) becomes

$$\begin{aligned} s' &= \mu(1-q) - \beta si - (\mu+p)s + \gamma i + [\mu q + ps(t-\tau)]\mathrm{e}^{-\mu\tau}, \\ i' &= \beta si - (\mu+\gamma)i, \\ v' &= (\mu q + ps) - [\mu q + ps(t-\tau)]\mathrm{e}^{-\mu\tau} - \mu v, \quad s+i+v = 1, \end{aligned} \tag{3.44}$$

which can be reduced to

$$\begin{aligned} s' &= \mu(1-q) - \beta si - (\mu+p)s + \gamma i + [\mu q + ps(t-\tau)]\mathrm{e}^{-\mu\tau}, \\ i' &= \beta si - (\mu+\gamma)i. \end{aligned} \tag{3.45}$$

Set

$$s_0 = \frac{\mu[1-q(1-\mathrm{e}^{-\mu\tau})]}{\mu+p(1-\mathrm{e}^{-\mu\tau})}.$$

Let $R_0 = \beta s_0/(\mu+\gamma)$. If $R_0 \le 1$, (3.45) has only the disease-free equilibrium $P_0 = (s_0, 0)$; if $R_0 > 1$, (3.45) has also an endemic equilibrium $P_e(s_e, i_e)$, where

$$s_e = \frac{\mu+\gamma}{\beta}, \quad i_e = \frac{(\mu+\gamma)[\mu+p(1-\mathrm{e}^{-\mu\tau})]}{\beta\mu}(R_0-1).$$

Theorem 3.4. *P_0 is globally asymptotically stable if $R_0 \le 1$, and P_e is globally asymptotically stable if $R_0 > 1$.*

Proof. (i) We show that the disease-free equilibrium is globally stable if $R_0 \le 1$. Let $x(t) = s(t) - s_0$. Then (3.45) becomes

$$\begin{aligned} x' &= -(\mu+p)x - (\beta s_0 - \gamma)i - \beta ix + p\mathrm{e}^{-\mu\tau}x(t-\tau), \\ i' &= [\beta s_0 - (\mu+\gamma)]i + \beta ix. \end{aligned} \tag{3.46}$$

When $\beta s_0 \le \gamma$, we define $W_{11} = |x|$. Then the right-hand upper derivative of W_{11} along (3.46) satisfies the inequality

$$D^+W_{11}|_{(3.46)} \le -(\mu+p)|x| + (\gamma - \beta s_0)i - \beta i|x| + p\mathrm{e}^{-\mu\tau}|x(t-\tau)|.$$

To remove the term with delay, we define

$$W_1 = W_{11} + i + p\mathrm{e}^{-\mu\tau}\int_{t-\tau}^{t}|x(\theta)|\mathrm{d}\theta.$$

Then

$$\begin{aligned} D^+W_1|_{(3.46)} &\le -(\mu+p)|x| - \mu i + \beta i(x-|x|) + p\mathrm{e}^{-\mu\tau}|x| \\ &\le -[\mu+p(1-\mathrm{e}^{-\mu\tau})]|x| - \mu i. \end{aligned}$$

It follows that P_0 is globally asymptotically stable if $\beta s_0 \le \gamma$.

When $\gamma < \beta s_0 \leq \mu + \gamma$, we define

$$W_{22} = (\beta s_0 - \gamma)i + \frac{\beta}{2}x^2.$$

Then the derivative of W_{22} along (3.46) is given by

$$\begin{aligned}\left.\frac{\mathrm{d}W_{22}}{\mathrm{d}t}\right|_{(3.46)} &= -(\mu+p)\beta x^2 - (\beta s_0 - \gamma)[(\mu+\gamma) - \beta s_0]i \\ &\quad - \beta^2 i x^2 + \beta p \mathrm{e}^{-\mu\tau} x(t)\cdot x(t-\tau) \\ &\leq -(\mu+p)\beta x^2 - (\beta s_0 - \gamma)[(\mu+\gamma) - \beta s_0]i \\ &\quad + \beta p \mathrm{e}^{-\mu\tau} x(t)\cdot x(t-\tau). \end{aligned} \tag{3.47}$$

Using the inequality

$$x(t)\cdot x(t-\tau) \leq \frac{x^2(t) + x^2(t-\tau)}{2},$$

inequality (3.47) becomes

$$\begin{aligned}\left.\frac{\mathrm{d}W_{22}}{\mathrm{d}t}\right|_{(3.46)} &\leq -\beta(\mu+p)x^2 - (\beta s_0 - \gamma)[(\mu+\gamma) - \beta s_0]i \\ &\quad + \frac{\beta p \mathrm{e}^{-\mu\tau}}{2}[x^2(t) + x^2(t-\tau)].\end{aligned}$$

Let us define

$$W_2 = W_{22} + \frac{\beta p \mathrm{e}^{-\mu\tau}}{2}\int_{t-\tau}^{t} x^2(\theta)\mathrm{d}\theta.$$

Then

$$\left.\frac{\mathrm{d}W_2}{\mathrm{d}t}\right|_{(3.46)} \leq -\beta[\mu + p(1-\mathrm{e}^{-\mu\tau})]x^2 - (\beta s_0 - \gamma)[(\mu+\gamma) - \beta s_0]i \leq 0,$$

where $\beta s_0 - \gamma > 0$ and $\mu + \gamma \geq \beta s_0$ are used. It follows from Theorems 3.2 and 3.3 that P_0 is globally asymptotically stable for $\gamma < \beta s_0 \leq \mu + \gamma$.

(ii) We show that the endemic equilibrium is globally stable when $R_0 > 1$. Let us define

$$x(t) = s(t) - s_e, \quad y(t) = -\ln i.$$

Then (3.45) becomes

$$\begin{aligned} x' &= -(\mu+p)x + \mu(\mathrm{e}^{-y^*} - \mathrm{e}^{-y}) + px(t-\tau)\mathrm{e}^{-\mu\tau} - \beta x\mathrm{e}^{-y}, \\ y' &= -\beta x, \end{aligned} \tag{3.48}$$

where $y^* = -\ln i_e$. Thus, it suffices to consider the global stability of $(0, y^*)$ for (3.48).

Let us define

$$W_{33} = \frac{\beta}{2}x^2 + \mu\int_{y^*}^{y}(\mathrm{e}^{-y^*} - \mathrm{e}^{-u})\mathrm{d}u.$$

Then the derivative of W_{33} along (3.48) is given by

$$\left.\frac{\mathrm{d}W_{33}}{\mathrm{d}t}\right|_{(3.48)} = -(\mu+p)\beta x^2(t) + \beta p\mathrm{e}^{-\mu\tau}x(t)\cdot x(t-\tau) - \beta^2 x^2(t)\mathrm{e}^{-y(t)}.$$

Using the inequalities

$$x(t)\cdot x(t-\tau) \le \frac{x^2(t)+x^2(t-\tau)}{2},$$

we have

$$\left.\frac{\mathrm{d}W_{33}}{\mathrm{d}t}\right|_{(3.48)} \le -(\mu+p)\beta x^2(t) + \frac{\beta p\mathrm{e}^{-\mu\tau}}{2}[x^2(t)+x^2(t-\tau)] - \beta^2 x^2(t)\mathrm{e}^{-y(t)}.$$

Let

$$W_3 = W_{33} + \frac{\beta p\mathrm{e}^{-\mu\tau}}{2}\int_{t-\tau}^{t} x^2(u)\mathrm{d}u.$$

We have

$$\left.\frac{\mathrm{d}W_3}{\mathrm{d}t}\right|_{(3.48)} \le -\beta[\mu + p(1-\mathrm{e}^{-\mu\tau}) + \beta\mathrm{e}^{-y(t)}]x^2 \le 0.$$

Notice that

$$\left.\frac{\mathrm{d}W_3}{\mathrm{d}t}\right|_{(3.48)} = 0 \quad \text{if and only if } x = 0,$$

and that $x = 0, y = y^*$ is the unique solution of (3.48) on the set $D' = \{(x,y)\colon x = 0\}$. It follows from the LaSalle's invariance principle (Theorem 3.3) that the equilibrium $(0, y^*)$ of (3.48) is globally asymptotically stable; that is, the endemic equilibrium P_e of (3.45) is globally asymptotically stable for $R_0 > 1$. □

3.4. An *SIS* Epidemic Model for Vector-Borne Diseases

Vector-borne diseases such as malaria and dengue fever are notorious infectious diseases. A fundamental model for the dynamics of the transmission of malaria between mosquitoes and humans was proposed by Ross, who was awarded his second Nobel prize in medicine.

Jin and Ma (2006) studied an SIR model with continuous delays, which incorporates the variations of incubation period of vectors.

Let h be the maximal length of latent period of vector. It is assumed that there are both disease transmissions between susceptible human individuals and infectious vectors, and disease transmissions from direct contacts of human individuals. Then the model takes the form:

$$\begin{aligned} S'(t) &= -\beta_1 S(t)\int_0^h f(s)I(t-s)\mathrm{d}s - \beta_2 S(t)I(t) - \mu S(t) + b,\\ I'(t) &= \beta_1 S(t)\int_0^h f(s)I(t-s)\mathrm{d}s + \beta_2 S(t)I(t) - (\mu+\lambda+c)I(t),\\ R'(t) &= \lambda I(t) - \mu R(t), \end{aligned} \tag{3.49}$$

where b is the recruitment rate of human population, μ is the per capita death-rate, c is the disease-induced death-rate, λ is the recovery rate, β_1 is the valid contact coefficient between susceptible human individuals and infectious vectors, β_2 is the valid contact coefficient between susceptible human individuals and infectious human individuals, and the kernel f is nonnegative, continuous, and satisfies $\int_0^h f(s)\mathrm{d}s = 1$.

The disease-free equilibrium is $E_0 = (b/\mu, 0, 0)$. When

$$\frac{b}{\mu} > \frac{\mu+\lambda+c}{\beta_1+\beta_2}, \tag{3.50}$$

Eq. (3.49) has a unique endemic equilibrium

$$E_+ = (S^*, I^*, R^*) = \left(\frac{\mu+\lambda+c}{\beta_1+\beta_2}, \frac{(b-\mu S^*)}{(\beta_1+\beta_2)S^*}, \frac{\lambda(b-\mu S^*)}{\mu(\beta_1+\beta_2)S^*}\right).$$

Our objective is to analyze the stability of the disease-free equilibrium and the endemic equilibrium by means of Liapunov functionals.

Theorem 3.5. *The disease-free equilibrium E_0 of* (3.49) *is globally stable if*

$$\frac{b}{\mu} < \frac{\mu + \lambda + c}{\beta_1 + \beta_2}. \tag{3.51}$$

The endemic equilibrium E_+ of (3.49) *is asymptotically stable if* (3.50) *holds.*

Proof. We begin by showing E_0 is globally stable when (3.51) holds.

Let us define the following Liapunov functional:

$$V(x_t) = I(t) + w_1 R(t) + w_2 \int_0^h f(s) \int_{t-s}^t I(u)\mathrm{d}u\mathrm{d}s + \frac{w_3}{2}(S(t) - S_0)^2, \tag{3.52}$$

where $S_0 = b/\mu$ and w_i are positive constants to be chosen. Then we have

$$V(x_t) > \min\left\{1, w_1, \frac{w_3}{2}\right\}(I(t) + R(t) + (S(t) - S_0)^2).$$

The time derivative of $V(x_t)$ along the solutions of system (3.49) is given by

$$\begin{aligned}
\dot{V}(x_t)|_{(3.49)} = {} & \beta_1 S(t) \int_0^h f(s) I(t-s)\mathrm{d}s + \beta_2 S(t) I(t) - (\mu + \lambda + c) I(t) \\
& + w_1(\lambda I(t) - \mu R(t)) + w_2 I(t) - w_2 \int_0^h f(s) I(t-s)\mathrm{d}s \\
& + w_3(S - S_0)[-\beta_1 S(t) \int_0^h f(s) I(t-s)\mathrm{d}s \\
& - \beta_2 S(t) I(t) - \mu(S(t) - S_0)].
\end{aligned}$$

After algebraic transformations, we obtain

$$\begin{aligned}
\dot{V}(x_t)|_{(3.49)} = {} & -w_3\mu(S - S_0)^2 + [w_1\lambda + w_2 + \sigma - (\mu + c + \lambda)] I(t) \\
& - w_1 \mu R(t) + I(t)[\beta_2 S(t)(1 - w_3(S - S_0)) - \sigma] \\
& + [\beta_1 S - w_2 - w_3 \beta_1 S(S - S_0)] \int_0^h f(s) I(t-s)\mathrm{d}s,
\end{aligned} \tag{3.53}$$

where σ is a positive constant. If σ and w_i satisfy

$$w_1\lambda + w_2 + \sigma < \mu + c + \lambda, \tag{3.54}$$

$$\beta_2(1 + w_3S_0)^2 < 4w_3\sigma, \tag{3.55}$$

$$\beta_1(1 + w_3S_0)^2 < 4w_2w_3, \tag{3.56}$$

then $\dot{V}(x_t)|_{(3.49)}$ is negative definite. In fact, (3.54) means that the coefficient of $I(t)$ in the second term of right-hand side of (3.53) is negative, (3.55) ensures that the coefficient of $I(t)$ in the fourth term of right-hand side of (3.53) is negative for all $S > 0$, and (3.56) ensures that the coefficient of the integral in the last term of right-hand side of (3.53) is negative for all $S > 0$. Hence, it suffices to show that we can choose σ and w_i such that (3.54), (3.55) and (3.56) are satisfied.

Note that (3.55) holds if $w_2 > \beta_1S_0$. Indeed, (3.55) can be rewritten as

$$\beta_1{S_0}^2w_3^2 + 2(\beta_1S_0 - 2w_2)w_3 + \beta_1 < 0. \tag{3.57}$$

It is easy to see that we can select $w_3 > 0$ such that (3.57) is satisfied if $\beta_1S_0 - 2w_2 < 0$ and $(\beta_1S_0 - 2w_2)^2 > (\beta_1S_0)^2$. The last two inequalities are valid if we select $w_2 > \beta_1S_0$. Similarly, (3.56) is satisfied if $\sigma > \beta_2S_0$. Finally, we prove the existence of w_1 such that (3.54) is satisfied. Since we require $w_2 > \beta_1S_0$ and $\sigma > \beta_2S_0$, it follows from (3.54) that

$$\mu + c + \lambda - w_1\lambda > w_2 + \sigma > (\beta_1 + \beta_2)S_0 = \frac{b(\beta_1 + \beta_2)}{\mu},$$

which is valid because of (3.51).

We now show that the endemic equilibrium is asymptotically stable if (3.50) holds. First, we linearize (3.49) at E_+ to obtain

$$u_1' = -((\beta_1 + \beta_2)I^* + \mu_1)u_1 - \beta_1S^*\int_0^h f(s)u_2(t-s)\mathrm{d}s - \beta_2S^*u_2,$$

$$u_2' = (\beta_1 + \beta_2)I^*u_1 + \beta_1S^*\int_0^h f(s)u_2(t-s)\mathrm{d}s + \beta_2S^*u_2 - (\mu + \lambda + c)u_2,$$

$$u_3' = \lambda u_2 - \mu u_3. \tag{3.58}$$

We consider the following Liapunov functional

$$V(u_t) = \frac{1}{2}w_1(u_1 + u_2)^2 + \frac{1}{2}u_2^2 + \frac{1}{2}w_3u_3^2 + \frac{1}{2}\beta_1S^*\int_0^h f(s)\int_{t-s}^t u_2^2(v)\mathrm{d}v\mathrm{d}s,$$

where w_i are positive constants to be chosen later.

Note that

$$V(u_t) \geq \frac{1}{2}w_1(u_1+u_2)^2 + \frac{1}{2}u_2^2 + \frac{1}{2}w_3u_3^2.$$

The time derivative of $V(u_t)$ along solutions of (3.58) is

$$\begin{aligned} V'(u_t) &= w_1(u_1+u_2)[-\mu u_1 - (\lambda+\mu+c)u_2] + (\beta_1+\beta_2)I^*u_1u_2 \\ &\quad - (\lambda+\mu+c-\beta_2S^*)u_2^2 + \beta_1S^*u_2\int_0^h f(s)u_2(t-s)\mathrm{d}s + w_3u_3u_3' \\ &\quad + \frac{1}{2}\beta_1S^*u_2^2 - \frac{1}{2}\beta_1S^*\int_0^h f(s)u_2^2(t-s)\mathrm{d}s. \end{aligned}$$

After some algebraic manipulations, we obtain

$$\begin{aligned} V'(u_t) &= -w_1\mu u_1^2 - [w_1(\lambda+\mu+c) + (\lambda+\mu+c-\beta_2S^*)]u_2^2 \\ &\quad + [-w_1\mu - w_1(\lambda+\mu+c) + (\beta_1+\beta_2)I^*]u_1u_2 + w_3\lambda u_2u_3 \\ &\quad - w_3\mu u_3^2 + \beta_1S^*u_2\int_0^h f(s)u_2(t-s)\mathrm{d}s + \frac{1}{2}\beta_1S^*u_2^2 \\ &\quad - \frac{1}{2}\beta_1S^*\int_0^h f(s)u_2^2(t-s)\mathrm{d}s. \end{aligned} \tag{3.59}$$

We select positive constants w_i such that the right-hand side of (3.59) is negative definite. First, let w_1 satisfy

$$w_1(\lambda+2\mu+c) = (\beta_1+\beta_2)I^*.$$

Note that

$$(\beta_1+\beta_2)S^* = \lambda+\mu+c,$$

and that

$$\beta_1S^*u_2\int_0^h f(s)u_2(t-s)\mathrm{d}s \leq \frac{1}{2}\beta_1S^*u_2^2 + \frac{1}{2}\beta_1S^*\int_0^h f(s)u^2(t-s)\mathrm{d}s.$$

It follows from (3.59) that

$$V'(u_t) \leq -w_1\mu u_1^2 - w_1(\lambda+\mu+c)u_2^2 - w_3\mu u_3^2 + w_3\lambda u_2u_3. \tag{3.60}$$

The right-hand side of (3.60) is negative definite if $w_3 > 0$ satisfies

$$(\lambda w_3)^2 - 4w_1(\lambda+\mu+c)\mu w_3 < 0.$$

This means that w_3 should be selected in the interval

$$0 < w_3 < \frac{4(\lambda+\mu+c)\mu w_1}{\lambda^2} = \frac{4(\lambda+\mu+c)\mu(\beta_1+\beta_2)I^*}{\lambda^2(\lambda+2\mu+c)}.$$

The proof is complete. □

From above discussions, we see that the construction of Liapunov functionals for delayed epidemic models is delicate. It would be nice if more techniques such as the compound matrix methods (see, for example, [Li *et al.* (2001)]) for ordinary differential equations models were applicable.

3.5. Stability Switches and Ultimate Stability

In the general case, an endemic equilibrium of an epidemic model is stable in the absence of delay. This means that all the characteristic roots of the model at the equilibrium have negative real parts. When a delay τ is introduced and increases, these roots continuously move in the complex plane. The equilibrium becomes unstable if one root crosses the pure imaginary axis from the left to the right. If this root stays in the right of the pure imaginary axis afterwards, the equilibrium remains unstable. If it goes back to the left and all the other roots always stay in the left, the equilibrium becomes stable again. This phenomenon of stability transitions is called stability switches. Multiple stability switches can occur in epidemic models. Beretta and Kuang (2002) proposed criteria to determine stability switches for models with delay-dependent coefficients. We begin from a typical characteristic equation:

$$D(\lambda,\tau) := a(\tau)\lambda + b(\tau) + c(\tau)\mathrm{e}^{-\lambda\tau} = 0, \tag{3.61}$$

where a, b, and c are real smooth functions of τ with continuous derivatives in τ. We assume

$$b(\tau) + c(\tau) \neq 0, \quad \forall \tau \geq 0, \tag{3.62}$$

to preclude the case that $\lambda = 0$ is a characteristic root.

Next, we look for conditions such that (3.61) has pure imaginary roots. First, assume that $\lambda = i\omega$ is a pure imaginary root of (3.61). Without loss of generality, we consider only $\lambda = i\omega$ with $\omega > 0$. Substituting it into

(3.61), we have

$$P(i\omega,\tau)+Q(i\omega,\tau)\mathrm{e}^{-i\omega\tau}=0, \tag{3.63}$$

where

$$P(i\omega,\tau)=b(\tau)+i\omega a(\tau), \qquad Q(i\omega,\tau)=c(\tau).$$

It follows that

$$\begin{aligned}\cos(\omega\tau)&=-\frac{b(\tau)}{c(\tau)},\\ \sin(\omega\tau)&=\frac{\omega(\tau)a(\tau)}{c(\tau)}.\end{aligned} \tag{3.64}$$

Hence, we obtain

$$F(\omega,\tau):=|P(i\omega,\tau)|^2-|Q(i\omega,\tau)|=\omega^2a^2+b^2-c^2=0. \tag{3.65}$$

By (3.65) we obtain necessary conditions that (3.61) admits pure imaginary roots:

$$\begin{aligned}&|c(\tau)|>|b(\tau)|,\\ &a(\tau)\neq 0,\\ &\omega(\tau)=\left(\frac{c^2-b^2}{a^2}\right)^{1/2}.\end{aligned} \tag{3.66}$$

Now, we assume that (3.66) holds and look for the set of τ in which (3.61) has pure imaginary roots. If $\theta(\tau)$ is a solution of the following system:

$$\begin{aligned}\cos(\theta(\tau))&=-\frac{b(\tau)}{c(\tau)},\\ \sin(\theta(\tau))&=\frac{\omega(\tau)a(\tau)}{c(\tau)},\end{aligned} \tag{3.67}$$

so is $\theta(\tau)+2n\pi$, where n is an integer. Hence, if $\omega(\tau)\tau$ satisfies (3.64), we have

$$\tau\omega(\tau)=\theta(\tau)+2n\pi,$$

which leads to

$$\tau=\frac{\theta(\tau)+2n\pi}{\omega(\tau)}.$$

Set

$$\tau_n = \frac{\theta(\tau) + 2n\pi}{\omega(\tau)}.$$

Then it is clear that (3.61) has a pure imaginary root if τ satisfies

$$S_n(\tau) := \tau - \tau_n(\tau) = 0. \tag{3.68}$$

The following theorem from Beretta and Kuang (2002) gives a criterion to compute the direction of a characteristic root that crosses the pure imaginary axis.

Theorem 3.6. *Let* (3.66) *and* (3.68) *hold. Then*

$$\operatorname{sign} \frac{\mathrm{d}Re\lambda}{\mathrm{d}\tau}\bigg|_{\lambda=i\omega} = \operatorname{sign} R(\tau),$$

where

$$\begin{aligned} R(\tau) = {} & a^2(\tau)\omega(\tau)\omega'(\tau)(a(\tau)b(\tau) + c^2(\tau)\tau) \\ & + \omega^2(\tau)a^2(\tau)(a'(\tau)b(\tau) - a(\tau)b'(\tau) + c^2(\tau)). \end{aligned}$$

We present a model of innovation diffusion with a time delay that represents an evaluation stage [Wang *et al.* (2006)] to illustrate the application of above methods. An innovation diffusion model describes how new products spread in a market through contacts between adopters and potential users, which is similar to transmissions of epidemics through contacts between infectious and susceptible individuals.

Let $A(t)$ be the number of adopters of a new product at time t, $N(t)$ be the number of potential consumers at time t, δ be the birth rate and the death rate of a population, γ be the intensity of advertisement of product, λ be the valid contact rate of adopters of the product with potential adopters, and ν be the discontinuance rate of adopters of the product. It is assumed that the rate of awareness of the new product for potential users is split into two parts: $\gamma N(t)$ which is from influences of advertisement of the product and $\lambda A(t)N(t)$ which is from contacts of adopters with potential users. We suppose that τ is the average time for an individual to evaluate the product. Specifically, if an individual is aware of the product at time $t - \tau$, the individual may leave the evaluation class in the interval $[t - \tau, t]$ due to the death or because individual is not interested in the product. Note that the survival probability through the stage is $\mathrm{e}^{-\delta\tau}$. Further, if ρ is the rate that individuals leave the evaluation class since they have decided not

to buy the product, $e^{-\rho\tau}$ is the fraction that individuals are still interested in the product at the end of the test period. Thus, the success probability through the evaluation stage, that is, the probability that an individual who is aware of the product at time $t-\tau$ does not die and remains interested in the product at time t, is $e^{-(\delta+\rho)\tau}$. Note that the awareness rate at time $t-\tau$ is $(\gamma+\lambda A(t-\tau))N(t-\tau)$. Then $(\gamma+\lambda A(t-\tau))N(t-\tau)e^{-(\delta+\rho)\tau}$ members in those persons successfully pass the evaluation stage $[t-\tau,t]$. We suppose that the individuals who pass the evaluation stage enter into the adopter class. Thus, the transfer rate from the potential consumer class to the adopter class at time t is $(\gamma+\lambda A(t-\tau))N(t-\tau)e^{-(\delta+\rho)\tau}$. Therefore, we obtain the following model:

$$\begin{aligned}\frac{dN(t)}{dt} &= \delta(N(t)+A(t)) - \delta N(t) + \nu A(t)\\ &\quad - (\gamma+\lambda A(t-\tau))N(t-\tau)e^{-(\delta+\rho)\tau},\\ \frac{dA(t)}{dt} &= (\gamma+\lambda A(t-\tau))N(t-\tau)e^{-(\delta+\rho)\tau} - (\delta+\nu)A(t).\end{aligned} \tag{3.69}$$

We suppose that δ, ν, and λ are positive constants.

From system (3.69), we obtain

$$\frac{d}{dt}(N(t)+A(t)) = 0,$$

which implies $N(t)+A(t)\equiv C$, where C is a positive constant. Thus, it suffices to consider

$$\frac{dA(t)}{dt} = p(\gamma+\lambda A(t-\tau))(C-A(t-\tau)) - \alpha A(t), \tag{3.70}$$

where $\alpha=\delta+\nu$ and $p=e^{-(\delta+\rho)\tau}$, and it is easy to see that (3.70) admits a unique positive equilibrium

$$A^* = (-p\gamma + p\lambda C - \alpha + \sqrt{(p\gamma - p\lambda C+\alpha)^2 + 4p^2\lambda\gamma C})/(2p\lambda). \tag{3.71}$$

We now look for stability switches of (3.70). Linearizing (3.70) at A^*, we obtain

$$\frac{dx(t)}{dt} = -\alpha x(t) + qx(t-\tau), \tag{3.72}$$

where

$$q = p(\lambda C - 2\lambda A^* - \gamma).$$

By substituting $x = \mathrm{e}^{\xi t}$ into (3.72), we obtain its characteristic equation

$$\xi = -\alpha + q\mathrm{e}^{-\xi\tau}. \tag{3.73}$$

From (3.65) we obtain

$$F(\omega, \tau) = \omega^2 + \alpha^2 - q^2.$$

If $\alpha^2 < q^2$, this equation admits a positive solution

$$\omega(\tau) = \sqrt{q^2 - \alpha^2}. \tag{3.74}$$

Then (3.67) becomes

$$\sin(\theta(\tau)) = -\frac{\omega(\tau)}{q(\tau)}, \quad \cos(\theta(\tau)) = \frac{\alpha}{q(\tau)}. \tag{3.75}$$

Assume that $\theta(\tau) \in (0, 2\pi)$ satisfies (3.75). Then we have

$$\tau_n = \frac{\theta(\tau) + 2n\pi}{\omega(\tau)}, \quad S_n(\tau) = \tau - \tau_n. \tag{3.76}$$

We need to show the existence of multiple zeros of $S_n(\tau)$ to confirm stability switches. However, it is difficult to verify this analytically. Then we fix the parameters and demonstrate it by numeric examples.

Example 3.1. Let us fix $C = 20, \alpha = 0.2, \lambda = 0.1, \gamma = 0.1, p = \mathrm{e}^{-0.2\tau}$. Then numeric calculations show that $\omega(\tau)$ exists when $0 \le \tau \le 6.5047$ and

$$\omega(\tau) = \sqrt{p^2\left(1.9 - 0.1\frac{19.0\,p - 2.0 + \sqrt{441.0\,p^2 - 76.0\,p + 4.0}}{p}\right)^2 - 0.04}.$$

Furthermore, $q(\tau) < 0$ when τ varies in the interval. Thus, we define

$$\theta(\tau) = \pi + \arctan\left(-\frac{\omega(\tau)}{\alpha}\right),$$

$$\tau_n(\tau) = \frac{\theta(\tau) + 2n\pi}{\omega(\tau)}.$$

By numeric calculations, we see that only $S_0(\tau) = 0$ has two roots $\tau_{01} = 1.50164$ and $\tau_{02} = 4.41394$ (see Fig. 3.4).

Calculating the term $R(\tau)$ in Theorem 3.6, we have $R(\tau_{01}) = 1$ and $R(\tau_{02}) = -1$. This shows that the real part of a characteristic root turns positive from negative sign when τ crosses 1.50164, and the real part of the

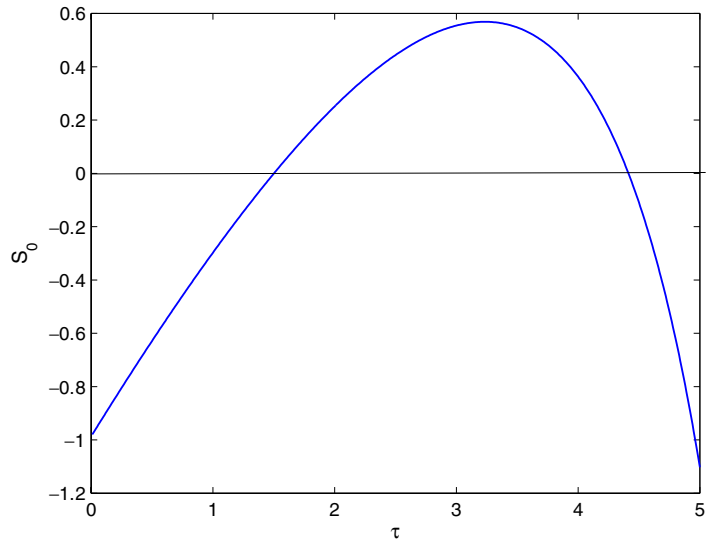


Fig. 3.4. Two roots of $S_0(\tau)$.

root turns negative from positive sign when τ crosses 4.41394. Consequently, the equilibrium becomes unstable when τ crosses 1.50164 and becomes stable when τ crosses 4.41394 such that stability switches occur.

From the above discussions, we see that it is not easy to use analytic methods to determine stability switches. Li and Ma (2006b) extended the geometric method [Beretta and Kuang (2002)], by which ultimate stability can be derived analytically.

We consider

$$D(\lambda, \tau) := P(\lambda, \tau) + Q(\lambda, \tau)\mathrm{e}^{-\lambda\tau} = 0, \tag{3.77}$$

where

$$P(\lambda, \tau) = \lambda^2 + a(\tau)\lambda + c(\tau), \quad Q(\lambda, \tau) = b(\tau)\lambda + d(\tau),$$

with $\tau \geq 0$. We make the following assumptions:

(A1) $a(\tau), b(\tau), c(\tau)$, and $d(\tau)$ are continuously differentiable in $R_{+0} = [0, +\infty)$.
(A2) $c(\tau) + d(\tau) \neq 0$ for any $\tau \in R_{+0}$.
(A3) $P(iy, \tau) + Q(iy, \tau) \neq 0$ for any $\tau \in R_{+0}$.

(A4) Every pure imaginary root of (3.77) is simple.
(A5) All roots of (3.77) have negative real parts when $\tau = 0$.

Assumption (A1) ensures that the solutions of (3.77) are continuous in τ; (A2) means that $\lambda = 0$ is not a root of (3.77); (A3) implies that $P(\lambda, \tau) = 0$ and $Q(\lambda, \tau) = 0$ do not have a common pure imaginary root; (A4) guarantees the transection of pure imaginary roots with the imaginary axis; and (A5) indicates that (3.77) is stable when $\tau = 0$.

We begin from conditions for the occurrence of pure imaginary roots of (3.77). Substituting $\lambda = iy$ into (3.77) and separating its real and imaginary parts, we obtain

$$\begin{aligned} b(\tau)y \sin y\tau + d(\tau) \cos y\tau &= -[c(\tau) - y^2], \\ d(\tau) \sin y\tau - b(\tau)y \cos y\tau &= a(\tau)y. \end{aligned} \tag{3.78}$$

It follows that

$$F(y, \tau) := y^4 - f_1(\tau)y^2 + f_2(\tau) = 0, \tag{3.79}$$

where

$$\begin{aligned} f_1(\tau) &= b^2(\tau) + 2c(\tau) - a^2(\tau), \\ f_2(\tau) &= c^2(\tau) - d^2(\tau), \\ f_3(\tau) &= f_1^2(\tau) - 4f_2(\tau). \end{aligned}$$

To determine positive solutions of (3.79) easily, we assume

(A6) Each of $f_j(\tau) = 0$ $(j = 1, 2, 3)$ has at most one positive root for any $\tau \in R_+$.

When $f_3(\tau) > 0$, if $F(y, \tau) = 0$ has roots y_+^2 and y_-^2, we have

$$y_+^2 = \frac{1}{2}\left[f_1(\tau) + \sqrt{f_3(\tau)}\right], \quad y_-^2 = \frac{1}{2}\left[f_1(\tau) - \sqrt{f_3(\tau)}\right]. \tag{3.80}$$

Assume that $y(\tau)$ is a positive root of (3.79). To make $iy(\tau)$ a pure imaginary root of (3.77), $y(\tau)$ must satisfy (3.78). From (3.78), we have

$$\begin{aligned} \sin y\tau &= \frac{-b(\tau)y(c(\tau) - y^2) + a(\tau)d(\tau)y}{b^2(\tau)y^2 + d^2(\tau)}, \\ \cos y\tau &= -\frac{d(\tau)(c(\tau) - y^2) + a(\tau)b(\tau)y^2}{b^2(\tau)y^2 + d^2(\tau)}. \end{aligned} \tag{3.81}$$

If $\tau = \tau^*$ satisfies (3.81), then $iy(\tau^*)$ is a pure imaginary root of (3.77). Now, we replace $y(\tau)\tau$ in (3.81) by $\theta(\tau)$ to obtain

$$\begin{aligned}\sin\theta(\tau) &= \frac{-b(\tau)y(c(\tau)-y^2)+a(\tau)d(\tau)y}{b^2(\tau)y^2+d^2(\tau)} \triangleq \varphi(y,\tau),\\ \cos\theta(\tau) &= -\frac{d(\tau)(c(\tau)-y^2)+a(\tau)b(\tau)y^2}{b^2(\tau)y^2+d^2(\tau)} \triangleq \psi(y,\tau).\end{aligned} \tag{3.82}$$

System (3.82) determine a function:

$$\theta(\tau) = \begin{cases} \arctan\dfrac{\varphi}{\psi}, & \text{if } \sin\theta > 0, \quad \cos\theta > 0;\\ \dfrac{\pi}{2}, & \text{if } \sin\theta = 1, \quad \cos\theta = 0;\\ \pi + \arctan\dfrac{\varphi}{\psi}, & \text{if } \cos\theta < 0;\\ \dfrac{3\pi}{2}, & \text{if } \sin\theta = -1, \quad \cos\theta = 0;\\ 2\pi + \arctan\dfrac{\varphi}{\psi}, & \text{if } \sin\theta < 0, \quad \cos\theta > 0. \end{cases} \tag{3.83}$$

If $\tau = \tau^*$ satisfies (3.81), it follows from (3.81) and (3.82) that there exists $k \in N_0 = \{0, 1, 2, 3, \ldots\}$ such that

$$y(\tau^*)\tau^* = \theta(\tau^*) + 2k\pi. \tag{3.84}$$

Now, we define

$$S(\tau) \triangleq \frac{y(\tau)\tau - \theta(\tau)}{2\pi}. \tag{3.85}$$

For convenience, we assume also

(A7) There exist at most finite solutions to equation $S(\tau) = k$ for any $k \in N_0$, and every solution is simple.

Let (A1)–(A7) hold. By the above discussions, we see that the necessary and sufficient condition that $\pm iy(\tau^*)$ are roots of (3.77) is that τ^* is a root of

$$\frac{y(\tau)\tau - \theta(\tau)}{2\pi} = k, \quad \text{that is,} \quad S(\tau) = k,$$

where $\theta(\tau)$ is defined by (3.83), and $y(\tau)$, $\tau \in (\alpha, \beta)$, is a positive root of (3.79).

The next theorem gives the direction that a pair of pure imaginary roots crosses the imaginary axis as τ varies.

Theorem 3.7. *Let* (A1) – (A7) *hold. If* $\tau^* \in (\alpha, \beta)$ *such that* $\lambda = iy(\tau^*)$ *is a root of* (3.77)*, the direction of* $\lambda(\tau)$*, when* τ *increases in a neighborhood of* $\tau = \tau^*$*, depends on*

$$V = \operatorname{sign}\left\{ f_3^{\frac{1}{2}}(\tau^*) \right\} \operatorname{sign}\left\{ \left. \frac{dS(\tau)}{d\tau} \right|_{\tau=\tau^*} \right\}.$$

(1) *If* $V = 1$ *and* τ *passes through* $\tau = \tau^*$*, then* $\lambda = \lambda(\tau)$ *passes through the imaginary axis from the left to the right.*
(2) *If* $V = -1$ *and* τ *passes through* $\tau = \tau^*$*, then* $\lambda = \lambda(\tau)$ *passes through the imaginary axis from the right to the left.*

The following two theorems give criteria for determining the stability and ultimate stability of delay-dependent equations.

Theorem 3.8. *Let* (A1)–(A7) *hold. If there is no positive solution to equation* $F(y,) = 0$ *for any* $\in (0, \infty)$*, or there is no positive solution to equation* $S(\tau) = k$ *for any* $k \in N_0$*, then* (3.77) *is stable for every* $\tau \in [0, +\infty)$.

Theorem 3.9. *Let* (A1)–(A7) *hold and* (3.77) *have pure imaginary roots for some* $\tau \in (0, +\infty)$*. Suppose that the equation*

$$F(y, \tau) = y^4 - f_1(\tau)y^2 + f_2(\tau) = 0$$

has a unique positive root $y_+(\tau)$*. Then we have*

(i) (3.77) *is ultimately stable if* $y_+(\tau)$ *is defined on a finite interval.*
(ii) *Assume that* $y_+(\tau)$ *is defined in an infinite interval. Then* (3.77) *is ultimately stable if* $\limsup_{\tau\to+\infty} S_+(\tau) < 0$*, and is ultimately unstable if* $\limsup_{\tau\to+\infty} S_+(\tau) > 0$.

Example 3.2. Let us consider an $SEIS$ model:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= (b-d)S(t) - \beta S(t)I(t) + \gamma I(t),\\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \beta S(t)I(t) - \beta S(t-\tau)I(t-\tau)\mathrm{e}^{-d\tau} - dE(t), \qquad (3.86)\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t-\tau)I(t-\tau)\mathrm{e}^{-d\tau} - (d+\alpha+\gamma)I(t),
\end{aligned}$$

where b is the birth rate of the population, d is the death rate of the population, β is the disease transmission coefficient, τ is the incubation

period, α is the disease-induced death-rate, and γ is the recovery rate of infected individuals.

When $g = b - d > 0$ and $\omega := d + \alpha + \gamma > \gamma e^{-d\tau}$, (3.86) has a unique endemic equilibrium P^*. Its characteristic equation is:

$$(\lambda + gf(\tau))(\lambda + \omega) - \omega(\lambda + g(f(\tau) - 1))e^{-\lambda\tau} = 0, \tag{3.87}$$

where

$$f(\tau) = \frac{\gamma e^{-d\tau}}{\omega - \gamma e^{-d\tau}}.$$

It is easy to see that P^* is stable when $\tau = 0$. Set

$$F(y, \tau) := y^4 + g^2 f^2(\tau) y^2 - \omega^2 g^2 [1 - 2f(\tau)] = 0. \tag{3.88}$$

When $\omega \geq 3\gamma$, (3.88) has a unique positive root $y(\tau)$, which is defined in $\tau \in (0, +\infty)$. If $\gamma < \omega < 3\gamma$, (3.88) has a unique positive root $y(\tau)$, defined in $\tau \in ((\ln(3\gamma/\omega))/d, +\infty)$. Thus, the existence interval for $y(\tau)$ is infinite in each case. Since $\lim_{\tau\to\infty} f(\tau) = 0$, we have $\lim_{\tau\to\infty} y(\tau) = \sqrt{\omega g}$. Note that

$$S(\tau) \triangleq \frac{y(\tau)\tau - \theta(\tau)}{2\pi}.$$

Then, it follows that

$$\lim_{\tau\to\infty} S(\tau) = +\infty.$$

Consequently, Theorem 3.9 shows that P^* is ultimately unstable.

3.6. An SEIRS Epidemic Model with Two Delays

Cooke and van den Driessche (1996) proposed an SEIRS model with two time delays. By neglecting disease-induced death-rate in the SEIRS model by Cooke and van den Driessche (1996), we obtain the following SEIRS epidemic model:

$$\begin{aligned} s' &= b - \lambda s(t) i(t) + \beta i(t - \tau) - b s(t), \\ i' &= \lambda\alpha s(t - \omega) i(t - \omega) - (\gamma + b) i(t), \end{aligned} \tag{3.89}$$

where s is the fraction of susceptible individuals, i is the fraction of infectious individuals, b is the birth rate and death rate of the population, λ is the average number of adequate contacts of an infectious individual per

unit time, ω is the latent period of the disease, τ is the temporary immune period of the population, γ is the recovery rate of infectious individuals, $\alpha = \exp(-b\omega)$, and $\beta = \gamma e^{-b\tau}$. Suppose $e(t)$ and $r(t)$ are the fractions of exposed individuals and recovered individuals, respectively. Since the population is divided into susceptible individuals, exposed individuals, infectious individuals and recovered individuals, we have $s(t)+e(t)+i(t)+r(t)=1$.

Wang (2002) studied the global dynamics of (3.89). Set $T=\max\{\tau,\omega\}$. Due to our background, we will consider (3.89) in the set

$$D \triangleq \left\{(\phi_1,\phi_2,\phi_3,\phi_4)\colon 0\le\phi_i(\theta), \sum_i \phi_i(\theta)=1, \theta\in[-T,0], i=1,2,3,4\right\}.$$

It is easy to show that D is positively invariant for (3.89). It is clear that $(1,0)$ is the disease free equilibrium of (3.89).

Theorem 3.10. *If $R_0=\lambda\alpha/(\gamma+b)\le 1$, the disease-free equilibrium $(1,0)$ is globally stable.*

Proof. Note that the second equation of (3.89) can be rewritten as

$$\begin{aligned} i' &= \lambda\alpha s(t)i(t) - (\gamma+b)i(t) + \lambda\alpha[s(t-\omega)i(t-\omega) - s(t)i(t)] \\ &= i(t)[\lambda\alpha s(t) - (\gamma+b)] - \lambda\alpha\frac{\mathrm{d}}{\mathrm{d}t}\int_{t-\omega}^{t}(s(u)i(u))\mathrm{d}u. \end{aligned}$$

If

$$x_t = (s(t+\theta), e(t+\theta), i(t+\theta), r(t+\theta)), \quad \theta\in[-T,0],$$

we define

$$V_0(x_t) = i(t) + \lambda\alpha\int_{t-\omega}^{t} s(\theta)i(\theta)\mathrm{d}\theta.$$

The derivative of V_0 along solutions of (3.89) is

$$V_0'(x_t) = i(t)[\lambda\alpha s(t) - (\gamma+b)] = (\gamma+b)i(t)[R_0 s(t) - 1].$$

Let $S=\{\phi\in D\colon \dot{V}_0(\phi)=0\}$ and let M be the maximal invariant set in S. If $R_0<1$, since $s(t)\le 1$, we have

$$V_0'(x_t)\le(\gamma+b)(R_0-1)i(t)\le 0.$$

It follows that $M = (1, 0)$. If $R_0 = 1$, we have

$$V_0'(x_t) = (\gamma + b)i(t)[s(t) - 1].$$

It follows that $M = (1, 0)$. We conclude from Theorems 3.2 and 3.3 that $(1, 0)$ is globally stable. □

The next theorem indicates that the disease is persistent if $R_0 > 1$.

Theorem 3.11. *Suppose $R_0 = \lambda\alpha/(\gamma + b) > 1$. Then there is a positive constant ϵ such that each positive solution $(s(t), i(t))$ of (3.89) satisfies $i(t) \geq \epsilon$, if t is large.*

Proof. Let us consider a positive solution $(s(t), i(t))$ of (3.89). According to this solution, we define

$$V_1(t) = i(t) + \lambda\alpha \int_{t-\omega}^{t} s(\theta)i(\theta)\mathrm{d}\theta.$$

Then we have

$$V_1'(t) = i(t)[\lambda\alpha s(t) - (\gamma + b)] = (\gamma + b)i(t)(R_0 s(t) - 1). \tag{3.90}$$

Since $R_0 > 1$, we have

$$I_1 := \frac{bR_0}{\lambda}\left(1 - \frac{1}{R_0}\right) > 0.$$

Claim: *For any $t_0 > 0$, it is impossible that $i(t) \leq I_1/2$, for all $t \geq t_0$.*

Suppose the contrary. Then there is a $t_0 > 0$ such that $i(t) \leq I_1/2$, for all $t \geq t_0$. The first equation of (3.89) is:

$$s' = b - \lambda s(t)i(t) + \beta i(t - \tau) - bs(t).$$

Then, for $t \geq t_0$,

$$s'(t) > b - (\lambda I_1/2 + b)s(t)$$

which implies

$$\begin{aligned} s(t) &> \mathrm{e}^{-(\lambda I_1/2+b)(t-t_0)}\left[s(t_0) + b\int_{t_0}^{t} \mathrm{e}^{(\lambda I_1/2+b)(\theta-t_0)}\mathrm{d}\theta\right] \\ &> \frac{b}{\lambda I_1/2 + b}(1 - \mathrm{e}^{-(\lambda I_1/2+b)(t-t_0)}), \end{aligned} \tag{3.91}$$

where $0 < s(t_0)$ is used. Since

$$\frac{b}{\lambda I_1/2 + b} = \frac{2}{R_0 + 1},$$

we have

$$s(t) > \frac{2}{R_0 + 1}(1 - \mathrm{e}^{-(\lambda I_1/2+b)(t-t_0)}). \tag{3.92}$$

Choose $T_1 > 0$ such that

$$\frac{1}{4}\left(1 - \frac{1}{R_0}\right) = \mathrm{e}^{-(\lambda I_1/2+b)T_1}. \tag{3.93}$$

Then (3.92) implies

$$s(t) > \frac{3R_0 + 1}{2R_0(R_0 + 1)} \triangleq \bar{R}, \quad \text{for } t \geq t_0 + T_1. \tag{3.94}$$

It is easy to see $\bar{R} > \frac{1}{R_0}$. Then, from (3.90), we have

$$V_1'(t) > (\gamma + b)i(t)(\bar{R}R_0 - 1), \quad \text{for } t \geq t_0 + T_1. \tag{3.95}$$

Set

$$\underline{i} = \min_{\theta\in[-\omega,0]} i(t_0 + T_1 + \omega + \theta).$$

Statement: *$i(t) \geq \underline{i}$, for all $t \geq t_0 + T_1$.*

Suppose the contrary. Then there is $T_2 \geq 0$, such that

$$\begin{aligned} &i(t) \geq \underline{i}, \quad \text{for } t_0 + T_1 \leq t \leq t_0 + T_1 + \omega + T_2, \\ &i(t_0 + T_1 + \omega + T_2) = \underline{i}, \\ &i'(t_0 + T_1 + \omega + T_2) \leq 0. \end{aligned}$$

However, the second equation of the model is:

$$i' = \lambda\alpha s(t - \omega)i(t - \omega) - (\gamma + b)i(t).$$

(3.94) implies that for $t = t_0 + T_1 + \omega + T_2$, we have

$$i'(t) \geq [\lambda\alpha s(t - \omega) - (\gamma + b)]\underline{i} > (\gamma + b)[R_0\bar{R} - 1]\underline{i} > 0.$$

This is a contradiction. Thus, $i(t) \geq \underline{i}$, for all $t \geq t_0 + T_1$. As a consequence, (3.95) leads to

$$V_1'(t) > (\gamma + b)\underline{i}(R_0\bar{R} - 1), \quad \text{for } t \geq t_0 + T_1,$$

which implies that as $t \to \infty, V_1(t) \to \infty$. This contradicts $V_1(t) \leq 1 + \lambda\alpha\omega$. Hence, the claim is proved.

From the claim, we are left to consider two possibilities. First, $i(t) \geq I_1/2$, for all large t. Secondly, $i(t)$ oscillates about $I_1/2$, for all large t.

Define

$$I_2 = \frac{I_1}{2} \mathrm{e}^{-(\gamma+b)(T_1+\omega)}. \tag{3.96}$$

We hope to show that $i(t) \geq I_2$ for all large t. The conclusion is evident in the first case. For the second case, let t_1 and t_2 satisfy

$$i(t_1) = i(t_2) = I_1/2,$$

$$i(t) < I_1/2 \quad \text{for } t_1 < t < t_2.$$

If $t_2 - t_1 \leq T_1 + \omega$, since $i'(t) > -(\gamma + b)i(t)$ and $i(t_1) = I_1/2$, it is obvious that $i(t) \geq I_2$, for $t_1 < t < t_2$. If $t_2 - t_1 \geq T_1 + \omega$, by the second equation of the model

$$i' = \lambda\alpha s(t - \omega)i(t - \omega) - (\gamma + b)i(t),$$

we obtain

$$i' > -(\gamma + b)i(t).$$

It leads to $i(t) \geq I_2$, for $t \in [t_1, t_1 + T_1 + \omega]$. For $t_1 + T_1 + \omega \leq t \leq t_2$, we have

$$S(t) > \bar{R}, \quad \text{for } t \in [t_1 + T_1, t_2].$$

Set

$$i_* = \min_{\theta \in [-\omega, 0]} i(t_1 + T_1 + \omega + \theta) \geq I_2.$$

Proceeding exactly as the proof for above claim, we see that $i(t) \geq i_* \geq I_2$ for $t_1 + T_1 + \omega \leq t \leq t_2$. Consequently, $i(t) \geq I_2$ for $t \in [t_1, t_2]$.

Since this kind of interval $[t_1, t_2]$ is chosen in an arbitrary way (we only need t_1 and t_2 are large), we conclude that $i(t) \geq I_2$ for all large t in the second case.

In view of our above discussions, the choices of T_1 and I_2 are independent of the positive solution, we have actually proved that any positive solution of (3.89) satisfies $i(t) \geq I_2$ for all large t. The proof is complete. □

3.7. Quiescence of Epidemics in a Patch Model

In this section, we consider the global stability of the disease-free equilibrium of model (3.19), where patchy structure and age structure are incorporated. Its difficulty is that the disease-free equilibrium cannot be solved analytically. Thus, we are forced to use abstract theory to deduce its existence and uniqueness.

For simplicity, we neglect the recovery rates in (3.19) to obtain

$$\begin{aligned}
&\frac{\mathrm{d}S_i}{\mathrm{d}t} = R_i(t) - d_i S_i - \beta_i S_i I_i + \sum_{j=1}^{n} a_{ij} S_j,\\
&\frac{\mathrm{d}I_i}{\mathrm{d}t} = \beta_i S_i I_i - d_i I_i + \sum_{j=1}^{n} b_{ij} I_j, \quad i = 1, \ldots, n. \qquad (3.97)\\
&(R_1(t), \ldots, R_n(t))^{\mathrm{T}} = \exp(C_J r) G(A(t-r)),
\end{aligned}$$

Here we recall that

$$C_J = \begin{bmatrix} -\mu_1 + c_{11} & c_{12} & \cdots & c_{1n} \\ c_{21} & -\mu_2 + c_{22} & \cdots & c_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ c_{n1} & c_{n2} & \cdots & -\mu_n + c_{nn} \end{bmatrix},$$

where c_{ij} are dispersal rates of juveniles and μ_i are the death rates of juveniles, and that

$$G(A) = (B_1(A_1)A_1, \ldots, B_n(A_n)A_n)^{\mathrm{T}},$$

where B_i is the per capita birth rate of adult population in patch i. In addition to assumptions (A1) and (A2) in Sec. 3.1.2, we further assume that all of a_{ij} and b_{ij}, $i \neq j$, are positive constants.

Our objective is to establish sufficient conditions for the existence and uniqueness of a disease-free equilibrium of (3.97).

We start with the introduction of cooperative systems of delay differential equations. For $x, y \in R^n$, we write $x \geq y$, if $x - y \in R^n_+$, $x > y$, if $x - y \in R^n_+ \backslash \{0\}$, and $x \gg y$, if $x - y \in \mathrm{int}(R^n_+)$. Let r be a nonnegative real number and $x(t)$ be a continuous function from $[-r, \sigma)$ to $R^n (\sigma > 0)$. For each $t \in [0, \sigma)$, we define $x_t \in C([-r, 0], R^n)$

by $x_t(\theta) = x(t+\theta)$, $\forall\theta \in [-r, 0]$. Consider an autonomous delay system

$$\frac{\mathrm{d}x(t)}{\mathrm{d}t} = f(x_t) \tag{3.98}$$

where $f: D \to R^n$ is Lipschitz continuous and D is an open subset of $C([-r, 0], R^n)$. For any $\phi \in D$, let $x(t, \phi)$ be the unique solution of (3.98) satisfying $x(\theta, \phi) = \phi(\theta)$, $\forall\theta \in [-r, 0]$. For $\phi, \psi \in C([-r, 0], R^n)$, we write $\phi \leq \psi$, if $\phi(\theta) \leq \psi(\theta)$, $\forall\theta \in [-r, 0]$. System (3.98) is said to be cooperative if the following quasimonotone condition holds:

(Q) Whenever $\phi \leq \psi$ and $\phi_i(0) = \psi_i(0)$ holds for some i, then $f_i(\phi) \leq f_i(\psi)$.

In particular, system (3.98) with $r = 0$, an autonomous ordinary differential system, is cooperative if off-diagonal elements of Jacobian matrix of f at any point in the domain are nonnegative. A typical example is the cooperative Lotka–Volterra system:

$$\frac{\mathrm{d}x_i(t)}{\mathrm{d}t} = x_i \left[r_i + \sum_{j=1}^{n} a_{ij} x_j \right], \quad i = 1, \ldots, n$$

where a_{ij} are nonnegative constants for $i \neq j$. For cooperative delayed system, we give an example from Takeuchi *et al.* (2006):

$$\begin{aligned} &\dot{x}_i(t) = x_i(t)[a_i - b_i x_i(t)] + \sum_{j=1}^{n} \{\epsilon_{ij} d_{ij} x_j(t - \tau_{ij}) - d_{ji} x_i(t)\}, \\ &i = 1, 2, \ldots, n. \end{aligned} \tag{3.99}$$

This models describes the population dispersal among n patches. Here, x_i is the density of a population in patch i, $d_{ij}(t)$ is the dispersal coefficient of the population from patch j to patch i, τ_{ij} represents a constant time for an individual to disperse from patch j to i, $\gamma_{ij} \geq 0$ denotes the per capita death rate of travelers from patch j to i, $\epsilon_{ij} = \mathrm{e}^{-\gamma_{ij}\tau_{ij}}$ gives the survival probability that an individual travels from patch j to patch i, a_i is the intrinsic growth rate of population in patch i, and b_i is the density-dependent coefficient.

One of the main advantages in the analysis of cooperative systems is that the comparison principle holds [Smith (1995)]. This means that if

$\phi \leq \psi$, we have $x(t,\phi) \leq x(t,\psi)$ for those $t \geq 0$, for which both solutions exist.

We are now ready to consider the existence and uniqueness of disease-free equilibrium of (3.97). If $(S_1^*, \ldots, S_n^*, 0, \ldots, 0)$ is a disease-free equilibrium of (3.97), then it is easy to see that $(S_1^*, \ldots, S_n^*)$ is an equilibrium of the following ordinary differential system:

$$\frac{\mathrm{d}S_i}{\mathrm{d}t} = \bar{R}_i(S) - d_i S_i + \sum_{j=1}^{n} a_{ij} S_j, \quad i = 1, \ldots, n, \tag{3.100}$$

where

$$S = (S_1, \ldots, S_n) \in R_+^n, (\bar{R}_1(S), \ldots, \bar{R}_n(S))^{\mathrm{T}} := \exp(C_J r) G(S).$$

Thus, we look for conditions such that (3.100) has a unique positive equilibrium. Note that $\exp(C_J t)$ is the fundamental solution matrix of the following cooperative system:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = C_J x.$$

If $\exp(C_J r) = (p_{ij})$, we have $p_{ij} \geq 0$, $\forall 1 \leq i, j \leq n$ (see, for example, [Smith (1995)]), and

$$\bar{R}_i(S) = \sum_{j=1}^{n} p_{ij} G_j(S_j). \tag{3.101}$$

We assume

$$\frac{\mathrm{d}G_i(A_i)}{\mathrm{d}A_i} \geq 0, \quad \forall A_i \in (0, \infty), \ \ i = 1, \ldots, n. \tag{3.102}$$

Then, (3.100) becomes cooperative. To find conditions that (3.100) has a unique positive equilibrium, we need the following notion and technical lemma from Zhao (2003). Let us consider

$$\frac{\mathrm{d}x}{\mathrm{d}t} = F(x), \tag{3.103}$$

where $F: U \to R^n$ is continuously differentiable.

Definition 3.1. System (3.103) is said to be strongly sublinear in U, if $F(\lambda x) \gg \lambda F(x)$, for any $x \in U$ with $x \gg 0$, and $\lambda \in (0, 1)$.

Lemma 3.1. *Suppose that* (3.103) *is cooperative and strongly sublinear in* R^n_+. *If every positive orbit has a compact orbit closure in the positive cone, then it converges to a unique positive equilibrium.*

To apply Lemma 3.1 to (3.100), we define $H = (H_1, \dots, H_n)$: $R^n_+ \to R^n$ by

$$H_i(S) = \bar{R}_i(S) - d_i S_i + \sum_{j=1}^{n} a_{ij} S_j, \quad \forall S \in R^n_+, \ 1 \le i \le n.$$

For any $\alpha \in (0,1)$ and $S \gg 0$, by (3.101) and (A2), we have

$$\bar{R}_i(\alpha S) - d_i \alpha S_i + \sum_{j=1}^{n} a_{ij} \alpha S_j > \alpha \left[\bar{R}_i(S) - d_i S_i + \sum_{j=1}^{n} a_{ij} S_j \right],$$

for each $i = 1, 2, \dots, n$, and hence, $H(\alpha S) \gg \alpha H(S)$, which means that H is strongly sublinear on R^n_+.

To find conditions such that (3.100) has a compact orbit closure in the positive cone, for $S \gg 0$, we denote the following matrix by $M(S)$:

$$\begin{bmatrix} p_{11}B_1(S_1) - d_1 + a_{11} & a_{12} + p_{12}B_2(S_2) & \cdots & a_{1n} + p_{1n}B_n(S_n) \\ p_{21}B_1(S_1) + a_{21} & p_{22}B_2(S_2) - d_2 + a_{22} & \cdots & p_{2n}B_n(S_n) + a_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ p_{n1}B_1(S_1) + a_{n1} & p_{n2}B_2(S_2) + a_{n2} & \cdots & p_{nn}B_n(S_n) - d_n + a_{nn} \end{bmatrix}.$$

Recall that the stability modulus of the matrix M, denoted by $s(M)$, is defined by

$$s(M) := \max\{Re\,\lambda \colon \lambda \text{is an eigenvalue of } M\}.$$

Since M has positive off-diagonal elements, by nonnegative matrix theory, we see that $s(M)$ is a simple eigenvalue of M with a (componentwise) positive eigenvector.

In what follows we use notation $K = (k, \dots, k) \in R^n$ for each $k \in R$, and let $H'(S)$ be the Jacobian matrix of H at $S \in R^n_+$.

Theorem 3.12. *Let* (A1), (A2) *and* (3.102) *hold. Assume that* a_{ij} *and* b_{ij}, $i \neq j$, *are positive constants. If* $s(H'(0)) > 0$ *and* $s(M(K)) < 0$ *for all large* k, *then* (3.97) *has a unique disease-free equilibrium*

$$E_0 = (S_1^*, S_2^*, \ldots, S_n^*, 0, \ldots, 0).$$

Proof. Let k be large enough such that $s(M(K)) < 0$, and $\bar{v} = (\bar{v}_1, \ldots, \bar{v}_n)$ be a positive eigenvector associated with $s(M(K))$. Choose $l > 0$ large enough such that $l\bar{v}_i > k$, $i = 1, 2, \ldots, n$. By (A2) we have

$$0 > s(M(K))l\bar{v} = M(K)l\bar{v} > H(l\bar{v}), \quad \forall t \geq 0. \tag{3.104}$$

Let $S(t, l\bar{v})$ be the solution of (3.100) satisfying $S(0, l\bar{v}) = l\bar{v}$. Since (3.100) is cooperative, it follows from (3.104) that $S(t, l\bar{v})$ is nonincreasing in $t \geq 0$, and converges to an equilibrium as t approaches infinity (see, for example, Corollary 5.2.2 of Smith (1995)). Similarly, since $s(H'(0)) > 0$, we can find a point on the unstable manifold of equilibrium 0 in the interior of R_+^n such that the solution starting from this point is increasing. Note also that the point can be chosen as close to the origin as we wish. We see that the origin repels positive solutions of (3.100). Therefore, every positive orbit of (3.100) has a positive lower bound and a positive upper bound. It follows from Lemma 3.1 that system (3.100) has one positive equilibrium, which is globally asymptotically stable for $S \in R_+^n \setminus \{0\}$. Consequently, (3.97) has a unique disease-free equilibrium. □

Let M_1 denote the matrix

$$\begin{bmatrix} \beta_1 S_1^* - d_1 + b_{11} & b_{12} & \cdots & b_{1n} \\ b_{21} & \beta_2 S_2^* - d_2 + b_{22} & \cdots & b_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ b_{n1} & b_{n2} & \cdots & \beta_n S_n^* - d_n + b_{nn} \end{bmatrix}.$$

Clearly, M_1 is irreducible since b_{ij}, $j \neq i$, are positive. Then $s(M_1)$ is a simple eigenvalue of M_1 with a positive eigenvector. It is easy to see that the disease-free equilibrium E_0 is asymptotically stable if $s(M_1) < 0$. The next theorem gives sufficient conditions that the equilibrium is globally stable.

Theorem 3.13. *Let the assumptions of Theorem* 3.12 *hold. Suppose that* $a_{ij} = b_{ij}$ *for* $i = 1, \ldots, n, j = 1, \ldots, n$. *Then* E_0 *is globally stable if* $s(M_1) < 0$.

Proof. Note that $A_i = S_i + I_i$, $\forall 1 \leq i \leq n$. By (3.97), we have

$$\frac{\mathrm{d}A_i}{\mathrm{d}t} = \bar{R}_i(A(t-r)) - d_i A_i + \sum_{j=1}^{n} a_{ij} A_j, \quad i = 1, \ldots, n. \tag{3.105}$$

Note that (3.105) is a delayed cooperative system. Proceeding essentially the same as in the proof of Theorem 3.12, we see that (3.105) admits a positive equilibrium $(S_1^*, S_2^*, \ldots, S_n^*)$, that is globally stable. (See [Wang, Fergola and Tenneriello (1997)] for details.) Since $A_i = S_i + I_i$, $\forall 1 \leq i \leq n$, for any $\epsilon > 0$, there exists $t_0 > 0$ such that $S_i(t) \leq S_i^* + \epsilon$, $\forall t \geq t_0$, $i = 1, \ldots, n$. It follows that

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} \leq (\beta_i(S_i^* + \epsilon) - d_i)I_i + \sum_{j=1}^{n} b_{ij} I_j, \quad \forall t \geq t_0, \ \ i = 1, \ldots, n. \tag{3.106}$$

Let us consider an auxiliary system

$$\frac{\mathrm{d}I_i}{\mathrm{d}t} = (\beta_i(S_i^* + \epsilon) - d_i)I_i + \sum_{j=1}^{n} b_{ij} I_j, \quad i = 1, \ldots, n. \tag{3.107}$$

Let $\epsilon > 0$ be small enough such that $s(M_1 + \epsilon\beta) < 0$. It follows that all the solutions of (3.107) tend to the origin as t tends to infinity. Since (3.107) is cooperative, it follows from the comparison principle that $I_i(t) \to 0$ as $t \to \infty, i = 1, \ldots, n$. Again, using $A_i = S_i + I_i$, we have $S_i(t) \to S_i^*$, as $t \to \infty, i = 1, \ldots, n$. □

3.8. Basic Reproductive Numbers in ODE Models

The basic reproductive number for an infectious disease is a fundamental concept in the study of disease transmissions. It is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual. Usually, the basic reproductive number defines the threshold for classic epidemic models. In a common case, a disease dies out if the basic reproductive number is less than unity and the disease is established in the population if the basic reproductive number is greater than unity (see, for example, Li *et al.* (2004)). The purpose of this section is to present mathematical methods to calculate basic reproductive numbers of epidemic models with patchy structures described by ordinary differential equations.

If a model has only one infected compartment, the basic reproductive number, denoted by R_0, is just the infection rate times the expectation of infection period. van den Driessche and Watmough (2002) proposed a general framework to compute basic reproductive numbers for epidemic models with multiple infected compartments.

Let $x = (x_1, \ldots, x_n)^{\mathrm{T}}$, with each $x_i \geq 0$, be the state of individuals in each compartment. We assume that the compartments can be divided into two types: infected compartments, labeled by $i = 1, \ldots, m$, and uninfected compartments, labeled by $i = m+1, \ldots, n$. Define X_s to be the set of all disease-free states:

$$X_s := \{x \geq 0 : \ x_i = 0, \ \forall i = 1, \ldots, m\}.$$

Let $\mathcal{F}_i(x)$ be the input rate of newly infected individuals in the ith compartment, $\mathcal{V}_i^+(x)$ be the input rate of individuals by other means (for example, births, immigrations), and $\mathcal{V}_i^-(t, x)$ be the rate of transfer of individuals out of compartment i (for example, deaths, recovery and emigrations). Thus, the disease transmission model is governed by an autonomous ordinary differential system:

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = \mathcal{F}_i(x) - \mathcal{V}_i(x) \triangleq f_i(x), \quad i = 1, \ldots, n, \tag{3.108}$$

where $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$.

Suppose that x_0 is a disease-free equilibrium. By direct calculations, we obtain

$$D_x\mathcal{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, \quad D_x\mathcal{V}(x_0) = \begin{pmatrix} V & 0 \\ J & -M \end{pmatrix},$$

where F and V are two $m \times m$ matrices defined by

$$F = \left(\frac{\partial \mathcal{F}_i(x_0)}{\partial x_j}\right)_{1 \leq i,j \leq m}, \quad V = \left(\frac{\partial \mathcal{V}_i(x_0)}{\partial x_j}\right)_{1 \leq i,j \leq m}, \tag{3.109}$$

respectively, and J is an $(n-m) \times n$ matrix. Furthermore, F is nonnegative, and $-V$ is cooperative in the sense that the off-diagonal elements of $-V$ are nonnegative.

Let $\psi(0)$ be the distribution of infected individuals at time 0, and $\psi(t)$ be the distribution of remaining individuals of those members after t time units. In a small neighborhood of the disease-free equilibrium, F is the infection rate matrix, and e^{-Vt} describes the evolution of infected

individuals driven by internal forces such as deaths, immigrations, and transitions among infected compartments. Thus, $\psi(t) = \mathrm{e}^{-Vt}\psi(0)$. As a consequence, $F\mathrm{e}^{-Vt}\psi(0)$ gives the new infection rate reproduced by remaining infected members at time t. Integrating it from 0 to infinity gives $FV^{-1}\psi(0)$. For this reason, van den Driessche and Watmough (2002) call FV^{-1} as the next infection matrix and define its spectral radius as the basic reproductive number; that is,

$$R_0 := \rho(FV^{-1}). \tag{3.110}$$

It is shown by van den Driessche and Watmough (2002) that the disease-free equilibrium is stable if $R_0 < 1$, and is unstable if $R_0 > 1$. This means that the basic reproductive number really acts as a threshold quantity for disease invasion in a small neighborhood of the disease-free equilibrium.

Example 3.3. By setting $\tau = 0$ in (3.6), we obtain

$$\begin{aligned}
\frac{\mathrm{d}I}{\mathrm{d}t} &= \beta S(t)I(t) - dI(t) - \gamma I(t),\\
\frac{\mathrm{d}S}{\mathrm{d}t} &= A - dS(t) - \beta S(t)I(t),\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \gamma I(t) - dR(t).
\end{aligned} \tag{3.111}$$

Its disease-free equilibrium is $(0, A/d, 0)$. Since there is only one infected compartment for (3.111), it is easy to obtain $F = \beta A/d$ and $V = d + \gamma$. Consequently,

$$R_0 = \frac{\beta A}{d} \times \frac{1}{d+\gamma} = \frac{\beta A}{d(d+\gamma)}.$$

Example 3.4. Let us consider the staged progression model:

$$\begin{aligned}
\dot{I}_1 &= \sum_{k=1}^{m-1} \beta_k S I_k/N - (\nu_1 + d_1)I_1,\\
\dot{I}_i &= \nu_{i-1}I_{i-1} - (\nu_i + d_i)I_i, \quad i = 1, \ldots, m-1,\\
\dot{I}_m &= \nu_{m-1}I_{m-1} - d_m I_m,\\
\dot{S} &= b - bS - \sum_{k=1}^{m-1} \beta_k S I_k/N,
\end{aligned} \tag{3.112}$$

which was proposed by Hyman *et al.* (1999). Here, S is the number of susceptible individuals. The infected population is subdivided into m subgroups, $I_1, I_2, \ldots, I_m$, with different infection stages such that infected susceptible individuals enter the first subgroup I_1 and then gradually progress from subgroup I_1 finally to subgroup I_m. ν_i is the average rate of progression from subgroup i to subgroup $i+1$. d_i is the death rate of infectious individuals in stage i, and b is the birth rate and death rate of susceptible individuals. It is assumed that individuals in subgroup I_m are no longer transmit the disease.

The unique disease-free equilibrium has $I_i = 0, i = 1, \ldots, m$, and $S = 1$. For simplicity, we define $\nu_m = 0$. Then $F = (F_{ij})$ and $V = (V_{ij})$, where

$$F_{ij} = \begin{cases} \beta_j, & i = 1, j \le m-1, \\ 0, & \text{otherwise}, \end{cases}$$

$$V_{ij} = \begin{cases} \nu_j + d_i, & j = i, \\ -\nu_j, & i = 1 + j, \\ 0, & \text{otherwise}. \end{cases}$$

Set $V^{-1} = (a_{ij})$. Then

$$a_{ij} = \begin{cases} 0, & i < j, \\ 1/(\nu_i + d_i), & i = j, \\ \displaystyle\prod_{k=j}^{i-1} \nu_k / \prod_{k=j}^{i} (\nu_k + d_k), & j < i. \end{cases}$$

It follows from (3.110) that

$$R_0 = \frac{\beta_1}{\nu_1 + d_1} + \frac{\beta_2 \nu_1}{(\nu_1 + d_1)(\nu_2 + d_2)} + \cdots + \frac{\beta_{m-1} \nu_1 \cdots \nu_{m-2}}{(\nu_1 + d_1) \cdots (\nu_{m-1} + d_{m-1})}.$$

Example 3.5. We consider model (3.12) where there are only two patches and the per capita birth rates are given by

$$B_i(N_i) = \frac{r_i}{N_i} + c_i, \quad c_i < \mu_i, \ \ 1 \le i \le 2.$$

Then we have

$$\begin{aligned}
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta_1 S_1 I_1 - (\mu_1 + \gamma_1 - b_{11}) I_1 - b_{22} I_2, \\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \beta_2 S_2 I_2 - (\mu_2 + \gamma_2 - b_{22}) I_2 - b_{11} I_1, \\
\frac{\mathrm{d}S_1}{\mathrm{d}t} &= r_1 + c_1 I_1 - (\mu_1 - c_1 - a_{11}) S_1 - \beta_1 S_1 I_1 + \gamma_1 I_1 - a_{22} S_2, \\
\frac{\mathrm{d}S_2}{\mathrm{d}t} &= r_2 + c_2 I_2 - (\mu_2 - c_2 - a_{22}) S_2 - \beta_2 S_2 I_2 + \gamma_2 I_2 - a_{11} S_1,
\end{aligned} \tag{3.113}$$

where a_{ii} and b_{ii} are negative constants.

The disease-free equilibrium $(0, 0, S_1^*, S_2^*)$ for this model can be solved explicitly as

$$\begin{aligned}
S_1^* &= \frac{r_2 a_{22} - \mu_2 r_1 + c_2 r_1 + r_1 a_{22}}{-\mu_2\mu_1 + \mu_2 c_1 + \mu_2 a_{11} + c_2\,\mu_1 - c_2\,c_1 - c_2\,a_{11} + \mu_1\,a_{22} - c_1 a_{22}}, \\
S_2^* &= \frac{-\mu_1 r_2 + c_1 r_2 + a_{11} r_2 + a_{11} r_1}{-\mu_2\mu_1 + \mu_2\,c_1 + \mu_2 a_{11} + c_2\mu_1 - c_2 c_1 - c_2 a_{11} + \mu_1 a_{22} - c_1 a_{22}}.
\end{aligned}$$

For model (3.113), we have

$$F = \begin{bmatrix} \beta_1 S_1^* & 0 \\ 0 & \beta_2 S_2^* \end{bmatrix}$$

and

$$V = \begin{bmatrix} \mu_1 + \gamma_1 - b_{11} & b_{22} \\ b_{11} & \mu_2 + \gamma_2 - b_{22} \end{bmatrix}.$$

It follows that

$$FV^{-1} = \begin{bmatrix} \dfrac{\beta_1 S_1^*(-\mu_2 - \gamma_2 + b_{22})}{\mathrm{w}} & \dfrac{\beta_1 S_1^* b_{22}}{\mathrm{w}} \\ \dfrac{\beta_2 S_2^* b_{11}}{\mathrm{w}} & -\dfrac{\beta_2 S_2^*(\mu_1 + \gamma_1 - b_{11})}{\mathrm{w}} \end{bmatrix},$$

where

$$\mathrm{w} = -\mu_1\mu_2 - \mu_1\gamma_2 + \mu_1 b_{22} - \gamma_1\mu_2 - \gamma_1\gamma_2 + \gamma_1 b_{22} + b_{11}\mu_2 + b_{11}\gamma_2.$$

Then it is easy to obtain an explicit formula for the basic reproductive number

$$R_0 = \frac{1}{2}\left(\mathrm{tr}(FV^{-1}) + \sqrt{(\mathrm{tr}(FV^{-1}))^2 - 4\det(FV^{-1})}\right). \tag{3.114}$$

To reveal the influences of population dispersal on the spread of epidemic diseases, we fix $r_1 = 1, r_2 = 5$, which means that there are different population birth coefficients in the two patches; fix $\beta_1 = 1.5, \beta_2 = 0.1$, which means that the two patches have different disease transmission coefficients; and fix $c_1 = c_2 = 1, \mu_1 = \mu_2 = 2, \gamma_1 = \gamma_2 = 0$. Then when two patches are disconnected, we see that the basic reproductive number of the epidemic disease is 0.75 in the first patch, and 0.25 in the second patch. By means of techniques of persistence of dynamic systems (see, for example, Thieme (1993)), it is shown by Wang and Zhao (2004) that the disease dies out in each patch when the two patches are isolated.

Then, we take $a_{11} = b_{11} = -0.3, a_{22} = b_{22} = -0.3k$, where k is a positive constant. This means susceptible individuals and infected individuals in each patch have the same dispersal rate, but different patch may have different migration rates. Then by direct calculations from (3.114), we see that $R_0 < 1$ if $0 < k < 0.7139$, $R_0 > 1$ if $k > 0.7139$. It is shown by Wang and Zhao (2004) that $R_0 > 1$ implies that the disease persists in the two patches. Thus, the disease spreads in the two patches if $k > 0.7139$, even though the disease cannot spread in any patch when they are isolated.

3.9. Basic Reproductive Numbers of Models with Delays

We start by considering the basic reproductive number of (3.97). If we let $x_i = I_i$, for $i = 1, \ldots, n$, and $x_{n+i} = S_i$, for $i = 1, \ldots, n$, then we have

$$\frac{\mathrm{d}x_i}{\mathrm{d}t} = f_i(x) = \mathcal{F}_i(x) - \mathcal{V}_i(x), \quad i = 1, \ldots, n,$$

where

$$\mathcal{F}_i(x) = \beta_i x_i x_{n+i}, \quad \mathcal{V}_i(x) = d_i x_i - \ b_{ij} x_j, \ \text{ for } \ i = 1, \ldots, n.$$

Here we do not write the equations for $i = n+1, \ldots, 2n$, since they are not important at this moment. Furthermore, the disease free equilibrium E_0 now becomes $(0, \ldots, 0, S_1^*, S_2^*, \ldots, S_n^*)$. For $i = 1, \ldots, n$, $\mathcal{F}_i(x)$ is the rate of appearance of new infections in compartment i, and $\mathcal{V}_i(x)$ is the net

decreasing rate of infectives in compartment i due to infective flows inside the system of infected compartments.

If $\mathcal{F} = (\mathcal{F}_1, \ldots, \mathcal{F}_{2n})$ and $\mathcal{V} = (\mathcal{V}_1, \ldots, \mathcal{V}_{2n})$, let us partition the derivatives $D\mathcal{F}(E_0)$ and $D\mathcal{V}(E_0)$ as

$$D\mathcal{F}(E_0) = \begin{bmatrix} F & 0 \\ 0 & 0 \end{bmatrix}, \quad D\mathcal{V}(E_0) = \begin{bmatrix} V & 0 \\ J_3 & J_4 \end{bmatrix},$$

where

$$F = \left[\frac{\partial \mathcal{F}_i}{\partial x_j}(E_0)\right]_{n\times n}, \quad V = \left[\frac{\partial \mathcal{V}_i}{\partial x_j}(E_0)\right]_{n\times n}.$$

Then it is easy to obtain

$$F = \begin{bmatrix} \beta_1 S_1^* & 0 & \cdots & 0 \\ 0 & \beta_2 S_2^* & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & \cdots & \beta_n S_n^* \end{bmatrix},$$

and

$$V = \begin{bmatrix} d_1 - b_{11} & -b_{12} & \cdots & -b_{1n} \\ -b_{21} & d_2 - b_{22} & \cdots & -b_{2n} \\ \vdots & \vdots & \vdots & \vdots \\ -b_{n1} & -b_{n2} & \cdots & d_n - b_{nn} \end{bmatrix}.$$

Following Diekmann *et al.* (1990) and van den Driessche and Watmough (2002), the matrix FV^{-1} is called the next infection matrix, and its spectral radius is defined as the basic reproductive number for (3.97); that is,

$$R_0 := \rho(FV^{-1}). \tag{3.115}$$

Example 3.6. Let us consider model (3.97) where there are only two patches and per capita birth rates are given by (B3) in Sec. 3.1.2:

$$B_i(A_i) = \frac{k_i}{A_i} + l_i$$

with $k_i > 0, l_i > 0$. Then (3.97) is reduced to:

$$\begin{aligned}
\frac{\mathrm{d}S_i}{\mathrm{d}t} &= R_i(t) - (d_i + a_i)S_i - \beta_i S_i I_i + a_j S_j, \quad i, j = 1, 2, \ \ i \neq j, \\
\frac{\mathrm{d}I_i}{\mathrm{d}t} &= \beta_i S_i I_i - (d_i + b_i)I_i + b_j I_j, \quad i, j = 1, 2, \ \ i \neq j,
\end{aligned} \tag{3.116}$$

where a_i and b_i are the migration rates of adult susceptibles and infectives, respectively. If c_i is the migration rate of juveniles in patch i, that is, $c_1 = -c_{11} = c_{21}$ and $c_2 = -c_{22} = c_{12}$, and $\exp(C_J r)$ is written as (p_{ij}), we have

$$\begin{aligned}
R_1(t) &= p_{11}(k_1 + l_1 A_1(t - r)) + p_{12}(k_2 + l_2 A_2(t - r)), \\
R_2(t) &= p_{21}(k_1 + l_1 A_1(t - r)) + p_{22}(k_2 + l_2 A_2(t - r)).
\end{aligned}$$

Let $E_0 = (S_1^*, S_2^*, 0, 0)$ be the disease-free equilibrium of (3.116). Then S_1^* and S_2^* can be easily obtained by solving the following linear system:

$$\begin{aligned}
p_{11}(k_1 + l_1 S_1^*) + p_{12}(k_2 + l_2 S_2^*) - (d_1 + a_1)S_1^* + a_2 S_2^* = 0, \\
p_{21}(k_1 + l_1 S_1^*) + p_{22}(k_2 + l_2 S_2^*) - (d_2 + a_2)S_2^* + a_1 S_1^* = 0.
\end{aligned}$$

For model (3.116), we have

$$F = \begin{bmatrix} \beta_1 S_1^* & 0 \\ 0 & \beta_2 S_2^* \end{bmatrix}$$

and

$$V = \begin{bmatrix} d_1 + b_1 & -b_2 \\ -b_1 & d_2 + b_2 \end{bmatrix}.$$

By direct calculations, we obtain

$$M := FV^{-1} = \begin{bmatrix} \dfrac{\beta_1 S_1^*(d_2 + b_2)}{w} & \dfrac{\beta_1 S_1^* b_2}{w} \\ \dfrac{\beta_2 S_2^* b_1}{w} & \dfrac{\beta_2 S_2^*(d_1 + b_1)}{w} \end{bmatrix},$$

where

$$w = d_1\, d_2 + d_1\, b_2 + b_1\, d_2.$$

By (3.115), we have

$$R_0 = \frac{1}{2}\left(\mathrm{tr}(M) + \sqrt{(\mathrm{tr}(M))^2 - 4\det(M)}\right).$$

For the illustration purpose, we fix $a_1 = a_2 = b_1 = b_2 = 0.2$, $\mu_1 = \mu_2 = 2$, $d_1 = d_2 = 0.5$, $l_1 = l_2 = 1$, $k_1 = k_2 = 1$, $r = 1$, $\beta_1 = 1.4$, $\beta_2 = 1.25$, $c_1 = 0.6$. This means that the two patches have the same migration rates for susceptible and infected adults, the same death rates for juveniles, the same death rates for adults, the same birth coefficients, but distinct disease transmission coefficients. If we take the migration rate of juveniles in the first patch is 0.6, as c_2 increases from 0, numeric calculations (see Fig. 3.5) show that $R_0 > 1$, when $0 < c_2 < 0.1064$ or $0.7607 < c_2$, and $R_0 < 1$, when $0.1064 < c_2 < 0.7607$. It is shown by Wang and Zhao (2005) that the disease persists in the two patches when $R_0 > 1$, and dies out in the two patches when $R_0 > 1$. Thus, the disease undergoes a transition from the uniform persistence to extinction and a second transition from extinction to the uniform persistence; that is, there exists a persistence–extinction–persistence switches, as the dispersal rate c_2 increases from 0.

Now, we consider the basic reproductive number of (3.29). For simplicity, we assume henceforth that two birth functions of populations in two patches are

$$B_i(N_i) = \frac{A_i}{N_i} + B_i, \quad i = 1, 2.$$

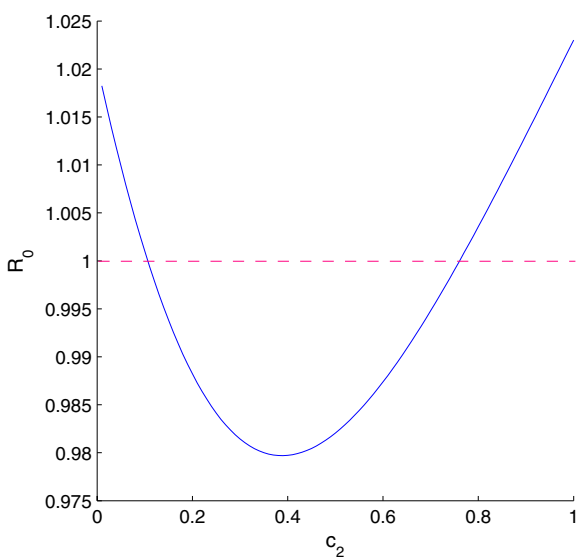


Fig. 3.5. The graph of the basic reproductive number R_0 versus the migration rate from the second patch c_2.

Then the model (3.29) reduces to

$$\begin{aligned}
&\frac{\mathrm{d}\mathbf{P}}{\mathrm{d}t} = \mathbf{Q}(t) - \exp(\mathbf{B}\tau)\mathbf{Q}(t-\tau) + \mathbf{B}\mathbf{P}(t),\\
&\frac{\mathrm{d}S_1}{\mathrm{d}t} = A_1 + B_1 N_1(t) - (\mu_1 + d_1)S_1(t) - Q_1(t) + d_2 S_2(t),\\
&\frac{\mathrm{d}S_2}{\mathrm{d}t} = A_2 + B_2 N_2(t) - (\mu_2 + d_2)S_2(t) - Q_2(t) + d_1 S_1(t),\\
&\frac{\mathrm{d}R_1}{\mathrm{d}t} = \gamma_1(t) - (\mu_1 + c_1)R_1(t) + c_2 R_2(t),\\
&\frac{\mathrm{d}R_2}{\mathrm{d}t} = \gamma_2(t) - (\mu_2 + c_2)R_2(t) + c_1 R_1(t),\\
&N_i(t) = S_i(t) + R_i(t) + P_i(t), \quad i = 1, 2, \ \ t \geq 0,
\end{aligned} \tag{3.117}$$

where

$$\mathbf{P}(t) = (P_1(t), P_2(t))^{\mathrm{T}}$$

with

$$P_i(t) = \int_0^\tau I_i(a,t)\mathrm{d}a, \quad \mathbf{Q}(t) = (Q_1(t), Q_2(t))^{\mathrm{T}},$$

and

$$\mathbf{B} = \begin{bmatrix} -\mu_1 - r_1 - b_1 & b_2 \\ b_1 & -\mu_2 - r_2 - b_2 \end{bmatrix}.$$

If $B_i < \mu_i, i = 1, 2$, then (3.117) has a unique disease-free equilibrium $E_0 = (0, 0, S_1^*, S_2^*, 0, 0)$, where

$$S_1^* = -\frac{-B_2 A_1 + \mu_2 A_1 + d_2 A_1 + d_2 A_2}{-B_1 B_2 + B_1\mu_2 + B_1 d_2 + \mu_1 B_2 - \mu_1\mu_2 - \mu_1 d_2 + d_1 B_2 - d_1\,\mu_2},$$

$$S_2^* = -\frac{d_1 A_1 - B_1 A_2 + \mu_1 A_2 + d_1 A_2}{-B_1 B_2 + B_1\mu_2 + B_1 d_2 + \mu_1 B_2 - \mu_1\mu_2 - \mu_1 d_2 + d_1 B_2 - d_1\mu_2}.$$

To determine the basic reproductive number for model (3.117), we assume that the population is at the disease-free equilibrium E_0. Expressing the first two equations of (3.117) in the form of integral equations (3.25) and

then linearizing them at E_0, we obtain

$$P_1(t) = k_1 S_1^* \int_0^\tau b_{11}(a)P_1(t-a)da + k_2 S_2^* \int_0^\tau b_{12}(a)P_2(t-a)\mathrm{d}a,$$
$$P_2(t) = k_1 S_1^* \int_0^\tau b_{21}(a)P_1(t-a)da + k_2 S_2^* \int_0^\tau b_{22}(a)P_2(t-a)\mathrm{d}a. \tag{3.118}$$

Set

$$\mathbf{U} = \begin{bmatrix} k_1 S_1^* \int_0^\tau b_{11}(a)\mathrm{d}a & k_2 S_2^* \int_0^\tau b_{12}(a)\mathrm{d}a \\ k_1 S_1^* \int_0^\tau b_{21}(a)\mathrm{d}a & k_2 S_2^* \int_0^\tau b_{22}(a)\mathrm{d}a \end{bmatrix}.$$

Since $\mathbf{U}$ is a positive matrix, its spectral radius $\rho(\mathbf{U})$ is a simple eigenvalue with a positive eigenvector. Let $\boldsymbol{\psi}(a) = (\psi_1, \psi_2)^{\mathrm{T}}$ be an initial distribution of the infected members in the patches during the infection period $[0, \tau]$, where ψ_1 and ψ_2 are constants. If we set

$$\mathcal{F} = \begin{bmatrix} k_1 S_1^* & 0 \\ 0 & k_2 S_2^* \end{bmatrix},$$

then $\mathcal{F}\boldsymbol{\psi}$ represents the emerging rate of new infectious individuals in the patches. Remember $(b_{ij}(a)) = \exp(\mathbf{B}a)$. Then $b_{ij}(a)$ gives the probability that an infective, initially in patch j with infection-age 0, is in patch i with infection-age a. Hence $\mathbf{U}\boldsymbol{\psi} = \int_0^\tau \exp(\mathbf{B}a)\mathcal{F}\boldsymbol{\psi}\mathrm{d}a$ provides the numbers of infected individuals in the patches when the infection period ends. Following [Diekmann Heesterbeek, and Metz (1990)] and [van den Driessche and Watmough (2002)], we call $\mathbf{U}$ the next infection matrix and define $\rho(\mathbf{U})$ as the basic reproductive number, R_0, for (3.117).

If the two patches are disconnected, by applying the above approach, we see that the basic reproductive number R_{0i} of patch i is:

$$R_{0i} = k_i S_{0i}^* \int_0^\tau \mathrm{e}^{-(\mu_i + r_i)a}\mathrm{d}a = \frac{k_i A_i(1 - \exp(-(\mu_i + r_i)\tau))}{(\mu_i - B_i)(\mu_i + r_i)}.$$

It is shown by Wang and Zhao (2006) that the disease dies out in the isolated patch i, if $R_{0i} < 1$. Furthermore, if the basic reproductive number R_0 is greater than unity, the disease persists in the two connected patches; if the basic reproductive number R_0 is less than unity, the disease dies out in every patch for small epidemic invasions.

Example 3.7. We fix $A_1 = 1$, $A_2 = 0.6$, $\tau = 1$, $k_1 = 0.1$, $k_2 = 0.1$, $\mu_1 = \mu_2 = 0.2$, $B_1 = 0.05$, $B_2 = 0.1$, $r_1 = 0$, $r_2 = 0$ and, $b_1 = 0.01d$, $b_2 = 0.002d$, $d_1 = d$, $d_2 = 0.01d$, where d is a parameter to vary. Then $R_{01} = 0.6432$ and $R_{02} = 0.5438$. This means that if the two patches are disconnected, the disease dies out in each patch. When population dispersal occurs, with the aid of numeric calculations, we obtain $R_0 > 1$ when $d > 0.1574$. Thus, the disease spreads in the two patches when $d > 0.1574$. Hence, the mobility of individuals in this case facilitates the spread of the disease. What is its biological mechanism? Note that the disease transmission coefficients of the two patches are the same. We turn to check the demography of the two patches.

When the patches are disconnected, the condition for the prevalence of the disease in the ith patch is $S_i^* > 11.0333$. When $d > 0$, we see that S_1^* is a decreasing function of d and S_2^* is an increasing function of d. Thus, when d increases from 0, individuals aggregate toward the second patch, and S_2^* reaches 11.0333 at $d = 0.1573$, above which the disease could break out in the second patch. However, because of the spatial heterogeneity, the basic reproductive number R_0 for the whole space remains less than 1 for $0.1573 < d < 0.1574$, which implies that the disease remains inactive. Only when $d > 0.1574$, R_0 is greater than 1, which means that the disease spreads in the two patches due to the aggregation of individuals in the second patch.

More works on epidemic transmissions in the framework of patchy structures can be found by Arino and van den Driessche (2006), Liu and Takeuchi (2006), and Wang (2007).

3.10. Fisher Waves in an Epidemic Model

In this section, we consider the geographic spread of epidemics via traveling waves. We confine ourselves to showing the existence of Fisher-type monotone traveling waves for a reaction–diffusion system modeling man–environment–man epidemics proposed by Capasso and Wilson (1997).

The mathematical model proposed by Capasso and Wilson (1997) was to describe the evolution of fecally–orally transmitted diseases, such as cholera, typhoid fever, and infectious hepatitis A, in the coastal regions of the Mediterranean Sea. Let $u_1(x,t)$ denote the spatial density of an infectious agent at a point x in the habitat at time $t \geq 0$, and $u_2(x,t)$ denote the spatial density of the infective human population at time t. For simplicity, we assume that the coastline is a straight line from $-\infty$ to ∞, which means

$x \in (-\infty, \infty)$. Then the model by Capasso and Wilson (1997) becomes

$$\begin{aligned} &\frac{\partial}{\partial t}u_1(x,t) = d\frac{\partial^2}{\partial x^2}u_1(x,t) - a_{11}u_1(x,t) + a_{12}u_2(x,t), \\ &\frac{\partial}{\partial t}u_2(x,t) = -a_{22}u_2(x,t) + g(u_1(x,t)), \\ &x \in (-\infty, \infty), \end{aligned} \tag{3.119}$$

where d, a_{11}, a_{12}, and a_{22} are positive constants, $1/a_{11}$ is the mean lifetime of the infectious agent in the environment, $1/a_{22}$ is the mean infectious period of the human infectives, a_{12} is the multiplicative factor of the infectious agent due to the human population, and $g(z)$ is the force of infection on the human population due to a concentration z of the infectious agent, d is the diffusion coefficient of the infectious agent. Note that system (3.119) models random dispersal of the pollutant while ignoring the small mobility of the infective human population. Mathematically, it suffices to study the following dimensionless system:

$$\begin{aligned} &\frac{\partial}{\partial t}u_1(x,t) = d\frac{\partial^2}{\partial x^2}u_1(x,t) - u_1(x,t) + \alpha u_2(x,t), \\ &\frac{\partial}{\partial t}u_2(x,t) = -\beta u_2(x,t) + g(u_1(x,t)), \\ &x \in (-\infty, \infty), \end{aligned} \tag{3.120}$$

where

$$\alpha = \frac{a_{12}}{a_{11}}, \quad \beta = \frac{a_{22}}{a_{11}}.$$

To get a monostable case (one equilibrium is unstable and the other is stable), we make the following assumptions on the function g:

(G1) $g \in C^1(R_+, R_+)$, $g(0) = 0$, $g''(0)$ exists, and $g'(z) > 0$, $\forall z \geq 0$;
(G2) $\alpha g'(0) > \beta$, and there is a $\bar{z} > 0$ such that $\alpha g(\bar{z}) \leq \beta \bar{z}$;
(G3) $g(z)$ is strongly sublinear on R_+ in the sense that $g(sz) > sg(z)$, $\forall z > 0, s \in (0,1)$.

By similar discussions as those for Lemma 3.1, we see that the following system:

$$\begin{aligned} u_1' &= -u_1 + \alpha u_2, \\ u_2' &= -\beta u_2 + g(u_1) \end{aligned} \tag{3.121}$$

admits only two equilibria $(0,0)$ and (u_1^*, u_2^*), where $(0,0)$ is unstable and (u_1^*, u_2^*) is globally asymptotically stable. Thus, we get a monostable case.

Under above assumptions, Zhao and Wang (2004) analyzed the existence of traveling waves of model (3.120). To this end, we let $(u_1(x,t), u_2(x,t)) = (U_1(z), U_2(z))$, where $z = x + ct$, be a traveling wave front solution of (3.120) with positive wave speed c. Substituting this special solution into (3.120), we obtain

$$\begin{aligned} cU_1' &= dU_1'' - U_1 + \alpha U_2, \\ cU_2' &= g(U_1) - \beta U_2. \end{aligned} \tag{3.122}$$

Since we are interested in the traveling waves connecting $(0,0)$ and (u_1^*, u_2^*), we impose the following boundary condition on (U_1, U_2):

$$\begin{aligned} U_i(-\infty) &:= \lim_{z \to -\infty} U_i(z) = 0, \\ U_i(+\infty) &:= \lim_{z \to +\infty} U_i(z) = u_i^*. \end{aligned} \tag{3.123}$$

Now, our objective is to show that (3.122) has a solution satisfying (3.123). By the second equation of (3.122), we have

$$\begin{aligned} U_2(t) = {} & \mathrm{e}^{-(\beta/c)(t-t_0)} U_2(t_0) \\ & + \frac{1}{c} \int_{t_0}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(U_1(s)) \mathrm{d}s, \quad \forall t_0 \in R := (-\infty, \infty). \end{aligned}$$

Since $U_2(t)$ and $g(U_1(t))$ are bounded functions on R, by taking $t_0 \to -\infty$, we obtain

$$U_2(t) = \frac{1}{c} \int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(U_1(s)) \mathrm{d}s, \quad \forall t \in R. \tag{3.124}$$

Substituting (3.124) into the first equation of (3.122), we get

$$cU_1'(t) = dU_1''(t) - U_1(t) + \frac{\alpha}{c} \int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(U_1(s)) \mathrm{d}s, \quad \forall t \in R. \tag{3.125}$$

Assume that $U_1(t)$ is a monotone increasing solution of (3.125) with

$$U_1(-\infty) = 0, \quad U_1(+\infty) = u_1^*. \tag{3.126}$$

Let $U_2(t)$ be defined by (3.124). It then easily follows that $(U_1(t), U_2(t))$ is a solution of (3.122), and $U_2(t)$ is also a monotone increasing function with

$$U_2(-\infty) = 0, \quad U_2(+\infty) = u_2^*. \tag{3.127}$$

Consequently, it suffices to consider monotonic solutions of problem (3.125) subject to (3.126). We hope to use the method of upper and lower solutions for that purpose. Let us start with a technical result.

Lemma 3.2. *Suppose that $u \in C^2(R, R)$ and u, u', and u'' are bounded on R. If*

$$cu'(t) \geq du''(t) - u(t), \quad \forall t \in R,$$

then $u(t) \geq 0, \forall t \in R$.

Proof. Let

$$h(t) = cu'(t) - du''(t) + u(t), \quad t \in R.$$

Then $h(t)$ is a nonnegative, continuous, and bounded function on R, and $u(t)$ satisfies the following linear equation:

$$du''(t) - cu'(t) - u(t) + h(t) = 0, \quad t \in R. \tag{3.128}$$

From the theory of second-order linear ordinary differential equations, it follows that

$$\begin{aligned} u(t) = {} & c_1 \mathrm{e}^{\gamma_1 t} + c_2 \mathrm{e}^{\gamma_2 t} + \frac{1}{d(\gamma_2 - \gamma_1)} \\ & \times \left(\int_{-\infty}^{t} \mathrm{e}^{\gamma_1 (t-s)} h(s) \mathrm{d}s + \int_{t}^{\infty} \mathrm{e}^{\gamma_2 (t-s)} h(s) \mathrm{d}s \right) \end{aligned} \tag{3.129}$$

where

$$\gamma_1 = \frac{c - \sqrt{c^2 + 4d}}{2d} < 0, \quad \gamma_2 = \frac{c + \sqrt{c^2 + 4d}}{2d} > 0.$$

Since both $u(t)$ and $h(t)$ are bounded on R, we have $c_1 = c_2 = 0$. It follows from the nonnegativity of $h(t)$ on R that $u(t) \geq 0, \forall t \in R$. □

Let $X = BUC(R, R)$ be the Banach space of all bounded and uniformly continuous functions from R into R with the usual supremum norm. Define

a continuous mapping $S: X \to X$ by

$$S(\phi)(t) = \frac{\alpha}{cd(\gamma_2 - \gamma_1)} \left[\int_{-\infty}^{t} \mathrm{e}^{\gamma_1(t-s)} \mathrm{d}s \int_{-\infty}^{s} \mathrm{e}^{-(\beta/c)(s-\theta)} g(\phi(\theta)) \mathrm{d}\theta \right.$$
$$\left. + \int_{t}^{\infty} \mathrm{e}^{\gamma_2(t-s)} \mathrm{d}s \int_{-\infty}^{s} \mathrm{e}^{-(\beta/c)(s-\theta)} g(\phi(\theta)) \mathrm{d}\theta \right]. \tag{3.130}$$

By direct calculations, we see that the first- and second-order derivatives of $S(\phi)(t)$ with respect to t are bounded on R, and $S(\phi)(t)$ is the unique bounded solution on R to the linear ordinary differential equation

$$du''(t) - cu'(t) - u(t) + \frac{\alpha}{c} \int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(\phi(s)) \mathrm{d}s = 0. \tag{3.131}$$

It is clear that any fixed point of S in X is a solution of (3.125). By the monotonicity of g on R and Lemma 3.2, as applied to $u(t) := S(\phi)(t + s) - S(\phi)(t)$ with $s > 0$, it follows that S has the following properties:

(P1) S is a monotonic increasing operator on X with respect to the pointwise ordering;
(P2) If $\phi \in X$ is monotone increasing on R, so is $S(\phi)$.

Now, we are ready to present the following definition.

Definition 3.2. A function $\phi \in X$ is called an upper solution of (3.125) if $S(\phi)(t) \leq \phi(t)$, $\forall t \in R$. A lower solution of (3.125) is defined by reversing the inequality.

Note that if $\phi \in X$ is twice continuously differentiable on R, except at finitely many points t_i, with $\phi'(t_i+) \leq \phi'(t_i-)$, $1 \leq i \leq m$, and satisfies

$$d\phi''(t) - c\phi'(t) - \phi(t) + \frac{\alpha}{c} \int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(\phi(s)) \mathrm{d}s \leq 0,$$
$$\forall t \neq t_i,\ 1 \leq i \leq m,$$

it then easily follows that ϕ is an upper solution of (3.125); (see, for example, Wu and Zou (2001)). A similar note applies to lower solutions of (3.125) if we reverse the afore-mentioned two inequalities.

Now we are ready to establish the existence of monotone solutions to (3.125) and (3.126).

Theorem 3.14. *Suppose that* (3.125) *admits an upper solution* $\bar{\rho}(t)$ *and a lower solution* $\underline{\rho}(t)$ *such that*

(1) $\bar{\rho}(t)$ *is monotone increasing on* R *and* $\bar{\rho}(-\infty) = 0, \bar{\rho}(+\infty) = u_1^*$;
(2) $\underline{\rho} \not\equiv 0$ *and* $\underline{\rho}(t) \le \bar{\rho}(t)$, $\forall t \in R$.

Then (3.125) *and* (3.126) *have a monotone increasing solution on* R.

Proof. Let $\phi_m = S^m(\bar{\rho})$, $\forall m \ge 0$. By Definition 3.2 and (P1), it follows that

$$\underline{\rho}(t) \le \phi_m(t) \le \phi_{m-1}(t) \le \bar{\rho}(t), \quad \forall t \in R, \ \ m \ge 1. \tag{3.132}$$

In particular, for each $t \in R$, the sequence $\{\phi_m(t)\}$ is decreasing. Thus $\phi(t) = \lim_{m\to\infty} \phi_m(t)$ exists and

$$\underline{\rho}(t) \le \phi(t) \le \bar{\rho}(t), \quad \forall t \in R.$$

By property (P2), we see that the sequence $\{\phi_m(t)\}$ is increasing in t for each m. It follows that $\phi(t)$ is increasing in t and

$$0 = \phi(-\infty) \le \phi(\infty) \le u_1^*.$$

For each fixed t, since $\phi_m(t) = S(\phi_{m-1})(t)$, by Lebesque's convergence theorem, we obtain $\phi(t) = S(\phi)(t)$. Hence, ϕ is a fixed point of S. This means that $\phi(t)$ is a monotone solution of (3.125). We are now left to show $\phi(\infty) = u_1^*$. Note that

$$\underline{\rho}(t) \le \phi(t) \le \phi(\infty), \quad \forall t \in R,$$

and $\underline{\rho}(t) \not\equiv 0$. We then have $0 < \phi(\infty) \le u_1^*$. By (3.125), it follows that

$$\phi(\infty) = \frac{\alpha}{\beta} g(\phi(\infty)).$$

Thus the uniqueness of a positive equilibrium of (3.121) implies that $\phi(\infty) = u_1^*$. This completes the proof. □

Our next goal is to construct appropriate upper and lower solutions to (3.125). To this end, we linearize (3.125) at $U_1 = 0$ to obtain

$$cU_1'(t) = dU_1''(t) - U_1(t) + \frac{\alpha g'(0)}{c} \int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} U_1(s)\mathrm{d}s. \tag{3.133}$$

By substituting $U_1(t) = \mathrm{e}^{\lambda t}$ into (3.133), we get a characteristic equation

$$P(\lambda) := \lambda^3 + \left(\frac{\beta}{c} - \frac{c}{d}\right)\lambda^2 - \frac{1+\beta}{d}\lambda + \frac{\alpha g'(0) - \beta}{d\,c} = 0. \tag{3.134}$$

It can be shown (see [Zhao and Wang (2004)]) that there is $c^* > 0$ such that $P(\lambda)$ has two positive roots if $c > c^*$, two complex roots with positive real parts if $0 < c < c^*$, and only one positive root if $c = c^*$.

Theorem 3.15. *Assume* (G1)–(G3) *hold. Then* (3.120) *has a monotone traveling wave connecting* $(0,0)$ *and* (u_1^*, u_2^*) *with speed* c *if* $c > c^*$, *and no such a wave if* $0 < c < c^*$.

Proof. In the case where $c > c^*$, (3.134) has two positive roots $\lambda_1 < \lambda_2$. Based on these two roots, we define

$$\bar{\rho} = \min\{u_1^* \mathrm{e}^{\lambda_1 t}, u_1^*\}. \tag{3.135}$$

We now verify that $\bar{\rho}$ is an upper solution of (3.125). If $t < 0$, then $\bar{\rho} = u_1^* \mathrm{e}^{\lambda_1 t}$. It is easy to obtain

$$\begin{aligned}
&d\bar{\rho}''(t) - c\bar{\rho}'(t) - \bar{\rho}(t) + \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(\bar{\rho}(s))\mathrm{d}s \\
&\quad = u_1^* \mathrm{e}^{\lambda_1 t}[d\lambda_1^2 - c\lambda_1 - 1] + \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(u_1^* \mathrm{e}^{\lambda_1 s})\mathrm{d}s \\
&\quad \le u_1^* \mathrm{e}^{\lambda_1 t}[d\lambda_1^2 - c\lambda_1 - 1] + \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} u_1^* g'(0) \mathrm{e}^{\lambda_1 s} ds \\
&\quad = u_1^* \mathrm{e}^{\lambda_1 t}\left[d\lambda_1^2 - c\lambda_1 - 1 + \frac{\alpha g'(0)}{c(\lambda_1 + \beta/c)}\right] \\
&\quad = u_1^* \mathrm{e}^{\lambda_1 t} \frac{1}{dc(c\lambda_1 + \beta)} P(\lambda_1) = 0,
\end{aligned} \tag{3.136}$$

where the inequality is valid due to the fact that $g(u) \le g'(0)u$, $\forall u \ge 0$, which is implied by assumption (G3).

If $t > 0$, then $\bar{\rho} = u_1^*$. It is easy to obtain

$$\begin{aligned} d\bar{\rho}''(t) - c\bar{\rho}'(t) - \bar{\rho}(t) + \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(\bar{\rho}(s))\mathrm{d}s \\ \leq -u_1^* + \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-\beta/c(t-s)} g(u_1^*)\mathrm{d}s \\ = -u_1^* + \frac{\alpha g(u_1^*)}{\beta} = 0. \end{aligned} \tag{3.137}$$

Hence, $\bar{\rho}$ is an upper solution of (3.125).

From assumption (G1), it follows that there exist $k > 0$ and $\delta \in (0, u_1^*)$ such that

$$g(z) \geq g'(0)z - kz^2, \quad \forall z \in [0, \delta]. \tag{3.138}$$

In view of $0 < \lambda_1 < \lambda_2$, we first fix $\epsilon \in (0, \lambda_1]$ such that $\lambda_1 + \epsilon < \lambda_2$, and then define

$$\underline{\rho}(t) = \max\{0, \delta(1 - M\mathrm{e}^{\epsilon t})\mathrm{e}^{\lambda_1 t}\}, \tag{3.139}$$

where the constant $M \geq 1$ is to be determined. Since $\delta < u_1^*$, $t_0 := -\frac{\ln M}{\epsilon} \leq 0$, and $0 < \epsilon \leq \lambda_1$, it is easy to see that

$$0 \leq \underline{\rho}(t) \leq \bar{\rho}(t), \quad \underline{\rho}^2(t) \leq (u_1^*)^2 \mathrm{e}^{(\lambda_1+\epsilon)t}, \ \ \forall t \in R. \tag{3.140}$$

If $t > t_0$, then $\underline{\rho}(t) = 0$. It follows that

$$\begin{aligned} \mathrm{d}\underline{\rho}''(t) - c\underline{\rho}'(t) - \underline{\rho}(t) + \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(\underline{\rho}(s))\mathrm{d}s \\ = \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(\underline{\rho}(s))\mathrm{d}s \geq 0. \end{aligned} \tag{3.141}$$

Let L and H be two linear operators defined by

$$\begin{aligned} L(\phi)(t) &:= d\phi''(t) - c\phi'(t) - \phi(t), \\ H(\phi)(t) &:= \frac{\alpha g'(0)}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)}\phi(s)\mathrm{d}s. \end{aligned}$$

It then easily follows that

$$L(\mathrm{e}^{\lambda\cdot})(t) = (d\lambda^2 - c\lambda - 1)\mathrm{e}^{\lambda t}, \quad \forall t \in R, \ \lambda \in R;$$
$$L(\mathrm{e}^{\lambda\cdot})(t) + H(\mathrm{e}^{\lambda\cdot})(t) = \frac{P(\lambda)}{dc(c\lambda+\beta)}\mathrm{e}^{\lambda t}, \quad \forall t \in R, \ \lambda \geq 0. \tag{3.142}$$

If $t < t_0$, we then have

$$\underline{\rho}(t) = \delta \mathrm{e}^{\lambda_1 t} - \delta M \mathrm{e}^{(\lambda_1+\epsilon)t}.$$

This, together with (3.138), (3.140), and (3.142), implies that

$$\begin{aligned}
&d\underline{\rho}''(t) - c\underline{\rho}'(t) - \underline{\rho}(t) + \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} g(\underline{\rho}(s))\mathrm{d}s \\
&\quad \geq d\underline{\rho}''(t) - c\underline{\rho}'(t) - \underline{\rho}(t) + \frac{\alpha}{c}\int_{-\infty}^{t} \mathrm{e}^{-(\beta/c)(t-s)} \\
&\qquad \times [g'(0)\underline{\rho}(s) - k\underline{\rho}^2(s)]\mathrm{d}s \\
&\quad \geq d\underline{\rho}''(t) - c\underline{\rho}'(t) - \underline{\rho}(t) + H(\underline{\rho})(t) - \frac{k(u_1^*)^2}{g'(0)} H(\mathrm{e}^{(\lambda_1+\epsilon)\cdot})(t) \\
&\quad = \delta[L(\mathrm{e}^{\lambda_1\cdot})(t) + H(\mathrm{e}^{\lambda_1\cdot})(t)] - \delta M[L(\mathrm{e}^{(\lambda_1+\epsilon)\cdot})(t) + H(\mathrm{e}^{(\lambda_1+\epsilon)\cdot})(t)] \\
&\qquad - \frac{k(u_1^*)^2}{g'(0)} H(\mathrm{e}^{(\lambda_1+\epsilon)\cdot})(t) \\
&\quad = \frac{\delta P(\lambda_1)}{\mathrm{d}c(c\lambda_1+\beta)}\mathrm{e}^{\lambda_1 t} - \frac{\delta M P(\lambda_1+\epsilon)}{\mathrm{d}c(c(\lambda_1+\epsilon)+\beta)}\mathrm{e}^{(\lambda_1+\epsilon)t} - \frac{k(u_1^*)^2}{g'(0)} \\
&\qquad \times \left[\frac{P(\lambda_1+\epsilon)}{\mathrm{d}c(c(\lambda_1+\epsilon)+\beta)} - (d(\lambda_1+\epsilon)^2 - c(\lambda_1+\epsilon) - 1)\right]\mathrm{e}^{(\lambda_1+\epsilon)t} \\
&\quad = \mathrm{e}^{(\lambda_1+\epsilon)t}\left[\frac{k(u_1^*)^2}{g'(0)}(d(\lambda_1+\epsilon)^2 - c(\lambda_1+\epsilon) - 1)\right. \\
&\qquad \left. - \left(\delta M + \frac{k(u_1^*)^2}{g'(0)}\right)\frac{P(\lambda_1+\epsilon)}{\mathrm{d}c(c(\lambda_1+\epsilon)+\beta)}\right] > 0,
\end{aligned} \tag{3.143}$$

provided M is sufficiently large.

Note that, in (3.143), we have used the fact that $P(\lambda_1) = 0$ and $P(\lambda_1+\epsilon) < 0$. From (3.141) and (3.143), it then follows that there exist positive numbers δ, ϵ, and $M = M(\delta, \epsilon)$ such that $\underline{\rho}(t)$ is a lower solution of (3.125). Thus the existence of a monotone traveling wave of (3.120) with speed c follows from Theorem 3.14.

It remains to show that (3.120) admits no monotone traveling wave solution in the case where $0 < c < c^*$. Set $V_1 = U_1, V_2 = U_1', V_3 = U_2$. Then (3.122) becomes

$$\begin{aligned} V_1' &= V_2, \\ V_2' &= \frac{1}{d}[V_1 + cV_2 - \alpha V_3], \\ V_3' &= \frac{1}{c}[g(V_1) - \beta V_3]. \end{aligned} \tag{3.144}$$

Linearizing (3.144) at $(0, 0, 0)$, we obtain

$$\begin{aligned} V_1' &= V_2, \\ V_2' &= \frac{1}{d}[V_1 + cV_2 - \alpha V_3], \\ V_3' &= \frac{1}{c}[g'(0)V_1 - \beta V_3]. \end{aligned} \tag{3.145}$$

It is easy to verify that the characteristic equation associated with (3.145) is the same as (3.134). Let $0 < c < c^*$ be fixed. Then one root of (3.134) is negative and a pair of complex conjugate roots of (3.134) has positive real parts. Hence the unstable manifold of (3.144) at $(0, 0, 0)$ is two-dimensional. Let $(U_1(t), U_2(t))$ be a solution to (3.122) and (3.123). Then $U(t) = (U_1(t), U_1'(t), U_2(t))$ is a solution of (3.144) with $U(-\infty) = (0, 0, 0)$ and $U(+\infty) = (u_1^*, 0, u_2^*)$. Clearly, (3.144) can be rewritten as

$$\begin{aligned} V_1' &= V_2, \\ V_2' &= \frac{1}{d}[V_1 + cV_2 - \alpha V_3], \\ V_3' &= \frac{1}{c}[g'(0)V_1 - \beta V_3] + G(V_1), \end{aligned} \tag{3.146}$$

where

$$G(V_1) = \frac{1}{c}[g(V_1) - g'(0)V_1] = o(|V_1|).$$

By Theorems 13.4.3 and 13.4.5 of Coddington and Levinson (1955), there is a solution $V(t)$ of (3.145) such that

$$U(t) = V(t)(1 + o(1)) \quad \text{as } t \to -\infty.$$

Since $V(t)$ is a spiral on the unstable manifold of (3.145) at $(0,0,0)$, as $t \to -\infty$, $U(t)$ is an oscillating solution of (3.144) as $t \to -\infty$. Consequently, (3.122) and (3.123) admits no monotone solution. □

It is shown by Zhao and Wang (2004) that (3.120) has also a monotone traveling wave connecting $(0,0)$ and (u_1^*, u_2^*) with speed c when $c = c^*$. Therefore, c^* is the minimal wave speed.

3.11. Propagation of HBV with Spatial Dependence

In this section, we consider the propagation of hepatitis B virus (HBV) infection along a liver. We investigate the existence of traveling waves via the geometric singular perturbation method.

We start from the basic model of virus dynamics proposed by [Nowak *et al.* (1996)]:

$$\begin{aligned} \frac{\mathrm{d}u}{\mathrm{d}t} &= \lambda - au - \beta uv, \\ \frac{\mathrm{d}w}{\mathrm{d}t} &= \beta uv - bw, \\ \frac{\mathrm{d}v}{\mathrm{d}t} &= kw - mv, \end{aligned} \tag{3.147}$$

where u is the density of uninfected susceptible host cells, w is the density of infected host cells, and v is the density of free virus particles. Susceptible cells are produced at a rate λ, die at rate au, and become infected at rate βuv. Infected cells are produced at rate βuv and die at rate bw. Free viruses are produced from infected cells at rate kw and are removed at rate mv. It is assumed that λ, a, β, b, k, and m are positive constants.

Model (3.147) implicitly assumes that cells and viruses are well mixed, and ignores the mobility of cells and viruses. For the HBV infection, susceptible host cells and infected cells are hepatocyte and cannot move under normal conditions, but viruses move freely in the liver. Motivated by these observations, Wang and Wang (2007) introduces the random mobility of viruses into (3.147). It is assumed that the motion of virus obeys the *Fickian diffusion*; that is to say, the population flux of virus is proportional to the concentration gradient and the proportionality constant is taken to be negative [Gourley and So (2002)]. We also neglect the

mobility of susceptible cells and infected cells, and obtain the following model:

$$\begin{aligned}\frac{\partial u}{\partial t} &= \lambda - au - \beta uv,\\ \frac{\partial w}{\partial t} &= \beta uv - bw,\\ \frac{\partial v}{\partial t} &= d\Delta v + kw - mv.\end{aligned} \tag{3.148}$$

Here $u(t,x)$, $w(t,x)$, and $v(t,x)$ are the densities of uninfected cells, infected cells and free viruses at position x and time t, respectively, and d is the diffusion coefficient.

Since the size of free virus particles is much smaller than that of the liver and the process of infection is usually more than 10 years or a lifetime for chronically infected individuals with HBV, it is reasonable to assume that the domain of free virus particles is an infinite spatial domain. For mathematical simplicity, we consider only a one-dimensional space. To simplify the mathematical analysis, we rescale the model by letting

$$\begin{gathered}U = (a/\lambda)u, \quad W = (a/\lambda)w, \quad V = (\beta/a)v,\\ t' = at, \quad x' = x, \quad D = d/a,\\ \rho_1 = b/a, \quad \rho_2 = k\beta\lambda/a^3, \quad \rho_3 = m/a.\end{gathered}$$

This leads to (after dropping the primes) the following model:

$$\begin{aligned}\frac{\partial U}{\partial t} &= 1 - U - UV,\\ \frac{\partial W}{\partial t} &= UV - \rho_1 W,\\ \frac{\partial V}{\partial t} &= D\frac{\partial^2 V}{\partial x^2} + \rho_2 W - \rho_3 V.\end{aligned} \tag{3.149}$$

We assume that ρ_1, ρ_2, ρ_3, and D are all positive constants.

The basic reproductive number of virus in the absence of spatial dependence is given by $R_0 = (\rho_2)/(\rho_1\rho_3)$. To establish the existence of traveling waves of system (3.149), we assume that it has the solution of

form $U(x,t) = u(x+ct)$, $W(x,t) = w(x+ct)$, and $V(x,t) = v(x+ct)$. Then we have

$$\begin{aligned} cu' &= 1 - u - uv, \\ cw' &= uv - \rho_1 w, \\ cv' &= Dv'' + \rho_2 w - \rho_3 v. \end{aligned} \tag{3.150}$$

Here primes denote differentiation with respect to the wave variable, $s := x + ct$. Because of the biological background, we require that the traveling waves u, w, and v be nonnegative and satisfy the boundary conditions:

$$\begin{aligned} &u(-\infty) = 1, \quad u(+\infty) = \frac{\rho_1\rho_3}{\rho_2} \triangleq U^*, \\ &w(-\infty) = 0, \quad w(+\infty) = \frac{\rho_2 - \rho_1\rho_3}{\rho_1\rho_2} \triangleq W^*, \\ &v(-\infty) = 0, \quad v(+\infty) = \frac{\rho_2 - \rho_1\rho_3}{\rho_1\rho_3} \triangleq V^*. \end{aligned} \tag{3.151}$$

Set $v' = z$. Then we have

$$\begin{aligned} cu' &= 1 - u - uv, \\ cw' &= uv - \rho_1 w, \\ v' &= z, \\ Dz' &= cz + \rho_3 v - \rho_2 w. \end{aligned} \tag{3.152}$$

When $R_0 > 1$, that is, $\rho_2 > \rho_1\rho_3$, system (3.152) has two equilibria:

$$E_0' = (1,0,0,0) \quad \text{and} \quad E_1' = (U^*, W^*, V^*, 0).$$

A traveling wave front solution of (3.149) exists if there exists a heteroclinic orbit connecting these two critical points.

Calculating the Jacobian matrix of the right side of (3.152) at E_0', we obtain

$$J = \begin{pmatrix} -1/c & 0 & -1/c & 0 \\ 0 & -\rho_1/c & 1/c & 0 \\ 0 & 0 & 0 & 1 \\ 0 & -\rho_2/D & \rho_3/D & c/D \end{pmatrix}.$$

The eigenvalues of this matrix satisfy the characteristic equation

$$\left(\lambda + \frac{1}{c}\right)(\lambda^3 + A_1\lambda^2 - A_2\lambda + A_3) = 0, \tag{3.153}$$

where $A_1 = (D\rho_1 - c^2)/cD, A_2 = (\rho_1 + \rho_3)/D$ and $A_3 = (\rho_2 - \rho_1\rho_3)/cD$.

Set

$$P(\lambda) = \lambda^3 + A_1\lambda^2 - A_2\lambda + A_3.$$

By direct calculations [Wang and Wang (2007)], we see that there is $c^* > 0$ such that $P(\lambda)$ has two positive roots if $c > c^*$, two complex roots with positive real parts if $0 < c < c^*$, and only one positive root if $c = c^*$. As a consequence, there is no traveling wave of (3.149) when $0 < c < c^*$. Indeed, there is a two-dimensional unstable manifold through E_0'. The critical point E_0' is a spiral point on the unstable manifold. Therefore, a trajectory approaching E_0' must have $v(s) < 0$, for some s. This violates the requirement that the traveling waves are nonnegative.

For large c, we can obtain the existence of traveling waves by means of techniques from Faria *et al.* (2006). Indeed, by removing the diffusion effect from (3.149) we obtain

$$\begin{aligned} \frac{\mathrm{d}U}{\mathrm{d}t} &= 1 - U - UV, \\ \frac{\mathrm{d}W}{\mathrm{d}t} &= UV - \rho_1 W, \\ \frac{\mathrm{d}V}{\mathrm{d}t} &= \rho_2 W - \rho_3 V \end{aligned} \tag{3.154}$$

If $R_0 > 1$, (3.154) admits two equilibrium points $E_0 = (1, 0, 0)$ and $E_1 = (U^*, W^*, V^*)$. Then we consider Liapunov functions

$$L_{E_0} = (U - \ln U) + W + \frac{\rho_1}{\rho_2}V,$$

and

$$L_{E_1} = U^*\left(\frac{U}{U^*} - \ln\frac{U}{U^*}\right) + W^*\left(\frac{W}{W^*} - \ln\frac{W}{W^*}\right) + \frac{\rho_1}{\rho_2}V^*\left(\frac{V}{V^*} - \ln\frac{V}{V^*}\right),$$

for E_0 and E_1, respectively. Calculating the time derivative of L_{E_0}, L_{E_1} along the solutions of system (3.154) and using the fact that arithmetic mean is greater than or equal to the geometric mean, Korobeinikov (2004) obtained the following results.

Lemma 3.3. *If $R_0 > 1$, then the positive equilibrium E_1 is globally asymptotically stable. If $R_0 \leq 1$, then E_0 is globally asymptotically stable.*

If $R_0 > 1$, since $E_1 = (U^*, W^*, V^*)$ is globally asymptotically stable in the positive quadrant, solutions of (3.154) initially near the unstable equilibrium E_0 approach the coexisting equilibrium E_1 and there exists a heteroclinic orbit connecting these two equilibria. Consequently, it follows from Faria *et al.* (2006) that (3.149) has traveling wave solutions for a large wave speed c. Hence, we have

Proposition 3.1. *If $R_0 > 1$, there is $c_1^* > 0$ such that for each $c > c_1^*$, system* (3.149) *has a traveling wave solution connecting E_0 and E_1.*

Now, we consider the existence of traveling waves when $c^* \leq c \leq c_1^*$. We need to restrict diffusion coefficient D small enough so that the geometric singular perturbation techniques can be applied. Note that when D is very small, system (3.152) is a singularly perturbed system. Let $s = D\eta$. Then system (3.152) becomes

$$\begin{aligned} c\dot{u} &= D(1 - u - uv), \\ c\dot{w} &= D(uv - \rho_1 w), \\ \dot{v} &= Dz, \\ \dot{z} &= cz + \rho_3 v - \rho_2 w, \end{aligned} \tag{3.155}$$

where dots denote differentiation with respect to η. While these two systems are equivalent for $D > 0$, the different time-scales give rise to two different limiting systems.

Taking $D \to 0$ in (3.152), we obtain

$$\begin{aligned} cu' &= 1 - u - uv, \\ cw' &= uv - \rho_1 w, \\ v' &= z, \\ 0 &= cz + \rho_3 v - \rho_2 w. \end{aligned} \tag{3.156}$$

Thus, the flow of system (3.156) is confined to the set

$$\mathcal{M}_0 = \left\{ (u, w, v, z) \in \mathbb{R}^4 \colon z = \frac{\rho_2 w - \rho_3 v}{c} \right\}, \tag{3.157}$$

and its dynamics are determined by the first three equations only. On the other hand, taking $D \to 0$ in (3.155), we have

$$\begin{aligned} c\dot{u} &= 0, \\ c\dot{w} &= 0, \\ \dot{v} &= 0, \\ \dot{z} &= cz + \rho_3 v - \rho_2 w. \end{aligned} \tag{3.158}$$

Any points in $\mathcal{M}_0$ are the equilibria of system (3.158). System (3.152) is referred to as the *slow system*, since the time-scale s is slow and (3.155) is referred to as the *fast system*, since the time-scale η is fast. Hence u, w, and v are called *slow variables* and z is called a *fast variable*. $\mathcal{M}_0$ is the *slow manifold*.

If $\mathcal{M}_0$ is *normally hyperbolic*, then we can use the geometric singular perturbation theory [Fenichel (1979)] to obtain a three-dimensional invariant manifold $\mathcal{M}_D$ for the flow, when $0 < D \ll 1$, which implies the persistence of the slow manifold as well as the stable and unstable foliations. As a consequence, the dynamics in the vicinity of the slow manifold are completely determined by the dynamics on the slow manifold.

Recall that $\mathcal{M}_0$ is a normally hyperbolic manifold if the linearization of the fast system (3.155), restricted to $\mathcal{M}_0$, has exactly $\dim \mathcal{M}_0$ eigenvalues with zero real part. The eigenvalues of the linearization of the fast system restricted to $\mathcal{M}_0$ are $0, 0, 0, c$. Thus $\mathcal{M}_0$ is normally hyperbolic.

According to Fenichel's invariant manifold theorem [Fenichel (1979)], there exists a small $D_1 > 0$, such that for $0 \le D < D_1$, there exists a three-dimensional locally invariant manifold

$$\mathcal{M}_D = \left\{ (u, w, v, z) \in \mathbb{R}^4 \colon z = \frac{\rho_2 w - \rho_3 v}{c} + Dh(u, w, v; D) \right\},$$

for the fast system, where h is a smooth function defined on a compact domain and satisfy $h(1, 0, 0; D) = 0$. After changing back to the slow time, we see that the dynamics on $\mathcal{M}_D$ are given by

$$\begin{aligned} u' &= \frac{1 - u - uv}{c}, \\ w' &= \frac{uv - \rho_1 w}{c}, \\ v' &= \frac{\rho_2 w - \rho_3 v}{c} + Dh(u, w, v; D). \end{aligned} \tag{3.159}$$

When $D = 0$, the flow on $\mathcal{M}_0$ is given by

$$\begin{aligned} u' &= \frac{1 - u - uv}{c}, \\ w' &= \frac{uv - \rho_1 w}{c}, \\ v' &= \frac{\rho_2 w - \rho_3 v}{c}, \end{aligned} \tag{3.160}$$

which has the same qualitative behavior as (3.154). Thus, E_0 is unstable and E_1 is globally stable in the positive quadrant by Lemma 3.2. More precisely, the eigenvalues of the linearization of (3.160) at E_0 are:

$$\begin{aligned} \lambda_1 &= -\frac{1}{c}, \\ \lambda_2 &= -\frac{\rho_1 + \rho_3 + \sqrt{(\rho_1 + \rho_3)^2 + 4(\rho_2 - \rho_1\rho_3)}}{2c}, \\ \lambda_3 &= -\frac{\rho_1 + \rho_3 - \sqrt{(\rho_1 + \rho_3)^2 + 4(\rho_2 - \rho_1\rho_3)}}{2c}. \end{aligned}$$

Since $R_0 > 1$ and $c^* \le c \le c_1^*$, $\lambda_3 > 0$ is the unique eigenvalue with the positive real part. Thus, there is a one-dimensional unstable manifold through E_0. Since E_1 is globally stable in the positive quadrant, the positive branch of the one-dimensional unstable manifold of E_0 for system (3.160), $W_0^U(E_0)$, connects to E_1; that is, the heteroclinic orbit connecting E_0 and E_1 exists for system (3.160). Evidently, the manifolds $W_0^U(E_0)$ and $W_0^S(E_1)$ are transversally intersected. By direct calculations [Wang and Wang (2007)], we see that (3.159) is asymptotically stable, when $D > 0$ is small. Hence, the transversal intersection of the unstable manifold and the stable manifold persists for small $D > 0$. Consequently, by Szmolyan (1991), we can state

Theorem 3.16. *Let $R_0 > 1$. Then there exists $D_0 > 0$ such that for every $0 < D < D_0$, system (3.149) has a traveling wave connecting E_0 and E_1 with speed c for $c^* \le c \le c_1^*$.*

Chapter 4

The Epidemic Models with Impulsive Effects

Zhen Jin

The theory and applications of impulsive differential equations have developed very rapidly at the end of last century. Impulsive equations are widely applied to evolution processes with a short-term perturbation. In real life, many phenomena do exhibit impulsive effects, such as biological phenomena involving thresholds, bursting rhythm models in medicine and biology, optimal control models in economics, pharmacokinetics and frequency modulated systems. Impulsive effects in epidemiologic modeling are mainly described as the impulsive vaccination to the people, seasonal birth and removal of some animals, pulse control to infectious disease system and so on. In this chapter, we give a brief introduction to works done by Jin (2001), Zhou and Liu (2003), Gakkhar and Negi (2008), Roberts and Kao (1998), Cao and Jin (2007), Lin *et al.* (submitted), Zhang *et al.* (2008), and Gao *et al.* (2005).

4.1. Basic Theory on Impulsive Differential Equations

In this section, we introduce basic definitions and theorems of impulsive differential equations [Lakshmikantham *et al.* (1989), Bainov and Simeonov (1993), and Bainov and Simeonov (1995)].

4.1.1. *Differential equations with impulses*

Let us consider an evolution process described by

(i) a system of differential equations

$$x' = f(t, x), \tag{4.1}$$

where f: $R_+ \times \Omega \to R^n$, $\Omega \in R^n$ is an open set and R_+, the non-negative real line;

(ii) the sets $M(t), N(t) \in \Omega$ for each $t \in R_+$;

(iii) the operator $A(t)$: $M(t) \to N(t)$ for each $t \in R_+$.

Let $x(t) = x(t, t_0, x_0)$ be any solution of (4.1) starting at (t_0, x_0). The process goes as follows: the point $P_t = (t, x(t))$ starts at the initial point $P_{t_0} = (t_0, x_0)$ and moves along the curve $\{(t, x)\colon t \geq t_0, x = x(t)\}$ until the time $t_1 > t_0$, at which the point P_t meets the set $M(t)$. At $t = t_1$, the operator $A(t)$ transfers the point to $P_{t_1^+} = (t_1, x_1^+) \in N(t_1)$, where $x_1^+ = A(t_1)x(t_1)$. Then the point P_t continues its motion along the curve with $x(t) = x(t, t_1, x_1^+)$ as the solution of (4.1) starting at $P_{t_1} = (t_1, x_1^+)$ until it hits the set $M(t)$ again, at the next moment $t_2 > t_1$. Then, once again the point $P_{t_2} = (t_2, x(t_2))$ is transferred to the point $P_{t_2^+} = (t_2, x_2^+) \in N(t_2)$, where $x_2^+ = A(t_2)x(t_2)$. As before, the point P_t continues to move forward with $x(t) = x(t, t_2, x_2^+)$ as the solution of (4.1) starting at (t_2, x_2^+). Thus the evolution process continues forward as long as the solution of (4.1) exists.

We will call the set of relations (i), (ii), and (iii), that characterize the aforementioned evolution process, an impulsive differential system. The curve described by the point P_t is called the integral curve, and the function $x = x(t)$, that defines this curve, a solution of the system.

Solutions of an impulsive differential system have the following three types:

(a) A continuous function, if the integral curve does not intersect the set $M(t)$ or hits it at fixed points of the operator $A(t)$.

(b) A piecewise continuous function having a finite number of discontinuities of the first kind if the integral curve meets $M(t)$ at a finite number of points that are not the fixed points of the operator $A(t)$.

(c) A piecewise continuous function having a countable number of discontinuities of the first kind if the integral curve encounters the set $M(t)$ at a countable number of points that are not the fixed points of the operator $A(t)$.

The moments t_k at which the point P_t hits the set $M(t)$ are called moments of impulsive effect. We shall assume that the solution $x(t)$ of the impulsive differential system is left continuous at $t_k, k = 1, 2, \ldots$, that is, $x(t_k^-) = \lim_{h \to 0^+} x(t_k - h) = x(t_k)$.

The freedom we have in the choice of the set of relations (i), (ii), and (iii), that describe an impulsive differential system, gives rise to several

types of systems. In this chapter, we mainly discuss the system with impulses at the fixed times.

Let the set $M(t) = \{M_k \mid M_k = \{(t_k, x), x \in \Omega\}\}_{k=1}^{\infty}$ represent a sequence of planes, where $t_1 < t_2 < \cdots < t_k < \cdots$ and $\lim_{k\to+\infty} t_k = +\infty$. Define the operator $A(t)$ at $t = t_k$ by

$$A(k)\colon \Omega \to \Omega, x \to A(t)x = x + I_k(x),$$

where $I_k\colon \Omega \to \Omega$. Consequently, the set $N(t)$ is also defined for $t = t_k$ and $N(k) = A(k)M(k)$. With this choice of $M(t)$, $N(t)$, and $A(t)$, a mathematical model of a simple impulsive system in which impulses occur at fixed times can be described by

$$\begin{aligned} x' &= f(t,x), && t \neq t_k,\ \ k = 1,2,\ldots, \\ \Delta x &= I_k(x), && t = t_k, \end{aligned} \tag{4.2}$$

where $\Delta x(t_k) = x(t_k^+) - x(t_k)$ and $x(t_k^+) = \lim_{h\to 0^+} x(t_k + h)$. We see immediately that any solution $x(t)$ of (4.2) satisfies

(i) $x'(t) = f(t, x(t)), t \in (t_k, t_{k+1}]$,
(ii) $\Delta x(t_k) = I_k(x(t_k)), t = t_k, k = 1, 2, \ldots$.

4.1.2. *Existence and uniqueness of solutions*

Let $\Omega \subset R^n$ be an open set and $f\colon R \times \Omega \to R^n$, $I_k\colon \Omega \to R^n$, $(t_0, x_0) \in R \times \Omega$, and $\alpha < \beta$. Suppose that for each $k \in Z$ the functions $\tau_k\colon \Omega \to R$ are continuous in Ω such that

$$\tau_k(x) < \tau_{k+1}(x), \quad \lim_{k\to\pm\infty} \tau_k(x) = \pm\infty \ \ (x \in \Omega).$$

Consider the impulsive differential equation

$$\begin{aligned} x' &= f(t,x), && t \neq \tau_k(x), \\ \Delta x &= I_k(x), && t = \tau_k,\ \ k = 1,2,\ldots \end{aligned} \tag{4.3}$$

with initial condition

$$x(t_0^+) = x_0. \tag{4.4}$$

Definition 4.1. A function φ: $(\alpha, \beta) \to R^n$ is said to be a *solution* of (4.3) if:

(1) $(t, \varphi(t)) \in R \times \Omega$ for $t \in (\alpha, \beta)$;
(2) for $t \in (\alpha, \beta)$, $t \neq \tau_k(\varphi(t))$, $k \in Z$, the function $\varphi(t)$ is differentiable and $\mathrm{d}\varphi/\mathrm{d}t = f(t, \varphi(t))$;
(3) the function $\varphi(t)$ is continuous from the left in (α, β) and if $t \in (\alpha, \beta)$, $t = \tau_k(\varphi(t))$ and $t \neq \beta$, then $\varphi(t^+) = \varphi(t) + I_k(\varphi(t))$, and for each $j \in Z$ and some $\delta > 0$, $s \neq \tau_j(\varphi(s))$, for $t < s < t + \delta$.

Definition 4.2. Each solution $\varphi(t)$ of (4.3) which is defined in an interval (t_0, β) and satisfied the condition $\varphi(t_0^+) = x_0$ is said to be a *solution of the initial value problem* (4.3), (4.4) (or a *solution of the equation with initial values* (t_0, x_0)).

Theorem 4.1 [Lakshmikantham *et al.* (1989)]. *Let the following conditions hold:*

(1) *The function* f: $R \times \Omega \to R^n$ *is continuous in* $t \neq \tau_k(x)$ $(k \in Z)$;
(2) *For any* $(t, x) \in R \times \Omega$, *there exists a locally integrable function* l *such that in a small neighbourhood of* (t, x)

$$|f(s, y)| \leq l(s);$$

(3) *For each* $k \in Z$, *the condition* $t_1 = \tau_k(x_1)$ *implies the existence of* $\delta > 0$, *such that*

$$t \neq \tau_k(x),$$

for all $0 < t - t_1 < \delta$ *and* $|x - x_1| < \delta$.

Then for each $(t_0, x_0) \in R \times \Omega$, *there exists a solution* x: $(t_0, \beta) \to R^n$ *of the initial value problem* (4.3), (4.4), *for some* $\beta > t_0$.

Theorem 4.2 [Lakshmikantham *et al.* (1989)]. *If condition* (2) *in Theorem* 4.1 *is replaced by the following condition*:

(2)′ *for any* $k \in Z$ *and* (t, x) *belonging to the hypersurface* $\sigma_k \equiv t = \tau_k(x)$, *there exists a finite limit of* $f(s, y)$ *as* $(s, y) \to (t, x), s > \tau_k(y)$, *then Theorem* 4.1 *is still valid.*

Theorem 4.3 [Lakshmikantham *et al.* (1989)]. *The solution* $x(t)$ *of the initial value problem* (4.3), (4.4) *is unique if the function* f *is such that the solution of the initial value problem* $x' = f(t, x), x(t_0) = x_0$ *is unique.*

This requirement is met if, for instance, f is (locally) Lipschitz continuous with respect to x in a neighborhood of (t_0, x_0).

If the initial value problem (4.3), (4.4) has a unique solution, then we shall denote this solution by $x(t; t_0, x_0)$.

For the impulsive equation with fixed moments

$$\begin{aligned} x' &= f(t,x), \quad t \neq \tau_k, \\ \Delta x &= I_k(x), \quad t = \tau_k, \end{aligned} \tag{4.5}$$

where $\tau_k < \tau_{k+1} (k \in Z)$ and $\lim_{k\to\pm\infty} \tau_k = \pm\infty$, the following theorem is valid.

Theorem 4.4 [Lakshmikantham *et al.* (1989)]. *Let the function $f\colon R \times \Omega \to R^n$ be continuous in the sets $(\tau_k, \tau_{k+1}] \times \Omega$, $(k \in Z)$ and for each $k \in Z$ and $x \in \Omega$, suppose that there exists a finite limit of $f(t,y)$ as $(t,y) \to (\tau_k, x)$, $t > \tau_k$. Then for each $(t_0, x_0) \in R \times \Omega$, there exist $\beta > t_0$ and a solution $x\colon (t_0, \beta) \to R^n$ of the initial value problem* (4.5), (4.4).

If, moreover, the function f is locally Lipschitz continuous with respect to x in $R \times \Omega$, then this solution is unique.

4.1.3. *Comparison principle*

It is well known that the theory of differential inequalities plays an important role in dynamics of differential equations. The corresponding theory of impulsive inequalities is equally useful in the investigation of impulsive differential equations.

Theorem 4.5 [Lakshmikantham *et al.* (1989)]. *Assume that*

(1) *the sequence $\{t_k\}$ satisfies $0 \le t_0 < t_1 < t_2 < \cdots$, with $\lim_{k\to\infty} t_k = \infty$;*
(2) *$m \in PC'[R_+, R]$ and $m(t)$ is left-continuous at t_k, $k = 1, 2, \ldots$;*
(3) *for $k = 1, 2, \ldots$, $t \ge t_0$*

$$\begin{aligned} m'(t) &\le p(t)m(t) + q(t), \quad t \neq \tau_k, \\ m(t_k^+) &\le d_k m(t_k) + b_k, \quad t = \tau_k, \end{aligned} \tag{4.6}$$

where $q, p \in C[R_+, R]$, $d_k \ge 0$, and b_k are constants.

Then

$$m(t) \le m(t_0) \prod_{t_0<t_k<t} d_k \exp\left(\int_{t_0}^{t} p(s)\mathrm{d}s\right) + \sum_{t_0<t_k<t} \left(\prod_{t_k<t_j<t} d_j \exp\left(\int_{t_k}^{t} p(s)\mathrm{d}s\right)\right) b_k + \int_{t_0}^{t} \prod_{s<t_k<t} d_k \exp\left(\int_{s}^{t} p(\sigma)\mathrm{d}\sigma\right) q(s)\mathrm{d}s, \quad t \ge t_0.$$

To introduce the comparison principle of impulsive differential equations, we firstly give the definition of extremal solutions of

$$\begin{aligned} u'(t) &= g(t,u), && t \ne \tau_k, \\ u(t_k^+) &= \psi_k(u(t_k)), && t = \tau_k, \\ u(t_0) &= u_0, \end{aligned} \tag{4.7}$$

where $g \in C[R_+ \times R, R]$ and $\psi_k \colon R \to R$.

Definition 4.3. Let $r(t) = r(t, t_0, u_0)$ be a solution of (4.7) on $[t_0, t_0 + a)$. Function $r(t)$ is said to be the maximal solution of (4.7), if for any solution $u(t) = u(t, t_0, u_0)$ of (4.7) existing on $[t_0, t_0 + a)$, the inequality

$$u(t) \le r(t), \quad t \in [t_0, t_0 + a) \tag{4.8}$$

holds. A minimal solution $\rho(t)$ may be defined similarly by reversing the inequality (4.8).

Definition 4.4. Let $V \colon R_+ \times R^n \to R_+$. V is said to belong to class V_0 if V satisfies:

(1) V is continuous on $(t_{k-1}, t_k] \times R^n$ and $\lim_{(t,y)\to(t_k^+,x)} V(t,y) = V(t_k^+, x)$ for every $x \in R^n$, $k \in N$;
(2) V is locally Lipschitz continuous with respect to x.

Definition 4.5. Let $V \in V_0$, for $(t,x) \in (t_{k-1}, t_k] \times R^n$. Define

$$D^+V(t,x) = \lim_{h\to 0^+} \sup \frac{1}{h}[V(t+h, x+hf(t,x)) - V(t,x)],$$

and

$$D_-V(t,x) = \lim_{h\to 0^-} \inf \frac{1}{h}[V(t+h, x+hf(t,x)) - V(t,x)].$$

If impulsive differential equation (4.7) and

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= f(t,x), \quad t \neq \tau_k, \\ \Delta x &= I_k(x), \quad t = \tau_k, \\ x(t_0^+) &= x_0, \quad t_0 \geq 0, \end{aligned} \tag{4.9}$$

satisfy the conditions:

(1) $0 < t_1 < t_2 < \cdots < t_k < \cdots$, and $t_k \to \infty$ as $k \to \infty$;
(2) f: $R_+ \times R^n \to R^n$ is continuous on $(t_{k-1}, t_k] \times R^n$ and

$$\lim_{(t,y)\to(t_k^+,x)} f(t,y) = f(t_k^+, x)$$

for every $x \in R^n$, $k \in N$;
(3) I_k: $R^n \to R^n$;
(4) g: $R_+ \times R_+ \to R$ is continuous on $(t_{k-1}, t_k] \times R^n$ and

$$\lim_{(t,y)\to(t_k^+,x)} g(t,y) = g(t_k^+, x)$$

for every $x \in R_+$, $k \in N$; then the following comparison principle holds.

Theorem 4.6 [Lakshmikantham *et al.* (1989)]. *Let* V: $R_+ \times R^n \to R_+$, $V \in V_0$. *Suppose that*

(1) g: $R_+ \times R_+ \to R$ *and satisfies the above condition* (4), *and* ψ_k: $R \to R$ *is nondecreasing and for each* $k = 1, 2, \ldots,$

$$\begin{aligned} D^+V(t,x) &\leq g(t, V(t,x)), \quad t \neq \tau_k, \\ V(t, x + I_k(x)) &\leq \psi_k(V(t,x)), \quad t = \tau_k. \end{aligned} \tag{4.10}$$

(2) $r(t) = r(t, t_0, u_0)$ *is the maximal solution of* (4.7) *existing on* $[t_0, \infty)$.

Then $V(t_0^+, x_0) \leq u_0$ *implies that*

$$V(t, x(t)) \leq r(t), \quad t > t_0,$$

where $x(t) = x(t, t_0, x_0)$ *is any solution of* (4.9) *on* $[t_0, \infty)$.

Theorem 4.7 [Lakshmikantham *et al.* (1989)]. *The assumption* (1) *of Theorem* 4.6 *holds with inequalities reversed and* ψ_k *being nonincreasing. Let* $\rho(t)$ *be the minimal solution of* (4.7) *existing on* $[t_0, \infty)$. *Then*

$V(t_0^+, x_0) \geq u_0$ *implies that*

$$V(t, x(t)) \geq \rho(t), \quad t > t_0.$$

Theorem 4.8 [Lakshmikantham *et al.* (1989)]. *If the scalar functions V and g in Theorem* 4.6 *are changed to be vector functions and g is quasimonotone nondecreasing, then similar results hold.* (*See Theorem* 3.1.2 *in Lakshmikantham et al.* (1989).)

4.1.4. *Linear homogeneous impulsive periodic systems and Floquet theory*

Consider the linear T-periodic impulsive equation

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= A(t)x, \quad t \neq \tau_k, \ t \in R, \\ \Delta x &= B_k x, \qquad t = \tau_k, \ k \in Z. \end{aligned} \tag{4.11}$$

Following three hypotheses are introduced:

(H1) $A(\cdot) \in PC(R, C^{n\times n})$, $A(t+T) = A(t)$ $(t \in R)$;
(H2) $B_k \in C^{n\times n}$, $det(E + B_k) \neq 0$, $\tau_k < \tau_{k+1}$ $(k \in Z)$;
(H3) There exists a $q \in N$, such that

$$B_{k+1} = B_k, \quad \tau_{k+q} = \tau_k + T \quad (k \in Z).$$

Without loss of generality, we assume that $\tau_0 \leq 0 < \tau_1$. The following theorem is a generalization of Floquet's theorem.

Theorem 4.9 [Bainov and Simeonov (1993)]. *Let* (H1)–(H3) *hold. Then each fundamental matrix of* (4.11) *can be represented in the form*

$$X(t) = \phi(t)\mathrm{e}^{\Lambda t} \quad (t \in R), \tag{4.12}$$

where the matrix $\Lambda \in C^{n\times n}$ is constant and the matrix $\phi(\cdot) \in PC^1(R, C^{n\times n})$ is nonsingular and T-periodic.

Let $X(t)$ be a fundamental matrix of (4.11). Then the matrix $X(t+T)$ is also fundamental, and

$$X(t+T) = X(t)M \quad (t \in R), \tag{4.13}$$

where the constant matrix M is called the monodromy matrix of (4.11) corresponding to the fundamental matrix $X(t)$. All monodromy matrices of

(4.11) are similar and have the same eigenvalues. The eigenvalues $\mu_1, \ldots, \mu_n$ of the monodromy matrices are called (Floquet) multipliers of Eq. (4.11) and the eigenvalues $\lambda_1, \ldots, \lambda_n$ of the matrix Λ in Theorem 4.9 are called characteristic exponents (or Floquet exponents) of (4.11). Furthermore,

$$\lambda_j = \frac{1}{T} \ln \mu_j \quad (j = 1, \ldots, n).$$

To calculate the Floquet multipliers of (4.11), we choose an arbitrary fundamental matrix $X(t)$ of (4.11) and calculate the eigenvalues of the matrix

$$M = X(t_0 + T)X^{-1}(t_0), \tag{4.14}$$

where $t_0 \in R$ is fixed.

If $X(0) = E$ (or $X(0^+) = E$), then we can choose

$$M = X(T) \quad (M = X(T^+)) \tag{4.15}$$

as the monodromy matrix of (4.11). Usually, we calculate any monodromy matrix of (4.11) by using the following formula:

$$M = X(T^+) = \prod_{k=1}^{q} (E + B_k) \exp\left(\int_0^T A(t)\mathrm{d}t \right). \tag{4.16}$$

The following two theorems are simple corollaries of Theorem 4.9.

Theorem 4.10 [Bainov and Simeonov (1993)]. *Let conditions* (H1)−(H3) *hold. Then the number* $\mu \in C$ *is a multiplier of* (4.11), *if and only if there exists a nontrivial solution* $\varphi(t)$ *of* (4.11) *such that* $\varphi(t + T) = \mu\varphi(t)$, $(t \in R)$.

Theorem 4.11 [Bainov and Simeonov (1993)]. *Let conditions* (H1)−(H3) *hold. Then* (4.11) *has a nontrivial* kT*-periodic solution, if and only if the* k*th power of some of its multipliers equals* 1.

The Floquet multipliers of Eq. (4.11) completely characterize its stability. Considering the relation

$$\frac{1}{T} \ln |\mu_j| = Re\, \lambda_j, \quad j = 1, \ldots, n,$$

between the multipliers μ_j of (4.11) and real parts of the eigenvalues λ_j of the matrix Λ, we have the theory below.

Theorem 4.12 [Bainov and Simeonov (1993)]. *Let conditions* (H1)−(H3) *hold. Then the linear T-periodic impulsive equation* (4.11) *is*:

(1) *stable if and only if all multipliers μ_j $(j = 1, \ldots, n)$ of Eq.* (4.11) *satisfy the inequality $|\mu_j| \leq 1$ and, moreover, for those μ_j with $|\mu_j| = 1$, there correspond simple elementary divisors*;
(2) *asymptotically stable if and only if all multipliers μ_j $(j = 1, \ldots, n)$ of Eq.* (4.11) *satisfy the inequality $|\mu_j| < 1$*;
(3) *unstable if $|\mu_j| > 1$, for some $j = 1, \ldots, n$.*

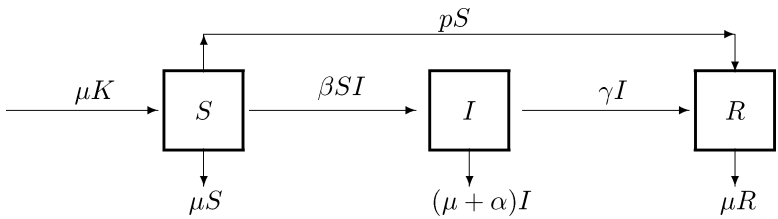
4.2. SIR Epidemic Model with Pulse Vaccination

Vaccination strategies are designed and applied to control or eradicate infectious diseases, among which there are constant vaccination and pulse vaccination. Pulse vaccination strategy (PVS) consists of periodic repetitions of impulsive vaccinations in a population, for all the age cohorts. At each vaccination time a constant fraction p of susceptibles is vaccinated. This kind of vaccination is called impulsive since all the vaccine doses are applied in a time period which is very short with respect to the dynamics of the target disease. Its theoretic study was done by Agur and coworkers in 1993. PVS allows to reach the eradication of a disease with some practical advantages, as discussed by Agur *et al.* (1993), Shulgin *et al.* (1998), Stone *et al.* (2000), d'Onofrio (2002), Zeng *et al.* (2003), Jin (2001), Zhou and Liu (2003), and Lu *et al.* (2002). In this section, SIR epidemic models with pulse vaccination are studied.

4.2.1. *SIR epidemic models with pulse vaccination and disease-induced death*

First, suppose an epidemic model with constant vaccination is given. We study a population that is composed of three classes of individuals: susceptibles (S), infectives (I), and recovereds (R). Vaccination gives life-long immunity to pS susceptibles who are, as a consequence, transferred to class R. Considering the incidence is bilinear, the relation of the three distinct epidemiologic classes for the pulse vaccination is shown in the following figure. The dynamics of the transmission are governed by the

following system:



$$\begin{aligned} S' &= \mu K - \beta SI - (\mu + p)S, \\ I' &= \beta SI - (\mu + \alpha)I - \gamma I, \\ R' &= \gamma I - \mu R + pS, \end{aligned} \tag{4.17}$$

where μ is the birth and the natural death rate, γ is the recovery rate, β is the effective contact rate, α is the death rate due to disease, p is the vaccination fraction, K is the carrying capacity, and the total population $N = S + I + R$.

Equations (4.17) have a disease-free equilibrium, given by

$$E_0 = \left(\frac{\mu K}{\mu + p}, 0, \frac{pK}{\mu + p} \right).$$

The basic reproductive number of the epidemic is defined as

$$R_0 = \frac{\beta}{\mu + \alpha + \gamma} \times \frac{\mu K}{\mu + p}. \tag{4.18}$$

When $R_0 > 1$, system (4.17) has an endemic equilibrium, $E_+ = (S_+, I_+, R_+)$, where

$$\begin{aligned} S_+ &= \frac{\mu + \alpha + \gamma}{\beta}, \\ I_+ &= \frac{\mu + p}{\beta}(R_0 - 1) = \frac{\gamma[\mu K - (\mu + p)S_+]}{\beta S_+}, \\ R_+ &= \frac{\gamma I_+ + pS_+}{\mu} = \frac{\gamma[\mu K - (\mu + p)S_+] + \beta p S_+^2}{\beta \mu S_+}. \end{aligned}$$

Moreover the equilibria of system (4.17) have the following character.

Theorem 4.13. *If $R_0 < 1$, the disease-free equilibrium E_0 is globally asymptotically stable. If $R_0 > 1$, the disease-free equilibrium E_0 is unstable, and the endemic equilibrium E_+ is globally asymptotically stable.*

The detailed proof of Theorem 4.13 can be found in the article by Jin (2001).

Assume the pulse scheme proposes to vaccinate a fraction ρ, $(0 < \rho < 1)$, of the entire susceptible population in a single pulse, applied every year. When pulse vaccination is incorporated into the SIR model (4.17), the system can be rewritten as

$$\begin{aligned} S' &= \mu K - \beta SI - \mu S, \\ I' &= \beta SI - (\mu + \alpha)I - \gamma I, \quad t \neq k, \\ R' &= \gamma I - \mu R, \qquad\qquad k = 0, 1, 2, \ldots, \end{aligned} \tag{4.19}$$

$$\begin{aligned} S(k^+) &= (1 - \rho)S(k), \\ I(k^+) &= I(k), \qquad\qquad t = k, \\ R(k^+) &= R(k) + \rho S(k), \quad k = 0, 1, 2, \ldots. \end{aligned} \tag{4.20}$$

Here $f(k^+) = \lim_{t \to k^+} f(t)$, $f(k) = \lim_{t \to k^-} f(t)$.

4.2.1.1. *Existence and local stability of the disease-free periodic solution*

Theorem 4.14. *Equations* (4.19) *and* (4.20) *have the disease-free periodic-one solution* $(S^*(t), 0, R^*(t))$, *where*

$$S^*(t) = K - \frac{K\rho \mathrm{e}^{-\mu t}}{1 - (1 - \rho)\mathrm{e}^{-\mu}}, \quad R^*(t) = \frac{K\rho \mathrm{e}^{-\mu t}}{1 - (1 - \rho)\mathrm{e}^{-\mu}}. \tag{4.21}$$

Proof. If $I(t) \equiv 0$, investigating the component $S^*(t)$ of periodic-one solutions is equivalent to finding solutions of the following boundary-value problem

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu K - \mu S, \\ S(0) &= (1 - \rho)S(1). \end{aligned} \tag{4.22}$$

The solution of first equation of (4.22) with the initial value $(0, S(0))$ is

$$S(t) = K + [S(0) - K]\mathrm{e}^{-\mu t}, \tag{4.23}$$

so we have

$$S(1) = K + [S(0) - K]\mathrm{e}^{-\mu}. \tag{4.24}$$

By substituting (4.24) into the second equation of (4.22), we obtain

$$S(0) - (1-\rho)[K + (S(0) - K)\mathrm{e}^{-\mu}] = 0.$$

Then

$$S(0) = \frac{(1-\rho)K(1-\mathrm{e}^{-\mu})}{1-(1-\rho)\mathrm{e}^{-\mu}}.$$

Substituting the expression of $S(0)$ into (4.23), we get

$$S^*(t) = K - \frac{K\rho\mathrm{e}^{-\mu t}}{1-(1-\rho)\mathrm{e}^{-\mu}}, \quad t \in [0,1).$$

If $I(t) \equiv 0$, investigating the component $R^*(t)$ of periodic-one solutions is equivalent to finding solutions of the following boundary-value problem:

$$\begin{aligned} \frac{\mathrm{d}R}{\mathrm{d}t} &= -\mu R, \\ R(0) &= R(1) + \rho S(1). \end{aligned}$$

Similarly, we obtain

$$R^*(t) = \frac{K\rho\mathrm{e}^{-\mu t}}{1-(1-\rho)\mathrm{e}^{-\mu}}, \quad t \in [0,1).$$

□

Define the basic reproductive number of system (4.19) and (4.20) as follows

$$R_{0p} = \frac{\beta}{\mu+\alpha+\gamma} \times \left[K - \frac{K\rho(\mathrm{e}^{\mu}-1)}{\mu(\mathrm{e}^{\mu}-1+\rho)}\right],$$

where

$$K - \frac{K\rho(\mathrm{e}^{\mu}-1)}{\mu(\mathrm{e}^{\mu}-1+\rho)} = \int_0^1 S^*(t)\mathrm{d}t.$$

Theorem 4.15. *The disease-free periodic-one solution* $(S^*(t), 0, R^*(t))$ *of system* (4.19) *and* (4.20) *is locally asymptotically stable if* $R_{0p} < 1$.

Proof. The local stability of the period-one solution $(S^*(t), 0, R^*(t))$ can be determined by that of the linearized SIR equation of (4.19) and (4.20) about the periodic solution $(S^*(t), 0, R^*(t))$. By setting $S(t) = S^*(t) + x(t)$, $I(t) = 0 + y(t)$, $R(t) = R^*(t) + z(t)$, where $x(t)$, $y(t)$, $z(t)$ are small

perturbations, every solution of the linearized equations can be written as

$$\begin{pmatrix} x(t) \\ y(t) \\ z(t) \end{pmatrix} = \Phi(t) \begin{pmatrix} x(0) \\ y(0) \\ z(0) \end{pmatrix}.$$

Here $\Phi(t) = (\varphi_{ij}(t))$, $i, j = 1, 2, 3$, is a fundamental matrix and satisfies

$$\frac{\mathrm{d}\Phi(t)}{\mathrm{d}t} = \begin{pmatrix} -\mu & -\beta S^*(t) & 0 \\ 0 & \beta S^*(t) - (\mu + \gamma + \alpha) & 0 \\ 0 & \gamma & -\mu \end{pmatrix} \Phi(t),$$

with $\Phi(0) = E$, where E is the identity matrix. Then

$$\begin{pmatrix} x(nT^+) \\ y(nT^+) \\ z(nT^+) \end{pmatrix} = \begin{pmatrix} 1-\rho & 0 & 0 \\ 0 & 1 & 0 \\ \rho & 0 & 1 \end{pmatrix} \begin{pmatrix} x(nT) \\ y(nT) \\ z(nT) \end{pmatrix},$$

and hence, if the absolute value of all eigenvalues of

$$M = \begin{pmatrix} 1-\rho & 0 & 0 \\ 0 & 1 & 0 \\ \rho & 0 & 1 \end{pmatrix} \Phi(1)$$

are less than one, the periodic-one solution $(S^*(t), 0, R^*(t))$ is locally stable. By simple calculation, we have

$$\Phi(t) = \begin{pmatrix} \mathrm{e}^{-\mu t} & \varphi_{12} & 0 \\ 0 & \varphi_{22} & 0 \\ 0 & \varphi_{32} & \mathrm{e}^{-\mu t} \end{pmatrix},$$

where

$$\begin{aligned} \varphi_{22} &= \exp\left\{ \int_0^t [\beta S^*(\tau) - (\mu + \gamma + \alpha)] \mathrm{d}\tau \right\}, \\ &= \exp\left[(\beta K - \mu - \gamma - \alpha)t + \frac{\beta K \rho \mathrm{e}^{\mu} (\mathrm{e}^{-\mu t} - 1)}{\mu(\mathrm{e}^{\mu} - 1 + \rho)} \right], \\ \varphi_{12} &= -\beta \mathrm{e}^{-\mu t} \int_0^t [S^*(\tau) \varphi_{22}(\tau) \mathrm{e}^{\mu\tau}] \mathrm{d}\tau, \\ \varphi_{32} &= \mathrm{e}^{-\mu t} \int_0^t \gamma \varphi_{22}(\tau) \mathrm{e}^{\mu\tau} \mathrm{d}\tau. \end{aligned}$$

Then the eigenvalues λ_i, $i = 1, 2, 3$, of M are

$$\lambda_1 = (1-\rho)\mathrm{e}^{-\mu}, \quad \lambda_2 = \varphi_{22}(1), \quad \lambda_3 = \mathrm{e}^{-\mu}.$$

Because $0 < \rho < 1$ and $\mu > 0$, then $0 < \lambda_1 < 1$, $0 < \lambda_3 < 1$, and

$$\begin{aligned}\lambda_2 = \varphi_{22}(1) &= \exp\left[\beta K - (\mu+\gamma+\alpha) + \frac{\beta K\rho(1-\mathrm{e}^{\mu})}{\mu(\mathrm{e}^{\mu}-1+\rho)}\right],\\ &= \exp\left\{\left[\frac{\beta K}{\mu+\gamma+\alpha}\left(1-\frac{\rho(\mathrm{e}^{\mu}-1)}{\mu(\mathrm{e}^{\mu}-1+\rho)}\right)-1\right](\mu+\gamma+\alpha)\right\},\\ &= \exp[(R_{0p}-1)(\mu+\gamma+\alpha)] < 1,\end{aligned}$$

if $R_{0p} < 1$.

From the Floquet theorem, we know that the disease-free periodic-one solution $(S^*(t), 0, R^*(t))$ is locally asymptotically stable if $R_{0p} < 1$. □

4.2.1.2. *Global stability of the disease-free periodic solution*

Theorem 4.16. *The disease-free periodic-one solution* $(S^*(t), 0, R^*(t))$ *of system* (4.19) *and* (4.20) *is globally asymptotically stable if* $R_{0p} < 1$.

Proof. From the first equation of (4.19) and (4.20), it follows that

$$\begin{aligned}S'(t) &= \mu K - \beta SI - \mu S \le \mu K - \mu S,\\ S(k^+) &= (1-\rho)S(k).\end{aligned}$$

By using Theorem 4.5 (the impulsive differential inequality), we have

$$\begin{aligned}S(t) &\le S(0^+)\left(\prod_{0<k<t}(1-\rho)\right)\exp\left(-\int_0^t \mu \mathrm{d}s\right)\\ &\quad + \int_0^t \left(\prod_{s<k<t}(1-\rho)\right)\mu K\exp(-\mu(t-s))\mathrm{d}s,\\ &= S(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + K\mathrm{e}^{-\mu t}\int_0^t\left(\prod_{s<k<t}(1-\rho)\right)\mu\mathrm{e}^{\mu s}\mathrm{d}s\end{aligned}$$

$$
\begin{aligned}
&= S(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + K\mathrm{e}^{-\mu t} \\
&\quad \times \left[\int_0^1 \left(\prod_{s<k<t}(1-\rho)\right)\mathrm{e}^{\mu s}\mathrm{d}(\mu s) + \int_1^2 \left(\prod_{s<k<t}(1-\rho)\right)\mathrm{e}^{\mu s}\mathrm{d}(\mu s) + \cdots\right. \\
&\quad + \int_{[t]-1}^{[t]} \left(\prod_{s<k<t}(1-\rho)\right)\mathrm{e}^{\mu s}\mathrm{d}(\mu s) \\
&\quad \left. + \int_{[t]}^{t} \left(\prod_{s<k<t}(1-\rho)\right)\mathrm{e}^{\mu s}\mathrm{d}(\mu s)\right] \\
&= S(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + K\mathrm{e}^{-\mu t}[(1-\rho)^{[t]}(\mathrm{e}^{\mu}-1) \\
&\quad + (1-\rho)^{[t]-1}(\mathrm{e}^{\mu}-1)\mathrm{e}^{\mu} + \cdots + (1-\rho)(\mathrm{e}^{\mu}-1)\mathrm{e}^{([t]-1)\mu} + \mathrm{e}^{\mu t} - \mathrm{e}^{[t]\mu}] \\
&= S(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + K\mathrm{e}^{-\mu t} \\
&\quad \times \left\{\frac{(1-\rho)^{[t]}(\mathrm{e}^{\mu}-1)[1-(\frac{\mathrm{e}^{\mu}}{1-\rho})^{[t]}]}{1-(\frac{\mathrm{e}^{\mu}}{1-\rho})} + \mathrm{e}^{\mu t} - \mathrm{e}^{[t]\mu}\right\} \\
&= \mathrm{e}^{-\mu t}\left[S(0^+)(1-\rho)^{[t]} - \frac{K(1-\rho)^{[t]+1}(\mathrm{e}^{\mu}-1)}{\mathrm{e}^{\mu}-1+\rho}\right] \\
&\quad + K\left[1 - \frac{\rho\mathrm{e}^{\mu([t]+1-t)}}{\mathrm{e}^{\mu}-1+\rho}\right] \\
&= r(t) + K\left[1 - \frac{\rho\mathrm{e}^{\mu([t]+1-t)}}{\mathrm{e}^{\mu}-1+\rho}\right], \qquad (4.25)
\end{aligned}
$$

where

$$
r(t) = \mathrm{e}^{-\mu t}\left[S(0^+)(1-\rho)^{[t]} - \frac{K(1-\rho)^{[t]+1}(\mathrm{e}^{\mu}-1)}{\mathrm{e}^{\mu}-1+\rho}\right].
$$

Then

$$
r(t) \le S(0^+)\mathrm{e}^{-\mu t}. \qquad (4.26)
$$

From the second equation of (4.19), (4.25), and (4.26), we obtain

$$
\begin{aligned}
I' &= (\beta S - \mu - \alpha - \gamma)I \\
&\le \left[\beta K\left(1 - \frac{\rho\mathrm{e}^{\mu}\mathrm{e}^{\mu([t]-t)}}{\mathrm{e}^{\mu}-1+\rho}\right) - \gamma - \mu - \alpha + \beta r(t)\right] I.
\end{aligned}
$$

Then

$$I(t) \le I(0)\exp\left[(K\beta-\gamma-\alpha-\mu)t-\frac{K\beta\rho\mathrm{e}^{\mu}}{\mathrm{e}^{\mu}-1+\rho}\int_0^t \mathrm{e}^{\mu([s]-s)}\mathrm{d}s + \beta\int_0^t r(s)\mathrm{d}s\right]. \tag{4.27}$$

Because

$$\begin{aligned}\int_0^t \mathrm{e}^{\mu([s]-s)}\mathrm{d}s &= \int_0^1 \mathrm{e}^{-\mu s}\mathrm{d}s+\int_1^2 \mathrm{e}^{\mu(1-s)}\mathrm{d}s+\cdots \\ &\quad+\int_{[t]-1}^{[t]} \mathrm{e}^{\mu([t]-1-s)}\mathrm{d}s+\int_{[t]}^t \mathrm{e}^{\mu([t]-s)}\mathrm{d}s \\ &= \frac{(1-\mathrm{e}^{-\mu})}{\mu}[t]+\frac{1}{\mu}(1-\mathrm{e}^{-\mu(t-[t])}),\end{aligned}$$

and $0 \le t-[t] \le 1$, we have

$$\int_0^t \mathrm{e}^{\mu([s]-s)}\mathrm{d}s \ge \frac{(1-\mathrm{e}^{-\mu})}{\mu}[t]. \tag{4.28}$$

Substituting (4.28) into (4.27), we get

$$\begin{aligned}I(t) &\le I(0)\exp\left\{(K\beta-\gamma-\alpha-\mu)t-\frac{K\beta\rho(\mathrm{e}^{\mu}-1)}{(\mathrm{e}^{\mu}-1+\rho)\mu}[t]+\beta\int_0^t r(s)\mathrm{d}s\right\} \\ &\le D(t)\exp\left\{\left[K\beta\left(1-\frac{\rho(\mathrm{e}^{\mu}-1)}{\mu(\mathrm{e}^{\mu}-1+\rho)}\right)-\gamma-\mu-\alpha\right]t\right\},\end{aligned} \tag{4.29}$$

where

$$D(t)=I(0)\exp\left\{-\frac{S(0)\beta}{\mu}\mathrm{e}^{-\mu t}+\frac{S(0)\beta}{\mu}\right\}\exp\left\{\frac{K\beta\rho(\mathrm{e}^{\mu}-1)}{(\mathrm{e}^{\mu}-1+\rho)\mu}(t-[t])\right\}>0.$$

Furthermore, it can be easily seen that $D(t)$ has an upper bound. From (4.29), we know that $I(t)\to 0$, as $t\to+\infty$, if $R_{0p}<1$.

In the following, we prove that

$$S(t)\to S^*(t),\quad R(t)\to R^*(t),\quad t\to+\infty,$$

for each solution $(S(t),I(t),R(t))$ of system (4.19) and (4.20).

In fact, let $V(t) = |S(t) - S^*(t)|$. Then

$$\begin{aligned} D^+V(t) &= \operatorname{sign}(S(t) - S^*(t))(S'(t) - S^{*'}(t)), \\ &\leq -\mu|S(t) - S^*(t)| + \beta S(t)I(t). \end{aligned} \tag{4.30}$$

For $S(t) < K$, from (4.29) and (4.30) we have

$$D^+V(t) \leq -\mu|S(t) - S^*(t)| + r_1(t), \quad t \neq k, \tag{4.31}$$

where

$$r_1(t) = \beta K D e^{-Ct}, \quad C = -\frac{K\beta(\mathrm{e}^{\mu} - 1)}{\mathrm{e}^{\mu} - 1 + \rho} + \gamma + \alpha + \mu > 0.$$

If $t = k$,

$$\begin{aligned} V(k^+) &= |S(k^+) - S^*(k^+)| \\ &= (1-\rho)|S(k) - S^*(k)| \\ &= (1-\rho)V(k). \end{aligned} \tag{4.32}$$

Applying Theorem 4.5 to (4.31) and (4.32), we obtain

$$\begin{aligned} V(t) &\leq V(0^+)(1-\rho)^{[t]}\exp(-\mu t) \\ &\quad + \int_0^t \left(\prod_{s<k<t}(1-\rho)\right) r_1(s)\exp(-\mu(t-s))\mathrm{d}s, \\ &= V(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + \mathrm{e}^{-\mu t} \\ &\quad \times \left[\int_0^1 (1-\rho)^{[t]}\mathrm{e}^{\mu s} r_1(s)\mathrm{d}(\mu s) + \int_1^2 (1-\rho)^{[t]-1}\mathrm{e}^{\mu s} r_1(s)\mathrm{d}(\mu s) + \cdots \right. \\ &\quad \left. + \int_{[t]-1}^{[t]} (1-\rho)\mathrm{e}^{\mu s} r_1(s)\mathrm{d}(\mu s) + \int_{[t]}^t \mathrm{e}^{\mu s} r_1(s)\mathrm{d}(\mu s)\right] \\ &\leq V(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + K\beta D\mathrm{e}^{-\mu t} \\ &\quad \times \left\{\frac{(1-\rho)^{[t]}(\mathrm{e}^{\mu-C} - 1)}{\mu - C} + \frac{(1-\rho)^{[t]-1}(\mathrm{e}^{\mu-C} - 1)\mathrm{e}^{\mu-C}}{\mu - C} + \cdots \right. \\ &\quad \left. + \frac{(1-\rho)(\mathrm{e}^{\mu-C} - 1)\mathrm{e}^{([t]-1)(\mu-C)}}{\mu - C} + \frac{\mathrm{e}^{(\mu-C)t} - \mathrm{e}^{(\mu-C)[t]}}{\mu - C}\right\} \end{aligned}$$

$$
\begin{aligned}
&= V(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + \frac{K\beta D\mathrm{e}^{-\mu t}}{\mu - C} \\
&\quad \times \left\{ \frac{(1-\rho)^{[t]}(\mathrm{e}^{\mu - C} - 1)[1 - (\frac{\mathrm{e}^{\mu-C}}{1-\rho})^{[t]}]}{1 - (\frac{\mathrm{e}^{\mu-C}}{1-\rho})} + \mathrm{e}^{(\mu-C)t} - \mathrm{e}^{(\mu-C)[t]} \right\} \\
&= V(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + \frac{K\beta D\mathrm{e}^{-\mu t}}{\mu - C} \\
&\quad \times \left\{ \frac{-(1-\rho)^{[t]+1}(\mathrm{e}^{\mu-C} - 1) - \rho\mathrm{e}^{\mu - C([t]+1)}}{\mathrm{e}^{\mu-C} - 1 + \rho} + \mathrm{e}^{(\mu-C)t} \right\} \\
&= V(0^+)(1-\rho)^{[t]}\mathrm{e}^{-\mu t} + \frac{K\beta D\mathrm{e}^{-Ct}}{\mu - C} - \frac{K\beta D(1-\rho)^{[t]+1}(\mathrm{e}^{\mu-C} - 1)\mathrm{e}^{-\mu t}}{\mathrm{e}^{\mu-C} - 1 + \rho} \\
&\quad - \frac{K\beta D\rho\mathrm{e}^{-\mu t + \mu[t] + \mu - C[t] - C}}{\mathrm{e}^{\mu-C} - 1 + \rho}.
\end{aligned}
$$

Hence $V(t) \to 0 (t \to +\infty)$. Consequently, we have $S(t) \to S^*(t) (t \to +\infty)$. Similarly, we can prove $R(t) \to R^*(t) (t \to +\infty)$. □

4.2.1.3. *Comparison between constant and pulse vaccinations*

The proportional constant and pulse vaccinations are compared by the basic reproductive numbers R_0 and R_{0p}.

Letting $R_{0p} = 1$, we have

$$
\rho = \frac{(\beta K - \mu - \alpha - \gamma)\mu}{\beta K\big(1 - \frac{\mu}{\mathrm{e}^{\mu}-1}\big) + \frac{\mu(\mu+\alpha+\gamma)}{\mathrm{e}^{\mu}-1}} \triangleq \rho_c, \tag{4.33}
$$

and letting $R_0 = 1$, we have

$$
p = \frac{\beta K - \mu - \alpha - \gamma}{\mu + \alpha + \gamma} \triangleq p_c. \tag{4.34}
$$

From (4.33) and (4.34), it follows that

$$
\rho_c = \frac{p_c}{\frac{\mu}{\mathrm{e}^{\mu}-1} + \frac{\beta K}{\mu+\alpha+\gamma}(1 - \frac{\mu}{\mathrm{e}^{\mu}-1})}. \tag{4.35}
$$

If $\mu \ll 1$, then $\rho_c \approx p_c$. Thus, we have the following conclusions.

(a) Assume $\beta K > \mu + \alpha + \gamma$. Then

$$\frac{\mu}{e^{\mu} - 1} + \frac{\beta K}{\mu + \alpha + \gamma}\left(1 - \frac{\mu}{e^{\mu} - 1}\right) > 1.$$

From (4.35) we have $\rho_c < p_c$. Notice that $\beta K > \mu + \alpha + \gamma$ implies that the disease becomes endemic if the vaccination is absent. Hence, the pulse vaccination can eradicate the disease in this case.

(b) Assume $\beta K < \mu + \alpha + \gamma$. Then

$$\frac{\mu}{e^{\mu} - 1} + \frac{\beta K}{\mu + \alpha + \gamma}\left(1 - \frac{\mu}{e^{\mu} - 1}\right) < 1.$$

From (4.35) we have $\rho_c > p_c$. The assumption $\beta K < \mu + \alpha + \gamma$ implies that the disease does not become endemic if the vaccination is absent. Then, vaccination is not necessary here.

4.2.2. *SIR epidemic model without disease-induced death*

The following standard SIR epidemic model was studied by Shulgin *et al.* (1998):

$$\begin{aligned} \frac{dS}{dt} &= \mu - (\beta I + \mu)S, \\ \frac{dI}{dt} &= \beta SI - (\mu + \gamma)I, \\ \frac{dR}{dt} &= \gamma I - \mu R, \end{aligned} \tag{4.36}$$

where the population has a constant size, which is normalized to unity $S(t) + I(t) + R(t) = 1$.

The first and second equations of (4.36) do not have variable R. So, we only study the following equations:

$$\begin{aligned} \frac{dS}{dt} &= \mu - (\beta I + \mu)S, \\ \frac{dI}{dt} &= \beta SI - (\mu + \gamma)I. \end{aligned} \tag{4.37}$$

Equation (4.37) has the disease-free equilibrium (1,0) and the endemic equilibrium (S_c, I_c), where

$$S_c = \frac{\mu + \gamma}{\beta}, \quad I_c = \frac{\mu}{\beta}(R_0 - 1),$$

where $R_0 = \beta/(\mu + \gamma)$ is the basic reproductive number.

The disease-free equilibrium is globally asymptotically stable if $R_0 < 1$, and the endemic equilibrium is globally asymptotically stable if $R_0 > 1$.

When pulse vaccination is incorporated into the SIR model (4.36), and is applied in equal intervals, the system becomes nonautonomous and can be rewritten as

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= \mu - (\beta I + \mu)S - p\sum_{n=0}^{\infty} S(nT^-)\delta(t - nT), \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= \beta SI - (\mu + \gamma)I, \end{aligned} \tag{4.38}$$

where

$$S(nT^-) = \lim_{\epsilon \to 0^+} S(nT - \epsilon), \quad \epsilon > 0,$$

is the left-hand limit of $S(t)$, and $\delta(t)$ is the Dirac delta-function. Pulse vaccination is applied as an impulse at the discrete times $t = nT$, $n = 0, 1, 2, \ldots$, and the moment immediately before the nth vaccination pulse is denoted by $t = nT^-$. Impulses generated by the delta-function in (4.38) create jump discontinuities in variable $S(t)$, which suddenly decreases by the proportion p, whenever $t = nT$.

Using the discrete dynamic system determined by the stroboscopic map, a complete expression for the disease-free periodic solution over the nth time-interval $t_0 = (n - l)T \le t \le nT$ is

$$\begin{aligned} \widetilde{S}(t) &= 1 - \frac{p\mathrm{e}^{\mu T}}{\mathrm{e}^{\mu T} - (1 - p)}\mathrm{e}^{-\mu(t - t_0)} \\ &\quad - p\left[1 - \frac{p\mathrm{e}^{\mu T}}{\mathrm{e}^{\mu T} - (1 - p)}\mathrm{e}^{-\mu T}\right]\int_{t_0}^{t} \delta(t - nT)\mathrm{d}t, \\ \widetilde{I}(t) &= 0. \end{aligned} \tag{4.39}$$

The solution is periodic in time $\widetilde{S}(t + T) = \widetilde{S}(t)$, $\widetilde{I}(t + T) = \widetilde{I}(t)$. The local stability of the disease-free solution follows from the Floquet theorem.

The disease-free solution to the SIR model under pulse vaccination (4.38) is locally stable if

$$\frac{1}{T}\int_0^T \widetilde{S}(t)\mathrm{d}t < \frac{m + \gamma}{\beta} = S_{\mathrm{c}}. \tag{4.40}$$

Thus, for the stability of the disease-free solution, the mean value of $S(t)$, averaged over a single-pulse period, must be less than the threshold level S_{c}.

The proof of the global stability of the disease-free solution is not given [Shulgin *et al.* (1998)]. Here, we can prove it by using impulsive differential inequalities. The concrete proof process is similar to that in Sec. 4.2.1.

The stability condition (4.40) can be fully specified by substituting the exact expression (4.39) for $\widetilde{S}(t)$ and integrating it. In terms of the model parameters, the stability condition is

$$\frac{(\mu T - p)(\mathrm{e}^{\mu T} - 1) + \mu p T}{\mu T(p - 1 + \mathrm{e}^{\mu T})} < \frac{\mu + \gamma}{\beta} = S_{\mathrm{c}}. \tag{4.41}$$

When the proportion p of vaccination is given, calculating the maximum allowable period of the pulse, $T_{\max}(p)$, for which the epidemic can be eliminated, is not simple. In Sec. 4 [Shulgin *et al.* (1998)], the authors give two ways to calculate it:

(1) *Calculation from stability conditions*
It is possible to obtain an expression for the maximum allowable period of the pulse, $T_{\max}(p)$ in which the stability criterion above is satisfied. The maximum value occurs when the inequality in (4.41) is replaced by an equality. To calculate $T_{\max}$ one can simplify (4.41) by using Taylor expansions by reasonably assuming the period of pulses is much shorter than the mean lifespan, $T \ll 1/\mu$, and that the mean lifespan of an individual is much longer than the duration of disease ($\mu \ll \gamma$). After neglecting higher order terms, we finally obtain

$$T_{\max} \approx \frac{2\gamma p}{\mu(2\beta - p - \gamma)}. \tag{4.42}$$

(2) *Calculation from the fact that the number of the infective is descending*
The pulses are applied frequently enough to ensure $\mathrm{d}I(t)/\mathrm{d}t < 0$, for all t, so that the number of infectious individuals is a decreasing function of time. According to the second equation of (4.36), it is possible to satisfy this condition if pulsing ensures that, for all t, $S(t) < S_{\mathrm{c}} = (\mu + \gamma)/\beta$; that is, pulse vaccination is applied every time $S(t)$ approaches the threshold S_{c}. At this moment the number of $S(t)$ drops to $(1-p)S(t)$. Thus, the maximum period of the pulse, $T_{\max}$, is the allowable time when $S(t) \leq S_{\mathrm{c}}$ holds with the initial value $S(0) = (1-p)S_{\mathrm{c}}$.

From the first equation of (4.37), we have

$$\frac{\mathrm{d}S}{\mathrm{d}t} = \mu - \mu S - \beta SI \leq \mu - \mu S.$$

Then $S(t)$ is smaller than the solution of the following boundary problem:

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \mu - \mu x, \quad x(0) = (1-p)S_{\mathrm{c}},$$

which is

$$x(t) = 1 + [(1-p)S_{\mathrm{c}} - 1]\mathrm{e}^{-\mu t}.$$

Hence,

$$S(t) \leq x(t) = 1 + [(1-p)S_{\mathrm{c}} - 1]\mathrm{e}^{-\mu t}.$$

If $x(t) \leq S_{\mathrm{c}}$, then $S(t) \leq S_{\mathrm{c}}$, and

$$0 \leq t \leq \frac{1}{\mu} \ln\left(1 + \frac{pS_{\mathrm{c}}}{1 - S_{\mathrm{c}}}\right).$$

Therefore,

$$T_{\max} = \frac{1}{\mu} \ln\left(1 + \frac{pS_{\mathrm{c}}}{1 - S_{\mathrm{c}}}\right). \tag{4.43}$$

The expression (4.43) can also be derived by the following method. Consider that the minimum number of the susceptibles occurs just after pulse vaccination and is given by S^*, which is the unique fixed point of $S_{n+1} = (1-p)[1 + (S_n - 1)\mathrm{e}^{-\mu t}]$, while the maximum number of the susceptibles occurs just before vaccination and is equal to $S^*/(1-p)$. Hence, $S(t) < S_{\mathrm{c}}$ is equivalent to

$$\frac{S^*}{1-p} < S_{\mathrm{c}}. \tag{4.44}$$

Then the expression (4.43) for $T_{\max}$ is obtained by evaluating at equality and making use of the value of S^*.

4.3. SIRS Epidemic Model with Pulse Vaccination

In many epidemiologic models, the mixing of susceptibles with infectives is often considered to be homogeneous and accordingly the incidence rate is assumed to be bilinear as βSI. However, if the total population is very large or to the gregarious animals, the standard incidence $\beta(S/N)I$ is more appropriate. In this section we introduce pulse vaccination in two SIRS epidemic models with standard and nonmonotonic incidence rates [Gakkhar and Negi (2008)], respectively.

4.3.1. *SIRS model with pulse vaccination and standard incidence rate*

The model with standard incidence rate and pulse vaccination is as follows.

$$\begin{aligned} S' &= bN - \beta\frac{S}{N}I + \theta I + dR - \mu S, \quad t \neq t_n, \\ I' &= \beta\frac{S}{N}I - (\mu + \alpha + \gamma + \theta)I, \quad t_{n+1} = t_n + T, \\ R' &= \gamma I - (\mu + d)R, \end{aligned} \tag{4.45}$$

$$\begin{aligned} S(t^+) &= (1-p)S(t^-), \qquad t = t_n, \\ I(t^+) &= I(t^-), \qquad\qquad n = 0, 1, 2, \ldots \\ R(t^+) &= R(t^-) + pS(t^-), \end{aligned} \tag{4.46}$$

where the parameters b, β, μ, θ, γ, d and p are all positive constants. The parameter b represents the birth rate, β is adequate contact rate, μ is the per capita death-rate, θ is the removed rate from the infectious to the susceptible, γ is the natural recovery rate of the infective population, d is the rate at which recovered individuals lose immunity and return to the susceptible class, p is the proportion of those vaccinated successfully, the nonnegative constant α is the death rate due to disease, t_n is the time of vaccination, and the positive constant T is the time period.

Denote the total population size by N, with $N = S + I + R$. Then

$$N'(t) = (b - \mu)N - \alpha I. \tag{4.47}$$

Let

$$s = \frac{S}{N}, \quad i = \frac{I}{N}, \quad r = \frac{R}{N}.$$

Then system (4.45), (4.46), and (4.47) can be written as

$$\begin{aligned} s' &= b - bs + dr + \theta i - (\beta - \alpha)si, \qquad t \neq t_n, \\ i' &= -(b + \alpha + \gamma + \theta)i + \beta si + \alpha i^2, \quad t_{n+1} = t_n + T, \\ r' &= -(b + d)r + \gamma i + \alpha ir, \end{aligned} \tag{4.48}$$

$$\begin{aligned} s(t^+) &= (1-p)s(t^-), \qquad t = t_n, \\ i(t^+) &= i(t^-), \qquad\qquad n = 0, 1, 2, \ldots \\ r(t^+) &= r(t^-) + ps(t^-), \end{aligned} \tag{4.49}$$

Since, $s(t)+i(t)+r(t)=1$, we only study the following two-dimensional system:

$$\begin{aligned} i' &= -(b+\alpha+\gamma+\theta)i+\beta i(1-i-r)+\alpha i^2, && t\neq t_n,\\ r' &= -(b+d)r+\gamma i+\alpha ir, && t_{n+1}=t_n+T, \end{aligned} \tag{4.50}$$

$$\begin{aligned} i(t^+) &= i(t^-), && t=t_n,\\ r(t^+) &= r(t^-)+p[1-i(t^-)-r(t^-)], && n=0,1,2,\ldots. \end{aligned} \tag{4.51}$$

4.3.1.1. *Existence and local stability of the disease-free periodic solution*

The existence of a disease-free periodic solution is equivalent to the existence of a T-periodic solution which satisfies Eqs. (4.50) and (4.51) when $i(t)=0$. In this case, (4.50) and (4.51) become

$$\begin{aligned} r' &= -(b+d)r, && t\neq t_n,\\ r(t^+) &= p+(1-p)r(t^-), && t=t_n. \end{aligned} \tag{4.52}$$

Solving (4.52) in the interval $t_n\le t\le t_{n+1}$, we have

$$r(t)=\begin{cases} r(t^+)\exp[-(b+d)(t-t_n)], & t_n\le t<t_{n+1},\\ r(t_{n+1}^+)=p+(1-p)r(t_{n+1}^-), & t=t_{n+1}. \end{cases} \tag{4.53}$$

Similarly to the calculation in Sec. 4.2.2, we can use the stroboscopic map to get the disease-free periodic solution

$$\widetilde{r}(t)=\begin{cases} \dfrac{p\mathrm{e}^{(b+d)T}}{\mathrm{e}^{(b+d)T}+p-1}\exp[-(b+d)(t-t_n)], & t_n\le t<t_{n+1},\\ r_0, & t=t_{n+1}, \end{cases} \tag{4.54}$$

$$\widetilde{i}(t)=0.$$

The proof of the local stability is also similar to that in Sec. 4.2. Using the same method we obtain the two Floquet multipliers

$$\begin{aligned} \lambda_1 &= \exp\{[\beta-(b+\alpha+\gamma+\theta)]T-\beta\int_0^T\widetilde{r}(t)\mathrm{d}t\},\\ \lambda_2 &= (1-p)\exp[-(b+d)T]<1. \end{aligned} \tag{4.55}$$

According to Floquet theory, the solution (4.54) is locally stable if the absolute value of all Floquet multipliers are less than unity.

From (4.55), we see that the disease-free periodic solution is locally stable if

$$\frac{1}{T}\int_0^T \widetilde{r}(t)\mathrm{d}t > 1 - \frac{b+\alpha+\gamma+\theta}{\beta}, \tag{4.56}$$

or by $\widetilde{s}(t) = 1 - \widetilde{r}(t)$,

$$\frac{1}{T}\int_0^T \widetilde{s}(t)\mathrm{d}t < \frac{b+\alpha+\gamma+\theta}{\beta}. \tag{4.57}$$

Define the basic reproductive number

$$\begin{aligned} R^* &= \frac{\beta}{b+\alpha+\gamma+\theta} \times \frac{1}{T}\int_0^T \widetilde{s}(t)\mathrm{d}t \\ &= \frac{\beta}{b+\alpha+\gamma+\theta} \times \frac{[T(b+d)-p][\mathrm{e}^{T(b+d)}-1]+T(b+d)p}{T(b+d)[\mathrm{e}^{(b+d)T}+p-1]}. \end{aligned}$$

We have the following theorem.

Theorem 4.17. *If $R^* < 1$, then the periodic disease-free solution $(\widetilde{s}(t), 0, \widetilde{r}(t))$ of system* (4.48) *and* (4.49) *is locally asymptotically stable.*

4.3.1.2. *Global stability of the disease-free periodic solution*

In the following, we consider the global stability of the disease-free periodic solution $(\widetilde{s}(t), 0, \widetilde{r}(t))$.

From (4.48) and (4.49), we have

$$\begin{aligned} &s' = b + d - (b+d)s - (d-\theta)i - (\beta-\alpha)si, && t \neq t_n, \\ &i' = -(b+\alpha+\gamma+\theta)i + \beta si + \alpha i^2, && t_{n+1} = t_n + T, \end{aligned} \tag{4.58}$$

$$\begin{aligned} &s(t^+) = (1-p)s(t^-), && t = t_n, \\ &i(t^+) = i(t^-), && n = 0, 1, 2, \ldots. \end{aligned} \tag{4.59}$$

From biological point of view, we have a basic assumption that $\beta \geq \alpha$ and $d \geq \theta$. It is noted that the systems (4.45) and (4.46) are general SIRS model. Based on this assumption we have the following theorem.

Theorem 4.18. *If $R^* < 1$, then the T-periodic disease-free solution $(\widetilde{s}(t), 0, \widetilde{r}(t))$ of systems* (4.48) *and* (4.49) *is globally asymptotically stable.*

Proof. From Theorem 4.17, we only need to prove that every solution of (4.58) and (4.59) converges to the periodic solution $(\widetilde{s}(t), 0)$ when $R^* < 1$.

First, we prove that $\lim_{t\to+\infty} i(t) = 0$ if $R^* < 1$. From the first equation of (4.58) and (4.59), we have

$$\begin{aligned} s' &\le b + d - (b+d)s, \quad && t \ne t_n, \\ s(t^+) &= (1-p)s(t^-), && t = t_n. \end{aligned} \tag{4.60}$$

By using Theorem 4.5, we obtain

$$s(t) \le r_1(t) + 1 - \frac{p\mathrm{e}^{T(b+d)(1+[t/T])-(b+d)t}}{\mathrm{e}^{(b+d)T} + p - 1}, \tag{4.61}$$

where

$$r_1(t) = \mathrm{e}^{-(b+d)t}\left\{ s(0^+)(1-p)^{[t/T]} - \frac{(1-p)^{[t/T]+1}(\mathrm{e}^{(b+d)T} - 1)}{\mathrm{e}^{(b+d)T} + p - 1} \right\}.$$

Substituting (4.61) to the second equation of (4.58) yields

$$i'(t) \le i\left\{ \beta - (b + \alpha + \gamma + \theta) + \beta r_1(t) - \frac{p\beta\mathrm{e}^{T(b+d)(1+[t/T])-(b+d)t}}{\mathrm{e}^{(b+d)T} + p - 1} + \alpha i \right\}. \tag{4.62}$$

Let

$$f(t) = \beta - (b + \alpha + \gamma + \theta) + \beta r_1(t) - \frac{p\beta\mathrm{e}^{T(b+d)(1+[t/T])-(b+d)t}}{\mathrm{e}^{(b+d)T} + p - 1}.$$

From (4.62) and the comparison principle, we have

$$i(t) \le \frac{i(0)\exp\{\int_0^t f(\tau)\mathrm{d}\tau\}}{1 - \alpha i(0)\int_0^t \exp\{\int_0^\tau f(\sigma)\mathrm{d}\sigma\}\mathrm{d}\tau}. \tag{4.63}$$

Because

$$\begin{aligned} \int_0^t f(\tau)\mathrm{d}\tau = {} & [\beta - (b + \alpha + \gamma + \theta)]t + \beta\int_0^t r_1(\tau)\mathrm{d}\tau \\ & - \frac{p\beta\mathrm{e}^{(b+d)T}}{\mathrm{e}^{(b+d)T} + p - 1}\int_0^t \mathrm{e}^{(b+d)(T[\tau/T]-\tau)}\mathrm{d}\tau, \end{aligned} \tag{4.64}$$

and

$$\int_0^t \mathrm{e}^{(b+d)(T[\tau/T]-\tau)}\mathrm{d}\tau = \frac{1 - \mathrm{e}^{-(b+d)T}}{b+d}[t/T] + \frac{1}{b+d}\{1 - \mathrm{e}^{-(b+d)(t-T[t/T])}\},$$

we have

$$\int_0^t \mathrm{e}^{(b+d)(T[\tau/T]-\tau)}\mathrm{d}\tau \geq \frac{1-\mathrm{e}^{-(b+d)T}}{b+d}[t/T],$$

and

$$\begin{aligned}\int_0^t f(\tau)\mathrm{d}\tau &\leq [\beta-(b+\alpha+\gamma+\theta)]t\\ &\quad -\frac{p\beta\mathrm{e}^{(b+d)T}}{\mathrm{e}^{(b+d)T}+p-1}\frac{1-\mathrm{e}^{-(b+d)T}}{b+d}[t/T]+\beta\int_0^t r_1(\tau)\mathrm{d}\tau\\ &\leq \left[\beta-(b+\alpha+\gamma+\theta)-\frac{p\beta(\mathrm{e}^{(b+d)T}-1)}{T(b+d)(\mathrm{e}^{(b+d)T}+p-1)}\right]t\\ &\quad +\beta\left\{\frac{s(0^+)(\mathrm{e}^{(b+d)T}-1)}{b+d}+\frac{s(0^+)}{b+d}[(1-p)\mathrm{e}^{-(b+d)T}]^{[t/T]}\right.\\ &\quad \left.\times(1-\mathrm{e}^{-(b+d)T(t/T-[t/T])})\right\}+g(t),\end{aligned} \tag{4.65}$$

where

$$\begin{aligned}g(t)&=\frac{p\beta(\mathrm{e}^{(b+d)T}-1)}{T(b+d)(\mathrm{e}^{(b+d)T}+p-1)}(t-T[t/T])\\ &\leq \frac{p\beta(\mathrm{e}^{(b+d)T}-1)}{(b+d)(\mathrm{e}^{(b+d)T}+p-1)}.\end{aligned} \tag{4.66}$$

It follows from (4.65), (4.66) and the condition $R^*<1$ that

$$\lim_{t\to+\infty}\exp\left\{\int_0^t f(\tau)\mathrm{d}\tau\right\}=0, \tag{4.67}$$

and then according to (4.63) and (4.67), we obtain $i(t)\to 0$, $t\to+\infty$, if $R^*<1$.

Next, we prove that $s(t)\to\widetilde{s}(t)$, $t\to+\infty$, for every solution $(s(t),i(t))$ of system (4.58) and (4.59).

In fact, let $W(t)=|s(t)-\widetilde{s}(t)|$, we have

$$\begin{aligned}D^+W(t)&=\mathrm{sign}(s(t)-\widetilde{s}(t))(s'(t)-\widetilde{s}'(t))\\ &\leq -(b+d)|s(t)-\widetilde{s}(t)|+(d-\theta)i+(\beta-\alpha)si\\ &\leq -(b+d)W(t)+(d-\theta)i+(\beta-\alpha)si,\quad t\neq nT.\end{aligned} \tag{4.68}$$

From (4.63) and $R^* < 1$, there exists a constant M satisfying

$$i(t) \leq M\mathrm{e}^{Ht}, \tag{4.69}$$

where

$$H = (b + \alpha + \gamma + \theta) - \beta + \frac{p\beta(\mathrm{e}^{(b+d)T} - 1)}{T(b+d)(\mathrm{e}^{(b+d)T} + p - 1)}.$$

Then, it follows from

$$W(t_n^+) = (1-p)W(t_n^-), \tag{4.70}$$

(4.68), (4.69), and Theorem 4.5, that $\lim_{t\to+\infty} W(t) = 0$, that is, $s(t) \to \widetilde{s}(t)$, as $t \to +\infty$. □

4.3.2. *SIRS model with pulse vaccination and nonmonotonic incidence rate*

This part is based on the work by Gakkhar and Negi (2008). The model to be studied has the following form:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}\tau} &= b - \frac{\kappa SI}{1 + \beta I + \alpha I^2} - \mu S + \delta R, \\
\frac{\mathrm{d}I}{\mathrm{d}\tau} &= \frac{\kappa SI}{1 + \beta I + \alpha I^2} - (\mu + \gamma)I, \qquad \tau \neq nT, \\
\frac{\mathrm{d}R}{\mathrm{d}\tau} &= \gamma I - (\mu + \delta)R,
\end{aligned} \tag{4.71}$$

$$\begin{aligned}
S(nT^+) &= (1-p)S(nT^-), \qquad \tau = nT, \\
I(nT^+) &= I(nT^-), \qquad n = 0, 1, 2, \ldots, \\
R(nT^+) &= R(nT^-) + pS(nT^-).
\end{aligned} \tag{4.72}$$

The constant b is the recruitment rate, μ is the natural death rate, κI measures the infection force of the disease, and $1/(1 + \beta I + \alpha I^2)$ measures the inhibition effect from the behavior change of the susceptible individuals. The natural recovery rate of the infective population is γ, δ is the rate at which recovered individuals lose immunity and return to the susceptible class. The parameter α is assumed to be positive. The parameter β is chosen to ensure $1 + \beta I + \alpha I^2 > 0$ for all $I \geq 0$, that is, $\beta > -2\sqrt{\alpha}$. The pulse vaccination proposes to vaccinate a fraction, p, of the entire susceptible population in a single pulse.

4.3.2.1. *Existence and stability of the disease-free solution*

For simplicity, we introduce a new set of variables and parameters as

$$x = \frac{\kappa}{\mu+\delta}S, \qquad y = \frac{\kappa}{\mu+\delta}I, \quad z = \frac{\kappa}{\mu+\delta}R, \quad t = (\mu+\delta)\tau,$$
$$B = \frac{b\kappa}{(\mu+\delta)^2}, \quad d = \frac{\mu}{\mu+\delta}, \quad q = \frac{\delta}{\mu+\delta}, \quad m = \frac{\beta(\mu+\delta)}{\kappa},$$
$$n = \frac{\alpha(\mu+\delta)^2}{\kappa^2}, \quad h = \frac{\mu+\gamma}{\mu+\delta}, \quad c = \frac{\gamma}{\mu+\delta}.$$

Further, observe that

$$x + y + z = \frac{\kappa}{\mu+\delta}(S+I+R) = \frac{\kappa b}{\mu(\mu+\delta)} \triangleq A. \tag{4.73}$$

Using the new variables, system (4.71) and (4.72) become

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= B - \frac{xy}{1+my+ny^2} - \mathrm{d}x + qz, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{xy}{1+my+ny^2} - hy, \quad t \neq nT, \\ \frac{\mathrm{d}z}{\mathrm{d}t} &= cy - z, \end{aligned} \tag{4.74}$$

$$\begin{aligned} x(nT^+) &= (1-p)x(nT^-), \qquad t = nT, \\ y(nT^+) &= y(nT^-), \qquad n = 0,1,2,\ldots \\ z(nT^+) &= z(nT^-) + px(nT^-). \end{aligned} \tag{4.75}$$

Using the stroboscopic map, the complete expression for the disease-free periodic solution over the nth time interval, $nT < t \leq (n+1)T$, is obtained as

$$\begin{aligned} \tilde{x}(t) &= (B+Aq)\left[1 - \frac{p\mathrm{e}^T}{\mathrm{e}^T - 1 + p}\mathrm{e}^{-(t-nT)}\right], \\ \tilde{y}(t) &= 0, \\ \tilde{z}(t) &= A - (B+Aq)\left[1 - \frac{p\mathrm{e}^T}{\mathrm{e}^T - 1 + p}\mathrm{e}^{-(t-nT)}\right]. \end{aligned}$$

The local stability of periodic solution, $(\tilde{x}(t), 0)$, in x-y plane, can be determined by the linearization of the system

$$\left.\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= (B + Aq) - \frac{xy}{1 + my + ny^2} - x, \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{xy}{1 + my + ny^2} - hy, \quad t \neq nT, \end{aligned}\right\} \tag{4.76}$$

$$\left.\begin{aligned} x(nT^+) &= (1-p)x(nT^-), \quad t = nT, \\ y(nT^+) &= y(nT^-), \qquad\quad n = 0, 1, 2, \ldots \end{aligned}\right\} \tag{4.77}$$

Similarly, to the proof of the local stability in Sec. 4.2.1.1, we prove that the disease-free period solution is locally asymptotically stable if

$$R_0 = \frac{B + Aq}{h} \frac{(\mathrm{e}^T - 1)(T - p) + Tp}{T(\mathrm{e}^T - 1 + p)} < 1. \tag{4.78}$$

By the comparison principle, it can be shown that the periodic disease-free solution of the system (4.76) and (4.77) is globally asymptotically stable in their biological sets as is stated below.

Theorem 4.19 [Gakkhar and Negi (2008)]. *The locally asymptotically stable disease-free periodic solution* $(\tilde{x}(t), 0)$ *of systems* (4.76) *and* (4.77) *is also globally asymptotically stable in the domain* $D = \{(x, y)\colon x > 0, y \geq 0, n \geq 0, m + ny \geq 0\}$.

4.3.2.2. *Bifurcation and existence of epidemic periodic solutions*

The following theorem establishes the existence of periodic solutions of systems (4.76) and (4.77) in the xyz space near $(\tilde{x}(t), 0, \tilde{z}(t))$.

Theorem 4.20 [Gakkhar and Negi (2008)]. *When* $R_0 = 1$, *the disease-free periodic solution* $(\tilde{x}(t), 0, \tilde{z}(t))$ *bifurcates to another periodic solution in the xyz space.*

Proof. Consider the following impulsive system:

$$\left.\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= (B + Aq) - \frac{xy}{1 + my + ny^2} - x = G_1(x, y), \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \frac{xy}{1 + my + ny^2} - hy = G_2(x, y), \end{aligned}\right\} \quad t \neq nT,$$

$$\left.\begin{aligned} x(nT^+) &= (1-p)x(nT^-),\\ y(nT^+) &= y(nT^-), \end{aligned}\right\} \quad t = nT. \tag{4.79}$$

Let ψ be the flow associated to (4.79). The following notations are used in further analysis:

$$F_1(x,y) = (1-p)x, \quad F_2(x,y) = y,$$

$$X = \psi(t, X_0), \quad X_0 = X(x(0), y(0)), \quad \zeta(t) = (\tilde{x}(t), 0)^T$$

$$\frac{\partial \psi_1(t,X_0)}{\partial x} = \exp\left(\int_0^t \frac{\partial G_1(\zeta(\varepsilon))}{\partial x}\mathrm{d}\varepsilon\right),$$

$$\frac{\partial \psi_2(t,X_0)}{\partial y} = \exp\left(\int_0^t \frac{\partial G_2(\zeta(\varepsilon))}{\partial y}\mathrm{d}\varepsilon\right),$$

$$\frac{\partial \psi_1(t,X_0)}{\partial y} = \int_0^t \exp\left(\int_\omega^t \frac{\partial G_1(\zeta(\varepsilon))}{\partial x}\mathrm{d}\varepsilon\right)\frac{\partial G_1(\zeta(\varepsilon))}{\partial y} \times \exp\left(\int_\omega^t \frac{\partial G_1(\zeta(\varepsilon))}{\partial y}\mathrm{d}\varepsilon\right)\mathrm{d}\omega.$$

Simple calculations yield

$$d_0' = 1 - \left(\frac{\partial F_2}{\partial y}\frac{\partial \psi_2}{\partial y}\right)_{(t_0,X_0)} = 1 - \exp\left[\int_0^{t_0}(\tilde{x}(t)-h)\mathrm{d}t\right].$$

Then the condition $d_0' = 0$ leads to

$$R_0 = \frac{(B+Aq)}{h}\frac{(\mathrm{e}^{t_0}-1)(t_0-p)+t_0 p}{t_0(\mathrm{e}^{t_0}-1+p)} = 1.$$

Furthermore, we have

$$a_0' = 1 - \left(\frac{\partial F_1}{\partial x}\frac{\partial \psi_1}{\partial x}\right)_{(t_0,X_0)} = 1-(1-p)\mathrm{e}^{-t_0},$$

$$b_0' = -\left(\frac{\partial F_1}{\partial x}\frac{\partial \psi_1}{\partial y} + \frac{\partial F_1}{\partial y}\frac{\partial \psi_2}{\partial y}\right)_{(t_0,X_0)} = \int_0^{t_0}\exp(-(t_0-\omega))\tilde{x}(\omega)\exp\left(\int_0^\omega(\tilde{x}(\varepsilon)-h)s\mathrm{d}\varepsilon\right)\mathrm{d}\omega > 0,$$

$$\begin{aligned}
\frac{\partial^2\psi_2(t,X_0)}{\partial y^2} &= \int_0^t \exp\left(\int_\omega^t \frac{\partial G_2(\zeta(\varepsilon))}{\partial y}\mathrm{d}\varepsilon\right)\frac{\partial^2 G_2(\zeta(\omega))}{\partial y^2}\\
&\quad\times\exp\left(\int_0^\omega \frac{\partial G_2(\zeta(\varepsilon))}{\partial y}\mathrm{d}\varepsilon\right)\mathrm{d}\omega\\
&\quad+\int_0^t\left\{\exp\left(\int_\omega^t \frac{\partial G_2(\zeta(\varepsilon))}{\partial y}\mathrm{d}\varepsilon\right)\frac{\partial^2 G_2(\zeta(\omega))}{\partial y\partial x}\right\}\\
&\quad\times\left\{\int_0^\omega \exp\left(\int_\rho^t \frac{\partial G_1(\zeta(\varepsilon))}{\partial x}\mathrm{d}\varepsilon\right)\frac{\partial G_1(\zeta(\rho))}{\partial y}\right.\\
&\quad\left.\times\exp\left(\int_0^\rho \frac{\partial G_1(\zeta(\varepsilon))}{\partial y}\mathrm{d}\varepsilon\right)\mathrm{d}\rho\right\}\mathrm{d}\omega,\\
\frac{\partial^2\psi_2(t_0,X_0)}{\partial y^2} &= \int_0^{t_0}\exp\left(\int_\omega^{t_0}(\tilde{x}(\varepsilon)-h)\mathrm{d}\varepsilon\right)(-2n\tilde{x}(\omega))\\
&\quad\times\exp\left(\int_0^\omega(\tilde{x}(\varepsilon)-h)\mathrm{d}\varepsilon\right)\mathrm{d}\omega\\
&\quad+\int_0^{t_0}\left\{\exp\left(\int_\omega^{t_0}(\tilde{x}(\varepsilon)-h)\mathrm{d}\varepsilon\right)\right\}\\
&\quad\times\left\{\int_0^\omega\exp\left(-\int_0^\omega\mathrm{d}\varepsilon\right)(-\tilde{x}(\nu))\right.\\
&\quad\left.\times\exp\left(\int_0^\nu(\tilde{x}(\varepsilon)-h)\mathrm{d}\varepsilon\right)\mathrm{d}\nu\right\}\mathrm{d}\omega<0,\\
\frac{\partial^2\psi_1(t_0,X_0)}{\partial y\partial\bar{t}} &= \frac{\partial F_2}{\partial y}\exp\left(\int_0^t\frac{\partial G_2(\zeta(\varepsilon))}{\partial y}\mathrm{d}\varepsilon\right)\\
&= [\tilde{x}(t_0)-h]\exp\left(\int_0^{t_0}(\tilde{x}(\varepsilon)-h)\mathrm{d}\varepsilon\right),\\
\frac{\partial\psi_1(t_0,X_0)}{\partial\bar{t}} &= \left(\frac{d\tilde{x}}{\mathrm{d}t}\right)_{t_0}>0.
\end{aligned}$$

Substituting them into

$$\begin{aligned}
C = -2\frac{\partial^2 F_2}{\partial x\partial y}&\left(-\frac{b_0'}{a_0'}\frac{\partial\psi_1(t_0,X_0)}{\partial x}\frac{\partial\psi_1(t_0,X_0)}{\partial y}\right)\frac{\partial\psi_2(t_0,X_0)}{\partial y}-\frac{\partial^2 F_2}{\partial y^2}\\
&\times\left(\frac{\partial\psi_2(t_0,X_0)}{\partial y}\right)^2+2\frac{\partial F_2}{\partial y}\frac{b_0'}{a_0'}\frac{\partial^2\psi_2(t_0,X_0)}{\partial x\partial y}-\frac{\partial F_2}{\partial y}\frac{\partial^2\psi_2(t_0,X_0)}{\partial y^2},
\end{aligned}$$

and after simplification, we have

$$C = 2\frac{b_0'}{a_0'}\frac{\partial^2\psi_2(t_0,X_0)}{\partial x\partial y} - \frac{\partial^2\psi_2(t_0,X_0)}{\partial y^2} > 0. \tag{5.5.34}$$

Moreover, we have

$$\begin{aligned}
B &= -\frac{\partial^2 F_2}{\partial x\partial y}\left(\frac{\partial\psi_1(t_0,X_0)}{\partial\bar{t}} + \frac{\partial\psi_1(t_0,X_0)}{\partial x}\frac{1}{a_0'}\frac{\partial F_1}{\partial x}\frac{\partial\psi_1(t_0,X_0)}{\partial\bar{t}}\right)\frac{\partial\psi_2(t_0,X_0)}{\partial y} \\
&\quad - \frac{\partial F_2}{\partial y}\left(\frac{\partial^2\psi_1(t_0,X_0)}{\partial\bar{t}\partial y} + \frac{\partial^2\psi_2(t_0,X_0)}{\partial x\partial y}\frac{1}{a_0'}\frac{\partial F_1}{\partial x}\frac{\partial\psi_1(t_0,X_0)}{\partial\bar{t}}\right), \\
&= -\frac{\partial F_2}{\partial y}\left(\frac{\partial^2\psi_1(t_0,X_0)}{\partial\bar{t}\partial y} + \frac{\partial^2\psi_2(t_0,X_0)}{\partial x\partial y}\frac{1}{a_0'}\frac{\partial F_1}{\partial x}\frac{\partial\psi_1(t_0,X_0)}{\partial\bar{t}}\right), \\
&= -\left([\tilde{x}(t_0)-h]\exp\left(\int_0^{t_0}(\tilde{x}(\tau)-h)\mathrm{d}\tau\right)\right. \\
&\quad \left. + \frac{(1-p)}{a_0'}\frac{\partial\psi_1(t_0,X_0)}{\partial\bar{t}}\frac{\partial^2\psi_2(t_0,X_0)}{\partial x\partial y}\right).
\end{aligned}$$

To determine the sign of B, we let $\theta(t) = \tilde{x}(t) - h$ and then $\frac{d\theta(t)}{\mathrm{d}t} = \tilde{x}'(t) > 0$. Since $\int_0^{t_0}\theta(t)\mathrm{d}t = \int_0^{t_0}(\tilde{x}(t)-h)\mathrm{d}t = 0$ and $\theta(t)$ is strictly increasing, that $\theta(t_0) > 0$. This implies $B < 0$ and hence $BC < 0$. Using Theorem 4.21 from the bifurcation theory, given below, we prove that there is a supercritical bifurcation at a nontrivial periodic solution of systems (4.76) and (4.77), for $BC < 0$. □

Theorem 4.21 [Lakmeeh and Arino (2000)]. *Suppose* $|1 - a_0'| < 1$ *and* $d_0' = 0$. *Then*

(a) *if* $BC \neq 0$, *there exists a bifurcation from a nontrivial periodic solution of* (4.76) *and* (4.77); *the bifurcation is supercritical if* $BC < 0$, *and subcritieal if* $BC > 0$;
(b) *if* $BC = 0$, *the case is undetermined.*

4.4. SIS Epidemic Model with Pulse Vaccination

In this section, we analyze the stability of the periodic eradication solution for the SIS epidemic model with pulse vaccination [Zhou and Liu (2003)].

Assume that a k fraction of susceptibles is vaccinated at discrete time $t = 1, 2, \ldots$. The pulse vaccination does not give life-long immunity, there is an immunity waning for the vaccinated individuals with the per capita

immunity waning rate θ. Let $S(t)$ denote the proportion of the susceptibles, $I(t)$ the proportion of the infectives, and $V(t)$ the proportion of the immune individuals by pulse vaccination at discrete time $t = 1, 2, \ldots$. Then the system is given by

$$\begin{aligned} S'(t) &= \mu(1-S) - \beta SI + \gamma I + \theta V, \\ I'(t) &= \beta SI - (\mu+\gamma)I, \qquad\qquad t \neq 1, 2, \ldots, \\ V'(t) &= -(\mu+\theta)V, \\ S(n) &= (1-k)S(n^-), \\ I(n) &= I(n^-), \\ V(n) &= V(n^-) + kS(n^-), \end{aligned} \tag{4.80}$$

where μ is the birth and the death rate, γ is the recover rate, and β is the effective contact rate. $S(t)$, $I(t)$, and $V(t)$ are continuous from right at the pulse moment and $S(t) + I(t) + V(t) = 1$.

Solving Eqs. (4.80) in the interval $n \leq t < n+1$ and by $S(t) = 1 - I(t) - V(t)$, we obtain

$$\begin{aligned} I(t) &= \frac{I(n)\pi(t, n, V(n))}{1 + \beta I(n) \int_n^t \pi(u, n, V(n))\mathrm{d}u}, \\ V(t) &= V(n)\mathrm{e}^{-\omega(t-n)}, \end{aligned} \tag{4.81}$$

where

$$\pi(t, n, V(n)) = \exp\left(\sigma(t-n) + \frac{\beta V(n)}{\omega}(\mathrm{e}^{-\omega(t-n)} - 1)\right),$$

$\sigma = \beta - \mu - \gamma$, and $\omega = \mu + \theta$. Using solutions (4.81), we arrive at the following discrete system for $I(n)$ and $V(n)$:

$$\begin{aligned} I(n+1) &= F(I(n), V(n)), \\ V(n+1) &= G(I(n), V(n)), \end{aligned} \qquad n = 0, 1, 2, \ldots, \tag{4.82}$$

where

$$\begin{aligned} F(I(n), V(n)) &= \frac{I(n)\pi(1, 0, V(n))}{1 + \beta I(n) \int_0^1 \pi(u, 0, V(n))\mathrm{d}u}, \\ G(I(n), V(n)) &= k + V(n)(1-k)\mathrm{e}^{-\omega} - kF(x, y). \end{aligned} \tag{4.83}$$

The existence of a periodic solution (with period 1) of (4.80) is equivalent to the existence of an equilibrium of the discrete system (4.82).

That is, we need to find the roots of the system

$$x = F(x, y), \quad y = G(x, y). \tag{4.84}$$

We have the following theorem.

Theorem 4.22. *The discrete system* (4.82) *has the trivial equilibrium* $E^0(0, k/(1-(1-k)\mathrm{e}^{-\omega}))$, *which corresponds to the disease-free equilibrium periodic solution* (*with Period* 1) *of* (4.80). *Define*

$$R_0 = \frac{\beta}{\mu+\gamma}\left(1 - \frac{k(1-\mathrm{e}^{-\omega})}{\omega(1-(1-k)\mathrm{e}^{-\omega})}\right).$$

There exists a positive equilibrium

$$E^*\left(I^*, \frac{(k(1-I^*))}{(1-(1-k)\mathrm{e}^{-\omega})}\right)$$

of (4.82), *if* $R_0 > 1$, *where* I^* *is the root of the equation* $x = F(x, (k(1-x)))/(1-(1-k)\mathrm{e}^{-\omega}))$. *The positive equilibrium of* (4.82) *is unique for small* $k > 0$, *and* E^* *corresponds to the endemic periodic solutions (with period* 1) *of* (4.80).

The disease-free periodic solution of the model (4.80) is

$$\begin{aligned}
&\tilde{S}(t) = 1 - \tilde{V}(t), \quad \tilde{I}(t) = 0,\\
&\tilde{V}(t) = \frac{k\mathrm{e}^{-\omega(t-n)}}{1-(1-k)\mathrm{e}^{-\omega}}, \quad n \le t < n+1, \ \ n = 0, 1, 2, \ldots,
\end{aligned}$$

and the positive periodic solution of (4.80) is

$$\begin{aligned}
S_p(t) &= 1 - I_p(t) - V_p(t),\\
I_p(t) &= \frac{I^*\pi(t, n, V^*)}{1 + \beta I^* \int_n^t \pi(u, n, V^*)\mathrm{d}u},\\
V_p(t) &= V^*\mathrm{e}^{-\omega(t-n)},\\
V^* &= \frac{k(1-I^*)}{1-(1-k)\mathrm{e}^{-\omega}}, \quad n \le t < n+1, \ \ n = 0, 1, 2, \ldots.
\end{aligned} \tag{4.85}$$

Using the Floquet theorem, the local stabilities of E^0 and E^* can be obtained as shown in Theorem 4.23.

Theorem 4.23. *The trivial equilibrium* E^* *of* (4.81) *is stable if* $R_0 < 1$, *and unstable if* $R_0 > 1$. *The positive equilibrium* E^* *of* (4.81) *is stable if* $R_0 > 1$ *and* k *is sufficiently small.*

By the comparison principle, the global stability of the disease-free solution when $\theta = 0$ can also be proved as shown in Theorem 4.24.

Theorem 4.24. *Assume that* $\theta = 0$. *The disease-free periodic solution of* (4.80) *is globally asymptotically stable if*

$$R_3 = \frac{\beta}{\mu + \gamma}\left(1 - \frac{k\mathrm{e}^{-\omega}}{1 - (1-k)\mathrm{e}^{-\omega}}\right) < 1.$$

The detailed proof can be found in the article by Zhou and Liu (2003).

4.5. SEIR Epidemic Model with Pulse Vaccination

For some diseases, there is a exposed period before infected susceptibles become infectious. The SEIR epidemic model with pulse vaccination to be discussed [d'Onofrio (2002)] is

$$\begin{aligned} S'(t) &= \mu(1-S) - \beta(t)SI, \\ S(nT^+) &= (1-p)S(nT^-), \quad n \in N_+, \\ E'(t) &= \beta(t)SI - (\varepsilon + \mu)E, \\ I'(t) &= \varepsilon E - (\gamma + \mu)I, \\ R(t) &= 1 - S(t) - E(t) - I(t), \end{aligned} \tag{4.86}$$

where $E(t)$ is the fraction of exposed individuals. The vaccination gives life-long immunity. $R(t)$ contains the vaccinated people also. p is the fraction of susceptibles to whom the vaccine is inoculated at $t = nT, n \in N_+$. μ is the mortality rate, ε is the inverse of latent period, γ is the inverse of infectious period, $\beta(t)$ is constant or is given by $\beta(t+1) = \beta(t)$, and T is the time between two consecutive pulse vaccinations. When the contact rate will be constant.

First, we study the model with a constant population size. As in the study in the preceding section, the disease-free equilibrium solution, $(S^*(t), 0, 0)$, exists, where

$$S^*(t; \mu, T, p) = 1 - \frac{p\,\exp(\mu(T - \mathrm{Mod}(t, T)))}{\exp(\mu T) - (1-p)}. \tag{4.87}$$

By numeric simulations, we have the condition for the local stability of the eradication solution

$$\frac{1}{T}\int_0^T \beta(\tau)S^*(\tau)\mathrm{d}\tau < \frac{(\mu+\varepsilon)(\mu+\gamma)}{\varepsilon}. \tag{4.88}$$

When $\beta(t)$ is constant, we recall that the basic reproductive number for the SEIR model is

$$R_0 = \frac{\varepsilon\beta}{(\mu+\varepsilon)(\mu+\gamma)}.$$

Then (4.88) can be rearranged as

$$R_0\frac{1}{T}\int_0^T S^*(\tau)\mathrm{d}\tau < 1. \tag{4.89}$$

Next, we consider an SEIR epidemic model with the variation population size. We let $\bar{S}$, $\bar{E}$, $\bar{I}$, and $\bar{R}$ denote the total numbers of individuals in the corresponding epidemiologic classes, and include disease-induced deaths. The dynamics of the total population size $N(t)$ are given by

$$N'(t) = (b-\mu_1(N))N - \alpha\bar{I}, \tag{4.90}$$

where b is the birth rate, $\mu_1(t)$ is the natural death-rate, and α is the disease-induced death-rate. We then consider the following two cases:

- $\mu_1(N) = \mu$ is constant. If $\alpha = 0$, the population can have exponential growth ($b > \mu$), zero-growth ($b = \mu$), or exponential decay ($b < \mu$).
- $\mu_1(N) = \mu(N)$ is a nondecreasing and follows the logistic dynamics with a positive equilibrium N^*. Note that, of course, $\mu(N) \geq \mu(0)$.

The SEIR model equations are given by

$$\begin{aligned}
\bar{S}'(t) &= bN - \mu_1\bar{S} - \frac{\beta(t)}{N}\bar{S}\bar{I}, && \bar{S}(0) = \bar{S}_0,\\
\bar{S}(nT^+) &= (1-p)\bar{S}(nT^-), && n \in N_+,\\
\bar{E}'(t) &= \frac{\beta(t)}{N}\bar{S}\bar{I} - (\varepsilon+\mu_1)\bar{E}, && \bar{E}(0) = \bar{E}_0,\\
\bar{I}'(t) &= \varepsilon\bar{E} - (\gamma+\mu_1+\alpha)\bar{I}, && \bar{I}(0) = \bar{I}_0,\\
\bar{R}(t) &= N(t) - \bar{S}(t) - \bar{E}(t) - \bar{I}(t).
\end{aligned} \tag{4.91}$$

Set $(\bar{S}(t), \bar{E}(t), \bar{I}(t), \bar{R}(t)) = N(t)(S(t), E(t), I(t), R(t))$. We obtain

$$N'(t) = (b - \alpha I - \mu(N))N, \tag{4.92}$$

and

$$\begin{aligned} S'(t) &= b(1-S) - (\beta(t) - \alpha)SI, & S(0) &= S^0, \\ S(nT^+) &= (1-p)S(nT^-), & n &\in N_+, \\ E'(t) &= \beta(t)SI + \alpha EI - (\varepsilon + b)E, & E(0) &= E^0, \\ I'(t) &= \varepsilon E + \alpha I^2 - (\gamma + b + \alpha)I, & I(0) &= I^0, \end{aligned} \tag{4.93}$$

which has the feasible set $\mho = \{(S, E, I) \in [0,1]^3 | 0 \leq S + I + E \leq 1\}$. The system has the disease-free solution $(S^*(t; b, T, p), 0, 0)$ which is called relative eradication solution. The approximate local asymptotic stability criterion is

$$R_0 \frac{1}{T} \int_0^T S^*(\tau; b, T, p) \mathrm{d}\tau < 1, \tag{4.94}$$

where, under the assumption of $\alpha > 0$, the basic reproductive number is

$$R_0 = \frac{\varepsilon\beta}{(b+\varepsilon)(b+\gamma+\alpha)}.$$

We then set $S(t) = (\bar{S}(t)/N(t))$, and obtain the system

$$\begin{aligned} S'(t) &= b(1-S) - (\beta(t) - \alpha)S\frac{\bar{I}}{N}, \\ S(nT^+) &= (1-p)S(nT^-), \\ \bar{E}'(t) &= \beta(t)S\bar{I} - (\varepsilon + \mu_1)\bar{E}, \\ \bar{I}'(t) &= \varepsilon\bar{E} - (\gamma + \mu_1 + \alpha)\bar{I}, \\ N'(t) &= (b - \mu_1(N))N - \alpha\bar{I}, \end{aligned} \tag{4.95}$$

with the invariant domain $\Xi = \{(S, \bar{E}, \bar{I}, N) | S \in [0,1], N > 0, \bar{E} \geq 0, \bar{I} \geq 0, \bar{E} + \bar{I} \leq N(1-S)\}$. It admits an eradication periodic solution $(S, \bar{E}, \bar{I}) = (S^*(t; b, T, p), 0, 0)$ which is called total eradication solution.

On the global stability of the equilibrium, several sufficient conditions are derived in the paper [d'Onofrio (2002)]. We list some main results here. The reader is referred to [d'Onofrio (2002)] for further details.

Theorem 4.25 [d'Onofrio (2002)]. *When $\beta(t) \geq \alpha \geq 0$, a sufficient condition for the global asymptotic stability (GAS) of the periodic free*

solution of (4.93) *in the set* $\mho$ *is*

$$\max\{|\phi_1|, |\phi_2|\} < 1, \tag{4.96}$$

where ϕ_1, ϕ_2 *are the Floquet's eigenvalues associated with the following linear system with* T*-periodic coefficients*:

$$\begin{aligned} y_1'(t) &= (\beta(t)S^*(t; b, T, p) + \alpha)y_2 - (b + \varepsilon)y_1, \\ y_2'(t) &= \varepsilon y_1 - (b + \gamma)y_2. \end{aligned} \tag{4.97}$$

When condition (4.96) holds and $b = m$, it follows from $N' = -\alpha I$ that $N(t) = N(0)\exp(-\alpha \int_0^{+\infty} I(u)\mathrm{d}u) > 0$.

Theorem 4.26 [d'Onofrio (2002)]. *If* $\alpha = 0$ *and the population follows the logistic dynamics, Theorem* 4.25 *also holds for the total eradication solution.*

For an exponentially growing population, the relative and total eradication cannot be guaranteed because $N \to +\infty$ and $I \to 0$. Then the behavior of $\bar{I} = I(t)N(t)$ cannot be determined. However, we have other conditions derived as follows.

Theorem 4.27 [d'Onofrio (2002)]. *Assume* $\beta(t) \geq \alpha > 0$, *and* $\mu_1 = \mu(0)$ *and* $\alpha \geq 0$, (*or* $\mu_1 = \mu$ *and* $\alpha > 0$). *Then a sufficient condition to have a GAS total eradication in* Ξ *is*

$$\max\{|\omega_1|, |\omega_2|\} < 1, \tag{4.98}$$

where ω_1, ω_2 *are the Floquet eigenvalues of the system*

$$\begin{aligned} y_1'(t) &= \beta(t)S^*(t; b, T, p)y_2 - (\mu_1 + \varepsilon)y_1, \\ y_2'(t) &= \varepsilon y_1 - (\mu_1 + \gamma + \alpha)y_2. \end{aligned} \tag{4.99}$$

4.6. SI Epidemic Model with Birth Pulse

Traditional mathematical models for population dynamics usually assume that species reproduce throughout the year, whereas some species, such as blue whale, polar bear, Orinoco crocodile, Yangtse alligator and Giant panda, only give births seasonally. To model such populations, we remove the continuous reproduction and replace it with a birth pulse. Consequently, impulsive differential equations provide a natural description for such systems.

There are extensive studies on epidemic models with pulse births in the literature [Roberts and Kao (1998); Cao and Jin (2007); Lin *et al.* (submitted); Zhang *et al.* (2008); Gao *et al.* (2005)]. In this and following sections, we illustrate such works, starting with the work by Roberts and Kao (1998).

4.6.1. *The model with constant births*

Let the host population density be N, the susceptibles be S, and the infectives be I, with $N = S + I$. The host birth and death rates, $B(N)$ and $D(N)$, are assumed to be nonincreasing and nondecreasing functions of population density, respectively, ($B'(N) \leq 0$ and $D'(N) \geq 0$), and infectious animals have the increased death rate $D(N) + \alpha$, where α is the death rate due to the disease. The dynamics of the host population are described by the equation

$$\frac{\mathrm{d}N}{\mathrm{d}t} = (B(N) - D(N))N - \alpha I. \tag{4.100}$$

For the population to grow from $N = 0$, it is also necessary that $B(0) > D(0)$. When no disease is present, the host population has carrying capacity K, defined by $B(K) = D(K)$, which exists and is unique provided that $\lim_{N\to\infty}(B(N) - D(N)) < 0$ and $B'(K) \neq D'(K)$.

Let $p \in [0, 1]$, $0 \leq p \leq 1$, be the proportion of the offspring who are infected vertically, $C(N)$, with $C'(N) \geq 0$, be a general contact rate. The equations for the dynamics of the disease transmission are

$$\begin{aligned} \frac{\mathrm{d}S}{\mathrm{d}t} &= [B(N) - D(N)]S + (1-p)B(N)I - \beta\frac{C(N)}{N}SI, \\ \frac{\mathrm{d}I}{\mathrm{d}t} &= pB(N)I + \beta\frac{C(N)}{N}SI - [\alpha + D(N)]I, \end{aligned} \tag{4.101}$$

where all parameters are nonnegative. Because $S + I = N$, Eq. (4.100) and the first equation in (4.101) only are considered. Taking the transformation $Z = I/N$, we have

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}t} &= (B(N) - D(N))N - \alpha I, \\ \frac{\mathrm{d}Z}{\mathrm{d}t} &= -(1-p)B(N)Z + [\beta C(N) - \alpha](1 - Z)Z. \end{aligned} \tag{4.102}$$

Model (4.102) has been studied in detail by Roberts and Jowett (1996), Diekmann and Kretzschmar (1991), and Zhou and Hethcote (1994). Some results are listed below.

Define the basic reproductive number (recall $B(K) = D(K))R_0$ by

$$R_0 = \frac{pB(K) + \beta C(K)}{\alpha + D(K)}, \tag{4.103}$$

and define

$$R_1 = \frac{pB(0) + \beta C(0)}{\alpha + B(0)}, \tag{4.104}$$

$$R_2 = \frac{pB(0) + \beta C(0)}{\alpha + B(0) + \frac{(\beta C(0) - \alpha)(B(0) - D(0))}{\alpha}}. \tag{4.105}$$

The system (4.102) has four steady states:

(1) $N = Z = 0$ (the trivial steady state, which is always unstable).
(2) $N = K$, $Z = 0$ (the disease-free steady-state, which is globally stable when $R_0 < 1$).
(3) $N = 0$, $Z = Z_0 = 1 - (1 - p)B(0)/(\beta C(0) - \alpha)$ (the host-extinction steady-state, which exists when $R_1 > 1$, and is globally stable when $R_2 > 1$; biologicalally this represents the limit as the disease drives the host population to extinction).
(4) $N = N^*$, $Z = Z^*$, $0 < N^* < K$, $0 < Z^* < 1$ (the endemic steady state, which exists and is stable when $R_0 > 1$, and $R_1 < 1$ and/or $R_2 < 1$. (N^*, Z^*) is the unique nontrivial solution of the system (4.102) with $\mathrm{d}N/\mathrm{d}t = \mathrm{d}Z/\mathrm{d}t = 0$).

4.6.2. *The model with birth pulse*

An assumption that lead to system (4.102) is that births are evenly distributed throughout the year. To model a single annual birth pulse, $B(N)$ is set to zero and the host population $N(t)$ is increased by an amount $B(N)N$, whenever t has an integer value. We require $B'(N) \leq 0$ and make following assumptions:

(H_1) $\ln(1 + B(0)) > D(0)$.
(H_2) $\lim_{N\to\infty} \ln(1 + B(N)) < \lim_{N\to\infty} D(N)$.

Assumption (H_1) ensures that the host population can persist in the absence of a disease, and (H_2) is regulated at a finite density.

The equations for the host population, and the proportion that are infected and infectious are

$$\begin{aligned}
\frac{\mathrm{d}N}{\mathrm{d}t} &= -(D(N)+\alpha Z)N, \quad t \neq m, \ \ m = 0,1,2,\ldots,\\
\frac{\mathrm{d}Z}{\mathrm{d}t} &= [\beta C(N)-\alpha](1-Z)Z,\\
N(m^+) &= [1+B(N(m))]N(m),\\
Z(m^+) &= \frac{1+\pi B(N(m))}{1+B(N(m))}Z(m).
\end{aligned} \tag{4.106}$$

The fourth equation in (4.106) arises directly from $I(m^+) = I(m)(1 + \pi B(N(m)))$, where π is the proportion of the infected offspring.

We now investigate the periodic-one solutions of system (4.106). This is equivalent to finding solutions of the boundary-value problem consisting of the first and second equations of system (4.106) on (0,1), with boundary conditions

$$\begin{aligned}
N(0) &= [1+B(N(1))]N(1),\\
Z(0) &= \frac{1+\pi B(N(1))}{1+B(N(1))}Z(1).
\end{aligned} \tag{4.107}$$

If $(N(t), Z(t))$ is a solution of the first and second equations of (4.106), for $t \in (0,1)$, and boundary condition (4.107), the system (4.106) have a periodic solution defined by $(N_p(t), Z_p(t)) = (N(t), Z(t))$ for $t \in (0,1)$, and $(N_p(t+1), Z_p(t+1)) = (N_p(t), Z_p(t))$ for all noninteger t.

In the absence of a disease the host population now has a periodically reset time-varying carrying capacity. Setting $Z(t) \equiv 0$, the first equations of (4.106) and (4.107) have solution $N(t) = K(t)$ for $t \in (0,1)$, where

$$\int_{K_1}^{K(t)} \frac{\mathrm{d}N}{ND(N)} = 1 - t \tag{4.108}$$

and

$$\int_{K_1}^{K_1(1+B(K_1))} \frac{\mathrm{d}N}{ND(N)} = 1. \tag{4.109}$$

Equation (4.108) defines the function $K(t)$ in terms of $K_1 = K(1)$, and Eq. (4.109) defines the value of K_1. The left-hand side of (4.109) is a strictly decreasing function of K_1, which is therefore defined uniquely.

Similarly to the three thresholds (R_0, R_1, R_2) for (4.102), we define the following three quantities for system (4.106):

$$R_0 = \frac{\ln(1+\pi B(K_1)) + \beta \int_0^1 C(K(t))\mathrm{d}t}{\alpha + \ln(1+B(K_1))}, \tag{4.110}$$

$$R_1 = \frac{\ln(1+\pi B(0)) + \beta C(0)}{\alpha + \ln(1+B(0))}, \tag{4.111}$$

$$R_2 = \frac{\ln(1+\pi B(0)) + \beta C(0)}{\alpha + \ln(1+B(0)) + \frac{\beta C(0)-\alpha}{\alpha}(\ln(1+B(0)) - D(0))}. \tag{4.112}$$

The system defined by the first and second equations of (4.106) and the boundary conditions (4.107) has at least three possible solutions:

(1) The trivial solution, $N = Z = 0$. This solution exists and is unstable for all parameter values.
(2) The disease-free solution, $Z = 0$, $N = K(t)$. This solution exists for all parameter values, but is unstable if $R_0 > 1$.
(3) The host-extinction solution, $N = 0$, $Z = Z_0(t)$, where

$$Z_0(t) = \frac{1}{1 + (1 - Z_0(1))/(Z_0(1))\mathrm{e}^{(\beta C(0)-\alpha)(1-t)}}$$

with

$$Z_0(1) = \frac{\mathrm{e}^{(\beta C(0)-\alpha)} - (1+B(0))/(1+\pi B(0))}{\mathrm{e}^{(\beta C(0)-\alpha)} - 1}.$$

If $R_1 > 1$ then

$$\mathrm{e}^{(\beta C(0)-\alpha)} > \frac{1+B(0)}{1+\pi B(0)} > 1,$$

which ensures that $0 < Z_0(1) < 1$ and the solution exists. It is stable if $R_2 > 1$.

Using the Floquet theorem, the local stability of the above solutions is proved.

Two methods for controlling an infectious disease in a wild animal population are introduced by Roberts and Kao (1998), which are the regular culling of animals and mass vaccination. Criteria for the eradication of a fatal disease in a population with periodic birth pulses is obtained there (see Roberts and Kao (1998) for details).

4.7. SIR Epidemic Model with Constant Recruitment and Birth Pulse

In this section, we develop an SIR epidemic model with a constant recruitment and a density-independent birth-rate aiming at a population descending. We analyze the dynamic behavior with constant and pulse birth, respectively.

4.7.1. *The model with constant birth*

Consider an SIR model, whose dynamics are described by the following differential equations:

$$\begin{aligned} S' &= A + b_1 S - \beta SI - \mu S + b_1 p_1 R + b_2 p_2 I, \\ I' &= \beta SI - (\mu + \gamma + \alpha) I + b_2 (1 - p_2) I, \\ R' &= \gamma I - \mu R + b_1 (1 - p_1) R. \end{aligned} \tag{4.113}$$

The total population size is denoted by N, with $N = S + I + R$.

In this model, the parameters A, β, μ, and γ are all positive constants; μ is the natural death rate, the nonnegative constant α is the death rate due to disease, β is the contact rate, the infectives recover at a rate γ, such that $1/\gamma$ is the mean infection period, and A is a constant recruitment of susceptible individuals.

Adding the three equations of model (4.113), one obtains

$$N'(t) = A - \mu N + b_1 N - (b_1 - b_2) I - \alpha I. \tag{4.114}$$

From the biological consideration and the fact that the population is descending, we make further hypotheses and give their explanations:

(1) Considering the effects of the infectious disease on the fertility of the infectives, we assume that the susceptibles and recovereds have the same birth rate b_1, which is higher than the infectives' birth-rate b_2 (that is, $b_1 > b_2$). We assume that all the offspring of susceptibles are susceptible, but a fraction p_1, $(0 < p_1 < 1)$, of the offsprings of

recovereds are susceptible, and the rest offspring have immunity. We also assume that a faction p_2, $(0 < p_2 < 1)$, of the infectives' offspring are susceptible, and the rest are infected. Due to the effects of the disease to the infectives, we assume $p_1 > p_2$. Furthermore, we assume that b_1, b_2, p_1, and p_2 are all positive constants.

(2) $\mu > b_1$.

(3) The constant recruitment A plays a role to balance the population. In the absence of the disease, Eq. (4.114) becomes $N'(t) = A - \mu N + b_1 N$. From the condition $\mu > b_1$, we get $N'(t) < 0$ without the recruitment A. This means that the population is unable to maintain itself without recruitment.

The dynamic system (4.113) has two equilibria, the disease-free equilibrium given by

$$S_0^* = \frac{A}{\mu - b_1}, \quad I_0^* = 0, \quad R_0^* = 0,$$

and the endemic equilibrium given by

$$\begin{aligned} S_+^* &= \frac{(\mu + \gamma + \alpha) - b_2(1 - p_2)}{\beta}, \\ I_+^* &= \frac{\beta A + [(\mu + \gamma + \alpha) - b_2(1 - p_2)](b_1 - \mu)}{\beta[(\mu + \gamma + \alpha) - b_2 - \frac{b_1 p_1 \gamma}{\mu - b_1(1 - p_1)}]}, \\ R_+^* &= \frac{\gamma I_+^*}{\mu - b_1(1 - p_1)}. \end{aligned} \tag{4.115}$$

When a newly infected individual enters the population at the disease-free equilibrium, the individual is infected for an average time $\phi = (\mu + \gamma + \alpha)^{-1}$. Then the average number of secondary infections produced by this infected individual through horizontal transmissions is

$$\frac{\beta \frac{A}{\mu - b_1}}{\mu + \gamma + \alpha},$$

and through vertical transmissions is $(b_2(1 - p_2))/(\mu + \gamma + \alpha)$. Consequently, the basic reproductive number of system (4.113) is defined as

$$R_0 = \frac{\beta \frac{A}{\mu - b_1} + b_2(1 - p_2)}{\mu + \gamma + \alpha}.$$

From (4.114), it follows that the total population $N(t)$ converges to the constant $A/(\mu - b_1)$ in the absence of infection. If $N > A/(\mu - b_1)$,

$N'(t) < 0$, and obviously, the set

$$\Omega_1 = \left\{(S, I, R)\colon 0 < S + I + R = N \le \frac{A}{\mu - b_1}, \quad S \ge 0, I \ge 0, R \ge 0\right\}$$

is positively invariant for system (4.113). We have the results below.

Theorem 4.28. *The disease-free equilibrium* (S_0^*, I_0^*, R_0^*) *of system* (4.113) *is locally stable in* Ω_1 *if and only if* $R_0 < 1$. *Furthermore, if* $R_0 < 1$, *the disease-free equilibrium is globally stable. If* $R_0 > 1$, *the disease-free equilibrium is unstable, and the endemic equilibrium is locally stable in the domain* Ω_1.

4.7.2. *The model with pulse birth*

Considering the births of some wild animals are seasonal or occur at regular pulses, we assume that the population give birth at a single pulse, every T time period. The birth rate is the same as in hypothesis (1) in Sec. 4.7.1.

When pulse births is incorporated into the SIR model (4.113), the system becomes

$$\begin{aligned} S' &= A - \beta SI - \mu S, \\ I' &= \beta SI - (\mu + \gamma + \alpha)I, \quad t \ne nT, \\ R' &= \gamma I - \mu R, \qquad\qquad n = 0, 1, 2, \ldots, \end{aligned} \tag{4.116}$$

$$\begin{aligned} S(nT^+) &= S(nT) + b_1 S(nT) + b_1 p_1 R(nT) \\ &\quad + b_2 p_2 I(nT), \\ I(nT^+) &= I(nT) + b_2(1 - p_2)I(nT), \qquad t = nT, \\ R(nT^+) &= R(nT) + b_1(1 - p_1)R(nT), \qquad n = 0, 1, 2, \ldots \end{aligned} \tag{4.117}$$

The dynamics of the total population size, $N(t)$, satisfy the equations

$$\begin{aligned} N'(t) &= A - \mu N - \alpha I, \quad t \ne nT, \\ N(nT^+) &= (1 + b_1)N(nT) - (b_1 - b_2)I(nT), \quad t = nT, \ n = 0, 1, 2, \ldots \end{aligned} \tag{4.118}$$

From biological considerations, we restrict our analysis in the domain

$$\Omega_2 = \{(S, I, R)\colon S \ge 0, I \ge 0, R \ge 0\},$$

and it is easy to see the set is positively invariant for system (4.116) and (4.117).

4.7.2.1. *Existence and local stability of the disease-free periodic solution*

We begin the analysis of (4.116) and (4.117) by first demonstrating the existence of a disease-free periodic solution, in which infectious individuals are entirely absent from the population permanently; that is,

$$I(t) = 0, \quad t \geq 0.$$

This is motivated by the fact that $I^* = 0$ is an equilibrium solution for the variable $I(t)$, as it gives $I'(t) = 0$.

Under these conditions and noting $R = N - S - I$, systems (4.116) and (4.117) change into following:

$$\begin{aligned} N' &= A - \mu N, \quad t \neq nT, \\ S' &= A - \mu S, \quad n = 0, 1, 2, \ldots \end{aligned} \tag{4.119}$$

$$\begin{aligned} N(nT^+) &= (1 + b_1)N(nT), \qquad t = nT, \\ S(nT^+) &= [1 + b_1(1 - p_1)]S(nT) \\ &\quad + b_1 p_1 N(nT), \qquad n = 0, 1, 2, \ldots. \end{aligned} \tag{4.120}$$

Solving Eqs. (4.119) between pulses, we have

$$N(t) = \frac{A}{\mu} + \left[N(nT^+) - \frac{A}{\mu}\right] \mathrm{e}^{-\mu(t-nT)}, \tag{4.121}$$

$$S(t) = \frac{A}{\mu} + \left[S(nT^+) - \frac{A}{\mu}\right] \mathrm{e}^{-\mu(t-nT)}, \tag{4.122}$$

$$nT < t \leq (n+1)T \quad (n = 0, 1, 2, \ldots).$$

Equation (4.121) holds between pulses. At each successive pulse, more births occur, which yields

$$\begin{aligned} N((n+1)T^+) &= (1 + b_1)\left\{\frac{A}{\mu} + \left[N(nT^+) - \frac{A}{\mu}\right] \mathrm{e}^{-\mu T}\right\} \\ &= F(N(nT^+)). \end{aligned} \tag{4.123}$$

Equation (4.123) has a unique fixed point

$$N^* = \frac{(1 + b_1)\frac{A}{\mu}\left(1 - \mathrm{e}^{-\mu T}\right)}{1 - (1 + b_1)\mathrm{e}^{-\mu T}}. \tag{4.124}$$

The fixed point N^* implies that there is a corresponding cycle of period T in the total population $N(t)$.

For N^* to be positive, we require

$$(1+b_1)\mathrm{e}^{-\mu T} < 1 \quad \left(\text{that is, } \mu > \frac{\ln(1+b_1)}{T}\right). \tag{4.125}$$

In fact, $(\ln(1+b_1))/T$ can be seen as the effective birth rate of the total population N. Due to the population's descending, the natural death-rate μ should be larger than its birth rate $(\ln(1+b_1))/T$. Then we have the inequality (4.125).

Furthermore, the fixed point N^* is locally stable because

$$\left|\frac{\mathrm{d}F(N(nT^+))}{\mathrm{d}N}\right|_{N(nT^+)=N^*} = (1+b_1)\mathrm{e}^{-\mu T} < 1. \tag{4.126}$$

By substituting $N(nT^+) = N^*$ into (4.121), we obtain the complete expression for the disease-free periodic solution, over the nth time-interval $nT < t \le (n+1)T$,

$$\widetilde{N}(t) = \frac{A}{\mu}\left[1 + \frac{b_1\mathrm{e}^{-\mu(t-nT)}}{1-(1+b_1)\mathrm{e}^{-\mu T}}\right], \tag{4.127}$$

$$\widetilde{I}(t) = 0. \tag{4.128}$$

Similarly, substituting

$$N(nT) = \frac{\frac{A}{\mu}\left(1-\mathrm{e}^{-\mu T}\right)}{1-(1+b_1)\mathrm{e}^{-\mu T}}$$

into the second equation of (4.120), we get

$$S(nT^+) = [1+b_1(1-p_1)]S(nT) + b_1p_1\frac{(A/\mu)\left(1-\mathrm{e}^{-\mu T}\right)}{1-(1+b_1)\mathrm{e}^{-\mu T}}.$$

Using the same method, we have

$$\widetilde{S}(t) = \frac{A}{\mu}\left[1 + \frac{b_1\mathrm{e}^{-\mu(t-nT)}}{1-(1+b_1)\mathrm{e}^{-\mu T}}\right], \tag{4.129}$$

$$nT < t \le (n+1)T.$$

Then $\widetilde{R}(t) = \widetilde{N}(t) - \widetilde{S}(t) - \widetilde{I}(t) = 0$.

The solution is periodic in time,

$$\widetilde{S}(t+T)=\widetilde{S}(t),\quad \widetilde{I}(t+T)=\widetilde{I}(t),\quad \widetilde{R}(t+T)=\widetilde{R}(t).$$

Similarly to the system with constant birth but changing the effective birth rate to $(1/T)\ln[1+b_2(1-p_2)]$, we define the basic reproductive number for model (4.116) and (4.117) as

$$R_{0p}=\frac{\beta\frac{1}{T}\int_0^T\widetilde{S}(t)\mathrm{d}t+\frac{1}{T}\ln[1+b_2(1-p_2)]}{\mu+\gamma+\alpha},$$

where $\widetilde{S}(t)$ is the periodic disease-free solution.

In the following, we prove the asymptotic stability of the disease-free solution $(\widetilde{S}(t),0,0)$.

Similarly to the proof of the local stability in Sec. 4.2, we have the monodromy matrix

$$M=\begin{pmatrix}1+b_1 & b_2p_2 & b_1p_1\\ 0 & 1+b_2(1-p_2) & 0\\ 0 & 0 & 1+b_1(1-p_1)\end{pmatrix}\begin{pmatrix}\mathrm{e}^{-\mu T} & \varphi_{12} & 0\\ 0 & \varphi_{22} & 0\\ 0 & \varphi_{32} & \mathrm{e}^{-\mu T}\end{pmatrix},$$

where

$$\varphi_{22}=\mathrm{e}^{\int_0^T\beta\widetilde{S}(\sigma)\mathrm{d}\sigma-(\mu+\gamma+\alpha)T},$$

$$\varphi_{12}=\mathrm{e}^{-\mu T}\int_0^T[-\beta\widetilde{S}(\sigma)]\mathrm{e}^{\mu\sigma}\varphi_{22}(\sigma)\mathrm{d}\sigma,$$

$$\varphi_{32}=\mathrm{e}^{-\mu T}\int_0^T\gamma\varphi_{22}(\sigma)\mathrm{e}^{\mu\sigma}\mathrm{d}\sigma.$$

Then the eigenvalues λ_1, λ_2, and λ_3 of M are given by

$$\lambda_1=(1+b_1)\mathrm{e}^{-\mu T},\quad \lambda_3=[1+b_1(1-p_1)]\mathrm{e}^{-\mu T},$$

$$\lambda_2=[1+b_2(1-p_2)]\mathrm{e}^{\int_0^T\beta\widetilde{S}(t)\mathrm{d}t-(\mu+\gamma+\alpha)T}.$$

From (4.125), we have $\lambda_1<1$. Furthermore, because $\lambda_3<\lambda_1$, we obtain $\lambda_3<1$. $\lambda_2<1$ if and only if

$$\frac{1}{T}\int_0^T\beta\widetilde{S}(t)\mathrm{d}t+\frac{1}{T}\ln[1+b_2(1-p_2)]<\mu+\gamma+\alpha. \tag{4.130}$$

That is, the periodic disease-free solution $(\widetilde{S}(t),0,0)$ is asymptotically stable if $R_{0p}<1$. In summary, we have

Theorem 4.29. *If* $R_{0p}<1$, *then the periodic disease-free solution* $(\widetilde{S}(t),0,0)$ *of systems* (4.116) *and* (4.117) *is locally asymptotically stable.*

4.7.2.2. *Global asymptotic stability of the disease-free solution*

We further investigate the global stability of the disease-free solution.

Theorem 4.30. *The periodic disease-free solution* $(\widetilde{S}(t),0,0)$ *of systems* (4.116) *and* (4.117) *is globally asymptotically stable if* $R_{0p}<1$.

Proof. Since $R=N-S-I$, we reduce systems (4.116) and (4.117) into the following system:

$$\begin{aligned} N' &= A-\mu N-\alpha I,\\ S' &= A-\beta SI-\mu S, \qquad t\neq nT\\ I' &= \beta SI-(\mu+\gamma+\alpha)I, \quad n=0,1,2,\ldots, \end{aligned} \tag{4.131}$$

$$\begin{aligned} N(nT^+) &= (1+b_1)N(nT)-(b_1-b_2)I(nT)\\ S(nT^+) &= [1+b_1(1-p_1)]S(nT)+b_1p_1N(nT)\\ &\quad -(b_1p_1-b_2p_2)I(nT), \quad t=nT\\ I(nT^+) &= I(nT)+b_2(1-p_2)I(nT), \quad (n=0,1,2,\ldots). \end{aligned} \tag{4.132}$$

Then the global stability of systems (4.116) and (4.117) is equivalent to that of systems (4.131) and (4.132).

From the first equation of (4.131) and (4.132), it follows that

$$\begin{aligned} N'(t) &\le A-\mu N,\\ N(nT^+) &\le (1+b_1)N(nT). \end{aligned}$$

By using Theorem 4.5, we have

$$\begin{aligned} N(t) &\le N(0^+)\Bigg(\prod_{0<kT<t}(1+b_1)\Bigg)\exp\left\{\int_0^t(-\mu)\mathrm{d}s\right\}\\ &\quad+\int_0^t\Bigg(\prod_{s<kT<t}(1+b_1)\Bigg)\exp\left\{\int_s^t(-\mu)\mathrm{d}\sigma\right\}A\mathrm{d}s. \end{aligned} \tag{4.133}$$

If $t \neq nT$, setting $s = T\delta$ leads (4.133) to

$$\begin{aligned} N(t) &\leq N(0^+)\left\{\prod_{0<k<\frac{t}{T}}(1+b_1)\right\}\mathrm{e}^{-\mu t} \\ &\quad + A\mathrm{e}^{-\mu t}\int_0^t\left\{\prod_{\frac{s}{T}<k<\frac{t}{T}}(1+b_1)\right\}\mathrm{e}^{\mu s}\mathrm{d}s, \\ &= N(0^+)(1+b_1)^{[(t/T)]}\mathrm{e}^{-\mu t} + A\mathrm{e}^{-\mu t}\int_0^{\frac{t}{T}}\left\{\prod_{\delta<k<\frac{t}{T}}(1+b_1)\right\}\mathrm{e}^{\mu T\delta}\mathrm{d}(T\delta). \end{aligned}$$

If $t = nT$, (4.133) becomes

$$\begin{aligned} N(nT) &\leq N(0^+)\left\{\prod_{0<k<n}(1+b_1)\right\}\mathrm{e}^{-\mu nT} \\ &\quad + A\mathrm{e}^{-\mu nT}\int_0^{nT}\left\{\prod_{s<kT<nT}(1+b_1)\right\}\mathrm{e}^{\mu s}\mathrm{d}s, \\ &= N(0^+)(1+b_1)^{n-1}\mathrm{e}^{-\mu nT} + A\mathrm{e}^{-\mu nT}K_0, \end{aligned}$$

where

$$K_0 = \frac{1}{\mu}(\mathrm{e}^{\mu T}-1)\frac{\mathrm{e}^{(n-1)\mu T}\{1-[(1+b_1)\mathrm{e}^{-\mu T}]^n\}}{1-(1+b_1)\mathrm{e}^{-\mu T}}.$$

Thus,

$$\begin{aligned} N(nT) &\leq N(0^+)(1+b_1)^{n-1}\mathrm{e}^{-\mu nT} \\ &\quad + A\mathrm{e}^{-\mu nT}\frac{1}{\mu}(\mathrm{e}^{\mu T}-1)\frac{\mathrm{e}^{(n-1)\mu T}(1-[(1+b_1)\mathrm{e}^{-\mu T}]^n)}{1-(1+b_1)\mathrm{e}^{-\mu T}} \\ &= M_n + V, \end{aligned} \tag{4.134}$$

where

$$M_n = M[(1+b_1)\mathrm{e}^{-\mu T}]^n, \quad M = \frac{N(0^+)}{1+b_1} - V, \quad V = \frac{(A/\mu)\left(1-\mathrm{e}^{-\mu T}\right)}{1-(1+b_1)\mathrm{e}^{-\mu T}}.$$

From the second equation of systems (4.131) and (4.132), it follows that

$$\begin{aligned} S' &\le A - \mu S, \\ S(nT^+) &\le [1 + b_1(1-p_1)]S(nT) + b_1 p_1 N(nT) \\ &\le [1 + b_1(1-p_1)]S(nT) + b_1 p_1 M_n + b_1 p_1 V. \end{aligned}$$

Using Theorem 4.5, we have

$$\begin{aligned} S(t) &\le S(0^+)\left(\prod_{0<kT<t}[1 + b_1(1-p_1)]\right)\mathrm{e}^{-\mu t} \\ &\quad + \sum_{0<kT<t}\left\{\prod_{kT<jT<t}[1 + b_1(1-p_1)]\exp\left[\int_{kT}^{t}(-\mu)\mathrm{d}s\right]\right\}(b_1 p_1 M_k \\ &\quad + b_1 p_1 V) + \int_0^t \prod_{s<kT<t}[1 + b_1(1-p_1)]\exp\left[\int_s^t(-\mu)\mathrm{d}\sigma\right]A\mathrm{d}s \\ &= K_1 + K_2 + K_3, \end{aligned}$$

for $t \ne nT$, where

$$\begin{aligned} K_1 &= S(0^+)[1 + b_1(1-p_1)]^{[t/T]}\mathrm{e}^{-\mu t}, \\ K_2 &= M(1+b_1)\mathrm{e}^{-\mu t}((1+b_1)^{[t/T]} - [1 + b_1(1-p_1)]^{[t/T]}) \\ &\quad + \frac{b_1 p_1 V \mathrm{e}^{-\mu t}}{1 - [1 + b_1(1-p_1)]\mathrm{e}^{-\mu T}}(\mathrm{e}^{[t/T]\mu T} - [1 + b_1(1-p_1)]^{[t/T]}), \end{aligned}$$

$$\begin{aligned} K_3 &= \frac{(A/\mu)\left(1 - \mathrm{e}^{-\mu T}\right)\mathrm{e}^{-\mu t}([1 + b_1(1-p_1)]}{1 - [1 + b_1(1-p_1)]\mathrm{e}^{-\mu T}} \\ &\quad \times (\mathrm{e}^{[t/T]\mu T} - [1 + b_1(1-p_1)]^{[t/T]}) + \frac{A}{\mu} - \frac{A}{\mu}\mathrm{e}^{-\mu t}\mathrm{e}^{[t/T]\mu T}. \end{aligned}$$

Thus,

$$\begin{aligned} S(t) &\le P[1 + b_1(1-p_1)]^{[t/T]}\mathrm{e}^{-\mu t} + M(1+b_1)(1+b_1)^{[t/T]}\mathrm{e}^{-\mu t} \\ &\quad + Qe^{[t/T]\mu T}\mathrm{e}^{-\mu t} + \frac{A}{\mu}, \end{aligned}$$

where

$$P = S(0^+) - M(1+b_1) - \frac{b_1 p_1 V}{1-[1+b_1(1-p_1)]\mathrm{e}^{-\mu T}} - \frac{(A/\mu)(1-\mathrm{e}^{-\mu T})([1+b_1(1-p_1)]}{1-[1+b_1(1-p_1)]\mathrm{e}^{-\mu T}},$$

$$Q = \frac{b_1 p_1 V}{1-[1+b_1(1-p_1)]\mathrm{e}^{-\mu T}} + \frac{(A/\mu)\left(1-\mathrm{e}^{-\mu T}\right)([1+b_1(1-p_1)]}{1-[1+b_1(1-p_1)]\mathrm{e}^{-\mu T}} - \frac{A}{\mu}.$$

From the third equation of (4.131) and (4.132), it follows that

$$\begin{aligned} I' &= [\beta S(t) - (\mu+\gamma+\alpha)]I \\ &\le [\Psi(t) + \beta\frac{A}{\mu} - (\mu+\gamma+\alpha)]I, \\ I(nT^+) &\le [1+b_2(1-p_2)]I(nT), \end{aligned}$$

where

$$\Psi(t) = \beta P[1+b_1(1-p_1)]^{[t/T]}\mathrm{e}^{-\mu t} + \beta M(1+b_1)(1+b_1)^{[t/T]}\mathrm{e}^{-\mu t} + \beta Q\mathrm{e}^{[t/T]\mu T}\mathrm{e}^{-\mu t}.$$

By using Theorem 4.5 again, we obtain

$$\begin{aligned} I(t) &\le I(0^+)\left(\prod_{0<kT<t}[1+b_2(1-p_2)]\right)\exp\left\{\int_0^t \Psi(s)\mathrm{d}s + \int_0^t \left[\beta\frac{A}{\mu} - (\mu+\gamma+\alpha)\right]\mathrm{d}s\right\} \\ &= I(0^+)[1+b_2(1-p_2)]^{[t/T]}\exp\left[\int_0^t \Psi(s)\mathrm{d}s\right] \times \exp\left\{\beta\frac{A}{\mu}t - (\mu+\gamma+\alpha)t\right\}, \end{aligned}$$

where

$$\exp\left\{\int_0^t \Psi(s)\mathrm{d}s\right\} = \beta P K_4 + \beta M(1+b_1)K_5 + \beta Q K_6,$$

and

$$K_4 = \frac{1}{\mu}\left(1-\mathrm{e}^{-\mu T}\right)\frac{1-[(1+b_1(1-p_1))\mathrm{e}^{-\mu T}]^{[t/T]}}{1-(1+b_1(1-p_1))\mathrm{e}^{-\mu T}} + \frac{1}{\mu}\left([1+b_1(1-p_1)]\mathrm{e}^{-\mu T}\right)^{[t/T]}(1-\mathrm{e}^{-\mu T(t/T-[t/T])}),$$

$$K_5 = \frac{1}{\mu}\left(1-\mathrm{e}^{-\mu T}\right)\frac{1-[(1+b_1)\mathrm{e}^{-\mu T}]^{[t/T]}}{1-(1+b_1)\mathrm{e}^{-\mu T}} + \frac{1}{\mu}\left([1+b_1]\mathrm{e}^{-\mu T}\right)^{[t/T]}(1-\mathrm{e}^{-\mu T(t/T-[t/T])}),$$

$$K_6 = \frac{1}{\mu}\left(1-\mathrm{e}^{-\mu T}\right)[t/T] + \frac{1}{\mu}(1-\mathrm{e}^{-\mu T(t/T-[t/T])}).$$

Thus,

$$I(t) \le D\exp\left\{\frac{t}{T}\ln[1+b_2(1-p_2)] + \frac{\beta A}{\mu}t - (\mu+\gamma+\alpha)t + \frac{\beta Q}{\mu}\left(1-\mathrm{e}^{-\mu T}\right)\frac{t}{T}\right\},$$

where

$$D(t) = I(0^+)[1+b_2(1-p_2)]^{[t/T]-t/T} \times \exp\{\beta P K_4 + \beta M(1+b_1)K_5 + \beta Q K_6\}$$

is bounded for all $t \ge 0$.

If $R_{0p} < 1$, then

$$\frac{t}{T}\ln[1+b_2(1-p_2)] + \frac{\beta A}{\mu}t - (\mu+\gamma+\alpha)t + \frac{\beta Q}{\mu}\left(1-\mathrm{e}^{-\mu T}\right)\frac{t}{T} < 0.$$

Thus, $I(t) \to 0$ as $t \to \infty$.

In the following, we prove that

$$N(t) \to \widetilde{N}(t), \quad S(t) \to \widetilde{S}(t), \quad t \to \infty,$$

for any solution $(N(t), S(t), I(t))$ of systems (4.131) and (4.132).

Let $W(t) = |N(t) - \widetilde{N}(t)|$. Then we have

$$\begin{aligned} D^+W(t) &= \operatorname{sign}(N(t) - \widetilde{N}(t))(N'(t) - \widetilde{N}'(t)) \\ &\le -\mu|N(t) - \widetilde{N}(t)| + \alpha I(t) \\ &\le -\mu W(t) + r_1(t), \quad t \ne nT, \end{aligned} \tag{4.135}$$

where

$$\begin{aligned} r_1(t) &= \alpha D\mathrm{e}^{-Ct}, \\ C &= -\frac{t}{T}\ln[1 + b_2(1 - p_2)] - \frac{\beta A}{\mu}t + (\mu + \gamma + \alpha)t \\ &\quad - \frac{\beta Q}{\mu}\left(1 - \mathrm{e}^{-\mu T}\right)\frac{t}{T} > 0, \end{aligned}$$

if $R_{0p} < 1$. Furthermore, we have

$$\begin{aligned} W(nT^+) &= |N(nT^+) - \widetilde{N}(nT^+)| \\ &\le (1 + b_1)W(nT) + (b_1 - b_2)I(nT), \quad t = nT. \end{aligned}$$

From the preceding computation of $I(t)$, we know

$$\begin{aligned} I(nT) &\le I(0^+)[1 + b_2(1 - p_2)]^{-1} \\ &\quad \times \exp\left\{\frac{\beta P}{\mu}\left(1 - \mathrm{e}^{-\mu T}\right)\frac{1 - [(1 + b_1(1 - p_1))\mathrm{e}^{-\mu T}]^n}{1 - (1 + b_1(1 - p_1))\mathrm{e}^{-\mu T}}\right. \\ &\quad \left. + \frac{\beta}{\mu}M(1 + b_1)\left(1 - \mathrm{e}^{-\mu T}\right)\frac{1 - [(1 + b_1)\mathrm{e}^{-\mu T}]^n}{1 - (1 + b_1)\mathrm{e}^{-\mu T}}\right\} \\ &\quad \times \exp\left\{(\ln[1 + b_2(1 - p_2)] + \frac{\beta A}{\mu}T - (\mu + \gamma + \alpha)T\right. \\ &\quad \left. + \frac{\beta Q}{\mu}\left(1 - \mathrm{e}^{-\mu T}\right))n\right\} \\ &\le H\mathrm{e}^{-Cn}, \end{aligned}$$

where the constant

$$\begin{aligned} H &= I(0^+)[1 + b_2(1 - p_2)]^{-1} \\ &\quad \times \exp\left\{\frac{\beta P}{\mu}\left(1 - \mathrm{e}^{-\mu T}\right)\frac{1}{1 - (1 + b_1(1 - p_1))\mathrm{e}^{-\mu T}}\right\} \\ &\quad + \frac{\beta}{\mu}M(1 + b_1)\left(1 - \mathrm{e}^{-\mu T}\right)\frac{1}{1 - (1 + b_1)\mathrm{e}^{-\mu T}}. \end{aligned}$$

Then

$$W(nT^+) \le (1+b_1)W(nT) + (b_1-b_2)H\mathrm{e}^{-Cn}. \tag{4.136}$$

From (4.135) and (4.136), and using Theorem 4.5, we obtain

$$\begin{aligned}
W(t) &\le W(0^+)(1+b_1)^{[t/T]}\mathrm{e}^{-\mu t} \\
&\quad + \sum_{0<kT<t} ((1+b_1)^{[t/T]-k}\mathrm{e}^{-\mu t}\mathrm{e}^{-\mu kT}(b_1-b_2)H\mathrm{e}^{-Ck}) \\
&\quad + \int_0^t \prod_{s<kT<t} (1+b_1)\mathrm{e}^{-\mu t}\mathrm{e}^{\mu s} r_1(s)\mathrm{d}s \\
&= W(0^+)((1+b_1)\mathrm{e}^{-\mu t})^{[t/T]}\mathrm{e}^{-\mu T(t/T-[t/T])} \\
&\quad + \left((b_1-b_2)H + \frac{\alpha D}{\mu - C}(1-\mathrm{e}^{(\mu-C)T})(1+b_1)\right) \\
&\quad \times \frac{\mathrm{e}^{-\mu T(t/T-[t/T])}\mathrm{e}^{-[t/T]C}}{1-(1+b_1)\mathrm{e}^{-\mu T}\mathrm{e}^{C}} \\
&\quad - [(b_1-b_2)H + \frac{\alpha D}{\mu - C}(1-\mathrm{e}^{(\mu-C)T})(1+b_1)] \\
&\quad \times \frac{\mathrm{e}^{-\mu T(t/T-[t/T])}\left((1+b_1)\mathrm{e}^{-\mu t}\right)^{[t/T]}}{1-(1+b_1)\mathrm{e}^{-\mu T}\mathrm{e}^{C}} \\
&\quad + \frac{\alpha D}{\mu - C}\mathrm{e}^{-\mu T(t/T-[t/T])}\mathrm{e}^{-[t/T]CT}[\mathrm{e}^{(\mu-C)T(t/T-[t/T])}-1].
\end{aligned}$$

Hence $W(t) \to 0$, as $t \to \infty$, that is, $N(t) \to \widetilde{N}(t)$, as $t \to \infty$. Similarly, we can prove $S(t) \to \widetilde{S}(t)$ as $t \to \infty$. □

4.7.3. *The comparison between constant and pulse births*

It is interesting to compare the differences between the effects of the constant and pulse births.

For constant birth, the basic reproductive number is

$$R_0 = \frac{(\beta A/(\mu - b_1)) + b_2(1-p_2)}{\mu + \gamma + \alpha}.$$

For the pulse birth, the basic reproductive number is

$$R_{0p} = \frac{\beta\frac{1}{T}\int_0^T \widetilde{S}(t)\mathrm{d}t + \frac{1}{T}\ln[1+b_2(1-p_2)]}{\mu + \gamma + \alpha}.$$

By substituting the exact expression for $\widetilde{S}(t)$, (4.129), into R_{0p} and then integrating it, the expression of R_{0p} becomes

$$R_{0p} = \frac{\beta\frac{A}{\mu}\left\{T + \frac{b_1\left(1-\mathrm{e}^{-\mu T}\right)}{\mu[1-(1+b_1)\mathrm{e}^{-\mu T}]}\right\} + \ln[1+b_2(1-p_2)]}{(\mu+\gamma+\alpha)T}.$$

We denote

$$F(T) = \frac{\beta\frac{A}{\mu}\left\{T + \frac{b_1\left(1-\mathrm{e}^{-\mu T}\right)}{\mu[1-(1+b_1)\mathrm{e}^{-\mu T}]}\right\} + \ln[1+b_2(1-p_2)]}{(\mu+\gamma+\alpha)T}.$$

From the condition $\mu > (\ln(1+b_1))/T$, we have $T > (1/\mu)\ln(1+b_1)$. Hence

$$F\left(\frac{1}{\mu}\ln(1+b_1)\right) = \lim_{T\to\left[\frac{1}{\mu}\ln(1+b_1)\right]^+} F(T) = +\infty,$$

$$F(+\infty) = \lim_{T\to+\infty} F(T) = \frac{\beta\frac{A}{\mu}}{\mu+\gamma+\alpha},$$

and

$$\frac{\mathrm{d}F(T)}{\mathrm{d}T} = \frac{G(T)}{(\mu+\gamma+\alpha)^2T^2},$$

where

$$\begin{aligned} G(T) = &-\frac{\beta A b_1}{\mu}(\mu+\gamma+\alpha) \\ &\times\left\{\frac{b_1 T\mathrm{e}^{-\mu T}}{[1-(1+b_1)\mathrm{e}^{-\mu T}]^2} + \frac{b_1\left(1-\mathrm{e}^{-\mu T}\right)}{\mu[1-(1+b_1)\mathrm{e}^{-\mu T}]}\right\} \\ &-(\mu+\gamma+\alpha)\ln[1+b_2(1-p_2)] < 0. \end{aligned}$$

Clearly, $F'(T) < 0$, and as a consequence, $F(T)$ is a decreasing function of T.

It follows from

$$\begin{aligned} &\frac{\beta\frac{A}{\mu-b_1} + b_2(1-p_2)}{\mu+\gamma+\alpha} \\ &\quad = \frac{\beta\frac{A}{\mu}}{\mu+\gamma+\alpha}\left[1 + \frac{b_1}{\mu-b_1} + \frac{\mu b_2(1-p_2)}{\beta A}\right] > \frac{\beta\frac{A}{\mu}}{\mu+\gamma+\alpha}, \end{aligned}$$

that there exists unique constant T_c, such that

$$F(T_c) = \frac{\beta\frac{A}{\mu - b_1} + b_2(1 - p_2)}{\mu + \gamma + \alpha}.$$

If $T > T_c$, then $R_{0p} < R_0$, which implies that it is easier for the population with a pulse birth to eliminate the disease ($R_{0p} < 1$), whereas, if $T < T_c$, then $R_0 < R_{0p}$, which implies that it is easier for the population with a constant birth to eliminate the disease ($R_0 < 1$). If $T = T_c$, the constant and pulse births have the same effect. As a matter of fact, when the birth pulse period T gets very large, the births become less important and have little effect on the population. In this case, the basic reproductive number R_{0p} will get much smaller, which converges to $\beta(A/\mu)/(\mu + \gamma + \alpha)$. Consequently, the disease in the population with a pulse birth can be eliminated easily. However, as the birth pulse period T gets very small, the population gives births many times during a very short time period, which have stronger effect on the population than that with constant births when they have the same birth rate. In such a case, it becomes more difficult to eradicate the disease in the population with pulse births.

4.8. SIR Epidemic Models with Pulse Birth and Standard Incidence

Let us consider the following SIR epidemic model [Lin *et al.* (submitted)]:

$$\left.\begin{aligned} S' &= -\beta\frac{S}{N}I - \mu S - pS, \\ I' &= \beta\frac{S}{N}I - (\mu + \gamma + \alpha)I, \\ R' &= \gamma I - \mu R + pS, \end{aligned}\right\} \quad t \neq n\tau, \ \ n = 0, 1, 2, \ldots,$$

$$\left.\begin{aligned} S(n\tau^+) &= S(n\tau) + bN(n\tau), \\ I(n\tau^+) &= I(n\tau), \\ R(n\tau^+) &= R(n\tau), \end{aligned}\right\} \quad t = n\tau, \ \ n = 0, 1, 2, \ldots, \tag{4.137}$$

where the parameters β, μ, γ, p, b, and τ are positive constants. β is adequate contact rate, μ is the per capita death rate, θ is the removed rate, p is the proportion of the vaccinated individuals, b is the proportion of the offspring of the susceptibles, τ is the period of birth pulses, and the constant α, $\alpha \geq 0$, represents the death rate due to disease. The total

population size is $N = S + I + R$. We further assume $\beta \geq \alpha$. Let

$$s = \frac{S}{N}, \quad i = \frac{I}{N}, \quad r = \frac{R}{N},$$

then system (4.137) can be written as follows:

$$\left.\begin{aligned} s' &= -ps + (\alpha - \beta)si, \\ i' &= -(\gamma + \alpha)i + \beta si + \alpha i^2, \\ r' &= ps + \gamma i + \alpha ir, \end{aligned}\right\} \quad t \neq n\tau,$$

$$\left.\begin{aligned} s(n\tau^+) &= \frac{s(n\tau) + b}{1 + b}, \\ i(n\tau^+) &= \frac{i(n\tau)}{1 + b}, \\ r(n\tau^+) &= \frac{r(n\tau)}{1 + b}, \end{aligned}\right\} \quad t = n\tau. \tag{4.138}$$

By virtue of the equation $s(t) + i(t) + r(t) = 1$, we study the following two-dimensional system

$$\left.\begin{aligned} s' &= -ps + (\alpha - \beta)si, \\ i' &= -(\gamma + \alpha)i + \beta si + \alpha i^2, \end{aligned}\right\} \quad t \neq n\tau,$$

$$\left.\begin{aligned} s(n\tau^+) &= \frac{s(n\tau) + b}{1 + b}, \\ i(n\tau^+) &= \frac{i(n\tau)}{1 + b}, \end{aligned}\right\} \quad t = n\tau. \tag{4.139}$$

It is easily seen that the domain

$$\Omega = \{(s, i) \mid s \geq 0, i \geq 0, s + i \leq 1\}$$

is the positively invariant set of system (4.139).

4.8.1. *The existence and local stability of disease-free periodic solution*

Using the method similar to that in Sec. 4.2, we can prove the existence and local stability of disease-free periodic solutions.

From the stroboscopic map, we obtain a τ-periodic disease-free solution $(\widetilde{s}(t), 0)$ of system (4.139), where

$$\widetilde{s}(t) = \frac{b\mathrm{e}^{p\tau}}{(1+b)\mathrm{e}^{p\tau}-1}\mathrm{e}^{-p(t-n\tau)}, \quad n\tau < t \leq (n+1)\tau. \tag{4.140}$$

The eigenvalues of $\mathbf{M}$, denoted by λ_1, λ_2, are

$$\lambda_1 = \frac{1}{1+b}\exp(-p\tau) < 1, \quad \lambda_2 = \frac{1}{1+b}\exp\left\{\beta\int_0^\tau \widetilde{s}(t)\mathrm{d}t - (\gamma+\alpha)\tau\right\}.$$

It is easy to see that $\lambda_2 < 1$, if and only if $\beta\int_0^\tau \widetilde{s}(t)\mathrm{d}t < \ln(1+b)+(\gamma+\alpha)\tau$. Define the threshold of model (4.138) as

$$R^* = \frac{\beta\int_0^\tau \widetilde{s}(t)\mathrm{d}t}{\ln(1+b)+(\gamma+\alpha)\tau}, \tag{4.141}$$

where $\widetilde{s}(t)$ is the disease-free periodic solution. Then we have

Theorem 4.31. *If $R^* < 1$, then the τ-periodic disease-free solution $(\widetilde{s}(t), 0, \widetilde{r}(t))$ of system (4.138) is locally asymptotically stable.*

4.8.2. *The global stability of disease-free periodic solution*

We then investigate the global stability of disease-free periodic solution as follows.

Theorem 4.32. *If $R^* < 1$, then the τ-periodic disease-free solution $(\widetilde{s}(t), 0, \widetilde{r}(t))$ of system (4.138) is globally asymptotically stable.*

Proof. We prove the conclusion in the following two steps:

Step 1. We begin our analysis by demonstrating that $\lim_{t\to\infty} i(t) = 0$ if $R^* < 1$. In fact, from system (4.139) and the assumption $\beta \geq \alpha$, we obtain

$$\begin{aligned} s' &\leq -ps, && t \neq n\tau, \\ s(n\tau^+) &= \frac{s(n\tau)+b}{1+b}, && t = n\tau. \end{aligned}$$

By impulsive differential inequality, we see that

$$s(t) \leq \widetilde{s}(t) + s(0^+)(1+b)^{-[t/\tau]}\mathrm{e}^{-pt} + \frac{b(1+b)^{-[t/\tau]}\mathrm{e}^{p(\tau-t)}}{1-(1+b)\mathrm{e}^{p\tau}}.$$

Since

$$\lim_{t\to\infty}\left\{s(0^+)(1+b)^{-[t/\tau]}\mathrm{e}^{-pt}+\frac{b(1+b)^{-[\frac{t}{\tau}]}\mathrm{e}^{p(\tau-t)}}{1-(1+b)\mathrm{e}^{p\tau}}\right\}=0,$$

for any given

$$0<\epsilon_1<\frac{(1-R^*)[\ln(1+b)+(\gamma+\alpha)\tau]}{\beta\tau},$$

there exists $T_1>0$, such that

$$s(t)\le\widetilde{s}(t)+\epsilon_1, \tag{4.142}$$

for all $t>T_1$.

Next, we introduce the new variable $U=s+r$, and it follows from the equations of (4.138) that

$$\begin{aligned} U'&=(-\beta s+\alpha U+\gamma)(1-U), && t\neq n\tau,\\ U(n\tau^+)&=\frac{U(n\tau)+b}{1+b}, && t=n\tau. \end{aligned}$$

By (4.142), we see that

$$U^{'}\ge[\beta(\widetilde{s}(t)+\epsilon_1)+\alpha-\gamma]U-\alpha U^2+\gamma-\beta(\widetilde{s}(t)+\epsilon_1),\quad t>T_1,\ t\neq n\tau.$$

Consider the following equations

$$\begin{aligned} x'&=[\beta(\widetilde{s}(t)+\epsilon_1)+\alpha-\gamma]x\\ &\quad-\alpha x^2+\gamma-\beta(\widetilde{s}(t)+\epsilon_1), && t\neq n\tau,\\ x(n\tau^+)&=\frac{x(n\tau)+b}{1+b}, && t=n\tau. \end{aligned} \tag{4.143}$$

The first equation of (4.143) is called Riccati equation. It is easy to see that $x(t)=1$ is a solution of system (4.143). To prove the global asymptotic stability of the solution $x(t)=1$, we introduce new variable $y=x-1$, which transfers the system (4.143) to

$$\begin{aligned} y'&=[\beta\widetilde{s}(t)-(\gamma+\alpha)+\beta\epsilon_1]y-\alpha y^2, && t\neq n\tau,\\ y(n\tau^+)&=\frac{y(n\tau)}{1+b}, && t=n\tau. \end{aligned}$$

Letting $z = y^{-1}$, we obtain

$$\begin{aligned} z' &= -[\beta\widetilde{s}(t) - (\gamma+\alpha) + \beta\epsilon_1]z + \alpha, \quad && t \neq n\tau, \\ z(n\tau^+) &= (1+b)z(n\tau), && t = n\tau. \end{aligned} \tag{4.144}$$

Letting $q(t) = \beta\widetilde{s}(t) - (\gamma+\alpha) + \beta\epsilon_1$ and solving system (4.144) in interval $(T_1 + n\tau, T_1 + (n+1)\tau]$, we have

$$z(t) = \mathrm{e}^{-\int_{T_1+n\tau}^{t} q(\sigma)\mathrm{d}\sigma}\left[\alpha\int_{T_1+n\tau}^{t} \mathrm{e}^{\int_{T_1+n\tau}^{u} q(\sigma)\mathrm{d}\sigma}\mathrm{d}u + (1+b)z(T_1+n\tau)\right]. \tag{4.145}$$

When $t = T_1 + (n+1)\tau$, (4.145) can be written as

$$\begin{aligned} z(T_1+(n+1)\tau) = \mathrm{e}^{-\int_{T_1+n\tau}^{T_1+(n+1)\tau} q(\sigma)d\sigma}\Bigg[\alpha\int_{T_1+n\tau}^{T_1+(n+1)\tau} \mathrm{e}^{\int_{T_1+n\tau}^{u} q(\sigma)\mathrm{d}\sigma}\mathrm{d}u \\ + (1+b)z(T_1+n\tau)\Bigg]. \end{aligned}$$

Similarly, we can derive $z(T_1+n\tau)$, $z(T_1+(n-1)\tau), \ldots, z(T_1)$. Then using the iterative technique step by step,

$$\begin{aligned} z(T_1+n\tau) &= \mathrm{e}^{-\int_{T_1+(n-1)\tau}^{T_1+n\tau} q(\sigma)\mathrm{d}\sigma}\Bigg\{\alpha\int_{T_1+(n-1)\tau}^{T_1+n\tau} \mathrm{e}^{\int_{T_1+(n-1)\tau}^{u} q(\sigma)\mathrm{d}\sigma}\mathrm{d}u \\ &\quad + (1+b)z(T_1+(n-1)\tau)\Bigg\} \\ &\vdots \\ &= \mathrm{e}^{-\int_0^{n\tau} q(\sigma)\mathrm{d}\sigma}(1+b)^n\Bigg\{\alpha\sum_{k=1}^{n}(1+b)^{k-n-1}e^{\int_{T_1}^{T_1+(n-k)\tau} q(\sigma)d\sigma} \\ &\quad \times\int_{T_1+(n-k)\tau}^{T_1+(n-k+1)\tau} \mathrm{e}^{\int_{T_1+(n-k)\tau}^{u} q(\sigma)\mathrm{d}\sigma}\mathrm{d}u + z(T_1)\Bigg\}, \end{aligned}$$

where

$$\begin{aligned} &\mathrm{e}^{-\int_0^{n\tau} q(\sigma)\mathrm{d}\sigma}(1+b)^n \\ &\quad = \exp\left\{n\left[-\beta\int_0^{\tau}\widetilde{s}(\sigma)\mathrm{d}\sigma + \ln(1+b) + (\gamma+\alpha)\tau - \beta\epsilon_1\tau\right]\right\}. \end{aligned}$$

The condition $R^* < 1$ implies that $\lim_{n\to\infty} z(T_1 + n\tau) = \infty$. Hence, $\lim_{t\to\infty} x(t) = 1$. The comparison principle and the condition $U(t) \le 1$ then implies that $\lim_{t\to\infty}, U(t) = 1$. Therefore, we have $\lim_{t\to\infty}, i(t) = 0$.

Step 2. Then we show that $\lim_{t\to\infty} s(t) = \widetilde{s}(t)$ if $R^* < 1$.

Because we have that $\lim_{t\to\infty} i(t) = 0$, then for any given $\epsilon_2 > 0$, there exists $T_2 > 0$, such that

$$-\epsilon_2 \le i(t) \le \epsilon_2, \tag{4.146}$$

for all $t > T_2$. From (4.146) and system (4.139), we have

$$\begin{aligned} s' &\ge [-p + (\alpha - \beta)\epsilon_2]s, \quad && t \ne n\tau, \\ s(n\tau^+) &= \frac{s(n\tau) + b}{1 + b}, && t = n\tau. \end{aligned}$$

By impulsive differential inequality, we see that

$$\begin{aligned} s(t) \ge\ & s(T_2^+)(1+b)^{\left(\left[\frac{T_2}{\tau}\right]-\left[\frac{t}{\tau}\right]\right)} \mathrm{e}^{(-p+(\alpha-\beta)\epsilon_2)(t-T_2)} \\ & + \frac{b(1+b)^{\left(\left[\frac{T_2}{\tau}\right]-\left[\frac{t}{\tau}\right]\right)} \mathrm{e}^{(-p+(\alpha-\beta)\epsilon_2)\left(t-\left[\frac{T_2}{\tau}\right]\tau-\tau\right)}}{1-(1+b)\mathrm{e}^{-(-p+(\alpha-\beta)\epsilon_2)\tau}} \\ & + \frac{b\mathrm{e}^{p\tau}}{(1+b)\mathrm{e}^{p\tau}\mathrm{e}^{(\beta-\alpha)\epsilon_2\tau}-1} \mathrm{e}^{-p(t-[\frac{t}{\tau}]\tau)} \mathrm{e}^{(\alpha-\beta)\epsilon_2(t-[\frac{t}{\tau}]\tau-\tau)}. \end{aligned}$$

Since $\epsilon_2 > 0$ is arbitrary, it is obvious that

$$\begin{aligned} \lim_{t\to\infty} \Bigg\{ & s(T_2^+)(1+b)^{\left(\left[\frac{T_2}{\tau}\right]-\left[\frac{t}{\tau}\right]\right)} \mathrm{e}^{(-p+(\alpha-\beta)\epsilon_2)(t-T_2)} \\ & + \frac{b(1+b)^{\left(\left[\frac{T_2}{\tau}\right]-\left[\frac{t}{\tau}\right]\right)} \mathrm{e}^{(-p+(\alpha-\beta)\epsilon_2)\left(t-\left[\frac{T_2}{\tau}\right]\tau-\tau\right)}}{1-(1+b)\mathrm{e}^{-(-p+(\alpha-\beta)\epsilon_2)\tau}} \Bigg\} = 0, \end{aligned}$$

and

$$\lim_{t\to\infty} \frac{b\mathrm{e}^{p\tau}}{(1+b)\mathrm{e}^{p\tau}\mathrm{e}^{(\beta-\alpha)\epsilon_2\tau}-1} \mathrm{e}^{-p(t-[\frac{t}{\tau}]\tau)} \mathrm{e}^{(\alpha-\beta)\epsilon_2(t-[\frac{t}{\tau}]\tau-\tau)} = \widetilde{s}(t).$$

Hence, for any given $\epsilon_3 > 0$, there exists $T_3 > 0$, such that

$$s(t) \ge \widetilde{s}(t) - \epsilon_3, \tag{4.147}$$

for all $t > T_3$. Let $\epsilon = \min\{\epsilon_1, \epsilon_2, \epsilon_3\}$, $T = \max\{T_1, T_2, T_3\}$. Then from (4.142) and (4.147), we obtain $\widetilde{s}(t) - \epsilon \leq s(t) \leq \widetilde{s}(t) + \epsilon$; that is,

$$\lim_{t\to\infty} s(t) = \widetilde{s}(t),$$

for all $t > T$. Therefore, the disease-free periodic solution $(\widetilde{s}(t), 0, \widetilde{r}(t))$ is globally asymptotically stable. □

4.8.3. *The uniform persistence of the infection*

In this section, we will discuss the uniform persistence of the infection. First of all, we give two lemmas, which will be useful for our main results.

Lemma 4.1. *The impulsive equation*

$$\begin{aligned} x' &= -hx - l, \qquad t \neq n\tau, \\ x(n\tau^+) &= \frac{x(n\tau) + g}{1+g}, \quad t = n\tau, \end{aligned} \tag{4.148}$$

has a unique positive τ-periodic solution $\widetilde{x}(t)$, and $\widetilde{x}(t)$ is globally asymptotically stable in the sense that $\lim_{t\to\infty} |x(t) - \widetilde{x}(t)| = 0$, where $x(t)$ is any solution of system (4.148) *with positive initial value $x(0) > 0$. The parameters h, l, and g are all positive constants.*

Proof. Solving Eq. (4.148), we have

$$x(t) = W(t,0)x(0) - l\int_0^t W(t,\sigma)\mathrm{d}\sigma + \frac{g}{1+g}\sum_{0<n\tau<t} W(t, n\tau^+),$$

where

$$W(t, t_0) = \prod_{t_0 \leq n\tau < t} \frac{1}{1+g}\mathrm{e}^{-h(t-t_0)}.$$

Since $W(\tau, 0) = \frac{1}{1+g}\mathrm{e}^{-h\tau} < 1$, Eq. (4.148) has a unique positive τ-periodic solution $\widetilde{x}(t)$ with the initial value

$$\widetilde{x}(0) = \left(-l\int_0^\tau W(\tau^+, \sigma)\mathrm{d}\sigma + [g/(1+g)]W(\tau,\tau)\right)/(1 - W(\tau, 0)).$$

Next, we only need to prove that $\lim_{t\to\infty} |x(t) - \widetilde{x}(t)| = 0$. Since

$$|x(t) - \widetilde{x}(t)| = W(t,0)|x(0) - \widetilde{x}(0)|,$$

the result is obtained if $W(t,0) \to 0$, as $t \to \infty$. Suppose $t \in (n\tau, (n+1)\tau]$, then

$$W(t,0) = \prod_{0 \le j\tau < t} \frac{1}{1+g} \mathrm{e}^{-ht} = (1+g)^{-[t/\tau]} \mathrm{e}^{-ht}.$$

Thus $\lim_{t\to\infty} W(t,0) = 0$. The proof is completed. □

Lemma 4.2. *If $R^* > 1$, then the disease uniformly weakly persists in the population, in the sense that there exists $c > 0$ such that $\lim_{t\to\infty} \sup i(t) > c$ for all positive solutions of* (4.148).

Proof. Let us suppose that for every $\epsilon > 0$, there is a solution with $\lim_{t\to\infty} \sup i(t) < \epsilon$. From the first equation of (4.138), we have

$$s' = -ps + (\alpha - \beta)si \ge -ps + (\alpha - \beta)\epsilon, \quad t \ne n\tau.$$

Consider the following system:

$$\begin{aligned} u' &= -pu + (\alpha - \beta)\epsilon, \quad t \ne n\tau, \\ u(n\tau^+) &= \frac{u(n\tau) + b}{1+b}, \qquad t = n\tau. \end{aligned} \tag{4.149}$$

By Lemma 4.1, we see that system (4.149) has a unique positive τ-periodic solution $\widetilde{u}(t)$, and $\widetilde{u}(t)$ is globally asymptotically stable. Because $\widetilde{s}(t)$ is a τ-periodic solution of system (4.140), it is easy to see that

$$\widetilde{s}(t) - \widetilde{u}(t) = (\beta - \alpha)\epsilon \left(\frac{W(t,0) \int_0^\tau W(\tau^+, \sigma) \mathrm{d}\sigma}{1 - W(\tau, 0)} + \int_0^t W(t,\sigma) \mathrm{d}\sigma \right). \tag{4.150}$$

Let

$$\Delta = (\beta - \alpha) \max_{0 \le t \le \tau} \left\{ \frac{W(t,0) \int_0^\tau W(\tau^+, \sigma) \mathrm{d}\sigma}{1 - W(\tau, 0)} + \int_0^t W(t,\sigma) \mathrm{d}\sigma \right\}.$$

From (4.150), we have

$$\widetilde{u}(t) \ge \widetilde{s}(t) - \Delta\epsilon. \tag{4.151}$$

By the comparison principle, we know that $s(t) \ge u(t)$. Then from the second equation of system (4.138), we obtain

$$i' \ge -(\gamma + \alpha)i + \beta i u(t) + \alpha i^2, \quad t \ne n\tau. \tag{4.152}$$

Since $\widetilde{u}(t)$ is globally asymptotically stable, for the ϵ given above, there exists $T_4 > 0$, such that $u(t) \geq \widetilde{u}(t) - \epsilon$, $t > T_4$. From (4.151) and (4.152), we have

$$i' \geq [\beta\widetilde{s}(t) - (\gamma + \alpha) - (1 + \Delta)\beta\epsilon]i, \quad t > T_4, \ t \neq n\tau.$$

Consider the following system:

$$\begin{aligned} i' &\geq [\beta\widetilde{s}(t) - (\gamma + \alpha) - (1 + \Delta)\beta\epsilon]i, && t \neq n\tau, \\ i(n\tau^+) &= \frac{i(n\tau)}{1 + b}, && t = n\tau. \end{aligned}$$

By impulsive differential inequality, for $t \in (T_4 + n\tau, T_4 + (n + 1)\tau]$, we see that

$$\begin{aligned} i(t) &\geq i(T_4) \prod_{T_4 < j\tau < t} \frac{1}{1 + b} \exp\left\{ \int_{T_4}^{t} [\beta\widetilde{s}(\sigma) - (\gamma + \alpha) - (1 + \Delta)\beta\epsilon]\mathrm{d}\sigma \right\} \\ &= i(T_4)(1 + b)^{-n} \exp\left\{ \int_{T_4}^{T_4 + n\tau} [\beta\widetilde{s}(\sigma) - (\gamma + \alpha) - (1 + \Delta)\beta\epsilon]\mathrm{d}\sigma \right. \\ &\quad \left. + \int_{T_4 + n\tau}^{t} [\beta\widetilde{s}(\sigma) - (\gamma + \alpha) - (1 + \Delta)\beta\epsilon]\mathrm{d}\sigma \right\} \\ &\geq C \exp\{n[(R^* - 1)(\ln(1 + b) + (\gamma + \alpha)\tau) - (1 + \Delta)\beta\epsilon\tau]\}, \end{aligned}$$

where $C = i(T_4) \exp\{-[(\gamma + \alpha) + (1 + \Delta)\beta\epsilon]\tau\}$. Choose

$$0 < \epsilon < \frac{(R^* - 1)[\ln(1 + b) + (\gamma + \alpha)\tau]}{(1 + \Delta)\beta\tau}.$$

Thus $i(t) \to \infty$, as $t \to \infty$, a contradiction to the fact that $i(t)$ is bounded. The proof is completed. □

Theorem 4.33. *If $R^* > 1$, then the disease uniformly persists in the population, in the sense that there exists some $\varrho > 0$ such that $\lim_{t\to\infty} \inf i(t) \geq \varrho$ for all positive solutions of* (4.138).

Proof. Let

$$0 < \eta \leq \frac{1}{2}\left(1 - \frac{1}{R^*}\right)\frac{\widetilde{s}(t)}{M(\gamma+\alpha)},$$

where

$$M = \max_{0\leq t\leq\tau}\left\{\frac{W(t,0)\int_0^\tau W(\tau^+,\sigma)\mathrm{d}\sigma}{1-W(\tau,0)} + \int_0^t W(t,\sigma)\mathrm{d}\sigma\right\},$$

$$W(t,t_0) = \prod_{t_0\leq n\tau<t}\frac{1}{1+b}\mathrm{e}^{-p(t-t_0)}.$$

It can be shown from Lemma 4.1 that for any positive solution of (4.138) there exists at least one $t_0 > 0$, such that $i(t_0) > \eta > 0$. Then, we are left to consider two possible cases. The first one is $i(t) \geq \eta$, for all large $t \geq t_0$. The second one is $i(t)$ oscillates about η for large t.

It is easy to see, from the conclusion of Theorem 4.33, that the first case is its direct implication if we choose $\varrho = \eta$.

For the second case, let $t_1 > t_0$ and $t_2 > t_1$ satisfy

$$i(t_1) = i(t_2) = \eta, \quad \text{and} \quad i(t) < \eta \qquad \text{for } t_1 < t < t_2.$$

Then, we introduce the new variable $V = s + i$, and it follows from the equations of (4.138) that

$$\left.\begin{aligned} V' &= -pV - (\gamma+\alpha)i + (\alpha V + p)i, \\ i' &= -(\gamma+\alpha)i + \beta(V-i)i + \alpha i^2, \end{aligned}\right\} \quad t \neq n\tau,$$

$$\left.\begin{aligned} V(n\tau^+) &= \frac{V(n\tau)+b}{1+b}, \\ i(n\tau^+) &= \frac{i(n\tau)}{1+b}, \end{aligned}\right\} \quad t = n\tau. \tag{4.153}$$

If $i(t) \leq \eta$, then

$$V' \geq -pV - (\gamma+\alpha)\eta, \quad t \neq n\tau.$$

Consider the following system

$$\begin{aligned} x' &= -px - (\gamma+\alpha)\eta, \quad t \neq n\tau, \\ x(n\tau^+) &= \frac{x(n\tau)+b}{1+b}, \qquad t = n\tau. \end{aligned} \tag{4.154}$$

By Lemma 4.1, we see that Eq. (4.154) has a unique positive τ-periodic solution $\widetilde{x}(t)$, and $\widetilde{x}(t)$ is globally asymptotically stable. From the proof of Lemma 4.2, it is easy to see that

$$\widetilde{x}(t) - \widetilde{s}(t) = -(\gamma+\alpha)\eta\left(\frac{W(t,0)\int_0^\tau W(\tau^+,\sigma)\mathrm{d}\sigma}{1-W(\tau,0)} + \int_0^t W(t,\sigma)\mathrm{d}\sigma\right).$$

Then we obtain

$$\widetilde{x}(t) \geq \frac{1}{2}\left(1+\frac{1}{R^*}\right)\widetilde{s}(t).$$

The comparison principle and the global asymptotic stability of $\widetilde{x}(t)$ implies that there exists $T_5 > 0$, such that

$$V(t) \geq \frac{1}{2}\left(1+\frac{1}{R^*}\right)\widetilde{s}(t), \quad \text{for all } t > t_1 + T_5. \tag{4.155}$$

From (4.155) and the second equation of (4.153), we see that

$$i' \geq \left[\frac{\beta}{2}\left(1+\frac{1}{R^*}\right)\widetilde{s}(t) - (\gamma+\alpha)\right] i + (\alpha-\beta)i^2, \quad t > t_1+T_5, \ \ t \neq n\tau. \tag{4.156}$$

Consider the following system

$$\begin{aligned} y' &= \left[\frac{\beta}{2}\left(1+\frac{1}{R^*}\right)\widetilde{s}(t) - (\gamma+\alpha)\right] y + (\alpha-\beta)y^2, \quad && t \neq n\tau, \\ y(n\tau^+) &= \frac{y(n\tau)}{1+b}, && t = n\tau. \end{aligned} \tag{4.157}$$

Let $z = y^{-1}$. Then we have

$$\begin{aligned} z' &= \left[(\gamma+\alpha) - \frac{\beta}{2}\left(1+\frac{1}{R^*}\right)\widetilde{s}(t)\right] z + (\beta-\alpha), \quad && t \neq n\tau, \\ z(n\tau^+) &= (1+b)z(n\tau), && t = n\tau. \end{aligned} \tag{4.158}$$

It is similar to the proof of Lemma 4.1 that Eq. (4.158) has a unique positive τ-periodic solution $\widetilde{z}(t)$, and $\widetilde{z}(t)$ is globally asymptotically stable with the condition $R^* > 1$. Thus system (4.157) has a unique positive

τ-periodic solution $\widetilde{y}(t)$, and $\widetilde{y}(t)$ is globally asymptotically stable; that is,

$$\lim_{t\to\infty} |y(t) - \widetilde{y}(t)| = 0. \tag{4.159}$$

From (4.159), we see that there exists $T_6 > 0$ such that

$$y(t) > \rho \equiv \frac{1}{2} \min_{t_1+T_6\le t\le t_1+T_6+\tau} \widetilde{y}(t) > 0, \quad \text{for all } t > t_1 + T_6.$$

Let $T = \max\{T_5, T_6\}$, and define

$$\varrho = \min\{\rho, \eta \exp[-(\gamma + \alpha)\tau]\}.$$

If $t_2 - t_1 < \tau$, from the second equation of (4.153), we have the inequality

$$i'(t) \ge -(\gamma + \alpha)i,$$

and the comparison principle implies that $i(t) \ge \eta \exp\{-(\gamma+\alpha)(t-t_1)\} \ge \eta \exp\{-(\gamma+\alpha)\tau\}$: that is, $i(t) \ge \varrho$ for all $t \in (t_1, t_2)$.

If $t_2 - t_1 > \tau$, we divide the interval $[t_1, t_2]$ into two subintervals $[t_1, t_1 + \tau]$ and $[t_1+\tau, t_2]$. It is obvious that $i(t) \ge \varrho$ in interval $[t_1, t_1+\tau]$. In interval $[t_1 + \tau, t_2]$, we have the inequality (4.156). The comparison principle shows that $i(t) \ge y(t) \ge \rho \ge \varrho$ for $t \in [t_1+\tau, t_2]$. The analysis above is independent of any interval $[t_1, t_2]$, and the choice of ϱ is independent of any positive solution of (4.138). Hence the persistence is uniform to all positive solution. The proof is complete. □

4.9. SIR Epidemic Model with Nonlinear Birth Pulses

Consider an SIR model where all the newborn offspring are susceptible, and the density restrain $-(rN^2)/K$ influencing the birth rate b and death rate μ by a and $1 - a$. Using the impulsive differential equations for the model formulation, we have [Zhang *et al.* (2008)]

$$\left.\begin{aligned} S' &= -\left[\mu + (1-a)r\frac{N}{K}\right] S - \beta SI, \\ I' &= \beta SI - \gamma I - \alpha I - \left[\mu + (1-a)r\frac{N}{K}\right] I, \\ R' &= \gamma I - \left[\mu + (1-a)r\frac{N}{K}\right] R, \end{aligned}\right\} \quad t \ne nT,$$

$$\left.\begin{aligned} S(nT^+) &= S(nT) + \left[b - ar\frac{N(nT)}{K}\right] N(nT), \\ I(nT^+) &= I(nT), \\ R(nT^+) &= R(nT), \end{aligned}\right\} \quad t = nT, \tag{4.160}$$

where the parameters K, b, μ, a, γ, β, and r are all positive constants, α is a nonnegative constant and represents the death rate due to disease, γ is the removed rate, β is the infection rate, $r = b - \mu$, K represents a carrying capacity, or maximum possible population size. Because of the biological relevance, a natural restriction is $\beta - (1-a)\frac{r}{K} > 0$.

Adding the three equations in (4.160) together, we obtain

$$\begin{aligned} N' &= -\left[\mu + (1-a)r\frac{N(t)}{K}\right] N(t) - \alpha I, \quad t \neq nT, \\ N(nT^+) &= \left[1 + b - ar\frac{N(nT)}{K}\right] N(nT), \qquad t = nT. \end{aligned} \tag{4.161}$$

Again, the domain

$$\bar{S} = \{(S, I, R) \,|\, S > 0, I > 0, R > 0\}$$

is a positively invariant set for system (4.160).

4.9.1. *Existence and stability of the disease-free periodic solution*

In this section, we prove the existence, locally and globally asymptotic stability of the disease-free solution $(\tilde{N}(t), 0, 0)$.

We begin our analysis of (4.160) by showing the existence of an disease-free periodic solution, in which $I(t) = 0$, $R(t) = 0$. Then (4.161) becomes

$$\begin{aligned} N' &= -\left[\mu + (1-a)r\frac{N(t)}{K}\right] N(t), \quad t \neq nT, \\ N(nT^+) &= \left[1 + b - ar\frac{N(nT)}{K}\right] N(nT), \quad t = nT. \end{aligned} \tag{4.162}$$

Solving system (4.162), we have

$$\ln N(t) - \ln\left[1 + \frac{(1-a)r}{\mu K}N(t)\right] = -\mu t + c, \quad c \in R.$$

Let the initial value $N(0) = N_0$. Then we have

$$\frac{1}{N(t)} = \left[\frac{1}{N_0} + \frac{(1-a)r}{\mu K}\right]\exp(\mu t) - \frac{(1-a)r}{\mu K};$$

that is,

$$N(t) = \frac{1}{\left[\frac{1}{N_0} + \frac{(1-a)r}{\mu K}\right]\exp(\mu t) - \frac{(1-a)r}{\mu K}}. \tag{4.163}$$

In the interval $[0, T]$, $N(t)$ satisfies

$$N(0) = N(T^+) = \left[1 + b - \frac{ar}{K}N(T)\right]N(T);$$

that is,

$$N(0) = \frac{1 + b - \frac{ar}{K}\frac{1}{\left(\frac{1}{N_0} + \frac{(1-a)r}{\mu K}\right)\exp(\mu T) - \frac{(1-a)r}{\mu K}}}{\left(\frac{1}{N_0} + \frac{(1-a)r}{\mu K}\right)\exp(\mu T) - \frac{(1-a)r}{\mu K}}.$$

Hence,

$$\frac{(1-a)^2r^2[\exp(\mu T) - 1]^2}{\mu^2K^2}N_0^2 + mN_0 + [\exp(2\mu T) - (1+b)\exp(\mu T)] = 0, \tag{4.164}$$

where

$$m = \frac{ar}{K} - \frac{(1-a)(1+b)r[\exp(\mu T) - 1]}{\mu K} + \frac{2\exp(\mu T)(1-a)(\exp(\mu T) - 1)r}{\mu K}.$$

It follows from

$$\Delta = \left[\frac{ar}{K} - \frac{(1-a)r(1+b)[\exp(\mu T) - 1]}{\mu K} + \frac{2\exp(\mu T)(1-a)[\exp(\mu T) - 1]r}{\mu K}\right]^2 - \frac{4(1-a)^2r^2[\exp(\mu T) - 1]^2}{\mu^2K^2}[\exp(2\mu T) - (1+b)\exp(\mu T)]$$

$$= \left[\frac{(1-a)r[\exp(\mu T)-1](1+b)}{\mu K} - \frac{ar}{K}\right]^2 + \frac{4ar^2(1-a)[\exp(\mu T)-1]\exp(\mu T)}{\mu K^2} > 0,$$

that Eq. (4.164) has two distinct real solutions. Note

$$\begin{aligned} q &= \frac{\mu^2 K^2}{(1-a)^2 r^2(\exp(\mu T)-1)^2}[\exp(2\mu T) - (1+b)\exp(\mu T)] \\ &= \exp(\mu T)[\exp(\mu T) - 1 - b]\frac{\mu^2 K^2}{(1-a)^2 r^2[\exp(\mu T)-1]^2}, \\ p &= \left[\frac{r(1-a)(1+b)[\exp(\mu T)-1]}{\mu K} - \frac{2\exp(\mu T)(1-a)[\exp(\mu T)-1]r - ar\mu}{\mu K}\right] \\ &\quad \times \frac{\mu^2 K^2}{(1-a)^2 r^2[\exp(\mu T)-1]^2} \\ &= \left[\frac{r(1-a)[\exp(\mu T)-1][1+b-2\exp(\mu T)]}{\mu K} - \frac{ar}{K}\right] \\ &\quad \times \frac{\mu^2 K^2}{(1-a)^2 r^2[\exp(\mu T)-1]^2} \\ &= -\left[\frac{ar}{K} + \frac{r(1-a)[\exp(\mu T)-1][2\exp(\mu T)-1-b]}{\mu K}\right] \\ &\quad \times \frac{\mu^2 K^2}{(1-a)^2 r^2[\exp(\mu T)-1]^2}. \end{aligned}$$

If $\exp(\mu T) > 1+b$, then $q > 0$, $p < 0$. Hence Eq. (4.164) has two negative real solutions. On the other hand, if $\exp(\mu T) < 1+b$, then $q < 0$, which implies that Eq. (4.164) has only one positive solution, N_0^*. Thus, we obtain the following theorem.

Theorem 4.34. *If* $\mathrm{e}^{\mu T} < 1+b$ (*that is*, $\ln(1+b) > \mu T$), *system* (4.160) *has the disease-free periodic solution* $(\tilde{N}(t), 0, 0)$, *where*

$$\tilde{N}(t) = \frac{1}{\left(\frac{1}{N_0^*} + \frac{(1-a)r}{\mu K}\right)\exp[\mu(t-nT)] - \frac{(1-a)r}{\mu K}}, \quad nT < t \le (n+1)T. \tag{4.165}$$

Similarly to the proof of the local stability of period solutions, we have the monodromy matrix

$$M = \begin{pmatrix} 1+b-\frac{2ar}{K}\tilde{S}(t) & b-\frac{2ar}{K}\tilde{S}(t) & b-\frac{2ar}{K}\tilde{S}(t) \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \varphi_{11} & \varphi_{12} & \varphi_{13} \\ 0 & \varphi_{22} & 0 \\ 0 & \varphi_{32} & \varphi_{33} \end{pmatrix},$$

where

$$\varphi_{11} = \exp\left\{-\mu t - \frac{2(1-a)r}{K}\int_0^t \tilde{S}(u)\mathrm{d}u\right\},$$
$$\varphi_{22} = \exp\left\{-(\gamma+\alpha+\mu)t - \left[\frac{(1-a)r}{K}-\beta\right]\int_0^t \tilde{S}(u)\mathrm{d}u\right\},$$
$$\varphi_{33} = \exp\left\{-\mu t - \frac{(1-a)r}{K}\int_0^t \tilde{S}(u)\mathrm{d}u\right\}.$$

Then the eigenvalues of M are

$$\lambda_1 = \left[1+b-\frac{2ar}{K}\tilde{S}(T)\right]\exp\left\{-\mu T - \frac{2(1-a)r}{K}\int_0^T \tilde{S}(u)\mathrm{d}u\right\},$$
$$\lambda_2 = \varphi_{22} = \exp\left\{-(\gamma+\alpha+\mu)T - \left[\frac{(1-a)r}{K}-\beta\right]\int_0^T \tilde{S}(u)\mathrm{d}u\right\},$$
$$\lambda_3 = \varphi_{33} = \exp\left\{-\mu T - \frac{(1-a)r}{K}\int_0^T \tilde{S}(u)\mathrm{d}u\right\} < 1.$$

According to the first equation of (4.160), we have

$$\exp\left\{-\int_0^T \left[\mu + \frac{(1-a)r\tilde{N}(u)}{K}\right]\mathrm{d}u\right\} = \frac{\tilde{N}(T)}{\tilde{N}(0)},$$

and $\tilde{N}(0) = [1+b-ar(\tilde{N}(T))/K]\tilde{N}(T)$, and hence

$$\left[1+b-ar\frac{\tilde{N}(T)}{K}\right]\exp\left\{-\mu T - \frac{(1-a)r}{K}\int_0^T \tilde{N}(u)\mathrm{d}u\right\} = 1. \qquad (4.166)$$

Thus,

$$\begin{aligned}\phi_1 &= \left[1+b-\frac{2ar}{K}\tilde{S}(T)\right]\exp\left\{-\frac{(1-a)r}{K}\int_0^T \tilde{S}(u)\mathrm{d}u\right\}\\ &\quad\times\exp\left\{-\mu T-\frac{(1-a)r}{K}\int_0^T \tilde{S}(u)\mathrm{d}u\right\}\\ &= \frac{1+b-(2ar/K)\tilde{S}(T)}{1+b-ar(\tilde{S}(T)/K)}\exp\left\{-\frac{(1-a)r}{K}\int_0^T \tilde{S}(u)\mathrm{d}u\right\}<1.\end{aligned}$$

Therefore, the disease-free periodic solution $(\tilde{S}(t),0,0)$ is locally stable if and only if $\lambda_2<1$; that is,

$$\frac{[\beta-\frac{(1-a)r}{K}]\int_0^T \tilde{s}(u)\mathrm{d}u}{(\gamma+\alpha+\mu)T}<1.$$

Defining the basic reproductive number for (4.160) by

$$R_0=\frac{[\beta-\frac{(1-a)r}{K}]\int_0^T \tilde{s}(u)\mathrm{d}u}{(\gamma+\alpha+\mu)T},$$

we have following theorem.

Theorem 4.35. *If $R_0<1$, then the disease-free periodic solution $(\tilde{N}(t),0,0)$ of system (4.160) is locally stable.*

To prove the global stability of the disease-free periodic solution $(\tilde{S}(t),0,0)$, we need the following lemma.

Lemma 4.3 [Smith (1986b)]. *Let T: $R_+^n\to R_+^n$ be continuous, C^1 in int(R_+^n), and suppose $DT(0)$ exists with $\lim_{x\to 0^+}DT(x)=DT(0)$. In addition, we assume*

$$\begin{aligned}&\text{(a) } DT(x)>0, \quad \text{if } x>0;\\ &\text{(b) } DT(y)<0, \quad \text{if } 0<x<y.\end{aligned}$$

If $T(0)=0$, let $\lambda=\rho(DT(0))$. When $\lambda\le 1$, then for every $x\ge 0$, $T^n(x)\to 0$, as $n\to\infty$. When $\lambda>1$, then either $T^n(x)\to\infty$, as $n\to\infty$, for every $x>0$ or there exists a unique nonzero fixed point q of T. In the latter case, $q>0$ and for every $x>0$, $T^n(x)\to q$, as $n\to\infty$.

If $T(0)\ne 0$, then either $T^n(x)\to\infty$, as $n\to\infty$, for every $x\ge 0$, or there exists a unique fixed point q of T. In this latter case, $q>0$ and for every $x\ge 0$, $T^n(x)\to q$, as $n\to\infty$.

Theorem 4.36. *If $R_0 < 1$, then the disease-free periodic solution $(\tilde{S}(t), 0, 0)$ of system (4.160) with $\alpha = 0$ is globally asymptotically stable.*

Proof. When $nT < t \le (n+1)T$, Eq. (4.161) becomes

$$N(t) = \frac{1}{\left[\frac{1}{N(nT^+)} + \frac{(1-a)r}{\mu K}\right] \exp[\mu(t-nT)] - \frac{(1-a)r}{\mu K}}, \tag{4.167}$$

and

$$N((n+1)T^+) = \frac{1 + b - (ar/K)\frac{1}{(\frac{1}{N(nT^+)} + \frac{(1-a)r}{\mu K})\exp(\mu T) - \frac{(1-a)r}{\mu K}}}{[N(nT^+) + \frac{(1-a)r}{\mu K}]\exp(\mu T) - \frac{(1-a)r}{\mu K}}. \tag{4.168}$$

For simplicity, we rewrite (4.167)

$$N(t) = \frac{N(nT^+)}{\exp(\mu T) + \frac{(1-a)r}{\mu K}[\exp(\mu T) - 1]N(nT^+)} = \frac{x}{u + vx},$$

where

$$u = \exp(\mu T), \quad v = \frac{(1-a)r}{\mu K}[\exp(\mu T) - 1], \quad x = N(nT^+).$$

Then (4.168) has the form

$$N((n+1)T^+) = \frac{x}{u+vx}\left[1 + b - \frac{arx}{K(u+vx)}\right]. \tag{4.169}$$

To write (4.169) as a map, we define the map

$$F\colon R_+ \to R_+, \text{ by } F(x) = \frac{x}{u+vx}\left[1 + b - \frac{arx}{K(u+vx)}\right].$$

Then simple calculations yield

$$F'(x) = \frac{u}{(u+vx)^2}\left[1 + b - \frac{2arx}{K(u+vx)}\right]\mu x,$$

$$F''(x) = \left\{-\frac{2uv}{(u+vx)^3}\left[1 + b - \frac{2axr}{K(u+vx)}\right] - \frac{2aru^2}{K(u+vx)^4}\right\}\mu x.$$

We note that, in (4.163), when $N_0 \le K$, $N(T) \le K$. Then interval $[0, T]$ is an invariant set for (4.163). It is easy to see that

$1+b-\frac{ar}{K}N(T)\geq 1+b-ar=1+(1-a)b+a\mu>1$. Hence, $1+b-\frac{2ar}{K}x>0$. On the other hand, we have

$$\frac{x}{u+vx}-x=\frac{-[\exp(\mu T)-1]x-\frac{(1-a)r}{\mu K}[\exp(\mu T)-1]x}{\exp(\mu T)+\frac{(1-a)r}{\mu K}[\exp(\mu T)-1]x}<0.$$

From the analysis above, we obtain

$$1+b-\frac{2aru}{K(u+vx)}>1+b-\frac{2ar}{K}x>0.$$

Hence $F'(x)>0, F''(x)<0$. Moreover, from

$$DF(0)=\frac{1+b}{u}=\frac{1+b}{\exp(\mu T)},$$

we see that

$$\rho(DF(0))=\frac{1+b}{\exp(\mu T)}>1.$$

Then, from Lemma 4.3, we have either $F^n(x)\to\infty$, as $n\to\infty$, or there exists a unique nonzero fixed point q (that is, N_0^*) of F. In the latter case, $F^n(x)\to q$ as $n\to\infty$. Now, we need only to prove that the sequence $F^n(x)$ is bounded; that is, every point of F has a bounded orbit.

We already have

$$F(x)=\frac{x}{u+vx}\left[1+b-\frac{arx}{K(u+vx)}\right]<\frac{x}{u+vx}(1+b).$$

Then we consider the following map

$$H\colon[0,+\infty)\to[0,+\infty),\quad H(x)=\frac{(1+b)x}{u+vx}.$$

By simple calculations, we have

$$H'(x)=\frac{u(1+b)}{(u+vx)^2}>0;\quad H''(x)=-\frac{2uv(1+b)}{(u+vx)^3}<0.$$

Denote the fixed point of $H(x)$ by x^*. It is easy to see that

$$x^*=\frac{1+b-u}{v}=\frac{1+b-\exp(\mu T)}{v}>0.$$

Hence, $H(x)>x$, if $0<x<x^*$, and $H(x)<x$, if $x^*<x<+\infty$. Consequently, with the iterations of H, we see that $I=H^n([0,x^*])$ is a compact invariant interval in R_+ into which every point either eventually

enters and stays, or approaches. Moreover, since H is strictly increase, if $0 < x < x^*$, then $0 < H(x) < x^*$, and if $x > \max I = x^*$, then $H(x) < x$. Hence, the sequence $F^n(x)$ is bounded; that is, every point of F has a bounded orbit. From the analysis above, we know that

$$\lim_{n\to\infty} F^n(x) = q = N_0^*; \quad \text{that is, } \lim_{t\to\infty} N(t) = \tilde{N}(t).$$

It follows that, for any positive constant ϵ, there exists $T_1 > 0$, whenever $t > T_1$, $|N(t) - \tilde{N}(t)| < \epsilon$.

Using this inequality, $\tilde{N}(t) - \epsilon < N(t) < \tilde{N}(t) + \epsilon$, and integrating

$$\begin{aligned} I' &= \left[\beta S(t) - \gamma - \alpha - \mu - (1-a)r\frac{N(t)}{K}\right] I(t) \\ &< \left[\beta(\tilde{N}(t) + \epsilon) - \gamma - \alpha - \mu - (1-a)r\frac{\tilde{N}(t) - \epsilon}{K}\right] I, \end{aligned}$$

over interval $[T_1, t]$, we obtain

$$\begin{aligned} I(t) &< I(T_1^+) \exp\left\{ \int_{T_1}^t \left[\beta(\tilde{N}(u) + \epsilon) - \gamma - \alpha - \mu \right.\right. \\ &\quad \left.\left. - (1-a)r\frac{\tilde{N}(u) - \epsilon}{K}\right] \mathrm{d}u \right\} \\ &= I(T_1^+) \exp\left\{ \int_{T_1}^t \left[\beta\tilde{N}(u) - \gamma - \alpha - \mu - \frac{(1-a)r}{K}\tilde{N}(u)\right] \mathrm{d}u \right. \\ &\quad + \left(\left[\frac{t}{T}\right] - \left[\frac{T_1}{T}\right] - 1\right) \\ &\quad \times \int_0^T \left[\beta\tilde{N}(u) - \gamma - \alpha - \mu - \frac{(1-a)r}{K}\tilde{N}(u)\right] \mathrm{d}u \\ &\quad + \int_{[\frac{t}{T}]T}^t \left[\beta\tilde{N}(u) - \gamma - \alpha - \mu - \frac{(1-a)r}{K}\tilde{N}(u)\right] \mathrm{d}u \\ &\quad \left. + \epsilon \int_{T_1}^t \left[\beta + \frac{(1-a)r}{K}\right] \mathrm{d}u \right\} \\ &\leq I(T_1^+) \exp\left\{ \left(\left[\frac{t}{T}\right] - \left[\frac{T_1}{T}\right] - 1\right) \right. \\ &\quad \left. \times \int_0^T \left[\left(\beta - \frac{(1-a)r}{K}\right)\tilde{N}(u) - \gamma - \alpha - \mu\right] \mathrm{d}u \right. \end{aligned}$$

$$
\begin{aligned}
&+2\int_0^T \left[\beta - \frac{(1-a)r}{K}\right]\tilde{N}(u) + \left(\left[\frac{t}{T}\right] - \left[\frac{T_1}{T}\right] + 1\right)\\
&\times \int_0^T \left[\beta + \frac{(1-a)r}{K}\right]\epsilon \mathrm{d}u\Bigg\}\\
&= B\exp\Bigg\{\left(\left[\frac{t}{T}\right] - \left[\frac{T_1}{T}\right] - 1\right)\\
&\times \left[(R_0-1)(\gamma+\alpha+\mu)T + \epsilon\left(\beta + \frac{(1-a)r}{K}\right)T\right]\Bigg\}, \qquad (4.170)
\end{aligned}
$$

where

$$
B = I(T_1^+)\exp\left\{2\int_0^T \left[\beta - \frac{(1-a)r}{K}\right]\tilde{N}(u)\mathrm{d}u + 2\epsilon\left[\beta + \frac{(1-a)r}{K}\right]T\right\}.
$$

Taking

$$
0 < \epsilon \le \frac{(\gamma+\alpha+\mu)(1-R_0)}{2\left[\beta + \frac{(1-a)r}{K}\right]}.
$$

Then B is bounded. Then it follows from (5.8.11) that

$$
\begin{aligned}
I(t) &\le B\exp\left\{\left(\left[\frac{t}{T}\right] - \left[\frac{T_1}{T}\right] - 1\right)(\gamma+\alpha+\mu)T\right.\\
&\left.\times\left[(R_0-1) + \frac{1}{2}(1-R_0)\right]\right\}\\
&= B\exp\left\{\frac{1}{2}\left(\left[\frac{t}{T}\right] - \left[\frac{T_1}{T}\right] - 1\right)(\gamma+\alpha+\mu)T(R_0-1)\right\},
\end{aligned}
$$

which implies that when $R_0 < 1$, $\lim_{t\to\infty} I(t) = 0$.

Similarly, we can prove $R(t) \to 0$ as $t \to \infty$. This completes the proof. □

4.9.2. *Existence of positive T-periodic solutions and bifurcation*

Let $J \subset R$, and denote, by $PC(J,R)$, the set of functions $\psi : J \to R$ which are continuous for $t \in J$, $t \ne nT$, and have discontinuities of the first kind at the points $nT \in J$ where they are continuous from the left. Denote, by $PC'(J,R)$, the set of functions $\psi : J \to R$ with the derivative $(\mathrm{d}\psi/\mathrm{d}t) \in PC(J,R)$. We consider the Banach space of T-periodic functions $PC_T = \{\psi \in PC([0,T],R)|\ \psi(0) = \psi(T)\}$ with the supremum norm

$\|\psi\|_{PC_T} = \sup\{|\psi|: t \in [0,T]\}$, and $PC'_T = \{\psi \in PC'([0,T],R)|\ \psi(0) = \psi(T)\}$ with the supremum norm $\|\psi\|_{PC'_T} = \max\{\|\psi\|_{PC_T}, \|\psi'\|_{PC'_T}\}$. We also consider the product space $PC_T \times PC_T$ which is also a Banach space with the norm $\|(\psi_1,\psi_1)\|_{PC_T} = \|\psi_1\|_{PC_T} + \|\psi_2\|_{PC_T}$. Moreover, for any $f \in C_T$ (or PC_T) we define the average of f by $\bar{f} := (1/T)\int_0^T f(s)\mathrm{d}s$.

We need the following lemmas to study the existence of the positive T-periodic solutions and bifurcation.

Lemma 4.4. *Suppose $c_{ij}(t) \in PC_T$, and*

(1) *If*

$$\bar{c}_{11} \neq \frac{1}{T}\ln\frac{1}{1+b-\frac{2ar}{K}\tilde{N}(nT)}, \quad \bar{c}_{22} \neq 0 \quad \text{and} \quad \bar{c}_{33} \neq 0,$$

then the linear homogeneous periodic impulsive system

$$\begin{aligned}
x_1' &= c_{11}x_1(t) + c_{12}x_2(t), && t \neq nT,\\
x_2' &= c_{22}x_2(t), && n = 0,1,2,\ldots.\\
x_3' &= c_{33}x_3(t) + c_{32}x_2(t),\\
x_1(nT^+) &= \left[1+b-\frac{2ar}{K}\tilde{N}(nT)\right]x_1(nT), \quad t = nT,\\
x_2(nT^+) &= x_2(nT),\\
x_3(nT^+) &= x_3(nT),
\end{aligned} \tag{4.171}$$

has no nontrivial solution in $PC_T \times PC_T \times PC_T$. In this case, the nonhomogeneous system

$$\begin{aligned}
y_1' &= c_{11}y_1(t) + c_{12}y_2(t) + f_1, && t \neq nT,\\
y_2' &= c_{22}y_2(t) + f_2, && n = 0,1,2,\ldots.\\
y_3' &= c_{33}y_3(t) + c_{32}y_2(t) + f_3,\\
y_1(nT^+) &= \left[1+b-\frac{2ar}{K}\tilde{N}(nT)\right]y_1(nT) + g_{nT}, \quad t = nT,\\
y_2(nT^+) &= y_2(nT),\\
y_3(nT^+) &= y_3(nT)
\end{aligned} \tag{4.172}$$

has a unique solution $(y_1,y_2,y_3) \in PC_T \times PC_T \times PC_T$, for every $(f_1,f_2,f_3) \in PC_T \times PC_T \times PC_T$, $g_{nT} \in R$, and $g_{(n+1)T} = g_{nT}$, and the operator L: $PC_T \times PC_T \times PC_T \to PC_T \times PC_T \times PC_T$, defined by $(y_1,y_2,y_3) = L(f_1,f_2,f_3)$, is linear and relatively compact.

(2) *If*

$$\bar{c}_{11} \neq \frac{1}{T} \ln \frac{1}{1 + b - \frac{2ar}{K} \tilde{N}(nT)}, \quad \bar{c}_{22} = 0, \quad \textit{and} \quad \bar{c}_{33} \neq 0,$$

then (4.171) *has exactly one independent solution in* $PC_T \times PC_T \times PC_T$.

Proof. (1) Since

$$x_2(t) = x_2(0) \exp\left\{ \int_0^t c_{22}(s) \mathrm{d}s \right\}, \tag{4.173}$$

the condition $\bar{c}_{22} \neq 0$ implies that $x_2 \notin PC_T$, unless $x_2 \equiv 0$. Then $x_3(t) = x_3(0) \exp\{\int_0^t c_{33}(s) \mathrm{d}s\}$ and $\bar{c}_{33} \neq 0$, in turn, imply that $x_3 \notin PC_T$, unless $x_3 \equiv 0$. Similarly,

$$x_1(t) = x_1(0) \prod_{0 < nT \leq t} \left[1 + b - \frac{2ar}{K} \tilde{N}(nT) \right] \exp\left\{ \int_0^t c_{11}(s) \mathrm{d}s \right\}$$

and

$$\bar{c}_{11} \neq \frac{1}{T} \ln \frac{1}{1 + b - \frac{2ar}{K} \tilde{N}(nT)},$$

in turn, imply $x_1 \notin PC_T$, unless $x_1 \equiv 0$.

In this case, equation $y_2' = c_{22} y_2(t) + f_2$ has a unique solution $y_2(t) \in PC_T$, and the operator L_2: $PC_T \to PC_T$, defined by $y_2 = L_2 f_2$, is linear and relatively compact, and

$$\begin{aligned} y_3' &= c_{33} y_3(t) + f_4, \quad && t \neq nT, \\ y_3(nT^+) &= y_3(nT), && t = nT, \end{aligned}$$

for $f_4 = c_{32} L_2 f_2 + f_3 \in PC_T$, has a unique solution (since $\bar{c}_{33} \neq 0$) in PC_T and L_3: $PC_T \to PC_T$. Furthermore,

$$\begin{aligned} y_1' &= c_{11} y_1(t) + f_5, \quad && t \neq nT, \\ y_1(nT^+) &= \left[1 + b - \frac{2ar}{K} \tilde{N}(nT) \right] y_1(nT) + g_{nT}, && t = nT, \end{aligned}$$

for $f_5 = c_{12} L_2 f_2 + f_1 \in PC_T$, has a unique solution (since $\bar{c}_{11} \neq \frac{1}{T} \ln[1 + b - \frac{2ar}{K} \tilde{N}(nT)]$) in PC_T, and $y_1 = L_1 f_5$ defines a linear, relatively compact operator $L_1 : PC_T \to PC_T$. Thus (4.172) has a unique T-period solution

in $PC_T \times PC_T \times PC_T$, given by $(y_1, y_2, y_3) = L(f_1, f_2, f_3)$, where

$$L(f_1, f_2, f_3) = (L_1(c_{12}L_2f_2) + f_1, L_2f_2, L_3(c_{32}L_2f_2) + f_3). \tag{4.174}$$

(2) Under the stated assumptions, x_2, as given in (4.173), lies in PC_T for the initial condition $x_2(0)$. If $\bar{c}_{33} \neq 0$, then

$$\begin{aligned} x_3' &= c_{33}x_3(t) + c_{32}x_2(0)\exp\left\{\int_0^t c_{22}(s)\mathrm{d}s\right\}, && t \neq nT, \\ x_3(nT^+) &= x_3(nT), && t = nT, \end{aligned}$$

has a unique solution $\hat{x}_3(t)$. Now if

$$\bar{c}_{11} \neq \frac{1}{T}\ln\left[1 + b - \frac{2ar}{K}\tilde{N}(nT)\right],$$

then $x_1' = c_{11}x_1(t)$ has no nontrivial solution in PC_T and, hence

$$\begin{aligned} x_1' &= c_{11}x_1(t) + c_{12}x_2(0)\exp\left\{\int_0^t c_{22}(s)\mathrm{d}s\right\}, && t \neq nT, \\ x_1(nT^+) &= \left[1 + b - \frac{2ar}{K}\tilde{N}(nT)\right]x_1(nT), && t = nT, \end{aligned}$$

has a unique solution in PC_T. □

Lemma 4.5 [Lakshmikantham *et al.* (1989)]. *Suppose $a \in PC_T$ and $\bar{a} = (1/T)\ln\left[\prod_{n=1}^{q}\frac{1}{1+c_n}\right]$. Then*

$$\begin{aligned} z' &= az + f, && t \neq nT, \\ z(nT^+) &= (1 + c_n)z(nT), && t = nT, \end{aligned}$$

has a solution $z \in PC_T$, if and only if

$$\int_0^T \prod_{0 \leq nT < t} \frac{1}{1 + c_n}\exp\left\{\left[-\int_0^t a(u)\mathrm{d}u\right]f\right\}\mathrm{d}t = 0. \tag{4.175}$$

For the existence of positive periodic solution, we have the following theorem.

Theorem 4.37. *Suppose that there exists a constant $\epsilon_0 > 0$, which is sufficiently small, such that*

$$\gamma + \alpha + \mu < \beta\tilde{\tilde{N}}(t) - \frac{(1-a)r}{K}\tilde{\tilde{N}}(t) < \gamma + \alpha + \mu + \epsilon_0.$$

Then, there exists a solution $(N(t), I(t), R(t)) \in PC_T \times PC_T \times PC_T$ *of* (4.160), *satisfying* $N(t) < \widetilde{N}(t), I(t) > 0, R(t) > 0$ *for all* t.

Proof. Let $u_1 = N(t) - \widetilde{N}(t)$, $u_2 = I(t)$ and $u_3 = R(t)$ in (4.160) and (4.161), respectively. Then we have

$$\begin{aligned}
u_1' &= -\left[\mu + \frac{2r(1-a)\widetilde{N}}{K}\right] u_1 - \alpha u_2 + h_1(u_1, u_2, u_3), && t \neq nT,\\
u_2' &= \left[\beta\widetilde{N} - (\gamma + \alpha + \mu) - \frac{(1-a)r\widetilde{N}}{K}\right] u_2 + h_2(u_1, u_2, u_3),\\
u_3' &= \gamma u_2 - \left[\mu + \frac{r(1-a)\widetilde{N}}{K}\right] u_3 + h_3(u_1, u_2, u_3),\\
u_1(nT^+) &= \left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] u_1(nT) + l_{nT}, && t = nT,\\
u_2(nT^+) &= u_2(nT),\\
u_3(nT^+) &= u_3(nT),
\end{aligned} \tag{4.176}$$

where

$$\begin{aligned}
h_1(u_1, u_2, u_3) &= -\frac{(1-a)r}{K} u_1^2,\\
h_2(u_1, u_2, u_3) &= \beta(u_1 - u_2 - u_3)u_2 - \frac{(1-a)r}{K} u_1 u_2,\\
h_3(u_1, u_2, u_3) &= -\frac{(1-a)r}{K} u_1 u_3,
\end{aligned}$$

and

$$l_{nT} = -\frac{ar}{K} u_1^2(nT).$$

Define

$$\theta(t) = \beta\widetilde{N} - \frac{(1-a)r}{K}\widetilde{N} - p \quad \text{and} \quad p = \beta\bar{\widetilde{N}} - \frac{(1-a)r}{K}\bar{\widetilde{N}}.$$

Then

$$\beta\widetilde{N} - \frac{(1-a)r}{K}\widetilde{N} = \theta(t) + p, \quad \bar{\theta}(t) = 0,$$

and thus (4.176) becomes

$$\begin{aligned}
u_1' &= -\left[\mu + \frac{2r(1-a)\widetilde{N}}{K}\right] u_1 - \alpha u_2 + h_1(u_1,u_2,u_3), \quad t \neq nT,\\
u_2' &= [\theta(t) - (\gamma+\alpha+\mu)]\, u_2 + p u_2 + h_2(u_1,u_2,u_3),\\
u_3' &= \gamma u_2 - \left[\mu + \frac{r(1-a)\widetilde{N}}{K}\right] u_3 + h_3(u_1,u_2,u_3),\\
u_1(nT^+) &= \left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] u_1(nT) + l_{nT}, \qquad t = nT,\\
u_2(nT^+) &= u_2(nT),\\
u_3(nT^+) &= u_3(nT).
\end{aligned} \tag{4.177}$$

Now consider the linear homogeneous system

$$\begin{aligned}
v_1' &= -\left[\mu + \frac{2r(1-a)\widetilde{N}}{K}\right] v_1 - \alpha v_2, \quad t \neq nT,\\
v_2' &= [\theta(t) - (\gamma+\alpha+\mu)]\, v_2,\\
v_3' &= \gamma v_2 - \left[\mu + \frac{r(1-a)\widetilde{N}}{K}\right] v_3,\\
v_1(nT^+) &= \left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] v_1(nT), \qquad t = nT,\\
v_2(nT^+) &= v_2(nT),\\
v_3(nT^+) &= v_3(nT).
\end{aligned} \tag{4.178}$$

Note that

$$\begin{aligned}
\bar{c}_{22} &= \bar{\theta}(t) - (\gamma+\alpha+\mu) = -(\gamma+\alpha+\mu) \neq 0,\\
\bar{c}_{33} &= -\mu - (1-a)\frac{r}{K}\bar{\widetilde{N}}(t) < 0,\\
\bar{c}_{11} &= -\mu - 2(1-a)\frac{r}{K}\bar{\widetilde{N}}(t) < \frac{1}{T}\ln\frac{1}{1+b-(2ar/K)\widetilde{N}(nT)},
\end{aligned}$$

and hence (4.178) satisfies the hypotheses part (1) of Lemma 4.4. Consequently, we have the compact linear operator L: $PC_T \times PC_T \times PC_T \to$

$PC_T \times PC_T \times PC_T$, given by (4.174). Using L, we can equivalently write system (4.177) as the operator equation

$$(u_1, u_2, u_3) = pL^*(u_1, u_2, u_3) + G(u_1, u_2, u_3), \tag{4.179}$$

with

$$L^*(u_1, u_2, u_3) = (L_1(-\alpha L_2 u_2), L_2 u_2, L_3(\gamma L_2 u_2)),$$
$$G(u_1, u_2, u_3) = (L_1(-\alpha L_2 h_2 + h_1, L_2 h_2, L_3(\gamma L_2 h_2 + h_3)),$$

where L^*: $PC_T \times PC_T \times PC_T \to PC_T \times PC_T \times PC_T$ is linear and relatively compact, and $G : PC_T \times PC_T \times PC_T \to PC_T \times PC_T \times PC_T$ is quasiequicontinuous and relatively compact and satisfies $G = o(\|(u_1, u_2, u_3)\|_{PC_T})$ near $(0, 0, 0)$. The operator equation (4.179) is consequently of the type to which standard bifurcation theorems and techniques can be applied.

A nontrivial solution $(u_1, u_2, u_3) \neq (0, 0, 0)$ of (4.179) in $PC_T \times PC_T \times PC_T$, for some $p \in R$ (R is the set of the reals) gives a solution $(N, I, R) = (u_1 + \widetilde{N}, u_2, u_3)$ of systems (4.160) and (4.161) for $p = \beta\widetilde{\widetilde{N}} - \frac{(1-a)r}{K}\widetilde{\widetilde{N}}$. Solution $(N, I, R) \neq (\widetilde{N}(t), 0, 0)$ is called nontrivial solution of (4.160).

To prove Theorem 4.37, we apply the well-known local bifurcation techniques to (4.179). As is well known [Rabinowitz (1971)], bifurcation can occur only at the nontrivial solutions of the linearized problem

$$(v_1, v_2, v_3) = pL^*(v_1, v_2, v_3), \quad (v_1, v_2, v_3) \neq (0, 0, 0), \quad p \in R. \tag{4.180}$$

If $(v_1, v_2, v_3) \in PC_T \times PC_T \times PC_T$ is a solution of (4.180) for some $p \in R$, then, as long as L^* is defined, (v_1, v_2, v_3) satisfies the system

$$\begin{aligned}
v_1' &= -\left[\mu + \frac{2r(1-a)\widetilde{N}}{K}\right] v_1 - \alpha v_2, \quad t \neq nT, \\
v_2' &= [\theta(t) + p - (\gamma + \alpha + \mu)]\, v_2, \\
v_3' &= \gamma v_2 - \left[\mu + \frac{r(1-a)\widetilde{N}}{K}\right] v_3, \\
v_1(nT^+) &= \left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] v_1(nT), \quad t = nT, \\
v_2(nT^+) &= v_2(nT), \\
v_3(nT^+) &= v_3(nT),
\end{aligned} \tag{4.181}$$

and conversely, using Lemma 4.4 above, we see that (4.181), and hence (4.180), has a nontrivial solution in $PC_T \times PC_T \times PC_T$, if and only if $p = p^*$, where $p^* = \gamma + \alpha + \mu$. If $p = p^*$, then, by part (2) of Lemma 4.4, (4.181) has one independent solution in $PC_T \times PC_T \times PC_T$. A well-known result by Smith (1986b), Bainov and Simeonov (1995), and Shulgin *et al.* (1998) implies that a bifurcation occurs at this simple eigenvalue. Hence, there exists a continuum $U = \{(p, u_1, u_2, u_3)\} \subseteq R \times PC_T \times PC_T \times PC_T$ of nontrivial solutions of (4.179), such that the closure $\bar{U}$ of U contains $(p^*, 0, 0, 0)$. This continuum gives rise to a continuum $C = \{(p; N, I, R)\} \subseteq R \times PC_T \times PC_T \times PC_T$ of nontrivial solutions of (4.160) whose closure $\bar{C}$ contains the bifurcation point $(p^*; \widetilde{N}(t), 0, 0)$.

To see the solution in C corresponds to the solution (N, I, R) of (4.160) and (4.161) with the properties described in Theorem 4.37, we investigate the nature of the continuum C near the bifurcation point $(p^*, 0, 0)$, by expanding p and (u_1, u_2, u_3) into the Liapunov–Schmidt series (for small ε) (see [Vainberg and Trenogrn (1962)]):

$$p = p^* + p_1\varepsilon + \cdots, \quad u_i = u_{i1}\varepsilon + u_{i2}\varepsilon^2 + \cdots, \quad i = 1, 2, 3,$$

for $u_{ij} \in PC_T$. We substitute these series into the differential system (4.177) and equate the coefficients of ε and ε^2, respectively. Then we obtain

$$\begin{aligned}
u'_{11} &= -\left[\mu + \frac{2r(1-a)\widetilde{N}}{K}\right] u_{11} - \alpha u_{21}, \quad t \neq nT, \\
u'_{21} &= [\theta(t) + p^* - (\gamma + \alpha + \mu)]\, u_{21}, \\
u'_{31} &= \gamma u_{21} - \left[\mu + \frac{r(1-a)\widetilde{N}}{K}\right] u_{31}, \\
u_{11}(nT^+) &= \left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] u_{11}(nT), \qquad t = nT, \\
u_{21}(nT^+) &= u_{21}(nT), \\
u_{31}(nT^+) &= u_{31}(nT),
\end{aligned} \tag{4.182}$$

and

$$\begin{aligned}
u'_{12} &= -\left[\mu + \frac{2r(1-a)\widetilde{N}}{K}\right] u_{12} - \alpha u_{22} + \hat{h}_1(u_1, u_2, u_3), \quad t \neq nT, \\
u'_{22} &= [\theta(t) - (\gamma + \alpha + \mu)]u_{22} + p^* u_{22} + p_1 u_{21} + \hat{h}_2(u_1, u_2, u_3),
\end{aligned}$$

$$
\begin{aligned}
u'_{32} &= \gamma u_{22} - \left[\mu + \frac{r(1-a)\widetilde{N}}{K}\right] u_{32} + \hat{h}_3(u_1, u_2, u_3),\\
u_{12}(nT^+) &= \left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] u_{12}(nT) + \hat{l}_{nT}, \qquad t = nT,\\
u_{22}(nT^+) &= u_{22}(nT),\\
u_{32}(nT^+) &= u_{32}(nT),
\end{aligned}
\tag{4.183}
$$

where

$$
\begin{aligned}
\hat{h}_1(u_1, u_2, u_3) &= -\frac{(1-a)r}{K} u_{11}^2,\\
\hat{h}_2(u_1, u_2, u_3) &= \beta(u_{11} - u_{21} - u_{31})u_{21} - \frac{(1-a)r}{K} u_{11}u_{21},\\
\hat{h}_3(u_1, u_2, u_3) &= -\frac{(1-a)r}{K} u_{11}u_{31},
\end{aligned}
$$

and

$$
\hat{l}_{nT} = -\frac{ar}{K} u_{11}^2(nT).
$$

Thus $(u_{11}, u_{21}, u_{31}) \in PC_T \times PC_T \times PC_T$ must be a solution of (4.181).

We choose a specific solution satisfying the initial condition $u_{21}(0) = 1$. Then

$$
u_{21}(t) = \exp\left\{\int_0^t [\theta(s) + p^* - (\gamma + \alpha + \mu)]\mathrm{d}s\right\} > 0.
$$

Function $u_{31}(t)$ is the T-periodic solution of the linear equation

$$
\begin{aligned}
u'_{31} &= \gamma u_{21} - \left[\mu + (1-a)\frac{r\widetilde{N}}{K}\right] u_{31}, \quad t \neq nT,\\
u_{31}(nT^+) &= u_{31}(nT), \qquad\qquad\qquad\qquad\quad t = nT.
\end{aligned}
$$

Hence, $u_{31} = \int_0^T G(t,s)\gamma u_{21}(s)ds$, where $G(t,s)$ is a Green's function, given by

$$
G(t,s) = \begin{cases}
X(t)(1 - X(T))^{-1}/X(s), & 0 \le s \le t \le T,\\
X(t+T)(1 - X(T))^{-1}/X(s), & 0 \le t \le s \le T,\\
G(t - kT, s - jT), \quad kT < t \le (k+1)T, & jT < s \le (j+1)T,
\end{cases}
$$

where

$$X(t) = \exp\left\{\int_0^t \left[-\mu - (1-a)\frac{r\widetilde{N}(s)}{K}\right] \mathrm{d}s\right\} > 0.$$

Note that $u_{21} > 0$, for all t, and also since $X(T) = \exp\{\int_0^T [-\mu - (1 - a)\frac{r\widetilde{N}(s)}{K}]ds\} < 1$, we see that the Green's function $G(t, s) > 0$. Hence $u_{31} > 0$, for all t. Moreover, $u_{11}(t)$ is the T-periodic solution of the linear equation

$$u_{11}' = -\left[\mu + \frac{2(1-a)r\widetilde{N}}{K}\right] u_{11} - \alpha u_{21}, \quad t \neq nT,$$

$$u_{11}(nT^+) = \left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] u_{11}(nT), \qquad t = nT.$$

Hence, $u_{11} = -\int_0^T G(t, s)\alpha u_{21}(s)\mathrm{d}s$, and

$$\begin{aligned} X(t) = &\left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] \\ &\times \exp\left\{\int_0^t \left[-\mu - \frac{2(1-a)r\widetilde{N}(s)}{K}\right] \mathrm{d}s\right\} > 0, \\ X(T) = &\left[1 + b - \frac{2ar\widetilde{N}(nT)}{K}\right] \\ &\times \exp\left\{\int_0^T \left[-\mu - \frac{2(1-a)r\widetilde{N}(s)}{K}\right] \mathrm{d}s\right\} < 1. \end{aligned}$$

Then we have $u_{11} < 0$ for all t.

Applying Lemma 4.5 to the second equation of (4.183), we obtain

$$\begin{aligned} p_1 &= \frac{(1-a)r}{K}\bar{u}_{11} - \beta(\bar{u}_{11} - \bar{u}_{21} - \bar{u}_{31}) \\ &= \left[\frac{(1-a)r}{K} - \beta\right] \bar{u}_{11} + \beta(\bar{u}_{21} + \bar{u}_{31}) > 0. \end{aligned}$$

Thus, there exists a branch $C^+ = \{(p; u_1, u_2, u_3)\} \subseteq R \times PC_T \times PC_T \times PC_T$, where $p^* < p$, $u_1(t) < 0$, $u_2(t) > 0$, $u_3(t) > 0$, for all t, which corresponds to positive periodic solutions of (4.160), for p close to p^*. Therefore, there

exists a sufficiently small constant $\epsilon_0 > 0$, where $p^* < p < p^* + \epsilon_0$, such that we have the piecewise continuous branch U^+ of solutions of the from $(p; N, I, R) \in R \times PC_T \times PC_T \times PC_T$, satisfying $N(t) < \widetilde{N}(t)$, $I(t) > 0$, $R(t) > 0$, for all t. Since $p^* < p < p^* + \epsilon_0$ is equivalent to

$$\gamma + \alpha + \mu < \beta\widetilde{\widetilde{N}}(t) - \frac{(1-a)r}{K}\widetilde{\widetilde{N}}(t) < \gamma + \alpha + \mu + \epsilon_0, \quad R_0 \to 1^+.$$

Thus, we complete the proof of Theorem 4.37. □

4.10. SI Epidemic Model with Birth Pulses and Seasonality

In this section, we investigate the effect of birth pulses and seasonal prevention.

The following model is formulated and studied by Gao *et al.* (2005):

$$\begin{aligned} \dot{S}(t) &= B(N(t))S(t) + (1-k)B(N(t))I(t) - \beta\frac{S(t)I(t)}{N(t)} - \mu S(t), \\ \dot{I}(t) &= kB(N(t))I(t) + \beta\frac{S(t)I(t)}{N(t)} - \mu I(t), \\ \dot{N}(t) &= B(N(t))N(t) - \mu N(t), \end{aligned} \tag{4.184}$$

where $\mu > 0$ is the death rate constant, k, $0 < k < 1$, is the proportion of the infected offspring born vertically from infectives, and $B(N)N$ is a birth rate function with $B(N)$ satisfying the following basic assumptions, for $N \in (0, \infty)$:

(A_1) $B(N) > 0$;
(A_2) $B(N)$ is continuously differentiable with $B'(N) < 0$;
(A_3) $B(0^+) > \mu > B(\infty)$.

Assumptions (A_2) and (A_3) imply that $B^-(N)$ exists for $N \in (B(\infty), B(0^+))$, where B^- denotes the inverse function of B, and (A_3) implies the existence of a carrying capacity K such that $B(N) > \mu$, for $N < K$, and $B(N) < \mu$, for $N > K$.

Under these assumptions, nontrivial solutions of $\dot{N}(t) = B(N(t))N(t) - \mu N(t)$ approach the unique positive equilibrium $N^* = K = B^-(\mu)$, as $t \to \infty$. Examples of birth functions $B(N)$ in the biological literature, that

satisfy (A_1)–(A_3), are:

(B_1) $B_1(N) = be^{-N}$, with $b > \mu$;
(B_2) $B_2(N) = b/(c + N^n)$, with $b, c, n > 0$ and $(b/c) > \mu$;
(B_3) $B_3(N) = (A/N) + a$, with $A, \mu > a > 0$.

Functions B_1 and B_2 with $n = 1$ are used in fisheries, and are known as the Ricker function and Beverton–Holt function, respectively. Function $B_3(N)N$ represents a constant immigration rate A together with a linear birth term aN.

Let $i = I/N$. System (4.184) becomes

$$\begin{aligned} \dot{N}(t) &= [B(N(t)) - \mu]N(t), \\ \dot{i}(t) &= -(1-k)B(N(t))i(t) + \beta(1 - i(t))i(t). \end{aligned} \tag{4.185}$$

Using the similar methods as in [Jin (2001); Zhou and Liu (2003); Lu *et al.* (2002)], we investigate the dynamics of model (4.185) as follows.

Denote

$$\bar{R}_0 = \frac{kB(K) + \beta}{\mu}, \ (B(K) = \mu), \quad \bar{R}_1 = \frac{kB(0) + \beta}{B(0)},$$

where $\bar{R}_0$ is the basic reproductive number. Model (4.185) has the following four steady states:

(1) $N = i = 0$ (the trivial steady-state, which is always unstable).
(2) $N = K$, $i = 0$ (the disease-free steady-state, which is globally stale if $\bar{R}_0 < 1$).
(3) $N = 0$, $i = \bar{i} = 1 - ((1-k)B(0))/\beta$ (the host-extinction steady-state, which exists when $\bar{R}_1 > 1$, and is always unstable).
(4) $N = N^*$, $i = i^*$; $0 < N^* < K$, $0 < i^* < 1$ (the endemic steady state, which exists and is stable if $\bar{R}_0 > 1$ and $\bar{R}_1 < 1$, where (N^*, i^*) is the unique nontrivial solution of model (4.185) with $\dot{N}(t) = \dot{i}(t) = 0$).

4.10.1. *Existence and local stability of disease-free periodic solution*

Suppose that the reproduction takes place in a relatively short period each year, the population decreases in between these pulses of growth, a single annual birth pulse $B(N)$ in (4.185) is set to zero. We also suppose that the host population density $N(t)$ is increased by an amount $B(N)N$ whenever t has an integer value. From a biological point of view, it is reasonable that

the host population can persist in the absence of disease and it is regulated to a finite density. We further suppose $B'(N) \leq 0$ and make the following assumptions:

(H_1) $\ln(1 + B(0)) > \mu$;
(H_2) $\lim_{N\to\infty} \ln(1 + B(N)) < \mu$.

Since some infectious diseases may have different highly-infectious season, we assume that the infectious disease has high infection from T_1 to T_2 $(0 \leq T_1 < T_2 \leq 1)$ every year, and consider the following model for the transmission dynamics of a disease in a host population with pulse births

$$\begin{aligned} \dot{N}(t) &= -\mu N(t), \quad m \leq t < m+1, \\ \dot{i}(t) &= \begin{cases} \beta_1(1-i(t))i(t), & m \leq t < m+T_1, \\ \beta_1^*(1-i(t))i(t), & m+T_1 \leq t \leq m+T_2, \\ \beta_1(1-i(t))i(t), & m+T_2 \leq t < m+1, \end{cases} \\ N(m^+) &= (1+B(N(m)))N(m), \\ i(m^+) &= \frac{1+kB(N(m))}{1+B(N(m))}i(m), \end{aligned} \tag{4.186}$$

where m is an integer, $\beta_1 > 0$ and $\beta_1^* > 0$ are the infective rates of the disease in not a highly-infectious and a highly-infectious season, respectively.

If we further consider the effects of seasonal prevention in (4.184), we have the following SI model with birth pulse and seasonal prevention:

$$\begin{aligned} \dot{N}(t) &= -\mu N(t), \quad m \leq t < m+1, \\ \dot{i}(t) &= \begin{cases} \beta_1(1-i(t))i(t), & m \leq t < m+T_1, \\ \beta_2(1-i(t))i(t), & m+T_1 \leq t \leq m+T_2, \\ \beta_1(1-i(t))i(t), & m+T_2 \leq t < m+1, \end{cases} \\ N(m^+) &= (1+B(N(m)))N(m), \\ i(m^+) &= \frac{1+kB(N(m))}{1+B(N(m))}i(m), \end{aligned} \tag{4.187}$$

where β_2 is the infective rate in highly-infectious season due to the seasonal prevention. We assume $\beta_2^* > \beta_2$.

To investigate periodic solutions of period 1, period-doubling bifurcations, and chaotic behavior of system (4.187), we consider the special case with a Ricker function and deduce a stroboscopic map.

Integrating the first four equations of (4.187) and taking $B(N)$ as the form of a Ricker function, we obtain the following stroboscopic map:

$$\begin{aligned} N_{m+1} &= pN_m(1 + b\mathrm{e}^{-pN_m}), \\ i_{m+1} &= \frac{1 + kb\mathrm{e}^{-pN_m}}{1 + b\mathrm{e}^{-pN_m}} \frac{i_m}{(1-q)i_m + q}, \end{aligned} \tag{4.188}$$

where

$$p \doteq \mathrm{e}^{-\mu}, \quad q \doteq \exp[-\beta_1 + (\beta_1 - \beta_2)(T_2 - T_1)].$$

The assumption (H_2) holds and (H_1) leads to $bp/(1-p) > 1$, that is, $(1+b)\mathrm{e}^{-\mu} > 1$.

Define

$$R_0 = \frac{k+p}{q+kp}, \quad R_1 = \frac{1+kb}{q(1+b)}.$$

The dynamics behavior of system (4.188), coupled with (4.187), determine the dynamic behaviors of system (4.186).

System (4.188) has boundary equilibria $E_0 = (0,0)$, $E_{10} = (N^*, 0)$, and $E_{20} = (0, \bar{i})$, if $R_1 > 1$, and positive equilibrium $E^* = (N^*, i^*)$, if $R_0 > 1$, where

$$\bar{i} = \frac{1 + kb - q(1+b)}{(1+b)(1-q)}, \quad N^* = \frac{1}{p} \ln \frac{bp}{1-p}, \quad i^* = \frac{k + p - kp - q}{1-q}.$$

Using Jury criterion [Jury (1974)], it is easy to obtain the stability of E_0, E_{10}, E_{20}, and E^*, and all of the results are given in the following table:

Equilibria	Existence conditions	Stability conditions
E_0	Always existent	Always unstable
E_{10}	Always existent	$R_0 < 1$ and $b < b_\mathrm{c}$
E_{20}	$R_1 > 1$	Always unstable
E^*	$R_0 > 1$	$R_0 > 1$ and $b < b_\mathrm{c}$

Note that assumption (H_1) implies that E_0 and E_{20} are unstable, which ensure that the host population can not go to extinction. In the following, the existence and stability of positive equilibrium E^* are proved.

Theorem 4.38 [Gao *et al.* (2005)]. *Suppose* $R_0 > 1$ *and*

$$b < b_{\mathrm{c}} \doteq \frac{1-p}{p}\mathrm{e}^{\frac{2}{1-p}}. \tag{4.189}$$

Then system (4.188) *has a unique positive equilibrium, which is locally asymptotically stable.*

Proof. If system (4.188) has a positive equilibrium, it must satisfy

$$\begin{aligned} N^* &= pN^*(1 + b\mathrm{e}^{-pN^*}), \\ i^* &= \frac{1 + kb\mathrm{e}^{-pN^*}}{1 + b\mathrm{e}^{-pN^*}} \frac{i^*}{(1-q)i^* + q}. \end{aligned}$$

By simple calculation, if $R_0 > 1$, there exists a unique equilibrium $E^*(N^*, i^*)$, where

$$N^* = \frac{1}{p} \ln \frac{bp}{1-p}, \quad i^* = \frac{k + p - kp - q}{1-q}.$$

In the neighborhood of $(N, i) = (N^*, i^*)$, the dynamics of system (4.189) are determined by the linearization

$$X_{m+1} = BX_m$$

with

$$B = \begin{pmatrix} 1 - p(1-p)N^* & 0 \\ \Delta & \dfrac{q}{k + p - kp}, \end{pmatrix}$$

and $X = (N, i)$. There is no need to calculate the exact form of Δ as it is not required in the analysis. E^* is stable when the eigenvalues of B are less than one in magnitude. This holds only when B satisfies the three Jury conditions [Jury (1974)]:

$$\begin{aligned} 1 - \operatorname{tr} B + \det B &= p(1-p)N^* \left(1 - \frac{q}{k + p - kp}\right) > 0, \\ 1 + \operatorname{tr} B + \det B &= \left[2 - (1-p) \ln \frac{bp}{1-p}\right] \left(1 + \frac{q}{k + p - kp}\right) > 0, \\ 1 - \det B &= 1 - \frac{q}{k + p - kp} + \frac{(1-p)q}{k + p - kp} \ln \frac{bp}{1-p} > 0. \end{aligned}$$

It can be shown that the first and third inequalities are always satisfied, and that as b increases, the second inequality is violated at a critical point b_c. □

4.10.2. *Bifurcation analysis*

In the following, the changes of the numbers of equilibria and their stability as parameter b changes are investigated. Since R_0 has no relation with b, we fix $R_0 > 1$. Then equilibrium E_{10} is always unstable. $R_1 = 1$ is equivalent to

$$b = b_0 \doteq \frac{1-q}{q-k} \quad (q > k). \tag{4.190}$$

Note that if $b < b_0$ (that is, $R_1 > 1$), equilibrium E_{20} is always unstable. As b increases through b_0, E^* remains stable until b reaches another critical point $b = b_c$. A flip bifurcation results and the positive equilibrium loses stability to a stable two-cycle. As b increases beyond b_c, it passes through a series of bifurcations that eventually leads to chaotic dynamics. (See [Gao *et al.* (2005)] for detailed numeric simulations and analysis.)

The relationship between the solutions of system (4.186) and system (4.188) is illustrated as follows:

(i) The fixed points of the stroboscopic map correspond to the periodic solutions having the same period as the pulsing term.
(ii) The periodic points with period k of the stroboscopic map correspond to the entrained periodic solutions having exactly k times the period of the pulsing, which is often called subharmonic periodic solutions or subharmonic period k's.
(iii) The invariant circles correspond to the quasi-periodic solutions, tori T^2 for the original system of impulsive differential equations.
(iv) Possibly chaotic attractors correspond to strange attractors.

In the following, we show that the solutions of system (4.188) behave like the above three cases ((i), (ii), (iv)).

The trivial solution, $N(t) = i(t) = 0$, always exists and is unstable for all parameter values. If $R_0 < 1$ and $b < b_c$, the equilibrium E_{10} is stable. In this case, trajectories of model (4.188) approach the periodic solution

$E_{10}^*(t) = (N_p^*(t), 0)$ with period 1, where

$$N_p^*(t) = N^* \mathrm{e}^{-\mu(t-m)}, \quad m < t \le m+1,$$

with

$$N^* = \frac{1}{p} \ln \frac{bp}{1-p}.$$

That is, periodic solution $(N_p^*(t), 0)$ of system (4.188) is locally asymptotically stable.

If $R_1 > 1$, the equilibrium $E_{20} = (0, \bar{i})$ exists and is always unstable. In this case, the periodic solution of $(0, \bar{i}_p(t))$ of system (4.188) is unstable, where

$$\bar{i}_p(t) = \begin{cases} \dfrac{\bar{i}}{\bar{i} + (1-\bar{i}) \exp[-\beta_1(t-m)]}, & m \le t < m+T_1, \\ \dfrac{\bar{i}}{\bar{i} + (1-\bar{i}) \exp[-\beta_2(t-m) - (\beta_1 - \beta_2)T_1]}, & m+T_1 \le t < m+T_2, \\ \dfrac{\bar{i}}{\bar{i} + (1-\bar{i}) \exp[-\beta_1(t-m) + (\beta_1 - \beta_2)(T_2 - T_1)]}, & m+T_2 \le t < m+1. \end{cases}$$

If $R_0 > 1$, $R_1 < 1$, and $b < b_{\mathrm{c}}$, the positive equilibrium E^* exists and is stable. In this case, trajectories of system (4.188) approach the periodic solution $E_p^*(t) = (N_p^*(t), i_p^*(t))$ with period 1, where

$$N_p^*(t) = N^* \mathrm{e}^{-\mu(t-m)}, \quad m < t \le m+1,$$

$$i_p^*(t) = \begin{cases} \dfrac{i^*}{i^* + (1-i^*) \exp[-\beta_1(t-m)]}, & m \le t < m+T_1, \\ \dfrac{i^*}{i^* + (1-i^*) \exp[-\beta_2(t-m) - (\beta_1 - \beta_2)T_1]}, & m+T_1 \le t < m+T_2, \\ \dfrac{i^*}{i^* + (1-i^*) \exp[-\beta_1(t-m) + (\beta_1 - \beta_2)(T_2 - T_1)]}, & m+T_2 \le t < m+1. \end{cases}$$

That is, the periodic solution (4.186) of model (4.188) is locally asymptotically stable.

4.10.3. *Global stability of disease-free periodic solution*

In this section, we study the global stability of disease-free periodic solution $(N_p^*(t), 0)$.

Theorem 4.39 [Gao *et al.* (2005)]. *Assume* $R_0 < 1$, $b < b_c$, *and*

$$k + \frac{1-k}{1 + b(\frac{1-p}{bp})^{\frac{1}{p}}} < q. \tag{4.191}$$

Then the disease-free periodic solution $(N_p^*(t), 0)$ *of system* (4.186) *is globally asymptotically stable.*

Proof. Since $R_0 < 1$ and $b < b_c$, system (4.188) determined by (4.186) has an equilibrium $(N^*, 0)$, which is locally asymptotically stable. Then the corresponding periodic solution $(N_p^*(t), 0)$ is locally asymptotically stable.

From system (4.186), we have

$$\begin{aligned} \dot{N}(t) &= -\mu N(t), && t \neq m \in N, \\ N(m^+) &= (1 + b\mathrm{e}^{-N(m)})N(m). \end{aligned} \tag{4.192}$$

Solving the first equation of system (4.192) between pulses yields

$$N(t) = N_m \mathrm{e}^{-\mu(t-m)}, \quad m < t \leq m + 1.$$

Then

$$N_{m+1} = pN_m(1 + p\mathrm{e}^{-pN_m}) \doteq g(N_m), \tag{4.193}$$

where $g(N) = pN(1 + b\mathrm{e}^{-pN})$. It is easy to see that system (4.193) has unique positive equilibrium $N^* = (1/p)\ln(bp)/(1-p)$, which satisfies $g(N) > N$, if $0 \leq N < N^*$, and $g(N) < N$, if $N > N^*$. It follows from the results in Cull (1981), N^* is global asymptotically stable. Hence, the corresponding periodic solution of system (4.192)

$$N_p^*(t) = N^* \mathrm{e}^{-\mu(t-m)}, \quad m < t \leq m + 1,$$

is globally asymptotically stable.

From condition (4.191), we choose $\epsilon > 0$ sufficient small such that

$$\gamma \doteq k + \frac{1-k}{1 + b\mathrm{e}^{-\epsilon}(\frac{1-p}{bp})^{(1/p)}} < q. \tag{4.194}$$

Therefore, for any solution $(N(t), i(t))$ of system (4.186) with initial values $N_0 = N(0^+) > 0$, $i_0 = i(0^+)$, $0 < i_0 < 1$, there exists m^* such that

the following inequality holds for $m > m^*$:

$$N(t) \leq N_p^*(t) + \epsilon, \quad m < t < m + 1. \tag{4.195}$$

Furthermore, it follows from (4.195) that

$$N(t) \leq \frac{1}{p} \ln \frac{bp}{1-p} + \epsilon = N^* + \epsilon, \quad t > m^*. \tag{4.196}$$

At each successive pulse, the forth equation of model (4.186) gives

$$\begin{aligned} i(m^+) &= \left(k + \frac{1-k}{1+be^{-N(m)}}\right) i(m) \leq \left(k + \frac{1-k}{1+be^{-(N^*+\epsilon)}}\right) i(m) \\ &= \left(k + \frac{1-k}{1+be^{-\epsilon}[(1-p)/(bp)]^{(1/p)}}\right) i(m) = \gamma i(m), \end{aligned}$$

for $m > m^*$.

Consider following comparison system with impulsive

$$\begin{aligned} \dot{x}(t) &= \begin{cases} \beta_1[1-x(t)]x(t) & m \leq t < m + T_1, \\ \beta_2[1-x(t)]x(t) & m + T_1 \leq t < m + T_2, \\ \beta_1[1-x(t)]x(t) & m + T_2 \leq t < m + 1, \end{cases} \\ x(m^+) &= \gamma x(m), \end{aligned} \tag{4.197}$$

for $m > m^*$.

Integrating the equations of (4.197) between pulses, we have

$$x(t) = \begin{cases} \dfrac{x_m}{x_m + (1-x_m)\exp[-\beta_1(t-m)]}, & m \leq t < m + T_1, \\ \dfrac{x_m}{x_m + (1-x_m)\exp[-\beta_2(t-m) - (\beta_1 - \beta_2)T_1]}, & m + T_1 \leq t < m + T_2, \\ \dfrac{x_m}{x_m + (1-x_m)\exp[-\beta_1(t-m) + (\beta_1 - \beta_2)(T_2 - T_1)]}, & m + T_2 \leq t < m + 1, \end{cases} \tag{4.198}$$

for $m > m^*$, where x_m is the initial value at time $m (0 < x_m < 1)$.

Then

$$x_{m+1} = \frac{\gamma x_m}{(1-q)x_m + q}. \tag{4.199}$$

It follows from (4.191) that $\gamma < q$, and then Eq. (4.199) has a unique trivial equilibrium, which is locally asymptotically stable. It is obvious that,

to prove $\lim_{m\to\infty} x_m = 0$, we only need to prove that the zero solution of Eq. (4.199) is globally attractive.

Iterative method step by step, on Eq. (4.199), yields

$$x_m = \left[\left(\frac{q}{\gamma}\right)^m \frac{1}{x_0} + \frac{1-q}{\gamma-q}\left(1-\left(\frac{q}{\gamma}\right)^m\right)\right]^{-1},$$

where $x_0 = x(0^+)$ and $0 < x_0 < 1$. From (4.196), we then have $\gamma^{-1}q > 1$, and hence $\lim_{m\to\infty} x_m = 0$. Therefore, from (4.198) and (4.199), $\lim_{t\to\infty} x(t) = 0$.

Let $(N(t), i(t))$ be a solution of system (4.186) with $N(0^+) > N_0 > 0$ and $i(0^+) = i_0 (0 < i_0 < 1)$, $x(t)$ be the solution of impulsive differential equation system (4.197) with $x(0^+) = x_0 = i_0$. From the comparison principle for impulse differential equations, we obtain

$$\lim_{t\to\infty} \sup i(t) \le \lim_{t\to\infty} \sup x(t) = 0.$$

Incorporating it into the positivity of $i(t)$, $\lim_{t\to\infty} i(t) = 0$ follows.

Therefore, the disease-free periodic solution $(N_p^*(t), 0)$ is globally asymptotically stable. □

Chapter 5

Structured Epidemic Models

Yicang Zhou

Mathematical models are important tools for analyzing transmission process of infectious diseases. Any model is a kind of approximation to the real process due to necessary simplifying assumptions. The models in previous chapters have led to useful insights into the general transmission properties of infections even though some of them suffer from certain assumptions that may need to be more realistic. Those simplifying assumptions may make the models less helpful when it comes to understanding specific situations, such as infection depending on age groups. This leads to modifying models to better fit in the situations, which, of course, in turn, increases the model complexity.

The simplicity is based on the homogeneity assumption. The homogeneity assumption does not distinguish the variation between individuals in a population; that is, the individual differences in birth, death, and transmission are neglected. While there are advantages of using simplified models to make the model analysis more tractable, the disadvantage of the homogeneity assumption, however, is that those models may not give good descriptions to infectious diseases with strong stage- or age-dependent parameters. Hence, different structures are needed, and we introduce them into epidemic models to reflect the inhomogeneous phenomena in disease transmissions.

Stage structure is one of the simplest structures in epidemiology. A given population is divided into different stages according to their infectious status. Age is one of the most natural and important factors to structure a population group and to describe the differences in diseases transmissions. In fact, the transmission of many diseases is closely related to ages of

individuals because different ages mean different survival and infection probability. Age-structured epidemic models allow the mathematical models to take into account the vast amount of knowledge and data that biologists have collected, and to provide more information for disease prevention.

In this chapter we introduce basic theory and methods for stage- and age-structured epidemic models. The stage-structured epidemic model is considered in Sec. 5.1; the age-structured epidemic models are analyzed in Sec. 5.2; the infection-age-structured epidemic models are investigated in Sec. 5.3; and the discrete epidemic models are studied in Sec. 5.4. The main attention is paid to the dynamic behaviors of those epidemic models. The basic reproductive number for those models is defined, and used as the key parameter to study the asymptotic behavior of the epidemic dynamics.

5.1. Stage-Structured Models

To gain deeper insights into the mechanism of disease transmissions, more attention has been paid to the design and improvement of mathematical models. The classic epidemic models with mass action incidence rate or standard incidence rate are modified by introducing nonlinear incidence rate. Another issue that is critically significant in epidemiology modeling is the stage of infection. The fact is that there are many diseases that spread or have more effects on children, such as measles, mumps, chickenpox, and scarlet fever, while other infectious diseases such as gonorrhea and syphilis only spread among adults. Moreover, for diseases with long latent or infection periods, such as HIV/AIDS and tuberculosis, the probability of transmission varies in different infection periods. Consequently, stage structure needs to be included in models of disease transmissions.

There are two kinds of stage structures in epidemiologic models: the physiologic stage (mature or immature), and the epidemiologic stage (more or less infectious). There are a lot of works on population modeling with various stages in the literature [Aiello and Freedman (1990); Aiello *et al.* (1992); Wang and Chen (1997); Wood *et al.* (1989)]. Some of them are based on the infection-stage structure. Moghadas and Gumel studied a multistage model incorporating a generalized nonlinear incidence function [Moghadas and Gumel (2002)]. It is proved that the disease-free equilibrium is globally asymptotically stable if $R_0 < 1$, and the unique endemic equilibrium is globally asymptotically stable for $R_0 > 1$. McCluskey analyzed an epidemic model with multiple stages of infection, allowing infected individuals to move from advanced stages of infection back to previous stages of infection

[McCluskey (2003)]. A threshold parameter and the conditions on global stability were obtained. Li *et al.* discussed a stage-structured epidemic model [Li *et al.* (2008)] and determined the basic reproductive number by the method of next generation matrix. The global stability of the disease-free equilibrium and the local stability of the endemic equilibrium are also obtained. Xiao and Chen formulated a disease transmission model of the SIS type with stage structure and a delay [Xiao and Chen (2001b)], and investigated the global stability of the disease-free equilibrium and the stability of an endemic equilibrium. Xiao *et al.* considered an SIR model with two stages: the immature and mature stages [Xiao and Chen (2001b)]. It was also shown that there exists threshold phenomenon in that model [Xiao *et al.* (2002)]. Lu *et al.* presented an SI model with stage structure and studied the stability and existence of endemic equilibrium [Lu *et al.* (2003)].

In this section we introduce two discrete epidemic models: one with physiologic structure and the other with infection-stage structure.

5.1.1. *A discrete epidemic model with stage structure*

Consider an infectious disease which transmits only in mature population. The population is divided into two classes: immature individuals and mature individuals. Let $J(t)$ and $M(t)$ be densities of the immature and mature individuals, respectively. They satisfy the following equations:

$$\begin{aligned} J(t+1) &= \frac{bM(t)}{1+M(t)} + J(t) - (\mu_1 + c)J(t), \\ M(t+1) &= cJ(t) + M(t) - \mu_2 M(t), \\ N(t) &= J(t) + M(t), \end{aligned} \tag{5.1}$$

where μ_1 and μ_2 are the death rates of the immature and mature individuals, respectively, $B(t) = bM(t)/(1 + M(t))$ is the birth rate, and c is the maturation rate. The natural requirements on the parameters in model (5.1) are $\mu_1 + c \leq 1$ and $\mu_2 \leq 1$, since $\mu_1 + c$ is the proportion of the immature individuals who die or enter the mature group.

Since the disease transmits only among mature individual, we divide the mature individuals into susceptible group $S_m(t)$ and infective group $I_m(t)$. The susceptibles become infected after the contact with infectives. We assume that the recovered individuals enter the susceptible groups and can be infected again. The schematic diagram is shown in Fig. 5.1.

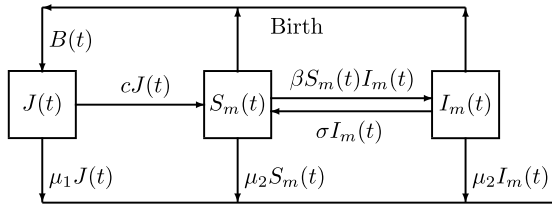


Fig. 5.1. The schematic diagram of the stage-structured SIS model.

Based on the assumptions, we have the following discrete SIS model with stage structure:

$$\begin{aligned} J(t+1) &= B(t) + J(t) - (\mu_1 + c)J(t), \\ S_m(t+1) &= cJ(t) + S_m(t) - \beta S_m(t)I_m(t) - \mu_2 S_m(t) + \sigma I_m(t), \\ I_m(t+1) &= \beta S_m(t)I_m(t) + I_m(t) - (\mu_2 + \sigma)I_m(t), \\ N(t) &= J(t) + S_m(t) + I_m(t), \end{aligned} \tag{5.2}$$

where β is the transmission rate by a mass action law and σ is the recovery rate of the infected individuals, The birth function $B(t)$ is taken as $B(t) = bM(t)/(1 + M(t))$, where $b > 0$ is the maximal birth rate of the mature individual.

Define the net reproductive number of the population model (5.1) to be

$$n_0 = \frac{bc}{\mu_2(\mu_1 + c)} = b \cdot \frac{1}{\mu_2} \cdot \frac{c}{\mu_1 + c},$$

where $1/\mu_2$ is the average time that an individual lives in the mature stage, and, $c/(\mu_1 + c)$ is the proportion that a newborn individual survives to the mature stage. Therefore, n_0 is the average number of offspring that an individual can produce during the whole life span with the maximal birth rate.

Theorem 5.1. *If $n_0 < 1$ system (5.1) has one equilibrium $P_0(0,0)$, and it is globally asymptotic stable. If $n_0 > 1$, then system (5.1) has two equilibria $P(0,0)$ and $P^*(J^*, M^*)$, with $J^* = \mu_2(n_0 - 1)/c$ and $M^* = n_0 - 1$, such that P_0 is unstable, and P^* is globally asymptotically stable.*

Proof. The Jacobian matrices of system (5.1) at the two equilibria are

$$L_0 = \begin{pmatrix} 1 - (\mu_1 + c) & b \\ c & 1 - \mu_2 \end{pmatrix}, \quad L^* = \begin{pmatrix} 1 - (\mu_1 + c) & b/n_0^2 \\ c & 1 - \mu_2 \end{pmatrix}.$$

If $n_0 < 1$, we define a Liapunov function $V(J, M) = cJ + (\mu_1 + c)M$. It is easy to get that

$$\begin{aligned} &V(J(t+1), M(t+1)) - V(J(t), M(t)) \\ &\quad = \frac{bcM(t)}{1 + M(t)} - \mu_2(\mu_1 + c)M(t) \\ &\quad = M(t)\mu_2(\mu_1 + c)\left(\frac{n_0}{1 + M(t)} - 1\right) \\ &\quad \leq 0. \end{aligned}$$

The well-known Liapunov stability theory implies the global stability of the equilibrium P_0 [Elaydi (1999)].

If $n_0 > 1$, the characteristic equation of matrix L_0 is

$$(\lambda - 1)^2 + (\mu_1 + \mu_2 + c)(\lambda - 1) + \mu_2(\mu_1 + c)(1 - n_0) = 0. \tag{5.3}$$

Using $\lambda - 1$ as the unknown variable, it is easy to see that Eq. (5.3) has a positive root. Hence the linearized system has a eigenvalue greater than 1. Therefore, the equilibrium P_0 is unstable.

If $n_0 > 1$, the characteristic equation of matrix L^* is

$$(\lambda - 1)^2 + (\mu_1 + \mu_2 + c)(\lambda - 1) + \mu_2(\mu_1 + c)\left(1 - \frac{1}{n_0}\right) = 0. \tag{5.4}$$

The two roots of Eq. (5.4) are

$$\lambda = 1 + \frac{1}{2}\big(-(\mu_1 + \mu_2 + c) \pm \sqrt{\Delta}\big),$$

where $\Delta = (\mu_1 + \mu_2 + c)^2 - 4\mu_2(\mu_1 + c)(1 - (1/n_0)) = (\mu_1 + c - \mu_2)^2 + (4\mu_2(\mu_1 + c)/n_0)$, and $0 < \sqrt{\Delta} < \mu_1 + \mu_2 + c < 2$. Then we see that the linearized system has two eigenvalues λ_1 and λ_2, with $|\lambda_i| < 1$, $i = 1, 2$, which implies the local stability of the equilibrium P^*.

Consider two solutions of (5.1), written in the vector form:

$$V_1(t) = \begin{pmatrix} J_1(t) \\ M_1(t) \end{pmatrix}, \quad V_2(t) = \begin{pmatrix} J_2(t) \\ M_2(t) \end{pmatrix},$$

where $J_1(t) \leq J_2(t)$ and $M_1(t) \leq M_2(t)$.

The recurrent equations in (5.1) lead to

$$\begin{aligned}
&J_2(t+1) - J_1(t+1)\\
&\quad = (1-\mu_1-c)(J_2(t)-J_1(t)) + \frac{b(M_2(t)-M_1(t))}{(1+M_2(t))(1+M_1(t))} \geq 0,\\
&M_2(t+1) - M_1(t+1)\\
&\quad = c(J_2(t)-J_1(t)) + (1-\mu_2)(M_2(t)-M_1(t)) \geq 0.
\end{aligned}$$

Those two inequalities imply that the two solutions of model (5.1) reserve their order; that is, if $J_2(0) \geq J_1(0)$ and $M_2(0) \geq M_1(0)$, then $J_2(t) \geq J_1(t)$ and $M_2(t) \geq M_1(t)$, for all $t \geq 0$.

Moreover, the solutions of (5.1) satisfy

$$\begin{aligned}
&J(t+1) - J(t)\\
&\quad = (1-\mu_1-c)(J(t)-J(t-1)) + \frac{b(M(t)-M(t-1))}{(1+M(t))(1+M(t-1))},\\
&M(t+1) - M(t)\\
&\quad = c(J(t)-J(t-1)) + (1-\mu_2)(M(t)-M(t-1)).
\end{aligned}$$

Hence the solutions of model (5.1) is monotone increasing (decreasing) if $J(1) \geq J(0)$ and $M(1) \geq M(0)$, ($J(1) \leq J(0)$ and $M(1) \leq M(0)$).

If $n_0 > 1$, for any positive initial value $J(0)$ and $M(0)$ of solutions of (5.1), we can choose two real numbers ε and L, where ε is sufficiently small and L is sufficiently large, such that $\varepsilon J^* < J(0) < LJ^*$ and $\varepsilon M^* < M(0) < LM^*$. Let $J_\varepsilon(t)$ and $M_\varepsilon(t)$ be the solution of (5.1) with the initial value $J_\varepsilon(0) = \varepsilon J^*$ and $M_\varepsilon(0) = \varepsilon M^*$. Let $J_L(t)$ and $M_L(t)$ be the solution of (5.1) with the initial value $J_L(0) = LJ^*$ and $M_L(0) = LM^*$. Then we have

$$\begin{aligned}
J_\varepsilon(1) &= (1-\mu_1-c)\varepsilon J^* + \frac{b\varepsilon M^*}{1+\varepsilon M^*}\\
&= \varepsilon J^* + \frac{b\varepsilon M^*(1-\varepsilon)M^*}{(1+\varepsilon M^*)(1+M^*)} \geq \varepsilon J^* = J_\varepsilon(0),\\
M_\varepsilon(1) &= c\varepsilon J^* + (1-\mu_2)\varepsilon M^* = \varepsilon M^* = M_\varepsilon(0),\\
J_L(1) &= (1-\mu_1-c)LJ^* + \frac{bLM^*}{1+LM^*}\\
&= LJ^* + \frac{bLM^*(1-L)M^*}{(1+LM^*)(1+M^*)} \leq LJ^* = J_L(0),\\
M_L(1) &= cLJ^* + (1-\mu_2)LM^* = LM^* = M_L(0).
\end{aligned}$$

Hence $(J_\varepsilon(t), M_\varepsilon(t))$ is an increasing solution of (5.1), and $(J_L(t), M_L(t))$ is a decreasing solution of (5.1), satisfying

$$J_\varepsilon(t) \le J(t) \le J_L(t), \quad M_\varepsilon(t) \le M(t) \le M_L(t).$$

The monotonic and bounded sequences $J_\varepsilon(t)$, $M_\varepsilon(t)$, $J_L(t)$ and $M_L(t)$ have limits:

$$\lim_{t\to\infty} J_\varepsilon(t) = J_\varepsilon^*, \quad \lim_{t\to\infty} M_\varepsilon(t) = M_\varepsilon^*, \quad \lim_{t\to\infty} J_L(t) = J_L^*, \quad \lim_{t\to\infty} M_L(t) = M_L^*.$$

It is easy to see that the limits $(J_\varepsilon^*, M_\varepsilon^*)$ and (J_L^*, M_L^*) are equilibria of model (5.1). The uniqueness of the positive equilibrium of (5.1) implies that

$$J_\varepsilon^* = J_L^* = J^*, \quad M_\varepsilon^* = M_L^* = M^*.$$

The monotonicity of the solution with respect to its initial value implies the global stability of the positive equilibrium P^*. □

From Theorem 5.1 we see that the population goes extinct if $n_0 < 1$, and tends to the positive equilibrium P^* if $n_0 > 1$. We assume that $n_0 > 1$ and that both the immature and mature individuals have reached their equilibrium states, that is, $J(t) = J^*$, $M(t) = M^*$, in the rest of this subsection.

Substituting these equilibrium values into the third equation of (5.2), we get a one-dimensional equation for infected mature individuals:

$$I_m(t+1) = \beta(M^* - I_m(t))I_m(t) + I_m(t) - (\mu_2 + \sigma)I_m(t), \tag{5.5}$$

The basic reproductive number of model (5.5) is defined by

$$R_0 = \frac{\beta M^*}{\mu_2 + \sigma}.$$

The dynamic behavior is given in the following theorem.

Theorem 5.2. *$I_0 = 0$ is the unique and global stable equilibrium of* (5.5)*, if $R_0 < 1$. There are two equilibria I_0 and $I^* = (\mu_2 + \sigma)(R_0 - 1)/\beta$, if $R_0 > 1$. The disease-free equilibrium I_0 is unstable if $R_0 > 1$, and the endemic equilibrium I^* is stable if $1 < R_0 < 1 + 2/(\mu_2 + \sigma)$. The endemic equilibrium becomes unstable and a periodic solution with period 2 appears if $R_0 > 1 + 2/(\mu_2 + \sigma)$.*

Proof. The existence of the equilibrium can be easily determined by the following equation:

$$I = \beta(M^* - I)I + I - (\mu_2 + \sigma)I.$$

If $R_0 < 1$ Eq. (5.5) leads to

$$\begin{aligned} I_m(t+1) - I_m(t) = &\ \beta(M^* - I_m(t))I_m(t) - (\mu_2 + \sigma)I_m(t) \\ \leq &\ (\mu_2 + \sigma)I_m(t)(R_0 - 1) < 0. \end{aligned}$$

Therefore, the disease-free equilibrium is globally stable.

When $R_0 > 1$, the endemic equilibrium exists, the stability changes as parameters change, and the dynamic behavior becomes more complicated. The linearization of (5.5) shows that the endemic equilibrium is stable if $1 < R_0 < 1 + 2/(\mu_2 + \sigma)$, and unstable if $R_0 > 1 + 2/(\mu_2 + \sigma)$. If $R_0 > 1 + 2/(\mu_2 + \sigma)$, straightforward calculations show that the periodic solutions with period 2 are

$$I_m^{**} = \frac{1}{2\beta}\Big(2 + (\mu_2 + \sigma)(R_0 - 1) \pm \sqrt{(\mu_2 + \sigma)^2(R_0 - 1)^2 - 4}\Big).$$

□

Let us consider the following example:

$$I_m(t+1) = 0.2(M^* - I_m(t))I_m(t) + I_m(t) - 0.2I_m(t). \tag{5.6}$$

The basic reproductive number for (5.6) is $R_0 = M^*$. The endemic equilibrium is $I^* = M^* - 1$, which is stable if $1 < M^* < 11$. It is unstable if $M^* > 11$. In this case, a periodic solution with period 2 appears. As M^* increases, the dynamics become more complicated. Figure 5.2 shows the trajectories of the model with different M^*.

For the stage-structured epidemic model (5.2), various incidence rates and birth rates can be used to describe the characteristics of different infectious diseases. More complicated situation are shown in [Jin *et al.* (2003); Li and Wang (2005)].

5.1.2. *Epidemic models with differential infectivity structure*

For diseases with long infectious periods or variable infectivities, it is more appropriate to introduce infection stages or progression stages into the models. For example, infected individuals of malaria, dengue fever, gonorrhea and other sexually transmitted diseases, may have different

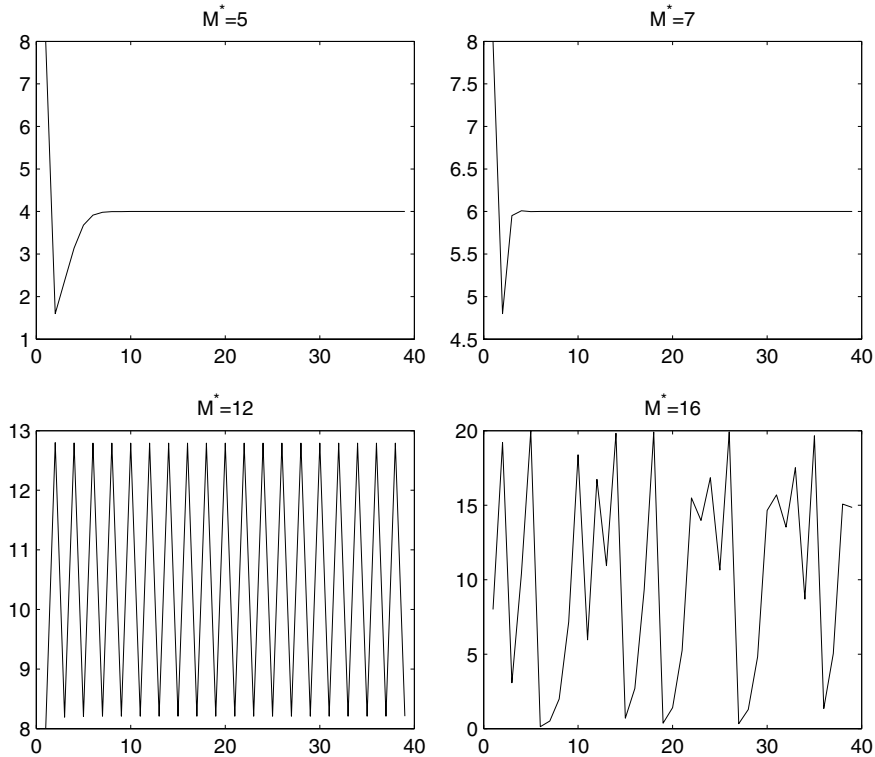


Fig. 5.2. The solution curves with different M^*.

infectivities in transmitting the disease in the different infection stages. Hepatitis B and schistosomiasis usually have a longer period of infection, and their infectiousness may vary in different progression stages.

In this subsection we consider a continuous-time epidemic model with infection-stage structure, where the period of infection is partitioned into two stages: the early and the later stages. We assume that the infected individuals in the early stage are transferred to the later stage, and individuals in both stages can recover or die. Then we divide the total population into three groups: the susceptibles S, the infectives in the early stage, I_1, and the infectives in the later stage, I_2. After contacts with infectives, a susceptible is infected and enters the early infection stage I_1, and then progresses to the later infection stage I_2. The infectives in both are infectious. We further assume that all the recruits are susceptible for

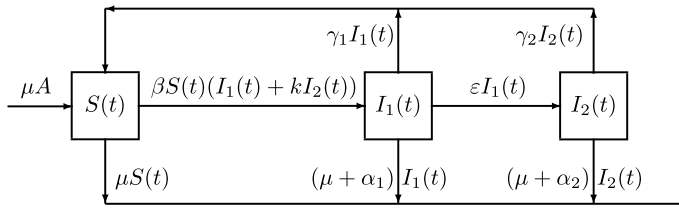


Fig. 5.3. The schematic diagram of stage progression.

infection. The relationship is schematically shown in Fig. 5.3, a transfer diagram.

The SIS model with two infection stages is described by the following system of ordinary differential equations:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \mu A - \mu S - \beta S(I_1 + kI_2) + \gamma_1 I_1 + \gamma_2 I_2, \\
\frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta S(I_1 + kI_2) - (\mu + \varepsilon + \gamma_1 + \alpha_1) I_1, \\
\frac{\mathrm{d}I_2}{\mathrm{d}t} &= \varepsilon I_1 - (\mu + \gamma_2 + \alpha_2) I_2,
\end{aligned} \tag{5.7}$$

where $S(t), I_1(t)$, and $I_2(t)$ denote the numbers of individuals in groups S, I_1, and I_2, at time t, respectively, μA is the recruitment rate of the population, μ is the natural death rate of the population, β and $k\beta$, with $k > 1$, are transmission coefficients for a susceptible through contacts with infectives in compartments I_1 and I_2, respectively, ε is the progression rate of the infectives from I_1 to I_2, γ_i are the natural recovery rates of the infectives in I_i, and α_i are the disease-induced death rates of the infectives in I_i, for $i = 1, 2$.

It is easy to check that the region

$$\Omega = \{(S, I_1, I_2) \mid S > 0,\ I_1 \geq 0,\ I_2 \geq 0,\ S + I_1 + I_2 \leq A\}$$

is a positively invariant set for model (5.7). Then we only consider the dynamic behavior of model (5.7) on Ω. The basic reproductive number for model (5.7) is

$$R_0 = \frac{(n + k\varepsilon)\beta A}{mn},$$

where we write $m := \mu + \varepsilon + \gamma_1 + \alpha_1$ and $n := \mu + \gamma_2 + \alpha_2$.

Straightforward calculations show that the disease-free equilibrium $P_0(A, 0, 0)$ is a unique equilibrium of model (5.7) if $R_0 \leq 1$. When $R_0 > 1$, model (5.7) has a unique endemic equilibrium $P^*(S^*, I_1^*, I_2^*)$, where

$$S^* = \frac{mn}{\beta(k\varepsilon + n)}, \quad I_1^* = \frac{\mu n A}{(m - \gamma_1)n - \gamma_2\varepsilon}\left(1 - \frac{1}{R_0}\right), \quad I_2^* = \frac{\varepsilon}{n} I_1^*.$$

From the definition of m and n we see that $(m - \gamma_1)n - \gamma_2\varepsilon > 0$. Then we have following stability results for equilibria P_0 and P^* [Li *et al.* (2008)].

Theorem 5.3. *The disease-free equilibrium, P_0, of model* (5.7) *is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$. The endemic equilibrium, P^*, of model* (5.7) *is locally asymptotically stable if $R_0 > 1$.*

Proof. The Jacobian matrices of model (5.7) at P_0 and P^* are, respectively,

$$J(P_0) = \begin{pmatrix} -\mu & -\beta A + \gamma_1 & -\beta k A + \gamma_2 \\ 0 & \beta A - m & \beta k A \\ 0 & \varepsilon & -n \end{pmatrix}$$

and

$$J(P^*) = \begin{pmatrix} -\mu - \dfrac{mI_1^*}{S^*} & -\beta S^* + \gamma_1 & -\beta k S^* + \gamma_2 \\ \dfrac{mI_1^*}{S^*} & \beta S^* - m & \beta k S^* \\ 0 & \varepsilon & -n \end{pmatrix}.$$

First, it is easy to check the eigenvalues of $J(P_0)$, and hence to see that P_0 is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Then, we let λ_i, $i = 1, 2, 3$, be the eigenvalues of $J(P^*)$ with $\operatorname{Re}\lambda_1 \leq \operatorname{Re}\lambda_2 \leq \operatorname{Re}\lambda_3$. From the expressions of m, n, and S^*, we see that $\det(J(P^*)) = -(mI_1^*/S^*)[n(m - \gamma_1) - \varepsilon\gamma_2] < 0$, and hence $\lambda_1\lambda_2\lambda_3 < 0$. There are two possible cases for the real part of the eigenvalues of $J(P^*)$: (1) $\operatorname{Re}\lambda_i < 0$ for all $i = 1, 2, 3$; (2) $\operatorname{Re}\lambda_1 < 0 \leq \operatorname{Re}\lambda_2 \leq \operatorname{Re}\lambda_3$. Since $\beta S^* < m$, we know that $\operatorname{tr}(J(P^*)) < 0$, and hence $\lambda_1 + \lambda_2 + \lambda_3 < 0$, which implies that $\operatorname{Re}(\lambda_1 + \lambda_2) < 0$ and $\operatorname{Re}(\lambda_1 + \lambda_3) < 0$.

Next, we consider the second additive compound matrix [Li *et al.* (1999)] of $J(P^*)$

$$J^{[2]}(P^*) = \begin{pmatrix} -\mu - m - \dfrac{m\mu I_1^*}{S^*} + \beta S^* & \beta k S^* & \beta k S^* - \gamma_2 \\ \varepsilon & -\mu - n - \dfrac{mI_1^*}{S^*} & -\beta S^* + \gamma_1 \\ 0 & \dfrac{mI_1^*}{S^*} & \beta S^* - m - n \end{pmatrix}.$$

The determination of $J^{[2]}(P^*)$ is

$$\begin{aligned} \det\big(J^{[2]}(P^*)\big) = &-(m+n-\beta S^*)\left[\mu(m-\beta S^*) + (\mu+n)\left(\mu + \frac{mI_1^*}{S^*}\right)\right] \\ &- \frac{mI_1^*}{S^*}\left[\frac{mI_1^*}{S^*}(m+n-\gamma_1) + (m-\gamma_1)\right. \\ &\left.\times(\mu+m-\beta S^*) + (\mu n + \varepsilon\gamma_2)\right]. \end{aligned}$$

Since $\beta S^* < m$ and $m > \gamma_1$, it is easy to see that $\det(J^{[2]}(P^*)) < 0$.

According to the property of the second additive compound matrix (see [Li *et al.* (1999)] for details), the eigenvalues of $J^{[2]}(P^*)$ are $\lambda_i + \lambda_j, 1 \le i < j \le 3$. Then $(\lambda_1+\lambda_2)(\lambda_1+\lambda_3)(\lambda_2+\lambda_3) < 0$. Notice that $\mathrm{Re}\,(\lambda_1+\lambda_2) < 0$ and $\mathrm{Re}\,(\lambda_1+\lambda_3) < 0$. Then $\mathrm{Re}\,(\lambda_2+\lambda_3) < 0$. This implies that case (2) is false. Therefore, $\mathrm{Re}\,\lambda_i < 0$, for all $i = 1, 2, 3$; that is, P^* is locally asymptotically stable if $R_0 > 1$. □

The global stability of the disease-free equilibrium of model (5.7) is given in the theorem below.

Theorem 5.4. *The disease-free equilibrium P_0 of* (5.7) *is globally stable on Ω if $R_0 < 1$.*

Proof. Let $V = (n + k\varepsilon)I_1 + kmI_2$. Then the derivative of V along solutions of system (5.7) is

$$\begin{aligned} \left.\frac{\mathrm{d}V}{\mathrm{d}t}\right|_{(5.7)} &= [(n+k\varepsilon)\beta S - mn](I_1 + kI_2) \\ &\le [(n+k\varepsilon)\beta A - mn](I_1 + kI_2) \\ &= mn(R_0 - 1)(I_1 + kI_2) < 0. \end{aligned}$$

Therefore, P_0 is globally asymptotically stable on Ω if $R_0 < 1$. □

The determination of the global stability of the endemic equilibrium of (5.7) is not analytically tractable. Here, we only consider a special case where $k = 1,\ \alpha_1 = \alpha_2 = 0$. Summing up the three equations in model (5.7), we have

$$\frac{\mathrm{d}(S + I_1 + I_2)}{\mathrm{d}t} = \mu(A - S - I_1 - I_2)$$

that yields

$$\lim_{t\to\infty}(S + I_1 + I_2) = A.$$

Substituting $S = A - I_1 - I_2$ into the second equation of model (5.7) and dropping the first one, we obtain

$$\begin{aligned} \frac{\mathrm{d}I_1}{\mathrm{d}t} &= \beta(A - I_1 - I_2)(I_1 + I_2) - (\mu + \varepsilon + \gamma_1)I_1, \\ \frac{\mathrm{d}I_2}{\mathrm{d}t} &= \varepsilon I_1 - (\mu + \gamma_2)I_2. \end{aligned} \tag{5.8}$$

The dynamic behavior of model (5.8) is the same as that of model (5.7).

The basic reproductive number for model (5.8) is

$$R_0 = \frac{\beta A(\varepsilon + \mu + \gamma_2)}{(\mu + \gamma_2)(\mu + \varepsilon + \gamma_1)}.$$

Then using the following transformation:

$$x = I_1 + I_2, \quad y = \frac{I_2}{I_1 + I_2},$$

system (5.8) becomes

$$\begin{aligned} \frac{\mathrm{d}x}{\mathrm{d}t} &= x[p - \beta x - (\gamma_2 - \gamma_1)y], \\ \frac{\mathrm{d}y}{\mathrm{d}t} &= \varepsilon - y[q - \beta x - (\gamma_2 - \gamma_1)y], \end{aligned} \tag{5.9}$$

where $p = \beta A - (\mu + \gamma_1),\ q = \beta A + \gamma_2 + \varepsilon - \gamma_1$. The transformation transfers the invariant domain and the endemic equilibrium of (5.8) to

$$G = \{(x, y) \mid 0 < x \le A, 0 < y < 1\}$$

and

$$Q^*(x^*, y^*), \quad x^* = A\left(1 - \frac{1}{R_0}\right), \quad y^* = \frac{\varepsilon}{\mu + \gamma_2 + \varepsilon}.$$

Then we have the following global stability results.

Theorem 5.5. *The positive equilibrium, $Q^*(x^*, y^*)$, of system (5.9) is globally asymptotically stable in G, if $R_0 > 1$.*

Proof. Define functions:

$$V_1 = x - x^* - x^* \ln \frac{x}{x^*} \quad \text{and} \quad V_2 = y - y^* - y^* \ln \frac{y}{y^*}.$$

Then the derivatives of V_1 and V_2 along the solutions of system (5.9) are, respectively,

$$\begin{aligned}
\left.\frac{\mathrm{d}V_1}{\mathrm{d}t}\right|_{(5.9)} &= -\beta(x - x^*)^2 - (\gamma_2 - \gamma_1)(x - x^*)(y - y^*), \\
\left.\frac{\mathrm{d}V_2}{\mathrm{d}t}\right|_{(5.9)} &= \frac{y - y^*}{y}[\varepsilon - y(q - \beta x - (\gamma_2 - \gamma_1)y)] \\
&= \frac{y - y^*}{y}[y^*(q - \beta x^* - (\gamma_2 - \gamma_1)y^*) - y(q - \beta x - (\gamma_2 - \gamma_1)y)] \\
&= \frac{y - y^*}{y}[(y^* - y)(q - \beta x^* - (\gamma_2 - \gamma_1)y^*) \\
&\quad + y(\beta(x - x^*) + (\gamma_2 - \gamma_1)(y - y^*))].
\end{aligned}$$

Since $q - \beta x^* - (\gamma_2 - \gamma_1)y^* = \varepsilon / y^* = \mu + \gamma_2 + \varepsilon$, then

$$\left.\frac{\mathrm{d}V_2}{\mathrm{d}t}\right|_{(5.9)} = -(y - y^*)^2 \left(\frac{\mu + \gamma_2 + \varepsilon}{y} + \gamma_1 - \gamma_2\right) + \beta(x - x^*)(y - y^*).$$

The fact that $y < 1$ implies

$$\left.\frac{\mathrm{d}V_2}{\mathrm{d}t}\right|_{(5.9)} \leq -(\mu + \gamma_1 + \varepsilon)(y - y^*)^2 + \beta(x - x^*)(y - y^*).$$

Let us consider the function $V = \eta V_1 + V_2$, where η is a positive value satisfying the inequality

$$(\gamma_1 - \gamma_2)^2 \eta^2 - 2\eta\beta[\gamma_1 + \gamma_2 + 2(\mu + \varepsilon)] + \beta^2 < 0.$$

The derivative of function V along the solutions of system (5.9) is

$$\begin{aligned}
\left.\frac{\mathrm{d}V}{\mathrm{d}t}\right|_{(5.9)} &\leq -\beta\eta(x - x^*)^2 - [\eta(\gamma_2 - \gamma_1) - \beta](x - x^*)(y - y^*) \\
&\quad - (\mu + \gamma_1 + \varepsilon)(y - y^*)^2.
\end{aligned}$$

By the definition of η, we have that

$$\left.\frac{\mathrm{d}V}{\mathrm{d}t}\right|_{(5.9)} \leq 0 \quad \text{and} \quad \left.\frac{\mathrm{d}V}{\mathrm{d}t}\right|_{(5.9)} = 0$$

if and only if $x = x^*$ and $y = y^*$. By the Liapunov asymptotic stability theorem, $Q(x^*, y^*)$ is globally stable in G. □

Theorem 5.5 implies that the endemic equilibrium, P^*, of model (5.7) is globally asymptotically stable in int$D$ when $R_0 > 1$, in the special case.

In HIV transmissions, an infected individual is highly infectious for the first few weeks after their infection. Then, they have low infectivity for many years, before they gradually become more infectious as their immune system finally breaks down and they progress to AIDS. Hence, It is natural to group infected individuals according their infection stages and study more complicated stage-structured models [McCluskey (2003); Hyman and Li (2005)].

5.2. Age-Structured Models

Age has been recognized as an important factor in dynamics of epidemic process for a long time. Age-structured epidemic models for different situations have been studied by many authors [Baily (1975); Hethcote (1994)]. Busenberg and his co-workers provided complete analysis for fairly general SIS models with age structure showing the existence of a threshold for endemic states [Busenberg *et al.* (1988); Busenberg *et al.* (1991); Busenberg and Cooke (1993)]. Iannelli and his co-workers further developed age-structured models by considering a special form of the force of infection. The explicitly computable threshold conditions are obtained in [Iannelli *et al.* (1992)].

Age-structured epidemic models are more complicated than compartmental differential equations models. In this section, we present an age-structured epidemic model with vertical transmission. The basic reproductive number is defined and the dynamic behavior is investigated. Stability conditions are obtained.

5.2.1. *Model formulation*

Horizontal transmission is the transmission of an infection through direct or indirect contacts with infected individuals. Vertical transmission is the

transmission of an infection from mother to child during the perinatal period. The studies of both horizontal and vertical transmissions are important.

We consider an age-structured population of variable size exposed to a communicable disease. The disease is both vertically and horizontally transmitted. Let $S(a,t)$ and $I(a,t)$, respectively, denote the age densities for susceptibles and infectives of age a at time t. Then $\int_{a_1}^{a_2} S(a,t)\mathrm{d}a$ and $\int_{a_1}^{a_2} I(a,t)\mathrm{d}a$ are the total number of susceptibles and infectives of ages between a_1 and a_2, respectively, at time t. We assume that the total population consists entirely of susceptibles and infectives, and that the horizontal transmission of the disease follows the proportionate mixing assumption: $k_1(a)S(a,t)\lambda(t)$, where $\lambda(t) = \int_0^{+\infty} k_2(u)I(u,t)\mathrm{d}u$. The age-structured epidemic model with vertical transmission is [El-Doma (1999)]

$$\begin{aligned}
&\frac{\partial S}{\partial a} + \frac{\partial S}{\partial t} = -k_1(a)S(a,t)\lambda(t) - \mu(a)S(a,t) + \gamma(a)I(a,t),\\
&\frac{\partial I}{\partial a} + \frac{\partial I}{\partial t} = k_1(a)S(a,t)\lambda(t) - (\mu(a) + \gamma(a))I(a,t),\\
&S(0,t) = \int_0^{\infty} \beta(a)(S(a,t) + (1-q)I(a,t))\mathrm{d}a,\\
&I(0,t) = q\int_0^{\infty} \beta(a)I(a,t)\mathrm{d}a,\\
&S(a,0) = S_0(a), \quad I(a,0) = I_0(a),
\end{aligned} \tag{5.10}$$

where q is the vertical transmission probability; that is, a portion, q, of newborns from infected parents are infective. $k_1(a)$ and $k_2(a)$ are bounded, nonnegative, continuous functions of a. The fertility rate, $\beta(a)$, is nonnegative and continuous function with compact support $[0, A]$, $(A > 0)$. The death rate $\mu(a)$ is the same for susceptibles and infectives, which is nonnegative, bounded, and continuous. We further assume that there exist nonnegative constants a_0 and $\bar{\mu}$ such that $\mu(a) > \bar{\mu} > 0$ when $a > a_0$, and $\mu(a_2) > \mu(a_1)$ for $a_2 > a_1 > a_0$. The cure rate $\gamma(a)$ is a bounded, nonnegative, and continuous function of a. The initial age distributions $S_0(a)$ and $I_0(a)$ are continuous, nonnegative, and integrable functions of a.

We define the age density of the total population $P(a,t) = S(a,t) + I(a,t)$. By adding the equations in (5.10), we find that $P(a,t)$ satisfies the

following equations:

$$\begin{aligned}
&\frac{\partial P(a,t)}{\partial a} + \frac{\partial P(a,t)}{\partial t} = -\mu(a)P(a,t),\\
&P(0,t) = \int_0^\infty \beta(a)P(a,t))\mathrm{d}a \triangleq B(t),\\
&P(a,0) = S_0(a) + I_0(a) \triangleq P_0(a).
\end{aligned} \tag{5.11}$$

System (5.11) is of McKendrick–VonForester type, and has a unique solution that exists for all time [Hoppensteadt (1975); Feller (1941)]. The unique solution of problem (5.11) is given by

$$P(a,t) = \begin{cases} \dfrac{P_0(a-t)\pi(a)}{\pi(a-t)}, & a > t,\\ B(t-a)\pi(a), & a < t, \end{cases} \tag{5.12}$$

where $\pi(a) = \exp(-\int_0^a \mu(u)\mathrm{d}u)$, and $B(t)$ has the following asymptotic behavior:

$$B(t) = |c + \theta(t)|\mathrm{e}^{p^* t}, \tag{5.13}$$

as $t \to \infty$. Here p^* is the unique real root of the following characteristic equation:

$$\int_0^\infty \beta(a)\pi(a)\mathrm{e}^{-pa}\mathrm{d}a = 1, \tag{5.14}$$

and $\theta(t)$ is a function such that $\theta(t) \to 0$ as $t \to \infty$, and c is a constant. The density of the infectives satisfies the following system of equations:

$$\begin{aligned}
&\frac{\partial I}{\partial a} + \frac{\partial I}{\partial t} = k_1(a)(P(a,t) - I(a,t))\lambda(t) - (\mu(a) + \gamma(a))I(a,t),\\
&I(0,t) = q\int_0^\infty \beta(a)I(a,t)\mathrm{d}a \triangleq V(t),\\
&I(a,0) = I_0(a).
\end{aligned} \tag{5.15}$$

5.2.2. *Existence of equilibrium*

We assume that the total population has already reached its steady-state distribution $P_\infty(a) = c\pi(a)$; that is, we assume that Eq. (5.14) is satisfied

when $p* = 0$ [Busenberg *et al.* (1988)]. We then look for the equilibrium solution of problem (5.15), $I^*(a)$, which satisfies the system

$$\begin{aligned}
&\frac{\mathrm{d}I^*(a)}{\mathrm{d}a} = k_1(a)(c\pi(a) - I^*(a))\lambda^* - (\mu(a) + \gamma(a))I^*(a),\\
&I^*(0) = q\int_0^\infty \beta(a)I^*(a)\mathrm{d}a,\\
&\lambda^* = \int_0^\infty k_2(a)I^*(a)\mathrm{d}a.
\end{aligned} \tag{5.16}$$

It is obvious that $I^*(a) = 0$, the disease-free equilibrium, is an equilibrium solution of (5.16). The endemic equilibrium and dynamic behavior of (5.15) is closely related to the basic reproductive number R_0, given by

$$\begin{aligned}
R_0 = {} & c\int_0^\infty\int_0^\infty \pi(a+u)\exp\left(-\int_u^{a+u}\gamma(v)\mathrm{d}v\right)k_2(a+u)k_1(u)\mathrm{d}u\mathrm{d}a\\
& + \frac{qc\sigma\int_0^\infty\int_0^\infty \beta(a+u)\pi(a+u)\exp(-\int_u^{a+u}\gamma(v)\mathrm{d}v)k_1(u)\mathrm{d}u\mathrm{d}a}{1 - q\int_0^\infty \beta(a)\pi(a)\exp(-\int_0^a\gamma(u)\mathrm{d}u)\mathrm{d}a},
\end{aligned}$$

where

$$\sigma = \int_0^\infty \pi(a)\exp\left(-\int_0^a\gamma(v)\mathrm{d}v\right)k_2(a)\mathrm{d}a.$$

The basic reproductive number R_0 is the average number of secondary infections that an infected individual can transmit during his/her whole infection period in a completely susceptible pool. The second term in the expression of R_0 means the vertical transmission will lead to more infection. The basic reproductive number $R_0 = 1$ is the threshold of the existence of the endemic equilibrium.

Theorem 5.6. *If $R_0 > 1$ system* (5.15) *has an endemic equilibrium $I^*(a)$, given by*

$$\begin{aligned}
I^*(a) = {} & v^*\pi(a)\exp\left(-\int_0^a\alpha(u)\mathrm{d}u\right)\\
& + c\lambda^*\pi(a)\int_0^a\exp\left(-\int_u^a\alpha(s)\mathrm{d}s\right)k_1(u)\mathrm{d}u,
\end{aligned} \tag{5.17}$$

where $\alpha(u) = \gamma(u) + \lambda^*k_1(u)$,

$$v^* = \frac{qc\lambda^*\int_0^\infty\int_0^\infty \beta(a+u)\pi(a+u)\exp(-\int_u^{a+u}\alpha(v)\mathrm{d}v)k_1(u)\mathrm{d}u\mathrm{d}a}{1 - q\int_0^\infty \beta(a)\pi(a)\exp(-\int_0^a\alpha(u)\mathrm{d}u)\mathrm{d}a},$$

and λ^* is the unique positive root of the equation $f(\lambda^*) = 1$, with

$$f(\lambda^*) = c\int_0^\infty\int_0^\infty \pi(a+u)\exp\left(-\int_u^{a+u}\alpha(v)\mathrm{d}v\right)k_2(a+u)k_1(u)\mathrm{d}u\mathrm{d}a + \frac{qc\sigma\int_0^\infty\int_0^\infty \beta(a+u)\pi(a+u)\exp\big(-\int_u^{a+u}\alpha(v)\mathrm{d}v\big)k_1(u)\mathrm{d}u\mathrm{d}a}{1-q\int_0^\infty \beta(a)\pi(a)\exp\big(-\int_0^a\alpha(u)\mathrm{d}u\big)\mathrm{d}a}.$$

Proof. From the first equation of (5.16) we obtain

$$I^*(a) = I^*(0)\pi(a)\exp\left(-\int_0^a\alpha(u)\mathrm{d}u\right) + c\lambda^*\pi(a)\int_0^a\exp\left(-\int_u^a\alpha(s)\mathrm{d}s\right)k_1(u)\mathrm{d}u.$$

Since $I^*(0) = q\int_0^\infty \beta(a)I^*(a)\mathrm{d}a$, we find that $I^*(0)$ satisfies

$$I^*(0) = \frac{qc\lambda^*\int_0^\infty\int_0^a \beta(a)\pi(a)\exp\big(-\int_u^a\alpha(v)\mathrm{d}v\big)k_1(u)\mathrm{d}u\mathrm{d}a}{1-q\int_0^\infty \beta(a)\pi(a)\exp\big(-\int_0^a\alpha(u)\mathrm{d}u\big)\mathrm{d}a}.$$

From the assumption that $\int_0^\infty \beta(a)\pi(a)\mathrm{d}a = 1$, $q\in(0,1)$, and $\alpha(a) > 0$, we see that the denominator in the expression of $I^*(0)$ is not zero. Substituting $I^*(a)$ into the last expression of (5.16), we know that λ^* satisfies $f(\lambda^*) = 1$. We can also check that $f(\lambda^*)$ is a decreasing function of λ^*. Therefore, $f(\lambda^*) = 1$ has a unique positive root λ^*, if $R_0 > 1$. The proof is complete. □

5.2.3. *Stability of equilibria*

To study the stability of the equilibrium we integrate problem (5.15) along the characteristics, $t = a +$ constant, and have

$$I(a,t) = \begin{cases} I_0(a-t)\exp(-\int_0^t\phi(u)\mathrm{d}u) + c\int_0^t\exp(-\int_u^t\phi(s)\mathrm{d}s) \\ \qquad\times\pi(a-t+u)k_1(a-t+u)\lambda(u)\mathrm{d}u, \quad a > t, \\ V(t-a)\pi(a)\exp(-\int_0^a\psi(s)\mathrm{d}s) + c\pi(a)\int_0^a\exp(-\int_u^a\psi(s)\mathrm{d}s) \\ \qquad\times k_1(u)\lambda(t-a+u)\mathrm{d}u, \quad a < t, \end{cases} \tag{5.18}$$

where $\phi(u) = \mu(a-t+u) + \gamma(a-t+u) + k_1(a-t+u)\lambda(u)$, and $\psi(u) = \gamma(u) + k_1(u)\lambda(t-a+u)$. Substituting $I(a,t)$ into the expression of $V(t)$

into (5.15), we see that $V(t)$ satisfies

$$\begin{aligned} V(t) = q &\int_0^t \beta(a)\pi(a)V(t-a) \\ &\times \exp\left(-\int_0^a \gamma(u) + k_1(u)\lambda(t-a+u)\mathrm{d}u\right) + q\int_0^\infty \beta(a+t)I_0(a) \\ &\times \exp\left(-\int_0^t (\mu(a+u) + \gamma(a+u) + k_1(a+u)\lambda(u))\mathrm{d}u\right)\mathrm{d}a \\ &+ cq\int_0^t\int_0^\infty \beta(a+u)\pi(a+u) \\ &\times \exp\left(-\int_a^{a+u} (\gamma(s) + k_1(s)\lambda(s+t-a+u))\mathrm{d}s\right) \\ &\times k_1(a)\lambda(t-u)\mathrm{d}u\mathrm{d}a. \end{aligned} \tag{5.19}$$

From the definition of $\lambda(a,t) = \int_0^\infty k_2(u)I(u,t)du$, we multiply the expression of $I(a,t)$ in (5.18) by $k_2(a)$, and integrate it from 0 to ∞, to obtain

$$\begin{aligned} \lambda(t) = &\int_0^\infty k_2(a)I_0(a) \\ &\times \exp\left(-\int_0^t (\mu(a+u) + \gamma(a+u) + k_1(a+u)\lambda(u))\mathrm{d}u\right)\mathrm{d}a \\ &+ \int_0^t V(t-a)\pi(a)k_2(a) \\ &\times \exp\left(-\int_0^a (\gamma(u) + k_1(u)\lambda(t-a+u))\mathrm{d}u\right)\mathrm{d}a \\ &+ c\int_0^t\int_0^\infty \pi(a+u)k_1(a)k_2(a+u)\lambda(t-u) \\ &\times \exp\left(-\int_a^{a+u} (\gamma(s) + k_1(s)\lambda(s+t-a-u))\mathrm{d}s\right)\mathrm{d}u\mathrm{d}a. \end{aligned} \tag{5.20}$$

By our assumptions on parameters and the dominant convergence theorem we have

$$\begin{aligned} q\int_0^t &\beta(a+t)I_0(a) \\ &\times \exp\left(-\int_0^t (\mu(a+u) + \gamma(a+u) + k_1(a+u)\lambda(u))\mathrm{d}u\right)\mathrm{d}a \to 0, \end{aligned}$$

$$\int_0^\infty k_2(a)I_0(a)$$
$$\times \exp\left(-\int_0^t (\mu(a+u)+\gamma(a+u)+k_1(a+u)\lambda(u))\mathrm{d}u\right)\mathrm{d}a \to 0,$$

as $t \to 0$. Consequently, $V(t)$ and $\lambda(t)$ satisfy the following limiting equations [Miller (1971)]

$$\begin{aligned} V(t) = q&\int_0^\infty \beta(a)\pi(a)V(t-a) \\ &\times \exp\left(-\int_0^a (\gamma(u)+k_1(u)\lambda(t-a+u))\mathrm{d}u\right)\mathrm{d}a \\ &+ cq\int_0^\infty\int_0^\infty \beta(a+u)\pi(a+u) \\ &\times \exp\left(-\int_a^{a+u} (\gamma(s)+k_1(s)\lambda(s+t-a+u))\mathrm{d}s\right) \\ &\times k_1(a)\lambda(t-u)\mathrm{d}u\mathrm{d}a, \end{aligned} \tag{5.21}$$

$$\begin{aligned} \lambda(t) = &\int_0^\infty V(t-a)\pi(a)k_2(a) \\ &\times \exp\left(-\int_0^a (\gamma(u)+k_1(u)\lambda(t-a+u))\mathrm{d}u\right)\mathrm{d}a \\ &+ c\int_0^\infty\int_0^\infty \pi(a+u)k_1(a)k_2(a+u)\lambda(t-u) \\ &\times \exp\left(-\int_a^{a+u} (\gamma(s)+k_1(s)\lambda(s+t-a-u))\mathrm{d}s\right)\mathrm{d}u\mathrm{d}a. \end{aligned}$$

The equilibrium solution of (5.15) corresponds to the equilibrium solution of (5.21). Then the disease-free equilibrium $I^*(a) = 0$ of (5.15) corresponds to the trivial solution $V(t) = 0$ and $\lambda(t) = 0$ of (5.21), and the endemic equilibrium of (5.15) corresponds to the positive equilibrium $V(t) = v^* = q\int_0^\infty \beta(a)I^*(a)\mathrm{d}a$ and $\lambda^* = \int_0^\infty k_2(a)I^*(a)\mathrm{d}a$ of (5.21). Moreover, the stability of (5.21) implies the stability of (5.15). By defining a function $F(\tau,\lambda)$ and studying the stability of the equilibrium of (5.21), El-Doma gives the following two stability theorems in [El-Doma (1999)]. The expression of function $F(\tau,\lambda)$ is very long, and the calculation is tedious.

They both are omitted here. Details could be found at reference [El-Doma (1999)].

Theorem 5.7. *The trivial equilibrium* $V = 0$ *and* $\lambda = 0$ *of* (5.21) *is globally stable if* (1) $R_0 < 1$, (2) $\beta(0) \neq 0$, *or there exists* $a_0 \in [0, \infty)$, *such that* $k_1(a_0)k_2(a_0) \neq 0$, *and* (3) $(dF(\tau, 0)/d\tau) \leq 0$. *The trivial equilibrium* $V = 0$ *and* $\lambda = 0$ *of* (5.21) *is unstable if* $R_0 > 1$.

Theorem 5.8. *The endemic equilibrium* $V = v^*$ *and* $\lambda = \lambda^*(a)$ *of* (5.21) *is locally asymptotically stable if* (1) $R_0 > 1$, (2) $\beta(0) \neq 0$, *or there exists a* $a_0 \in [0, \infty)$ *such that* $k_1(a_0)k_2(a_0) \neq 0$, *and* (3) $dF(\tau, 0)/d\tau \leq 0$.

5.3. Infection-Age-Structured Models

The homogeneous assumption is widely used in ordinary differential equation models of infectious diseases; that is, it is assumed that all individuals in each epidemiologic group are identical, and, especially, every infected individual is equally infectious during their period of infectivity. While the homogeneous assumption has proved to be appropriate in the study of the transmission of some diseases, to more accurately describe the transmission dynamics of most infectious diseases, it is necessary to include the transmission variations between individuals due to their age and/or infectious-age difference. In particular, the infectious-age-dependent infectivity needs to be introduced for diseases with long infectious period.

There are different ways to introduce infection-age structure into epidemic models. A simple one is to add infection-age structure only into infected groups (see, for example, [Kribs-Zaleta and Martcheva (2002); Inaba and Sekine (2004); Liu *et al.* (2007)]). More complicated models have chronologic age in all the population groups, and both chronologic age and infection-age for infected individuals [Inaba (1990); Zhou *et al.* (2001)]. In this section we give a brief introduction to both situations.

5.3.1. *An infection-age-structured model with vaccination*

Some diseases have high infectivity in the initial stage of infection, and the infectivity becomes low in the following stage since the immune response is stimulated to the infection. Infectivity and recovery rates may continue to vary during this latter stage.

Now, let us study the effects of a vaccination campaign upon the spread of a nonfatal disease which features both acute and chronic infective stages. We assume that infected individuals always pass through both stages

before recovery, and that the acute stage of infection is considerably more infectious than the chronic stage. We then assume that the vaccine being administered is permanently effective and provides complete protection against low-level infection for chronic stage individuals, but only partial protection against acutely infective contacts. We incorporate demographics via constant per capita birth and death rates, and assume that all newborns are susceptible. We divide the population into five compartments: susceptibles, $S(t)$; vaccinated individuals, $V(t)$; acute infectives, $I(t)$; chronic infectives, $C(t)$; and recovered individuals, $R(t)$. We further include the age of infection a in the compartment of chronic infectives such that $J(a,t)$ is the chronic infection-age density at time t, and $C(t) = \int_0^\infty J(a,t)\mathrm{d}a$, and then the total population is $N(t) = S(t) + V(t) + I(t) + C(t) + R(t)$.

Based on our assumptions, the following model is formulated and studied [Kribs-Zaleta and Martcheva (2002)]:

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= bN - \mu S - \gamma\frac{SI}{N} - \frac{S}{N}\int_0^\infty \delta(a)J(a,t)\mathrm{d}a - \psi S + cR,\\
\frac{\mathrm{d}V}{\mathrm{d}t} &= \psi S - \sigma\gamma\frac{VI}{N} - \mu V,\\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \gamma\left(\frac{S}{N} + \sigma\frac{V}{N}\right)I + \frac{S}{N}\int_0^\infty \delta(a)J(a,t)\mathrm{d}a - (\mu + k)I,\\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \int_0^\infty \alpha(a)J(a,t)\mathrm{d}a - (\mu + c)R,\\
\frac{\partial J}{\partial a} + \frac{\partial J}{\partial t} &= -(\mu + \alpha(a))J(a,t), \quad J(0,t) = kI(t),
\end{aligned} \tag{5.22}$$

where b is the per capita birth rate, μ is the per capita death rate, ψ is the per capita vaccination rate, σ, $0 \le \sigma \le 1$ is the infection reduction factor by vaccinating the acute infectives, γ is the effective per capita infection rate for acute infectives, $\delta(a)$ is the per capita infection rate for chronic infectives with infection age a, k is the per capita rate at which acute infectives progress into the chronic stage, $\alpha(a)$ is the per capita recovery rate for chronic infectives with infection age a, and c is the per capita rate for loss of immunity. We assume that all parameters are nonnegative with $b > 0$, $\mu > 0$, $\gamma > 0$, and that $\alpha(a)$, $\delta(a)$ are bounded functions of a. We also assume that $\int_0^\infty \alpha(a)\mathrm{d}a = \infty$, to guarantee that $\lim_{a\to\infty} J(a,t) = 0$ for all t.

The equation for the chronic class is

$$\frac{\mathrm{d}C}{\mathrm{d}t} = kI - \mu C - \int_0^\infty \alpha(a)J(a,t)\mathrm{d}t.$$

By adding the equations for the population subclasses we obtain the equation for the total population size

$$\frac{\mathrm{d}N}{\mathrm{d}t} = bN - \mu N.$$

This equation has the solution $N = N_0 \exp((b-\mu)t)$.

We normalize the model to consider the proportional dynamics of the system by introducing new variables

$$s = \frac{S}{N}, \quad v = \frac{V}{N}, \quad i = \frac{I}{N}, \quad j = \frac{J}{N}, \quad r = \frac{R}{N},$$

and the new variables satisfy the following equations:

$$\begin{aligned}
&\frac{\mathrm{d}s}{\mathrm{d}t} = b(1-s) - \gamma s i - s\int_0^\infty \delta(a) j(a,t)\mathrm{d}a - \psi s + cr,\\
&\frac{\mathrm{d}v}{\mathrm{d}t} = \psi s - \sigma\gamma v i - bv,\\
&\frac{\mathrm{d}i}{\mathrm{d}t} = \gamma i(s+\sigma v) + s\int_0^\infty \delta(a) j(a,t)\mathrm{d}a - (b+k)i,\\
&\frac{\mathrm{d}r}{\mathrm{d}t} = \int_0^\infty \alpha(a) j(a,t)\mathrm{d}a - (b+c)r,\\
&\frac{\partial j}{\partial a} + \frac{\partial j}{\partial t} = -(b+\alpha(a))j(a,t), \quad j(0,t) = ki(t),\\
&s + v + i + \int_0^\infty j(a,t)\mathrm{d}a + r = 1.
\end{aligned} \tag{5.23}$$

We set $\pi(a) := \exp\big(-\int_0^a \alpha(\theta)\mathrm{d}\theta\big)$, $d := \int_0^\infty \delta(a)\mathrm{e}^{-ba}\pi(a)\mathrm{d}a$, and define the vaccination-dependent reproductive number for (5.23) by

$$R(\psi) = \frac{b}{b+\psi}\frac{\gamma + kd}{b+k} + \frac{\psi}{b+\psi}\frac{\sigma\gamma}{b+k}.$$

Proportions, $b/(b+\psi)$ and $\psi/(b+\psi)$, of the contacts are with susceptibles and vaccinated individuals, respectively. An infective makes $\gamma/(b+k)$ infectious contacts while in the acute stage, and this number is reduced by a factor of σ when the contacts are with vaccinated individuals. In addition, a proportion, $k/(k+b)$, of infectives progresses to the chronic stage before dying, and those infectives then make an average of d infectious contacts while in the chronic stage. We can therefore interpret $R(\psi)$ as the sum of the proportions of infections made in the acute and chronic infective

stages. We note that $R(\psi)$ is a decreasing function of the vaccination rate ψ. The basic reproductive number becomes smaller due to the vaccination. When $\psi = 0$, we see that $R(0)$ is the basic reproductive number.

It is easy to see that $P_0(s_0, v_0, i_0, j_0(a), r_0)$ is the disease-free equilibrium of (5.23), where

$$s_0 = \frac{b}{b+\psi}, \quad v_0 = \frac{\psi}{b+\psi}, \quad i_0 = 0, \quad j_0(a) = 0, \quad r_0 = 0.$$

The characteristic equation of the linearized system of (5.23) at the disease-free equilibrium is

$$\lambda + b + k = \frac{\gamma(b+\sigma\psi)}{b+\psi} + \frac{bk}{b+\psi}\int_0^\infty \delta(a)\mathrm{e}^{-(\lambda+b)a}\pi(a)\mathrm{d}a. \tag{5.24}$$

For real value of λ, the expression on the left-hand side of (5.24) increases linearly in λ and is negative for $\lambda < -(b+k)$, whereas the expression on the right-hand side is positive and a monotone decreasing function of λ. This implies that the characteristic equation (5.24) has a unique real solution $\lambda = \lambda_0 > -(b+k)$. We can also verify that the real part of any complex solution of the characteristic equation (5.24) does not exceed the unique real solution λ_0. Indeed, if $\lambda = x + iy$ is a complex solution, then x satisfies the following inequality:

$$x + b + k \leq \frac{\gamma(b+\sigma\psi)}{b+\psi} + \frac{bk}{b+\psi}\int_0^\infty \delta(a)\mathrm{e}^{-(x+b)a}\pi(a)\mathrm{d}a. \tag{5.25}$$

We introduce the function

$$g(x) = \frac{\gamma(b+\sigma\psi)}{(b+\psi)(x+b+k)} + \frac{bk}{(b+\psi)(x+b+k)}\int_0^\infty \delta(a)\mathrm{e}^{-(x+b)a}\pi(a)\mathrm{d}a. \tag{5.26}$$

Clearly, $g(x) = 1$ for every solution of Eq. (5.24). Consequently, $g(\lambda_0) = 1 \leq g(x)$. The fact that $g(x)$ is a decreasing function of x implies that $x \leq \lambda_0$.

It is easy to verify that $\lambda_0 < 0$ is equivalent to $R(\psi) < 1$. Consequently, we know that the disease-free equilibrium, P_0, of (5.23) is stable if $R(\psi) < 1$. It is also proved that if $R(0) < 1$, the disease-free equilibrium of (5.23) is globally asymptotically stable [Kribs-Zaleta and Martcheva (2002)].

We now turn our attention to the existence of the endemic equilibrium $P^*(s^*, v^*, i^*, j^*(a), r^*)$ of (5.23). By setting the time derivatives to zero,

we have following expressions:

$$\begin{aligned} j^*(a) &= ki^*\mathrm{e}^{-ba}\pi(a), \qquad r^* = \frac{ki^*}{b+c}\int_0^\infty \alpha(a)\mathrm{e}^{-ba}\pi(a)\mathrm{d}a, \\ s^* &= \frac{b+cr^*}{b+\psi+(\gamma+kd)i^*}, \quad v^* = \frac{\psi s^*}{\sigma\psi i^*+b}. \end{aligned} \tag{5.27}$$

We can eliminate s^*, v^* $j^*(a)$ and r^* to obtain the following single quadratic equation for i^*:

$$Ai^2 + Bi + C = 0, \tag{5.28}$$

where

$$A = \sigma\gamma(\gamma+\mathrm{d}k)\left(1+\frac{k(1+c\tau)}{b+c}\right) \geq 0,$$

$$B = (b(\gamma+\mathrm{d}k)+\sigma\gamma\psi)\left(1+\frac{k(1+c\tau)}{b+c}\right)+\sigma\gamma(b+k-(\gamma+\mathrm{d}k)),$$

$$C = (b+k)(b+\psi)(1-R(\psi)),$$

and $\tau = \int_0^\infty \mathrm{e}^{-ba}\pi(a)\mathrm{d}a$.

We note that $A = 0$, if and only if $\sigma = 0$. $A = 0$ implies that the endemic equilibrium exists and is unique only if $R(\psi) > 1$. In what follows we assume $\sigma > 0$. In the case that $R(\psi) > 1$, we see that $C < 0$, so that the discriminant $B^2 - 4AC$ is positive and greater than B^2. Hence there is exactly one positive solution of (5.28). If, however, $R(\psi) < 1$, then $C > 0$, and (5.28) has either zero or two positive solutions. To have two positive solutions we need $B^2 - 4AC > 0$ and $B < 0$. Multiple endemic equilibria and backward bifurcation may appear. See [Kriba-Zaleta and Martcheva (2002)] for details.

A specific example is given below to illustrate the backward bifurcation. We use the following parameter values: $b = 1/1095$ days^{-1}, $\psi = 0.001$ days^{-1}, $\sigma = 0.5$, $k = 1/30$ days^{-1}, $\delta(a) = 0.000194$ days^{-1}, $\alpha(a) = 1/45$ days^{-1}, $c = 1000$ days^{-1}, and allowing γ to vary. The bifurcation diagram is shown in Fig. 5.4.

5.3.2. *An epidemic model with two age structures*

In this subsection we study an SIS model with two age structures. Chronologic age is introduced in every population groups. We assume that the total population reaches its steady state $p_\infty(a)$, and the total population be divided into two classes: the susceptibles with age density $s(a,t)$ and

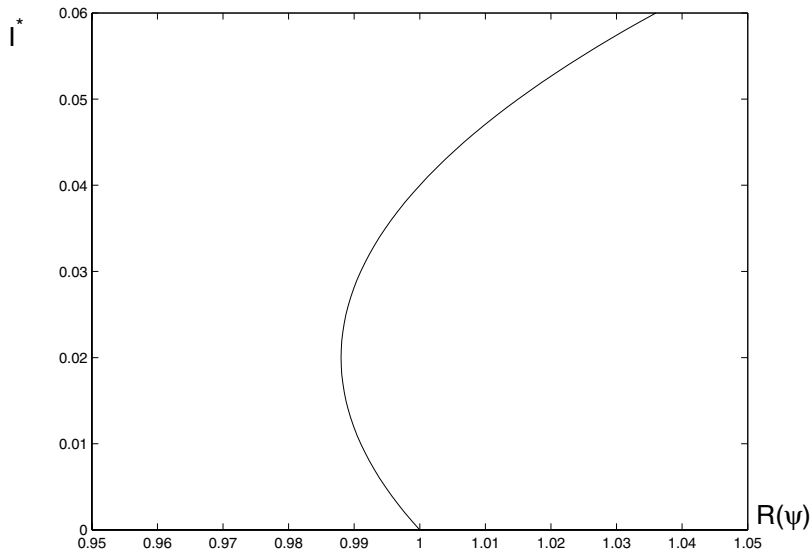


Fig. 5.4. The backward bifurcation of model (5.23).

the infectives with age and infection-age density $i(a, c, t)$, where a is the chronologic age and c is the infection age. Then the total numbers of the susceptibles $S(t)$ and the infectives $I(t)$, at time t, are given by

$$S(t) = \int_0^A s(a,t)\mathrm{d}a,$$

$$I(t) = \int_0^A \int_0^a i(a,c,t)\mathrm{d}c\mathrm{d}a,$$

where A is the maximal age that an individual can reach. We assume that the force of infection is given by

$$\begin{aligned} G(a,t) &= s(a,t)\int_0^A \int_0^{a'} \lambda(a,a',c)i(a',c,t)\mathrm{d}c\mathrm{d}a' \\ &= \left(p_\infty(a) - \int_0^a i(a,c,t)\mathrm{d}c\right)\int_0^A \int_0^{a'} \lambda(a,a',c)i(a',c,t)\mathrm{d}c\mathrm{d}a'. \end{aligned} \tag{5.29}$$

Since the density of the susceptibles can be obtained from the formula

$$s(a,t) = p_\infty(a) - \int_0^A i(a,c,t)\mathrm{d}c,$$

our main attention focuses on the density of the infected individuals. The density $i(a,c,t)$ of the infected individuals satisfies following system of equations:

$$\begin{aligned}
&\frac{\partial i(a,c,t)}{\partial a}+\frac{\partial i(a,c,t)}{\partial c}+\frac{\partial i(a,c,t)}{\partial t}=-(\mu(a)+\gamma(a))i(a,c,t),\\
&i(a,0,t)=G(a,t),\\
&i(a,c,0)=i_0(a,c),
\end{aligned}\tag{5.30}$$

where $\mu(a)$ and $\gamma(a)$ denote the age-specific death and recovery rates of the infective individuals, respectively, and $\lambda(a,a',c)$ is the rate at which an infective individual of age a' and infection-age c has a disease transmission contact with a susceptible of age a.

We assume that the disease does not significantly affect the death rate and the recovery rate of the infectives. For the parameters $\mu(a)$, $\gamma(a)$, $\lambda(a,a',c)$, and initial value $i_0(a,c)$, we make following assumptions:

(H1) $\mu(a)$ is a continuous function on $[0,A)$, $\mu(a)>0$ for $a\in[0,A)$, and $\lim_{a\to A^-}\int_0^a\mu(s)\mathrm{d}s=+\infty$.

(H2) $\gamma(a)$ is a nonnegative and continuous function on $[0,A]$.

(H3) $\lambda(a,a',c)$ is a bounded, positive, and continuous function on $0\le a\le A, 0\le c\le a'\le A$, and we define

$$\lambda^*=\max_{0\le a\le A,0\le c\le a'\le A}\lambda(a,a',c).$$

(H4) $i_0(a,c)$ is bounded, nonnegative, and continuous function on $0\le c\le a\le A$. And $i_0(a,c)$ satisfies the continuous compatible condition

$$\left(p_\infty(a)-\int_0^a i_0(a,c)\mathrm{d}c\right)\int_0^A\int_0^{a'}\lambda(a,a',c)i_0(a',c)\mathrm{d}c\mathrm{d}a'=i_0(a,0).$$

In the rest of this subsection we assume that assumptions (H1)–(H4) hold. The SIS model (5.30) has a unique continuous solution for all $t\ge0$ [Tucker and Zimmerman (1988)]. It is proved that the solution of the SIS model (5.30) is nonnegative if the initial condition $i_0(a,c)$ satisfies $\int_0^a i_0(a,c)\mathrm{d}c\le p_\infty(a)$ [Zhou *et al.* (2001)].

We next assume that $\lambda(a,a',c)=\lambda_1(a)\lambda_2(a',c)$, $0\le\lambda_1(a)<\lambda^*, 0\le\lambda_2(a',c)<\lambda^*$, and study the stability of the disease-free equilibrium and the existence of an endemic equilibrium.

By defining

$$w(t) = \int_0^A \int_0^{a'} \lambda_2(a', c) i(a', c, t) \mathrm{d}c\mathrm{d}a',$$

we see that

$$w(t) = \int_0^A \int_0^{a'} \lambda_2(a', c) G(a' - c, t - c) N(a')/N(a' - c) \mathrm{d}c\mathrm{d}a', \quad t \geq A,$$

where $N(a) = \exp\big(-\int_0^a \big(\mu(\tau) + \gamma(\tau)\big)\mathrm{d}\tau\big)$. From Eq. (5.29) we obtain

$$\begin{aligned} w(t) = & \int_0^A \int_0^{a'} \lambda_1(a' - c)\lambda_2(a', c) \\ & \times p_\infty(a' - c) \frac{N(a')}{N(a' - c)} w(t - c) \mathrm{d}c\mathrm{d}a' \\ & - \int_0^A \int_0^{a'} \lambda_1(a' - c)\lambda_2(a', c) \int_0^{a'-c} G(a' - c - \tau, t - c - \tau) \\ & \times \frac{N(a')w(t - c)}{N(a' - c - \tau)} \mathrm{d}\tau\mathrm{d}c\mathrm{d}a', \end{aligned} \tag{5.31}$$

and then

$$w(t) \leq \int_0^A \int_0^{a'} \lambda_1(a' - c)\lambda_2(a', c) p_\infty(a' - c) \frac{N(a')}{N(a' - c)} w(t - c) \mathrm{d}c\mathrm{d}a'.$$

We define the basic reproductive number of (5.30) to be

$$R_0 = \int_0^A \int_0^{a'} \lambda_1(a' - c)\lambda_2(a', c) p_\infty(a' - c) \frac{N(a')}{N(a' - c)} \mathrm{d}c\mathrm{d}a'.$$

The following threshold result for the stability of disease-free equilibrium model (5.30) is obtained [Zhou *et al.* (2001)].

Theorem 5.9. *Assume that assumptions* $(H1)$*–*$(H4)$ *hold. Then the disease-free equilibrium* (5.30) *is globally asymptotically stable if* $R_0 < 1$*. The disease-free equilibrium is unstable and there exists a unique endemic equilibrium if* $R_0 > 1$*.*

5.4. Discrete Models

While age-structured epidemic models provide good insight into the transmission process of infectious diseases, it is more difficult to study their

dynamic behavior and the determination of those continuous parameter functions for the continuous age-structured models is not an easy task. Nevertheless, compared to the continuous models, discrete age-structured epidemic models are simpler. The well-posedness of the discrete models is trivial, and the collection of statistic data is based on a discrete basis. Moreover, the dynamic behavior of the discrete models is richer and more complicated than their analogous continuous models. We present discrete age-structured epidemic models and investigate their dynamics in this section.

Discrete models in population dynamics have been extensively studied (see for example, [Cushing (1998); Zhou and Cushing (1998); Smith (2001)]), but the formulation and the analysis of discrete models in epidemiology are still at an infant stage. Allen studied discrete SI, SIS, and SIR epidemic models and found that the SI and SIR models are similar in behavior to their continuous analogues under some natural restrictions, but discrete SIS models can have more diverse behavior [Allen (1994)]. Castillo-Chavez and Yakubu studied a discrete SIS model which exhibits bistability over a wide range of parameter values [Castillo-Chavez and Yahubu (2001)]. Mendez and Fort investigated dynamic evolutions of discrete epidemic models by taking into account an intermediate class of population [Mendez and Fort (2000)]. Allen and Thrasher formulated an age-structured model for varicella and herpes zoster, and the effects of various control strategies are investigated [Allen and Thrasher (1998)]. Zhou and Fergola formulated a general discrete age-structured SIS model, and investigated the dynamic behavior of the model [Zhou and Fergola (2004)].

5.4.1. *The model formulation*

Suppose the maximal age of the population is A. We divide the population into $m+1$ subgroups according to their ages. Let $N_j(t)$, $j = 0, 1, 2, \ldots, m$, be the number of individuals with age $a \in [jA/(m+1), (j+1)A/(m+1)]$, at time t. To concentrate on the dynamics of disease transmissions, we assume that the total population reaches its stable distribution: that is, $N_j(t) = N_j$, $j = 0, 1, \ldots, m$, where N_j are constants. Then we consider an infectious disease spreading in the constant population.

We divide the population in each age group into susceptible and infectious classes. Let $S_j(t)$ and $I_j(t)$ denote the numbers of the susceptibles and infectives in age-group j, respectively. We assume that all the newborns are susceptible and in S_0. After one unit time, the susceptibles in class

S_j progress to class S_{j+1}, are infected and move to class I_{j+1}, or die. The infectives in class I_j can transfer to class I_{j+1}, recover to class S_{j+1}, or die. Then the discrete age-structured SIS model is described by the system

$$\begin{aligned}
&S_0(t+1) = N_0, \quad I_0(t+1) = 0,\\
&S_{j+1}(t+1) = p_j S_j(t) - \lambda_j \sum_{k=0}^{m} \beta_k I_k(t) \frac{S_j(t)}{N_j(t)} + \gamma_j I_j(t),\\
&I_{j+1}(t+1) = p_j I_j(t) + \lambda_j \sum_{k=0}^{m} \beta_k I_k(t) \frac{S_j(t)}{N_j(t)} - \gamma_j I_j(t),\\
&S_j(0) = S_{j0} \geq 0, \quad I_j(0) = I_{j0} \geq 0,
\end{aligned} \tag{5.32}$$

where $\beta_k \lambda_j$ is the transmission rate between an infective in group k and a susceptible in group j, γ_j is the recovery rate and p_j is the survival rate for individuals in group j, $j = 0, 1, \ldots, m$.

The existence and uniqueness of the solution of the initial value problem (5.32) is obvious. The nonnegativity of the solution is given in the following theorem.

Theorem 5.10. *If* $d_j + \gamma_j \leq 1$, $(d_j = 1 - p_j)$ *and* $d_j + (\lambda_j / N_j) \sum_{k=0}^{m} \beta_k N_k \leq 1$, $j = 0, 1, \ldots, m-1$, *then all solution of* (5.32) *are nonnegative.*

Proof. Let $0 < I_{j0} \leq N_j$, $0 < S_{j0} \leq N_j$, and the conditions of Theorem 5.10 hold. It is easy to see that $I_j(t) \geq 0$, for all t since $d_j + \gamma_j \leq 1$. We prove the nonnegativity of the solution by induction.

Suppose

$$S_{j+1}(1) = \left(p_j - \frac{\lambda_j}{N_j} \sum_{k=0}^{m} \beta_k I_k(0) \right) S_j(0) + \gamma_j I_j(0) \geq 0, \qquad j = 0, 1, \ldots, m-1.$$

From the fact that $S_j(t) + I_j(t) = N_j$, we have $I_j(1) \leq N_j (j = 0, 1, \ldots, m)$ and

$$d_j + \frac{\lambda_j}{N_j} \sum_{k=0}^{m} \beta_k I_k(1) \leq d_j + \frac{\lambda_j}{N_j} \sum_{k=0}^{m} \beta_k N_k \leq 1, \quad j = 0, 1, \ldots, m-1.$$

As a consequence, we have

$$S_{j+1}(2) = \left(p_j - \frac{\lambda_j}{N_j}\sum_{k=0}^{m}\beta_k I_k(1)\right) S_j(1) + \gamma_j I_j(1) \geq 0, \quad j = 0, 1, \ldots, m-1.$$

Hence $S_j(t) \geq 0$ for all $t \geq 0$ and $j \geq 0$, and all solutions of (5.32) are nonnegative. □

Remark. The conditions in Theorem 5.10 are epidemiologically meaningful. Condition $d_j + \gamma_j \leq 1$ means that the percentage of the infectives who die or recover is less than one, and $d_j + (\lambda_j/N_j)\sum_{k=0}^{m}\beta_k N_k \leq 1$ states that the percentage of the susceptibles who die or get infected is less than one.

Using the fact that $S_j(t) + I_j(t) = N_j$, the SIS model (5.32) can be reduced to

$$\begin{aligned} &I_0(t+1) = 0, \\ &I_{j+1}(t+1) = (p_j - \gamma_j) I_j(t) + \lambda_j \sum_{k=1}^{m}\beta_k I_k(t)\left(1 - \frac{I_j(t)}{N_j}\right), \\ &I_j(0) = I_{j0}. \end{aligned} \tag{5.33}$$

Define

$$\begin{aligned} &\vec{I}(t) = (I_1(t), I_2(t), \ldots, I_m(t))^\tau, \quad \tau \text{ stands for the transpose}, \\ &F = (F_{i,j})_{m\times m}, \quad F_{i,j} = \beta_j, \quad i, j = 1, 2, \ldots, m, \\ &T = (T_{i,j})_{m\times m}, \quad T_{i,i} = \lambda_{i-1}, \quad i = 1, 2, \ldots, m, \\ &B = (B_{i,j})_{m\times m}, \quad B_{i+1,i} = p_i - \gamma_i, \quad i = 1, 2, \ldots, m-1, \\ &M(\vec{I}(t)) = (M_{i,j})_{m\times m}, \quad M_{i+1,i} = \lambda_i I_i(t)/N_i, \quad i = 1, 2, \ldots, m-1, \end{aligned}$$

where the other entries in the matrices T, B, $M(\vec{I}(t))$ are zero. Then the equations for $I_j(t)$, in (5.33), can be written as

$$\vec{I}(t+1) = B\vec{I}(t) + TF\vec{I}(t) - M(\vec{I}(t))F\vec{I}(t), \quad t = 0, 1, 2, \ldots. \tag{5.34}$$

The expression in (5.34) can make our statement easier and simpler.

5.4.2. *The existence of the endemic equilibrium*

The equilibrium is the time-independent solution of (5.34), that is, a solution of the equation

$$\vec{I} = B\vec{I} + TF\vec{I} - M(\vec{I})F\vec{I}. \tag{5.35}$$

It is obvious that $\vec{I} = \vec{0}$ is a solution, which is the disease-free equilibrium.

Let $x = \sum_{k=1}^{m} \beta_k I_k$. Then $0 \le x \le \sum_{k=1}^{m} \beta_k N_k$. Equation (5.35) can be rewritten as

$$\vec{I} = B\vec{I} + xE\vec{\lambda} - xQ\vec{I}, \tag{5.36}$$

where E is the $m \times m$ identity matrix, and

$$\vec{\lambda} = (\lambda_0, \lambda_1, \lambda_2, \ldots, \lambda_{m-1})^\tau,$$
$$Q = (Q_{i,j})_{m\times m}, \quad Q_{i+1,i} = \lambda_i/N_i, \quad i = 1, 2, \ldots, m-1,$$

where the other entries in the matrix Q are zero.

Solving Eq. (5.36) for $\vec{I}$ yields

$$\vec{I} = x(E - B + xQ)^{-1}\vec{\lambda}.$$

Substituting $\vec{I}$ into the expression of x, we arrive at the equation

$$f(x) = (\beta_1, \beta_2, \ldots, \beta_m)(E - B + xQ)^{-1}\vec{\lambda} = 1.$$

A simple algebraic calculation gives the following explicit expression of $f(x)$:

$$\begin{aligned} f(x) = {} & \beta_1\lambda_0 + \beta_2(\lambda_1 + \lambda_0 q_1(x)) + \beta_3(\lambda_2 + \lambda_1 q_2(x) \\ & + \lambda_0 q_1(x)q_2(x)) + \cdots + \beta_m(\lambda_{m-1} + \lambda_{m-2}q_{m-1}(x) \\ & + \lambda_{m-3}q_{m-2}(x)q_{m-1}(x) + \cdots + \lambda_1 q_2(x)q_3(x)\cdots q_{m-1}(x) \\ & + \lambda_0 q_1(x)q_2(x)\cdots q_{m-1}(x)), \end{aligned}$$

where $q_j = q_j(x) = p_j - \gamma_j - x\lambda_j/N_j, j = 1, 2, \ldots, m-1$. Using the notations

$$a_j = (\beta_1, \beta_2, \ldots, \beta_m)[(E - B)^{-1}Q]^j((E - B)^{-1}\vec{\lambda}, \quad j = 0, 1, \ldots, m-1,$$

we have

$$\begin{aligned} a_0 - 1 = {} & a_1 x - a_2 x^2 + a_3 x^3 + \cdots \\ & + (-1)^{m-1} a_{m-2} x^{m-2} + (-1)^m a_{m-1} x^{m-1}. \end{aligned} \tag{5.37}$$

Define the basic reproductive number $R_0 = f(0) = a_0$. From Eq. (5.37), we obtain the following bifurcation theorem for the endemic equilibrium.

Theorem 5.11. *The age-structured SIS model* (5.34) *has an endemic equilibrium when R_0 is greater than and near one.*

Proof. The existence of an endemic equilibrium of (5.34) is equivalent to the existence of a positive root of (5.37). From the bifurcation theory it follows that there exists one and only one positive root of (5.37) if $R_0 > 1$ and $R_0 - 1$ is sufficiently small.

From the positive solution of (5.37) we can obtain the endemic equilibrium

$$\begin{aligned}
&I_1 = x\lambda_0,\\
&I_2 = x(\lambda_1 + \lambda_0 q_1(x)),\\
&\vdots\\
&I_m = x(\lambda_{m-1} + \lambda_{m-2}q_{m-1}(x) + \lambda_{m-3}q_{m-2}(x)q_{m-3}(x) + \cdots\\
&\qquad + \lambda_1 q_2(x)q_3(x)\cdots q_{m-1}(x) + \lambda_0 q_1(x)q_2(x)\cdots q_{m-1}(x)).
\end{aligned}$$

□

It is not easy to obtain the existence for large endemic equilibrium, the conjecture is that there exists an endemic equilibrium of (5.34) if $R_0 > 1$.

5.4.3. *The stability of the disease-free equilibrium*

To investigate the local stability of the disease-free equilibrium we use linearized system of (5.34)

$$\vec{I}(t+1) = B\vec{I}(t) + TF\vec{I}(t), \quad t = 0, 1, 2, \ldots. \tag{5.38}$$

Since

$$B+TF = B+\begin{bmatrix}
\lambda_0\beta_1 & \lambda_0\beta_2 & \lambda_0\beta_3 & \cdots & \lambda_0\beta_{m-1} & \lambda_0\beta_m\\
\lambda_1\beta_1 & \lambda_1\beta_2 & \lambda_1\beta_3 & \cdots & \lambda_1\beta_{m-1} & \lambda_1\beta_m\\
\lambda_2\beta_1 & \lambda_2\beta_2 & \lambda_2\beta_3 & \cdots & \lambda_2\beta_{m-1} & \lambda_2\beta_m\\
\vdots & \vdots & \vdots & \vdots & \vdots & \vdots\\
\lambda_{m-1}\beta_1 & \lambda_{m-1}\beta_2 & \lambda_{m-1}\beta_3 & \cdots & \lambda_{m-1}\beta_{m-1} & \lambda_{m-1}\beta_m
\end{bmatrix}$$

is a nonnegative matrix, the asymptotic behavior of (5.38) depends on the magnitude of the eigenvalues of $B + TF$. It follows from the Frebenius theorem for nonnegative matrices that $B + TF$ has one positive dominant eigenvalue ρ_0, and the module of each of the other eigenvalues, ρ, of $B+TF$ is not great than ρ_0: that is, $|\rho| \leq \rho_0$. Therefore, the stability of the disease-free equilibrium of (5.34) is determined by the dominant eigenvalue ρ_0.

To obtain the stability condition, we consider the linear system

$$(B+TF)\vec{v} = \rho E\vec{v}.$$

Matrix $B+TF$ has the dominant eigenvalue $\rho_0 = 1$ if and only if the equation

$$(E-B)^{-1}TF\vec{v} = \vec{v}$$

has a nonzero solution; that is, $(E-B)^{-1}TF$ has an eigenvalue 1. An algebraic calculation yields

$$(E-B)^{-1}TF = \begin{bmatrix} \beta_1 w_1 & \beta_2 w_1 & \beta_3 w_1 & \cdots & \beta_m w_1 \\ \beta_1 w_2 & \beta_2 w_2 & \beta_3 w_2 & \cdots & \beta_m w_2 \\ \beta_1 w_3 & \beta_2 w_3 & \beta_3 w_3 & \cdots & \beta_m w_3 \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ \beta_1 w_m & \beta_2 w_m & \beta_3 w_m & \cdots & \beta_m w_m \end{bmatrix},$$

where

$$\begin{aligned} &w_1 = \lambda_0, \quad w_2 = \lambda_1 + \lambda_0 q_1(0), \\ &w_3 = \lambda_2 + \lambda_1 q_2(0) + \lambda_0 q_1(0) q_2(0), \\ &\vdots \\ &w_m = \lambda_{m-1} + \lambda_{m-2} q_{m-1}(0) + \lambda_{m-3} q_{m-2}(0) q_{m-1}(0) + \cdots \\ &\qquad + \lambda_1 q_2(0) q_3(0) \cdots q_{m-1}(0) + \lambda_0 q_1(0) q_2(0) \cdots q_{m-1}(0). \end{aligned}$$

The characteristic equation of matrix $(E-B)^{-1}TF$ is

$$\rho^{m-1}(\beta_1 w_1 + \beta_2 w_2 + \cdots + \beta_m w_m - \rho) = 0.$$

The unique positive eigenvalue of $(E-B)^{-1}TF$ is

$$\rho = \beta_1 w_1 + \beta_2 w_2 + \cdots + \beta_m w_m = (\beta_1, \beta_2, \ldots, \beta_m)(E-B)^{-1}\vec{\lambda} = R_0.$$

From the linearization and comparison theory, we have following stability result.

Theorem 5.12. *The disease-free equilibrium* $\vec{I}^{\,0} = \vec{0}$ *of* (5.34) *is globally asymptotically stable if* $R_0 < 1$, *and is unstable if* $R_0 > 1$.

Proof. The linearized system (5.38) of (5.34) is stable if the dominant eigenvalue ρ_0 of $B+TF$ is less than 1, and unstable if the dominant eigenvalue is greater than 1. The above analysis shows that the dominant

eigenvalue equals to 1 if and only if $R_0 = 1$. From the theory on the discrete structured population models, it follows that [Cushing and Zhou (1994)]

$$\rho_0 < 1 \quad \text{if and only if} \quad R_0 < 1.$$

Therefore, the disease-free equilibrium is stable if $R_0 < 1$, and unstable if $R_0 > 1$.

From iterative relation (5.34), we see that $\vec{I}(t) \geq \vec{0}$, and

$$\vec{I}(t+1) \leq B\vec{I}(t) + TF\vec{I}(t), \quad t = 0, 1, 2, \ldots. \tag{5.39}$$

Then the comparison principle implies that the solution to the Eq. (5.34) is not greater than the solution to Eq. (5.38). We note that the zero solution of the linear system (5.38) is globally stable: that is, $\lim_{t\to\infty} \vec{I}(t) = \vec{0}$. Hence, all of the nonnegative solutions of (5.34) tend to zero as t approaches infinity, and the disease-free equilibrium is globally asymptotically stable. □

5.4.4. *The stability of the endemic equilibrium*

The linearized system of (5.34) at the endemic equilibrium, $\vec{I}^*$, is

$$\vec{z}(t+1) = \big(B + TF - M(\vec{I}^*)F - M(x^*)\big)\vec{z}(t), \quad t = 0, 1, 2, \ldots, \tag{5.40}$$

where

$$\begin{aligned}
&x^* = \beta_1 I_1^* + \beta_2 I_2^* + \cdots + \beta_m I_m^*,\\
&M(x^*) = (X_{i,j})_{m\times m},\\
&X_{i+1,i} = \lambda_i x^*/N_i, \quad i = 1, 2, \ldots, m-1,\\
&X_{i,j} = 0, \quad \text{if } i \neq j+1, \quad j = 1, 2, \ldots, m-1.
\end{aligned}$$

An algebraic calculation shows that the matrix $TF - M(\vec{I}^*)F$ is of the form

$$\begin{bmatrix}
\lambda_0\beta_1 & \lambda_0\beta_2 & \cdots & \lambda_0\beta_m\\
\lambda_1\beta_1\left(1 - \dfrac{I_1^*}{N_1}\right) & \lambda_1\beta_2\left(1 - \dfrac{I_1^*}{N_1}\right) & \cdots & \lambda_1\beta_m\left(1 - \dfrac{I_1^*}{N_1}\right)\\
\vdots & \vdots & \vdots & \vdots\\
\lambda_{m-1}\beta_1\left(1 - \dfrac{I_{m-1}^*}{N_{m-1}}\right) & \lambda_{m-1}\beta_2\left(1 - \dfrac{I_{m-1}^*}{N_{m-1}}\right) & \cdots & \lambda_{m-1}\beta_m\left(1 - \dfrac{I_{m-1}^*}{N_{m-1}}\right)
\end{bmatrix},$$

and the nonzero entries of matrix $B - M(x^*) = (Y_{i,j})_{m\times m}$ are

$$Y_{i+1,i} = p_i - \gamma_i - \lambda_i x^*/N_i, \quad i = 1, 2, \ldots, m-1.$$

If condition

$$p_j - \gamma_j - \lambda_j x^*/N_j \geq 0, \quad j = 0, 1, \ldots, m-1, \tag{5.41}$$

holds, then $B - M(x^*)$, $TF - M(\vec{I}^*)F$, and $B + TF - M(\vec{I}^*)F - M(x^*)$ are nonnegative matrices. The stability of the endemic equilibrium can be investigated in a similar manner as that for the disease-free equilibrium. In fact, the matrices $B - M(x^*)$ and $TF - M(\vec{I}^*)F$ in (5.40) play the same role as the matrices B and TF in (5.38). The stability of (5.40) can be determined by the dominant eigenvalue of the matrix $B + TF - M(\vec{I}^*)F - M(x^*)$, and equivalently, by the dominant eigenvalue of the matrix $(E - (B - M(\vec{I}^*)F))^{-1}(TF - M(x^*))$.

Define

$$\begin{aligned}
&u_1(x^*) = \lambda_0,\\
&u_2(x^*) = \lambda_1(1 - I_1^*/N_1) + \lambda_0 q_1(x^*),\\
&\vdots\\
&u_m(x^*) = \lambda_{m-1}(1 - I_{m-1}^*/N_{m-1}) + \lambda_{m-2}(1 - I_{m-2}^*/N_{m-2})q_{m-1}(x^*)\\
&\qquad\quad + \lambda_1(1 - I_1^*/N_1)q_2(x^*)\cdots q_{m-1}(x^*) + \lambda_0 q_1(x^*)\cdots q_{m-1}(x^*)
\end{aligned}$$

and

$$R_1 = \beta_1 u_1(x^*) + \beta_2 u_2(x^*) + \cdots + \beta_m u_m(x^*).$$

A similar argument as that in Theorem 5.12 leads to following result [Zhou and Fergola (2004)].

Theorem 5.13. *The endemic equilibrium,* $\vec{I}^*$, *of* (5.34) *is asymptotically stable if* $R_1 < 1$, *and it is unstable if* $R_1 > 1$.

From Theorem 5.13, we see that the endemic equilibrium is stable if $R_1 < 1$. This sufficient condition may not be necessary. We have the following global attraction result under certain conditions.

Let us assume that

$$(A)\ d_j + \gamma_j + \frac{\lambda_j}{N_j^*}\sum_{k=1}^{m}\beta_k N_k^* \leq 1, \quad p_j = 1 - d_j,\ \ j = 1, 2, \ldots, m-1.$$

We can show that the domain

$$D = \{(I_1, I_2, \ldots, I_m) \mid 0 \leq I_j \leq N_j, \quad j = 1, 2, \ldots, m\}$$

is positively invariant for model (5.33); that is, the solution of (5.33), with the initial value in D, stays in D, for all $t = 1, 2, \ldots$. In fact, if $0 \le I_j(t) \le N_j, j = 1, 2, \ldots, m$, then

$$I_{j+1}(t+1) = I_j(t)\left(1 - d_j - \gamma_j - \frac{\lambda_j}{N_j}\sum_{k=1}^{m}\beta_k I_k(t)\right) + \lambda_j \sum_{k=1}^{m}\beta_k I_k(t) \ge 0,$$

$$\begin{aligned} I_{j+1}(t+1) &\le (p_j - \gamma_j)I_j(t) + (p_j - \gamma_j)\left(N_j - I_j(t)\right) \\ &= (p_j - \gamma_j)N_j \le p_j N_j = N_{j+1}, \quad j = 0, 1, \ldots, m-1. \end{aligned}$$

Let $I_j = I_j^*$ be the endemic equilibrium of model (5.33); that is,

$$I_{j+1}^* = (p_j - \gamma_j)I_j^* + \lambda_j \sum_{k=1}^{m}\beta_k I_k^*\left(1 - \frac{I_j^*}{N_j}\right), \quad j = 0, 1, 2, \ldots, m-1.$$

Then it is easy to check that if $k \ne j$,

$$\frac{\partial I_{j+1}(t+1)}{\partial I_k(t)} = \lambda_j \beta_k \left(1 - \frac{I_j(t)}{N_j}\right),$$

and if $k = j$,

$$\frac{\partial I_{j+1}(t+1)}{\partial I_k(t)} = \lambda_j \beta_j \left(1 - \frac{I_j(t)}{N_j}\right) + 1 - d_j - \gamma_j - \frac{\lambda_j}{N_j}\sum_{k=1}^{m}\beta_k I_k(t).$$

Under the assumption (A), we see that

$$\frac{\partial I_{j+1}(t+1)}{\partial I_k(t)} \ge 0;$$

that is, the solutions of model (5.33) are monotone. For any solution of (5.33) with positive initial value $I_j(0)$, we can choose a small positive ε such that

$$\varepsilon I_j^* \le I_j(0), \quad j = 1, 2, \ldots, m.$$

It follows from the comparison principle that

$$I_j^{\varepsilon}(t) \le I_j(t), \quad j = 1, 2, \ldots, m, \ \ t = 1, 2, \ldots,$$

where $I_j^\varepsilon(t)$ is the solution of (5.33) with the initial value $I_j^\varepsilon(0) = \varepsilon I_j^*$. For the solution $I_j^\varepsilon(t)$ we see that

$$\begin{aligned} I_{j+1}^\varepsilon(1) &= (p_j - \gamma_j)\varepsilon I_j^* + \varepsilon\lambda_j \sum_{k=1}^m \beta_k I_k^* \left(1 - \frac{\varepsilon I_j^*}{N_j}\right) \\ &= \varepsilon I_{j+1}^* + \varepsilon\lambda_j \sum_{k=1}^m \beta_k I_k^* \frac{(1-\varepsilon) I_j^*}{N_j} \\ &\geq \varepsilon I_{j+1}^* \left(1 + \lambda_j \beta_{j+1} \frac{(1-\varepsilon) I_j^*}{N_j}\right) \\ &\geq \varepsilon I_{j+1}^* (1 + (1-\varepsilon)\sigma), \end{aligned} \tag{5.42}$$

where $\sigma < \sigma_0$ which is a positive number given by

$$\sigma_0 = \min\left\{\frac{1}{10},\ \lambda_1\beta_2\frac{I_1^*}{N_1},\ \lambda_2\beta_3\frac{I_2^*}{N_2}, \ldots, \lambda_{m-1}\beta_m\frac{I_{m-1}^*}{N_{m-1}}\right\}.$$

Similarly, we can show that

$$I_{j+1}^\varepsilon(2) \geq \varepsilon(1 + (1-\varepsilon)\sigma) I_{j+1}^* (1 + (1 - \varepsilon(1 + (1-\varepsilon)\sigma)\sigma).$$

The mathematical induction shows that

$$I_{j+1}^\varepsilon(t) \geq \varepsilon_t I_{j+1}^*, \quad t = 0, 1, 2, \ldots,$$

where ε_t is determined by following recurrent equation

$$\varepsilon_0 = \varepsilon, \quad \varepsilon_{t+1} = \varepsilon_t\big(1 + (1-\varepsilon_t)\sigma\big),\ \ t = 0, 1, 2, \ldots.$$

It is easy to see that $\{\varepsilon_t\}_{t=0}^{+\infty}$ is a monotone increasing sequence, satisfying $0 < \varepsilon_t < 1$, if $0 < \varepsilon_0 < 1$ and $0 < \sigma < \sigma_0 < 1/10$. Therefore,

$$\lim_{t\to+\infty} \varepsilon_t = 1.$$

Since $\sigma < \sigma_0$ is an arbitrary positive number, we can choose σ small enough and t large enough to let ε_t be close to 1. Hence, for any given positive number η, we have $I_{j+1}^\varepsilon(t) > (1-\eta) I_{j+1}^*$, if t is large enough.

Now let us consider the solution of (5.33)

$$I_1(1) = \lambda_0 \sum_{k=1}^{m} \beta_k N_k \le (p_0 - \gamma_0) N_0 < N_1,$$

$$I_{j+1}(1) = (p_j - \gamma_j) N_j < N_{j+1}, \quad j = 0, 1, \ldots, m-1,$$

with the initial value $I_j(0) = N_j$, $j = 1, 2, \ldots, m$. If we use $I_j(1)$, $j = 1, 2, \ldots, m$, as the new initial values, it follows from the comparison theorem that $I_j(2) \le I_j(1)$, $j = 1, 2, \ldots, m$. Then, from mathematical induction we have that the solutions of (5.33) with initial values, $I_j(0) = N_j$, are monotone decreasing sequences, $I_j(t+1) \le I_j(t)$, $j = 1, 2, \ldots, m$. The monotonicity of $I_j(t) \ge 0$ implies that $\lim_{t \to +\infty} I_j(t) = I_j^{**}$, $j = 1, 2, \ldots, m$, exist, and the limits I_j^{**}, $j = 1, 2, \ldots, m$, satisfy the equations

$$I_{j+1}^{**} = (p_j - \gamma_j) I_j^{**} + \lambda_j \sum_{k=1}^{m} \beta_k I_k^{**} \left(1 - \frac{I_j^{**}}{N_j}\right), \quad j = 0, 1, \ldots, m-1.$$

Therefore, $I_j = I_j^{**}$, $j = 1, 2, \ldots, m$, are also the equilibria of the model (5.33).

It follows from the comparison theorem again that $I_j^{**} \ge I_j^{*}$, $j = 1, 2, \ldots, m$. Now, suppose that there is one j_0 such that $I_{j_0}^{**} > I_{j_0}^{*}$. Then we can choose a sufficient small ξ, such that $\xi I_j^{**} < I_j^{*}$, $j = 1, 2, \ldots, m$ hold. Consider two solutions of model (5.33) with the initial values ξI_j^{**} and I_j^{*}, respectively. With the similar manner, we can show that the solution with the initial value ξI_j^{**} satisfies $I_{\xi j}(t) > (1-\eta) I_j^{**}$ for sufficiently large t, and a sufficiently small positive number η, which implies that $I_{\xi j}(t) \le I_j^{*}$, $j = 1, 2, \ldots, m$, $t = 1, 2, \ldots$; that is, $(1-\eta) I_j^{**} \le I_j^{*}$, and especially, $(1-\eta) I_{j_0}^{**} \le I_{j_0}^{*}$. This is a contradiction, which shows that $I_j^{**} = I_j^{*}$, $j = 1, 2, \ldots, m$.

For any given solution of (5.33) with a nonnegative initial value $I_j(0) > 0$, we can choose a small positive number ε such that $\varepsilon I_j^{*} \le I_j(0) \le N_j$. Then, from the comparison theorem, we have $\lim_{t \to \infty} I_j(t) = I_j^{*}$, $j = 1, 2, \ldots, m$. Therefore, following theorem is obtained.

Theorem 5.14. *Under assumption* (A) *the endemic equilibrium of* (5.34) *is globally attractive if it exists.*

5.4.5. *Special cases*

The dynamics of the general SIS model (5.34) are complex for arbitrary parameters. There are no satisfactory results for the uniqueness and global

stability of the endemic equilibrium for the general case. Hence we consider two special cases: $m = 2, 3$, as follows.

5.4.5.1. *The case of* $m = 2$

For the simplest case $m = 2$, the age-structured SIS model (5.33) becomes

$$\begin{aligned} I_1(t+1) &= \lambda_0 x(t), \\ x(t+1) &= x(t)\left[\beta_1\lambda_0 + \beta_2\lambda_1 + \beta_2(p_1-\gamma_1)\lambda_0 - \frac{\beta_2\lambda_0\lambda_1 x(t)}{N_1}\right], \qquad (5.43) \\ I_1(0) &= I_{10} > 0, \quad 0 < x(0) = \beta_1 I_{10} + \beta_2 I_{20} < \beta_1 N_1 + \beta_2 N_2. \end{aligned}$$

The endemic equilibrium of model (5.43) is

$$I_1 = \lambda_0 x, \quad x = \frac{N_1(R_{02}-1)}{\beta_2\lambda_0\lambda_1},$$

where $R_{02} = \beta_1\lambda_0 + \beta_2\lambda_1 + \beta_2(p_1-\gamma_1)\lambda_0$. Therefore, there exists one and only one endemic equilibrium of (5.43) if $R_{02} > 1$. The second equation of (5.43) is independent of $I_1(t)$. The dynamics of (5.43) are completely determined by the recurrence equation of $x(t)$. By introducing the new variable $x(t) = R_{02}N_1 y(t)/(\beta_2\lambda_0\lambda_1)$, the recurrence equation of $x(t)$ becomes

$$y(t+1) = R_{02}y(t)[1-y(t)], \quad y(0) = \beta_2\lambda_0\lambda_1 x(0)/N_1. \qquad (5.44)$$

The map in (5.44) is a famous quadratic difference equation. Theoretically, the simple difference equation (5.44) can display complicated dynamic behaviors. The zero fixed point $y = 0$ is globally stable if $R_{02} < 1$. The positive fixed point $y = (R_{02}-1)/R_{02}$ is bifurcated when $R_{02} > 1$. The zero fixed point $y = 0$ is unstable, whereas the positive fixed point $y = (R_{02}-1)/R_{02}$ is globally stable, if $1 < R_{02} < 3$. When R_{02} passes through 3, the positive fixed point loses its stability and a periodic cycle with period 2 appears. The fixed point $y = 0$ and $y = (R_{02}-1)/R_{02}$ are both unstable, whereas the period 2 cycle is globally stable, if $3 < R_{02} < 1+\sqrt{6}$. When R_{02} passes through $1+\sqrt{6}$, the period 2 cycle loses its stability and a period 4 cycle appears, and so on. The quadratic finite-difference equation (5.44) displays a sequence of period-doubling bifurcations and eventually shows chaotic behavior [Kaplan and Glass (1995); Elaydi (1999)].

With more realistic data and biological constraints, however, the complexity of the more general quadratic difference equation cannot occur, and the dynamics of the SIS model (5.33) are relatively simple. In fact, the

populations in different age classes satisfy $N_1 = p_0 N_0$ and $N_2 = p_0 p_1 N_0$. The conditions in Theorem 5.14 imply $\lambda_0(\beta_1 N_1 + \beta_2 N_2)/N_0 < p_0$ and $\lambda_1(\beta_1 N_1 + \beta_2 N_2)/N_1 < p_1$. Combining these conditions together, we have $\lambda_0(\beta_1 + \beta_2 p_1) < 1$, $\lambda_1(\beta_1 + \beta_2 p_1) < p_1$, and

$$R_{02} = \beta_1\lambda_0 + \beta_2\lambda_1 + \beta_2(p_1 - \gamma_1)\lambda_0 \le 2 - \lambda_0\gamma_1\beta_2 - \lambda_1\beta_1/p_1 < 2.$$

Hence, the period-doubling bifurcation does not appear. The disease-free equilibrium of (5.43) is globally stable if $R_{02} < 1$, and the endemic equilibrium of (5.43) exists and is globally stable if $R_{02} > 1$.

5.4.5.2. *The case of* $m = 3$

The analysis of the SIS model (5.33) for the case of $m = 3$ is similar to that for the case of $m = 2$, but the procedure is much more complicated. We use the following values of the parameters to make the calculation simple: $\beta_1 = \beta_2 = \beta_3 = 1$, $\gamma_1 = \gamma_2 = 0$, $N_1 = 1$, $N_2 = 9/10$, $N_3 = 81/100$, $p_0 = p_1 = p_2 = 9/10$, $\lambda_0 = \lambda_1 = \lambda_2 = \lambda$. The SIS model (5.33) with $m = 3$ is equivalent to the following system:

$$\begin{aligned} I_1(t+1) &= \lambda x(t), \\ I_2(t+1) &= \frac{9}{10}\lambda x(t) + \lambda x(t)(1 - \lambda x(t)), \\ x(t+1) &= \frac{10}{9}\lambda^3 x(t)^3 - \frac{361}{90}\lambda^2 x(t)^2 + \frac{561}{100}\lambda x(t), \\ I_1(0) &= I_{10}, \quad I_2(0) = I_{20}, \quad x(0) \le 2.71. \end{aligned} \tag{5.45}$$

The basic reproductive number of (5.45) is $R_{03} = 561\lambda/100$. The equilibrium solution of (5.45) satisfies following equations:

$$\begin{aligned} I_1 &= \lambda x, \\ I_2 &= \frac{9}{10}\lambda x + \lambda x(1 - \lambda x), \\ x_{1,2} &= \frac{1}{200}\,\frac{361\,\lambda \pm \sqrt{-71639\,\lambda^2 + 36000\,\lambda}}{\lambda^2}. \end{aligned} \tag{5.46}$$

Two positive real solutions x_1 and x_2, to Eq. (5.46), exist if $0 < \lambda \le 36000/71639 = 0.5025$. Solution x_1 is a decreasing function of λ and $x_1|_{\lambda=0.5025} = 3.5919 > 2.71$. Since we must have $x(t) \le \beta_1 N_1 + \beta_2 N_2 + \beta_3 N_3 = 2.7$,

x_1 cannot be the solution to system (5.45), that we need. Solution x_2 is an increasing function of λ and $0 \le x_2 \le 3.5919$ if $0.1783 \le \lambda \le 0.5025$.

The initial values $x(0)$ satisfy $x(0) \le 2.71$. The conditions $\lambda_j(\beta_1 N_1 + \beta_2 N_2 + \beta_3 N_3)/N_j < p_j$ $(j = 0, 1, 2)$ of Theorem 5.14 implies $\lambda < 2.9151$. The function $\phi(\lambda x) = 10\lambda^3 x^3/9 - 361\lambda^2 x^2/90 + 561\lambda x/100$ is a monotone increasing function of λx, and $\phi(1) = 2.71$. For any $0 < x(t) < 2.71$, the inequality $0 < \lambda x(t) < 1$ is necessary and sufficient to guarantee $0 < x(t+1) < 2.71$. This inequality implies that $\lambda < 1/2.71 = 0.369$.

We calculate the ratio $x(t+1)/x(t)$ to investigate the stability of the endemic equilibrium of (5.45). The function $\psi(x) = 10\lambda^3 x^2/9 - 361\lambda^2 x/90 + 561\lambda/100$ is a monotone decreasing function of x for any $\lambda \in (0.1783, 0.369)$, and $\psi(x_2) = 1$. Therefore, $x(t+1)/x(t) > 1$ for any $x(t) \in (0, x_2)$ and $\lambda \in (0.1783, 0.369)$, and $x(t+1)/x(t) < 1$ for any $x(t) \in (x_2, 2.71)$ and $\lambda \in (0.1783, 0.369)$. The global stability of the endemic equilibrium x_2 of (5.45) is obtained; that is, $\lim_{t\to\infty} x(t) = x_2$ for all $x(0) \in (x_2, 2.71)$ if $\lambda \in (0.1783, 0.369)$. Numeric simulation results are shown in Fig. 5.5 for $\lambda = 0.3$.

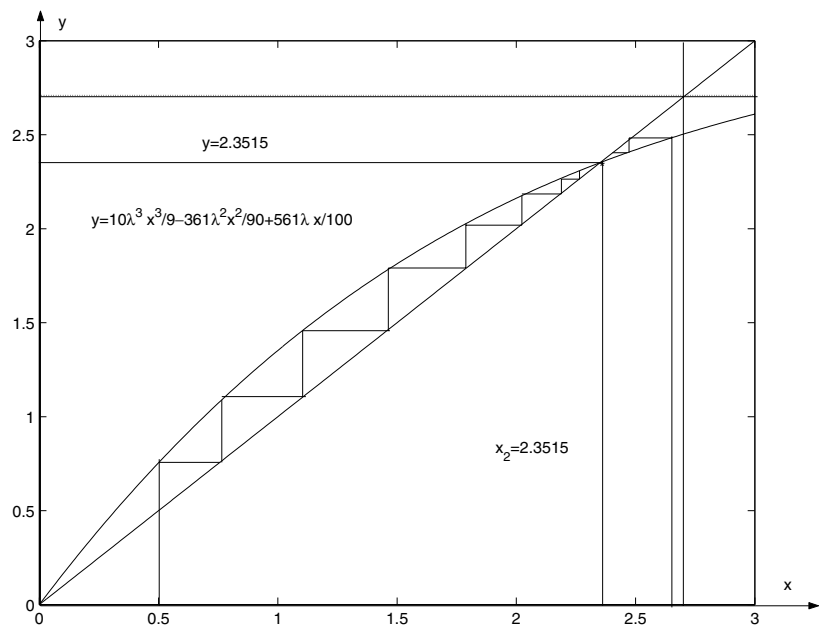


Fig. 5.5. The stability of the endemic equilibrium of (5.45) with $\lambda = 0.3$. The endemic equilibrium is $x_2 = 2.3515$, all the solution with initial value $0 < x(0) < 2.71$ converges to the endemic equilibrium x_2 of (5.45).

Epidemiologic modeling with age- and/or infection-age-structure gains good insight into transmission dynamics of infectious diseases. It provides useful guidance for data collection and programs for prevention and control of diseases. While the development and achievements of such modeling are promising, more appropriate formulations and more advanced analysis for age-structured epidemic models are still challenging. The materials presented in this chapter are only a brief introduction. We have a long way to go and far more to do in this field.

Chapter 6

Applications of Epidemic Modeling

Yicang Zhou

Epidemics can be described and predicted by mathematical models because infection and disease progression can be characterized by the transition of an individual from one state to another. Formulating a model involves classifying the possible infection states of an individual and the processes causing movement among those states. Mathematical models can provide predictions to contribute to the control of diseases [Ferguson (2005)].

Of course, the process of transmission has many epidemiologic complexities: (1) the nature of the transmission process, (2) heterogeneities in the pathogen populations, (3) patterns of host contacts, and (4) long and variable incubation periods of infections of some diseases. Incorporation of those complexities is often essential to generate a model that is not just qualitatively reasonable, but capable of quantitative predictions. Despite these challenges, many infectious diseases have been modeled, various models incorporate multiple parameters that must be estimated from available epidemiologic, clinical, and behavioral data, and mathematical modeling has made notable progresses during the past years [Ferguson (2005)].

Trends in the incidence of human immunodeficiency virus (HIV) in southern Africa in the past 5 years have validated the predictions made more than 10 years ago that acquired immune deficiency syndrome (AIDS) would reverse population growth in Sub-Saharan Africa in the 21st century. In the UK in 2001, mathematical models had a pivotal role in shaping disease-control policy during the foot and mouth epidemic in livestock. During the severe acute respiratory syndrome (SARS) epidemic in 2003, epidemiologic analysis and modeling quantified key and then unknown disease

parameters, such as incubation period distribution, case mortality rate, and transmissibility [Anderson *et al.* (1991, 2004); Kao (2002); Ferguson (2005)].

In this chapter we apply mathematical models to describe the transmission of three diseases: SARS, AIDS, and tuberculosis (TB). Although those models and their results are far more from satisfactory, it is certain that they have helped us to understand the transmission dynamics and to provide useful strategies for prevention and control of the diseases.

6.1. SARS Transmission Models

6.1.1. *SARS epidemics and modeling*

SARS is the first new contagious disease in the 21st century. Initial SARS cases occurred in southern China during November 2002, and international air travel quickly spread the disease through Asia, North America, and Europe [Bombardt (2006)]. SARS was first recognized as a global threat in mid-March 2003. By July 2003, the international spread of SARS-CoV resulted in 8098 SARS cases in 26 countries, with 774 deaths [WHO (2004)]. The epidemic caused significant social and economic disruption in areas with sustained local transmission of SARS.

SARS is a newly discovered infectious disease with a high potential for transmission to close contacts. SARS is caused by infection of the SARS virus. The main signs and symptoms of the SARS infected individuals are fever, respiratory compromise, chills, muscle aches, headache, and loss of appetite. The etiological agent of SARS is coronavirus. The virus is spread predominantly through droplet and through direct or indirect contacts.

SARS is highly contagious and spreads rapidly. There are many factors helping its transmission. The modern pharmaceuticals could neither prevent SARS infections nor abort the natural course of SARS cases. Each affected country controlled the spread of SARS in traditional ways: case identification and contact tracing, patient isolation, and exposure management. The disease surveillance shortcomings and public health capacity limitations constrained SARS responses. SARS has also taken advantage of easy international travel. Although much effort has been devoted to understanding that new health threat and much successful research has been done on the disease, there are still no effective drugs or vaccines for SARS during that period. Control has relied mainly on the rapid identification of cases and on effective isolation of probable cases and their contacts.

China is one of the countries most severely influenced by SARS. The cumulative number of diagnosed SARS cases is 5327 with 343 deaths in 2003 [Ministry of Health, China (2003)]. The diagnosed SARS cases were distributed over most provinces, and the number of SARS cases in China accounts for almost two-thirds of all reported cases worldwide. China was regarded as the epicenter of the SARS outbreak. SARS was transmitted mainly in Guangdong province in the southern part of China, before March 2003. There was a rapid spread of SARS in China beginning in April. Especially, in late April and early May, the number of daily new diagnosed SARS cases was over 100. The rapid growth in number of SARS cases set up a strong alarm to the government and the people. Public health authorities, physicians, and scientists all over the country began a campaign to cope with a severe and rapidly spreading infectious disease. Drastic measures and actions were taken to bring SARS under control since April 20 [Watts (2003)]. Newspapers, radios, TV stations, and posters campaigned to educate the public on SARS prevention. Disinfectant was sprayed in many public places, including streets, shopping centers, airports, railways, bus terminals, classrooms, offices, and transportation vehicles. Individuals who have had direct or indirect contacts with probable SARS infected cases have been quarantined in their homes, hospitals, or campuses. Stern travel advisories were issued to students and workers. A body temperature check is done for all air passengers and passengers who fail a therm-imaging check at the entrance are checked by nurses and doctors at quarantine centers. Many stock exchanges, cinemas, theaters, and internet cafes were closed temporarily. Quarantine outpatient departments were set up for fever patients in many large hospitals. Special hospitals for SARS treatment were specified in every large city. For example, the emergency quarantine center in Xiaotangshan, with a 1000-bed facility, was constructed within 8 days. The number of daily reported new diagnosed SARS cases were large in late April and early May, but the control measures taken were adequate and effective. SARS infection began to decline after the middle of May. The daily number of reported new probable cases of SARS in mainland China declined considerably from an average of 166 cases during the first week of May, to 90 cases during the second week, 27 cases in the third week, and 16 in the fourth week. The daily number of reported new cases dropped to an average of 2.5 and has decreased to zero later [Ministry of Health, China (2003)].

However, SARS transmission and all the measures to combat SARS have had strong negative side effects on daily life and development of

the economy. Can these strict control measures be relaxed, and when is a suitable time to begin the relaxation? Any change in control measures will have effects on the spread of SARS. Any relaxation of control measures must be done carefully to avoid a recurrence of infections. Therefore, it is important to know what will happen if some of the quarantine measures are canceled.

There are many questions about SARS transmission, which are: How many further infections will be produced by each infected person per day? How many people will become infected in the future? When will the infection peak arrive? How long does the infection peak last and how high is the peak? Will the current public health measures be enough to bring SARS under control?

By piecing together preliminary data on the infections and making use of accumulating case notifications, the quantitative assessment of the epidemic potential of SARS, and the effectiveness of control measures have been analyzed by Lipsitch *et al.* (2003); and Riley *et al.* (2003). Their main conclusion is that this new coronavirus is sufficiently transmissible to cause a very large epidemic if unchecked, but not so contagious as to be uncontrollable with good, basic public health measures. On the basis of several sources containing information on epidemiologic, demographic, and clinical variables in Hong Kong, the key epidemiologic time distributions from infection to onset, onset to admission, admission to death, and admission to discharge, and the relations between the SARS case fatality rate and patients' age have been estimated by Donnelly *et al.* (2003). By using global and regional data from the SARS epidemic, a mathematical model on SARS transmission was set up, and the average properties were extracted by Chowell *et al.* (2003). Hsieh and coworkers used SARS hospitalization and fatality data spanning one month to obtain parameter values for an epidemic model without quarantine or hospital isolation [Hsieh *et al.* (2004)]. Subsequently, these researchers included a two-level quarantine and hospital isolation in another system of ordinary differential equations and they performed a stability analysis that identified necessary quarantine rates for outbreak containment [Hsu and Hsieh (2006)].

In their study of SARS transmission and control in China, Zhou *et al.* assumed an inexhaustible supply of susceptible individuals, formulated a system of linear difference equations, and followed a process of trial and error in obtaining a time-varying transmission rate that enabled the model to closely match data on diagnosed cases per day [Zhou *et al.* (2004)]. A more complex model of the SARS outbreak in China was later put forward

by Zhang *et al.* (2005). They use 3 weeks of data on diagnosed SARS cases and then they obtained model results for the daily number of SARS patients. Gumel and coauthors studied a system of ordinary differential equations with constant parameters, and the chosen values of the two free parameters provided good agreement between calculated and reported cumulative SARS fatalities over time. After obtaining values of the two free parameters for four SARS outbreaks, calculations of cumulative probable cases over time generally conformed to reported data for each outbreak [Gumel *et al.* (2004)]. Bombardt described a semiempiric and deterministic epidemic modeling approach that focuses on time-varying rates of disease transmission in both unstructured and structured populations. He employed probability density functions to characterize disease progression and outbreak controls. Numeric results were obtained for the 2003 SARS outbreak in Taiwan, and the dynamic implications of time-varying transmission rates and scale-free contact networks were discussed [Bombardt (2006)].

We have mentioned a few of existing researches on SARS modeling. In the rest part of this section we will present a few simple models to describe the SARS epidemics in China.

6.1.2. *A simple model for SARS prediction*

SARS is a newly acute infective disease. It was not diagnosed correctly and promptly, and there had been no effective drugs or vaccines in 2003. Control measures in late spring 2003 was very strict in China. The daily life and development of economy had been affected greatly. All the people expected that SARS could be eradicated early and the normal social life could resume early.

Whether we can relax the strict control measure depends on the transmission tendency of SARS. A better model and prediction will be crucial to the decision-makers. The model and the decision rely on the mechanics and the data of SARS. Although we did not know much about the treatment of the SARS on patients, we have learnt the transmission process from experts in the medical field and public health departments. We have had very good data, since the number of newly infected, recovered, accumulated and deaths were released every day. These may be the best data in the history of infectious disease statistics!

Figures 6.1 and 6.2 give the daily and accumulative number of SARS transmission in China. The top left is the diagnosed SARS number, the top right is the suspicious SARS number, the bottom left is the recovered

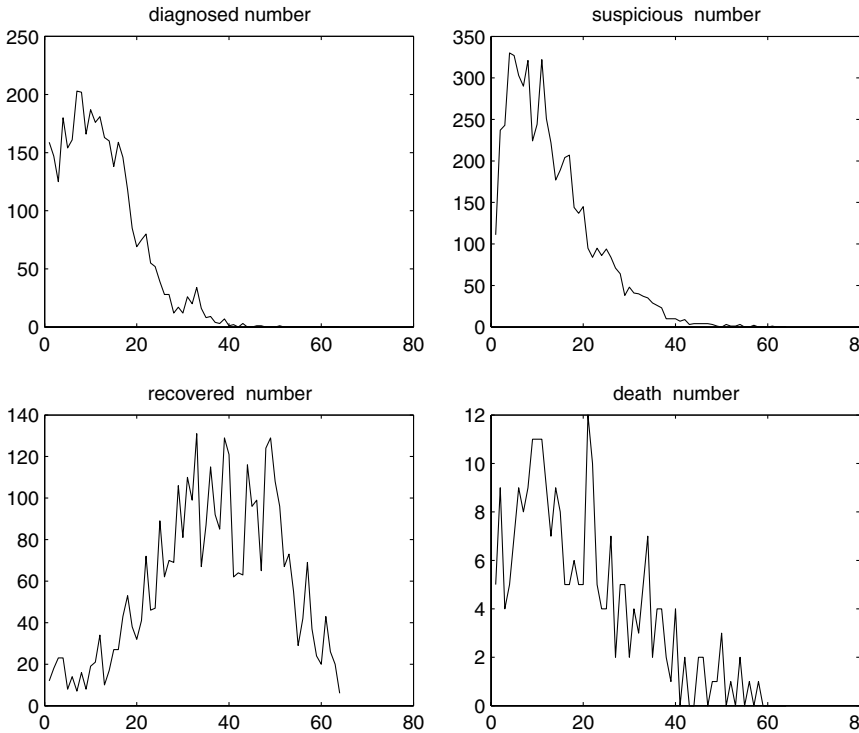


Fig. 6.1. The daily number of SARS transmission.

SARS number, the bottom right is the SARS death number. The abscissa is the date, starting from April 20, 2003.

Theoretically, all the individuals who have not been infected by SARS are susceptibles. Practically, there were quite a few SARS infected compared to the total population, and any infected individual is not allowed to contact all the susceptible individuals. Therefore, we pay our main attention to the SARS infected. Let $I(t)$ denote the SARS patients at time t, and we make the following assumptions:

(1) The newly infected is proportional to the accumulated SARS patients, and $\beta(t)$ is the time-dependent transmission rate.
(2) The daily recovered SARS patients is proportional to the accumulated SARS patients, and $\gamma(t)$ is the time-dependent recovery rate.
(3) The daily death number of SARS patients is proportional to the accumulated SARS patients, and $\mu(t)$ is the time-dependent death rate.

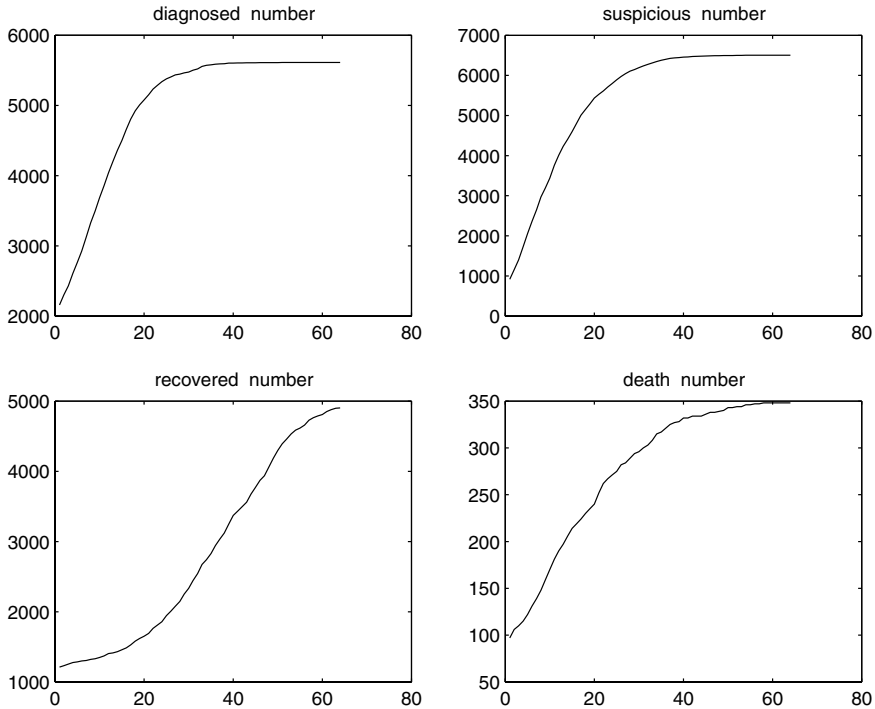


Fig. 6.2. The accumulated number of SARS transmission.

Why we use the time-dependent rates is that the control measure and the treatment experience kept changing daily. We can have a very simple model to describe SARS transmission in China:

$$\frac{\mathrm{d}I(t)}{\mathrm{d}t} = \beta(t)I(t) - (\gamma(t) + \mu(t))I(t), \quad I(t_0) = I_0. \tag{6.1}$$

Although model (6.1) is a very simple ordinary differential equation and it has analytic solution, we do not like to use it directly. Since all the statistic data are collected and released daily, we choose the time interval to be one day and discretize the simple model (6.1) to obtain the following model:

$$I(t+1) = I(t) + \beta(t)I(t) - (\gamma(t) + \mu(t))I(t), \quad I(t_0) = I_0. \tag{6.2}$$

The discretized model (6.2) is easy to understand and apply. The model says that the number of diagnosed SARS patients tomorrow equals the

number of today's SARS patients plus the newly diagnosed, and minus the sum of recovered and died patients. The newly infected, the recovered, the died, and the accumulated data were released every day by Ministry of Public Health. We can use the daily reported data to estimate our parameters, and then use the discretized model to give a prediction.

By definition we have

$$\beta(t) = \frac{\text{the number of daily diagnosed SARS patients at time } t}{\text{the number of the accumulated SARS patients at time } t},$$

$$\gamma(t) = \frac{\text{the number of daily recovered SARS patients at time } t}{\text{the number of the accumulated SARS patients at time } t},$$

$$\mu(t) = \frac{\text{the number of daily died SARS patients at time } t}{\text{the number of the accumulated SARS patients at time } t}.$$

In middle May 2003, we had 3 weeks data to estimate our parameters. The calculation result of the transmission rate $\beta(t)$ by above formulate is shown in Fig. 6.3.

The piecewise line is the curve we have got from the statistic data. After discussion with experts of epidemiology, statistics, and public health, we chose an exponential function $\beta(t) = a + b\mathrm{e}^{-ct}$ to fit the piecewise

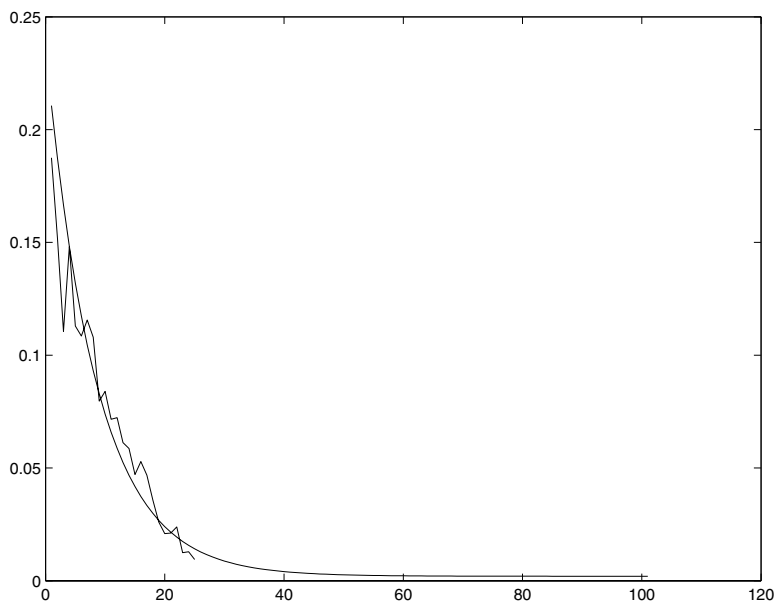


Fig. 6.3. The estimation of the SARS transmission rate.

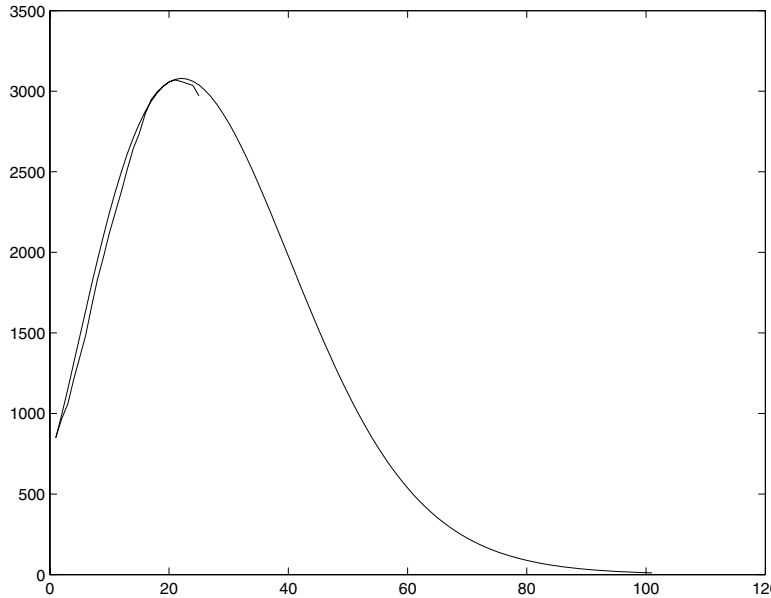


Fig. 6.4. The prediction of the accumulated SARS patients.

line. After calculation we obtained that $\beta(t) = 0.019 + 0.2231\mathrm{e}^{-0.1184t}$. The recovery rate and the death rate can be determined in the same way. After those three parameters were determined, we took April 20 as the initial date, and used the discrete model (6.2) to give the prediction. The result is shown in Figs. 6.4 and 6.5.

From those two figures we see that our prediction matched the statistic data quite well. After further improvement on our model we designed a software based on our simple ideas. After we prepared the daily reported number of SARS patients the software would give the prediction of the daily diagnosed and accumulated number of SARS patients quickly. We invited some medias and given a news release in May 21, 2003. Our prediction was warmly welcomed by the public and news medias. After the end of the SARS epidemic we compared our prediction with the whole data. The comparison is shown in Fig. 6.6.

From the comparison (Fig. 6.6), we see that the prediction done by the very simple model (6.2) is quite accurate. The estimation of the parameters here demonstrate the profound idea to treat the difficult problem in model formulation and application: how to estimate the model parameters from the real statistic data, especially, how to give a good estimation on the

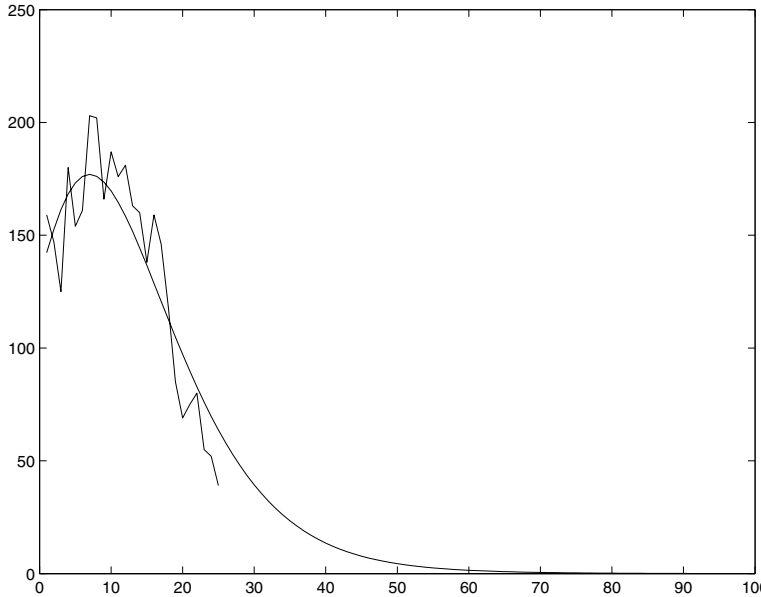


Fig. 6.5. The prediction of the daily diagnosed SARS patients.

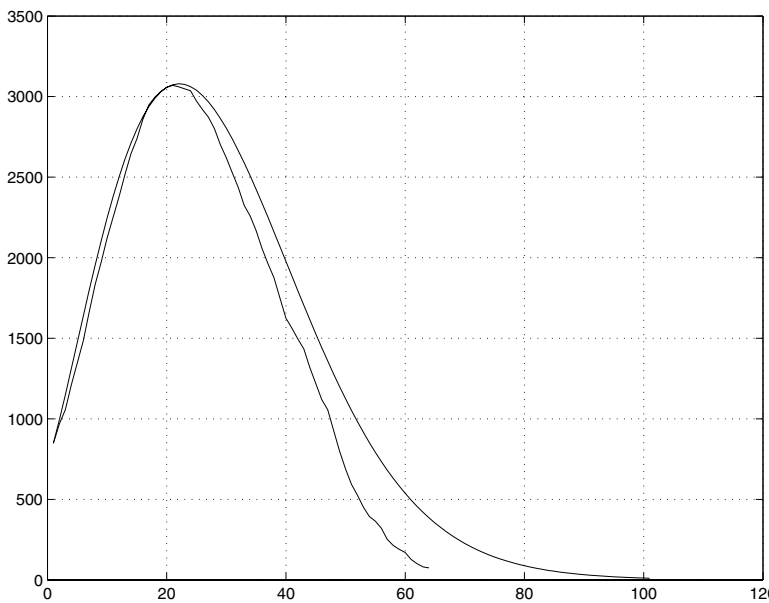


Fig. 6.6. The comparison of SARS prediction and real data.

transmission rate. The transmission rate is the key parameter in any modeling process. We usually have enough information to determine the recovery rate and the death rate. We do not have any direct and effective way to estimate the transmission rate, since it is dependent on many factors. The direct calculation based on limited real data provides the background to fit it mathematicly. Even we do not understand the mechanics of the disease transmission clearly, and we cannot identify how many factors do contribution to the transmission rate, we can give a better estimate by the "backward calculation" and the mathematical fit. The underline idea is that the real statistic data contain a lot information, and reflect the tendency of the disease transmission. Even though we cannot list all the factors that influence the disease transmission, and we cannot distinguish how important a factor contributes to the transmission rate, data demonstrate the influence and contribution of those factors. It is better to mine more information from data and to use limited data more efficiently.

6.1.3. *A discrete SARS transmission model*

The simplest model (6.1) has given satisfied prediction of SARS transmission in China. The model is too simple to give answers to questions we are interested in, such as, how much influence the quarantine will have on the control of the disease. In this section, we divide the population into more groups and study a discrete epidemic model. We follow the basic idea and structure of mathematical modelling on epidemiology [Baily (1975); Capasso (1993)]. We divide the population into the following six classes: susceptibles, exposed, infectives, quarantined, diagnosed, and recovered. The variables $S(t)$, $E(t)$, $I(t)$, $Q(t)$, $J(t)$, and $R(t)$ are the numbers of the individuals in the six classes at time t, respectively. Since all the data of the SARS infection are now announced daily, it is natural for us to use a discrete epidemic mode to describe the dynamics of the SARS transmission.

The numbers of exposed, infective, quarantined, and diagnosed members are very small compared to the numbers of the susceptibles. For example, the population size of China is over 1.3 billion, while the cumulative number of diagnosed SARS cases is under 6000.

We assume that all contacts sufficient to transmit infection by infectious members of the population are with susceptibles, neglecting contacts with exposed, infective, quarantined, and diagnosed members. Thus all these contacts produce new infections, and we concentrate our modeling and analysis on exposed, infective, quarantined, and diagnosed members.

An individual infected by SARS virus enters the exposed class and is in the incubation period. The incubation period lasts 2–12 days. It has not yet known whether individuals in the incubation period are able to transmit SARS. To be conservative in our estimates, we suppose that they have a lower infectivity. Some exposed individuals will enter the quarantined class as a result of prevention measures. The other exposed individuals will enter the infective class. Individuals in the quarantined and infective classes enter the diagnosed class after obvious symptoms of SARS appear and they are diagnosed definitely. Diagnosed individuals either recover and enter the recovered class or die due to the infection. The schematic representation of the individual flow between the different classes is shown in Fig. 6.7.

From the transmission mechanics and the schematic representation in Fig. 6.7, we obtain the recurrence relations for the numbers of individuals in the five classes. We formulate the following discrete mathematical model using the general principles of epidemiologic modelling [Hethcote (2000); Ma *et al.* (2004)].

$$\begin{aligned} E(t+1) &= E(t) + \beta(t)(kE(t) + I(t)) - (\varepsilon + \lambda)E(t), \\ I(t+1) &= I(t) + \varepsilon E(t) - (\alpha + \theta)I(t), \\ Q(t+1) &= Q(t) + \lambda E(t) - \sigma Q(t), \\ J(t+1) &= J(t) + \theta I(t) + \sigma Q(t) - (\alpha + \gamma)J(t), \\ R(t+1) &= R(t) + \gamma J(t), \\ E(0) > 0, &\quad I(0) > 0, \quad Q(0) > 0, \quad J(0) > 0, \quad R(0) > 0, \end{aligned} \tag{6.3}$$

where α is the SARS induced death rate, γ is the recovery rate, ε is the transfer rate from exposed to infective class, λ is the transfer rate from exposed to quarantined class, σ is the transfer rate from quarantined to diagnosed class, θ is the transfer rate from infective to diagnosed class,

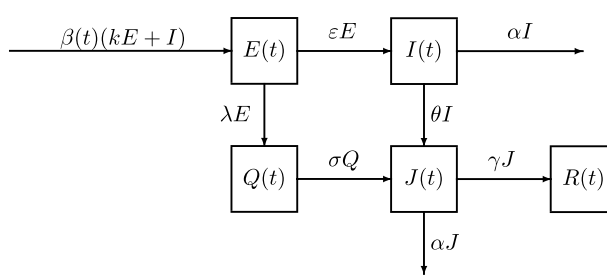


Fig. 6.7. The flow of individuals among different classes.

k is the infectivity fraction for the exposed individuals compared with individuals in the infective class, and $\beta(t)$ is the transmission rate per day.

The discrete SARS model (6.3) is a system of linear difference equations with time-dependent coefficients. We will determine the parameters in the model and do numeric simulations.

Even though much about the disease remains poorly understood, much data has been collected during the SARS epidemic. We use statistic data for SARS in China to estimate the parameters of the discrete SARS model (6.3). The average incubation period is taken as 6 days, divided into two parts: the first 3 days in the exposed class with less infectivity and the last 3 days with more infectivity. The fraction k is taken as 0.1. From the statistic data we estimate that a fraction 3/5 of the diagnosed SARS cases came from SARS suspected individuals, who had been quarantined and treated in hospitals, and a fraction 2/5 of the diagnosed SARS cases came from unquarantined individuals. We assume that a fraction 3/5 of the exposed individuals have been quarantined after they left the exposed class due to the stringent control measures. The transfer rate from the exposed class to the quarantined class is taken as a fraction 1/5, while 2/5 of the exposed individuals still have not been quarantined after they left the exposed class before obvious SARS symptoms appeared and they were diagnosed. The transfer rate from the exposed class to the infective class is taken as 2/15. Individuals in the infective and quarantined classes will enter the diagnosed class after 3 days on average and individuals in the diagnosed class will recover or die after 3 weeks in hospital on average. The SARS-induced death-rate is taken to be 1/140. Thus the values of parameters are estimated as follows:

$$\varepsilon = 2/15, \quad \lambda = 1/5, \quad \alpha = 1/140, \quad \theta = 1/3,$$
$$\sigma = 1/3, \quad \gamma = 1/21, \quad k = 0.1.$$

The infection rate $\beta(t)$ is the most important parameter in the model and model predictions are very sensitive to changes in the infection rate. From the statistic data we know that the infection rate $\beta(t)$ is a decreasing function after stringent control measures go into effect and cut down the infection gradually. We try to fit the function $\beta(t)$ by repeated numeric simulation and choose a fractional function of t, $\beta(t) = (31 + t)/(22 + 5t)$.

From the statistic data we estimate the initial values, as of April 21, 2003, $E(0) = 477, I(0) = 286, Q(0) = 191, J(0) = 848$ and $R(0) = 1213$. By using Matlab, we obtain the simulation result shown in Fig. 6.8.

In Fig. 6.8, the horizontal axis is the time measured in days starting from April 21, 2003, the dotted line is the statistic data, the continuous

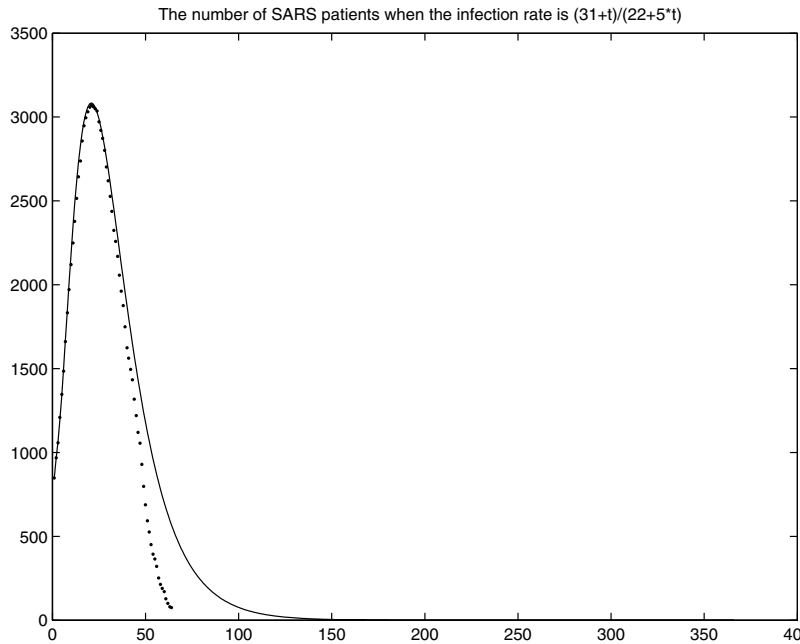


Fig. 6.8. The prediction and actual diagnosed SARS cases in China.

curve is the prediction of the model. We see that the number of the diagnosed SARS individuals (who are staying in hospitals) increases rapidly for the first 3 weeks and reaches a peak on May 11. The predicted number on May 11 is 3083. After May 11, the number decreases rapidly. This shows the effectiveness of the stringent control measures adopted in China. The prediction curve matches the actual data well.

Next we investigate the influence of delaying quarantine by fixing the infection rate $\beta(t)$, and all the parameters the same as given above. We vary the transfer rate θ to obtain different results. In Fig. 6.9, the transfer rate θ is taken to be $1/4$; that is, individuals stay in infective class one day longer. The simulation result shows that the peak will move to May 17, with maximum number 4111. Compared with the result shown in Fig. 6.8, the peak appears 6 days later, with 1028 individuals higher. In Fig. 6.10 the transfer rate θ is taken to be $1/5$; that is, individuals stay in infective class two day longer. The simulation result shows that the peak will move to May 24, with maximum number 5561. Compared with the result shown in Fig. 6.8, the peak appears 13 days later, with 2478 individuals more.

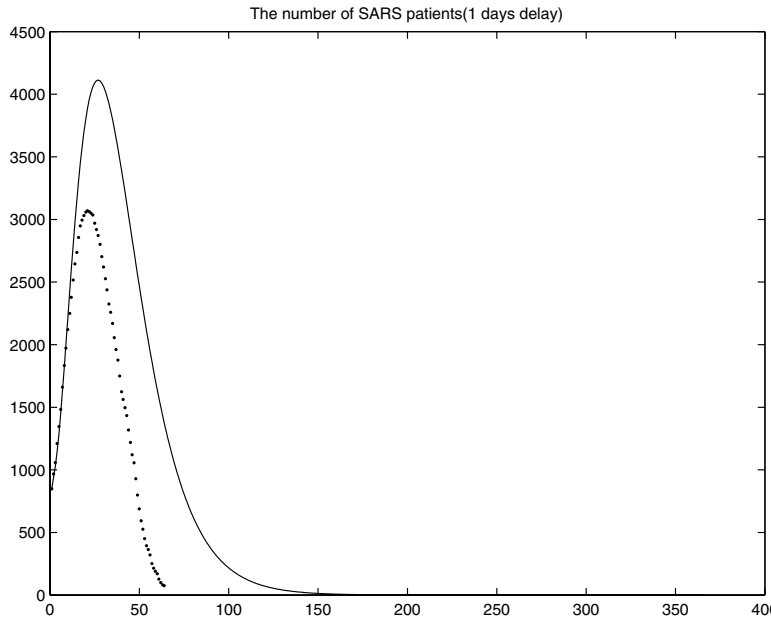


Fig. 6.9. The prediction and actual diagnosed SARS cases in China, $\theta = 1/4$.

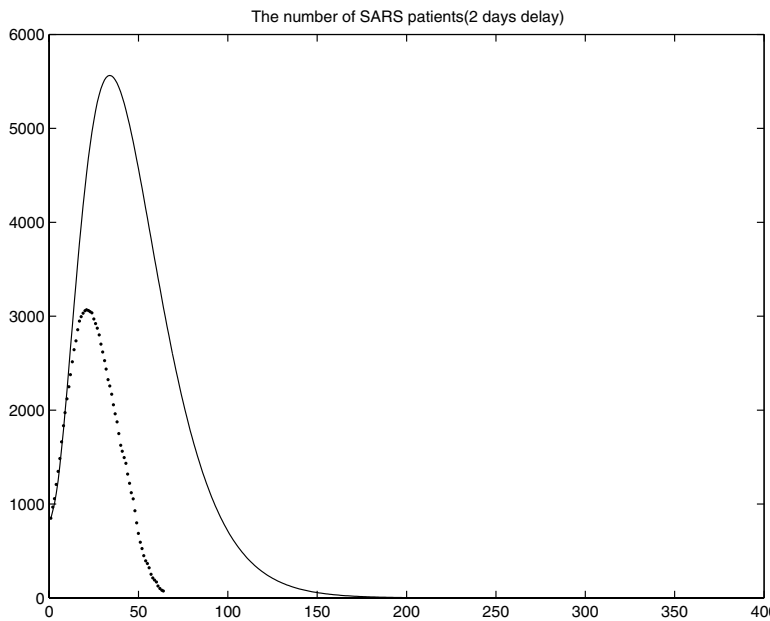


Fig. 6.10. The prediction and actual diagnosed SARS cases in China, $\theta = 1/5$.

The simulation results indicate that timely quarantine is significant for the control of SARS transmission.

Finally, we investigate the influence of k, the infectivity fraction of individuals in the class E compared to individuals in class I on SARS transmission. In the prediction of Fig. 6.8, the proportion is 0.1. Here we vary the proportion to be 0.2 and 0.3 (see Figs 6.11 and 6.12), and leave the other parameters unchanged. In Fig. 6.11, k is 0.2, and we see that the number of diagnosed SARS cases is higher than that in Fig. 6.8. The peak is reached on May 15 with maximum number 4682. The number of diagnosed SARS cases at the peak is 1599 higher than that in Fig. 6.8. In Fig. 6.12, k is 0.3 and we see that the number of diagnosed SARS cases is much higher than that in Fig. 6.8. The peak is reached on May 20, with maximum number 8227. The number of diagnosed SARS cases at the peak is 5144 more than that in Fig. 6.8.

The simulation results in Figs. 6.11 and 6.12 shows that infections transmitted by individuals in the exposed class can have great influence on SARS transmission. This indicates that determination of the infectivity for exposed individuals is essential for making good predictions. Early

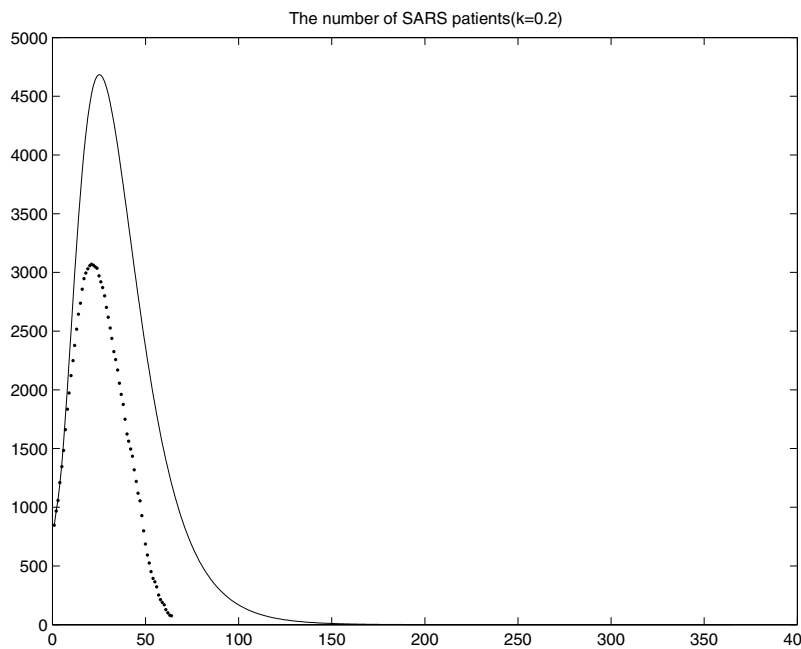


Fig. 6.11. The prediction and actual diagnosed SARS cases in China, $k = 0.2$.

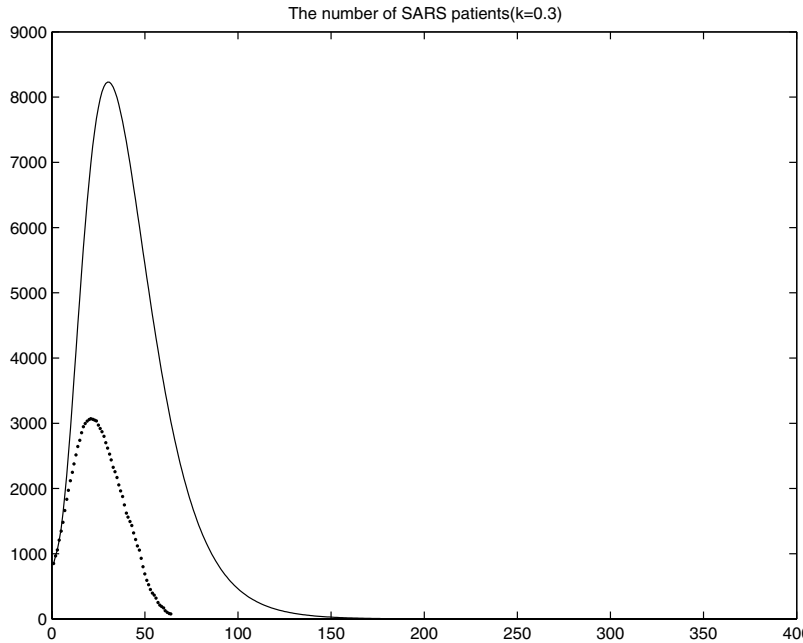


Fig. 6.12. The prediction and actual diagnosed SARS cases in China, $k = 0.3$.

identification, early tracing, and early quarantine are key factors in coping with the spread of SARS.

6.1.4. *A continuous SARS model with more groups*

SARS transmission is complicated and our previous modeling and analysis are based on simple assumptions. Many more factors should be take into account to develop a more realistic model. One topic that we have not considered is that numerous cases of infections to health-care workers have been reported in the early stages of the spread. Infected doctors and nurses account for roughly a quarter of the SARS cases in China before the middle of April. These medical-care workers have close contact with infectives and form a high-risk groups.

Now we divide the population into two related blocks: the free block in which the individuals may move freely, and the isolated block in which the individuals were isolated and can't contact with the individuals in the free block. Further, the free block is divided into four compartments: the susceptibles (S), the exposed (E), the infectious (I), and the removed (R);

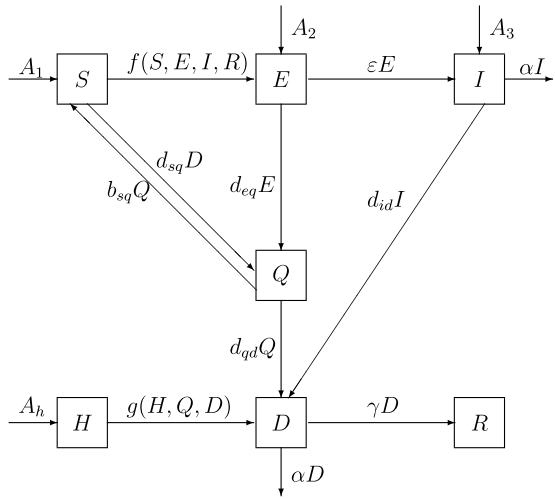


Fig. 6.13. Transfer diagram for the SARS in China.

the isolated block is divided into three compartments: the quarantined (Q), the diagnosed (D), and the health-care workers (H).

Stringent quarantine measures were taken to make SARS under control during the spring of 2003. Any individual who contacted a diagnosed patient of SARS directly or indirectly, or had the clinic symptoms similar to those of SARS would be quarantined as a possible SARS patient. These measures played a very important role to control the spread of SARS in China. On the other hand, inevitably, many individuals were misdiagnosed as SARS suspected and hence were mistakenly put in the Q-compartment due to the lack of fast and effective SARS diagnostic test. The transfer diagram of SARS is shown in Fig. 6.13.

Corresponding to the transfer diagram Fig. 6.13 we have the compartment model of SARS as follows:

$$\frac{\mathrm{dS}}{\mathrm{d}t} = A_1 - f(S,E,I,R) - d_{\mathrm{sq}}D + b_{\mathrm{sq}}Q,$$

$$\frac{\mathrm{dE}}{\mathrm{d}t} = A_2 + f(S,E,I,R) - \varepsilon E - d_{\mathrm{eq}}E,$$

$$\frac{\mathrm{dI}}{\mathrm{d}t} = A_3 + \varepsilon E - d_{\mathrm{id}}I - \alpha I,$$

$$\frac{\mathrm{dQ}}{\mathrm{d}t} = d_{\mathrm{eq}}E + d_{\mathrm{sq}}D - b_{\mathrm{sq}}Q - d_{\mathrm{qd}}Q,$$

$$\frac{\mathrm{dD}}{\mathrm{d}t} = g(H, Q, D) + d_{\mathrm{qd}}Q + d_{\mathrm{id}}I - \alpha D - \gamma D,$$

$$\frac{\mathrm{dH}}{\mathrm{d}t} = A_h - g(H, Q, D),$$

$$\frac{\mathrm{dR}}{\mathrm{d}t} = \gamma D, \tag{6.4}$$

where $f(S, E, I, R)$ and $g(H, Q, D)$ are the incidences in the free block and the isolated block, respectively.

We rewrite the incidence terms $f(S, E, I, R)$ as

$$f(S, E, I, R) = \beta(t)(k_1 E + I)$$

where $\beta(t)$ represents the infectious rate.

We took one day as the unit time, and assumed that the average latent period is 5 days. From the statistic data, in every day, 80% of the diagnosed SARS cases come from the Q-compartment, and 20% come from the I-compartment. So, we let

$$\varepsilon = \frac{1}{5} \times \frac{20}{100} = \frac{1}{25}, \quad d_{\mathrm{eq}} = \frac{1}{5} \times \frac{80}{100} = \frac{4}{25}.$$

Since the average number of days from entering the I-compartment to moving to the D-compartment is 3 days, $d_{\mathrm{id}} = 1/3$. On the other hand, if we assumed that the average transition times from the Q-compartment to the D-compartment and from the Q-compartment to the S-compartment are 3 days and 10 days, respectively, then by denoting the number of removed from quarantines to susceptibles and that of diagnosed from quarantines by q_{s} and q_{d}, respectively, with the daily reported data, we got the ratio of noninfected individuals in the Q-compartment, $q_{\mathrm{s}}/(q_{\mathrm{s}} + q_{\mathrm{d}}) = 0.6341$. Thus,

$$d_{\mathrm{qd}} = (1 - 0.6341) \times \frac{1}{3}, \quad b_{\mathrm{sq}} = 0.6341 \times \frac{1}{10}.$$

Since the period of recovery for an SARS patient is about 30 days and the statistic analysis shows that the ratio of the daily number of the new SARS suspected cases to the daily number of the new SARS diagnosed cases is 1.3:1, then

$$\gamma = \frac{1}{30}, \quad d_{\mathrm{sd}} = 1.3 \times 0.6341 \times \frac{1}{30}.$$

Finally, since the probability of SARS related death is 14%, $\alpha = 1/30 \times 0.14$.

The determination of the incidences in the free block and the isolated block is the key to analyze SARS model (6.4). It is difficult because of the poor understanding of the SARS virus and the difficulty in quarantines. Nevertheless, a significant amount of data have been collected during the course of SARS outbreak in China after the middle of April 2003. We used the backward calculation to estimate the adequate contact rate.

Let $\hat{f}(t)$ denote the number of new diagnosed SARS cases minus the number of new diagnosed SARS cases in the H-compartment at time t. $F(t) := f(S(t), E(t), I(t), R(t))$, the new infectives at time t in the free block should be $\hat{f}(t+8)$ because the average number of days from exposure to the SARS virus to the definite diagnosis is 8 days with the first 5 days in the E-compartment (with low infectivity) and the last 3 days in the I-compartment (with high infectivity). Therefore,

$$\beta(t) = \frac{F(t)}{I(t) + k_1 E(t)} = \frac{\hat{f}(t+8)}{\sum_{j=0}^{2} \hat{f}(t+j) + k_1 \sum_{j=3}^{7} \hat{f}(t+j)}.$$

Analogously, we can obtain the incidence in the isolated block. By regression analysis method from the data, we obtain

$$\beta(t) = 0.002 + 0.249\mathrm{e}^{-0.1303t}.$$

After the estimate of those parameters, we can do numeric simulations to validate the model (6.4), and discussed the effectiveness of control measures. The date of all the numeric simulations started from April 21, 2003; that is, the origin of abscissa corresponds to April 21, 2003. Figure 6.14 shows the simulated curve of the daily number of SARS patients in hospitals in reality. Figure 6.15 shows the case with no control measures. Figure 6.16 shows the case under which the prevention and control measures were relaxed from May 19, 2003. (In Figs. 6.15 and 6.16 we have assumed that the toxicity of SARS virus naturally declines at the rate of 0.01 per unit time.) Figure 6.17 shows the influence of the slow quarantine speed.

From the simulations above, we think that the rapid decrease of the SARS patients is attributed to the high successful quarantine rate and timely implementation of the quarantine measures, and indeed all of the prevention and control measures implemented in China are very effective.

We have presented three models to describe SARS transmission. The first one is very simple, and the other two add more factors in the models. Even though those models are formulated for SARS, the method of parameter estimate is based on the epidemiologic data from SARS, the principle and the idea can be applied to other diseases.

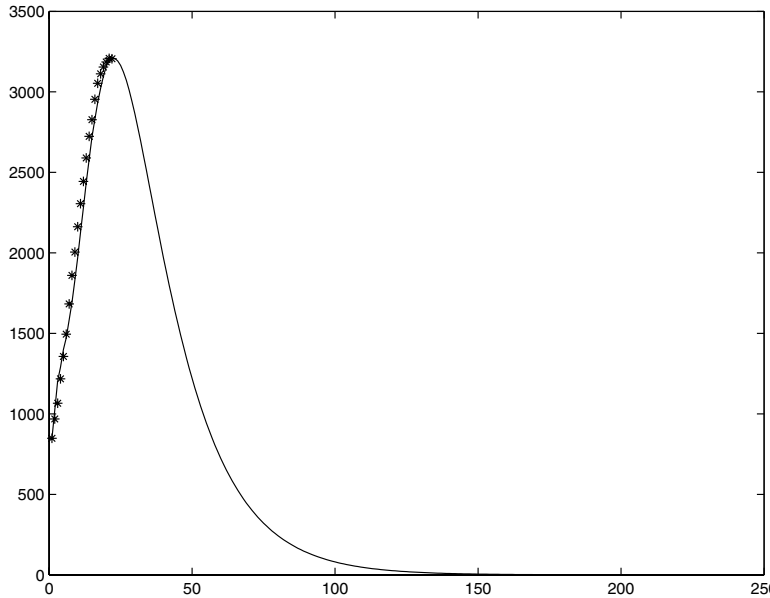


Fig. 6.14. The simulated and the reported daily number of SARS patients.

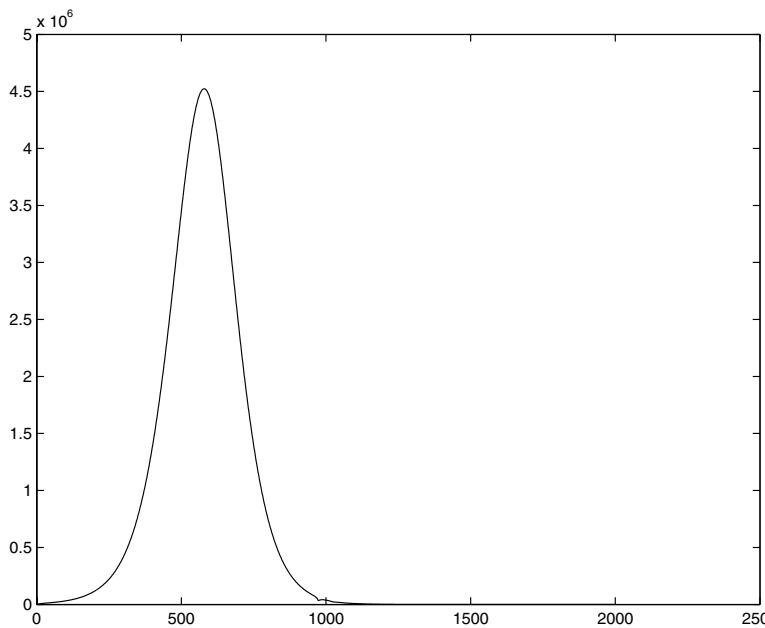


Fig. 6.15. The simulated transmission pattern in China without control measures: the outbreak will peak at the end of October 2004 with over 4.5 million individuals infected.

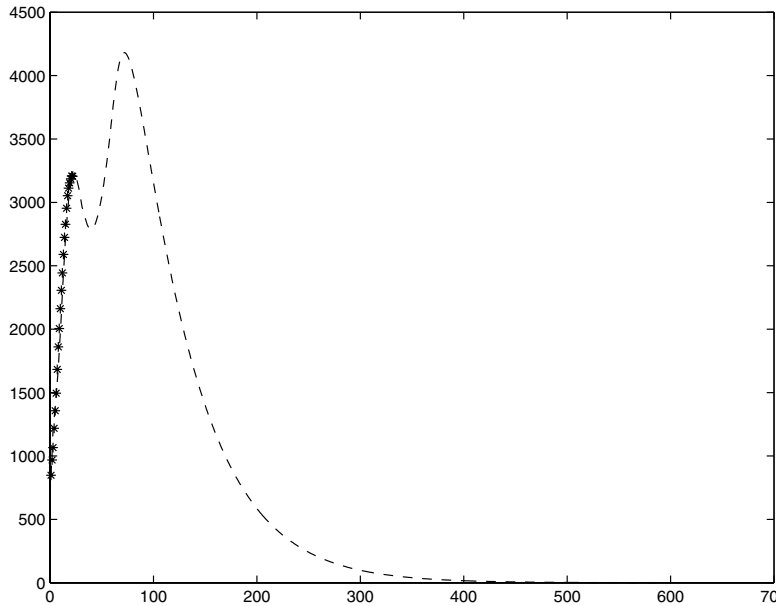


Fig. 6.16. The pattern of SARS transmission if the prevention and control measures were relaxed from May 19, 2003: there would be a second outbreak with the maximum number of SARS patients higher than that of the first outbreak.

Although SARS infected many individuals in more than 30 countries, it did not lead to the devastating health impact, but a rather disproportionate economic impact. Especially, the impact to the food industry and the tourists market were catastrophic during the SARS epidemic in China. The disproportionate scale and the nature of this impact had caused concern that outbreaks of more serious disease could cause catastrophic impacts on the global economy. We expect that mathematical models of the infectious diseases can help deal with the possible impact. The SARS epidemic in 2003 is short, but it is a sign that the emerging and reemerging diseases will still keep being a great threat to human life. We can use mathematical models to provide conceptual results such as thresholds, basic reproductive numbers, and contact numbers. Especially, mathematical models and computer simulations are useful experimental tools for assessing the control measures. Mathematical models can help us to understand the transmission characteristics of infectious diseases in communities, regions, and countries. They can provide prediction and lead to better approaches to decreasing the transmission of the infectious diseases. Mathematical models

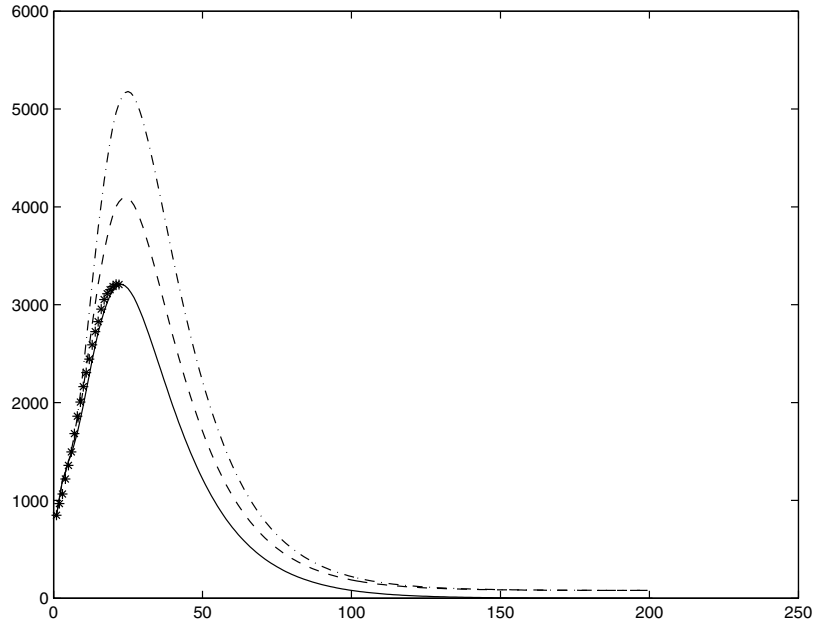


Fig. 6.17. The influence of the slow quarantine speed: the top and bottom lines show the number of daily SARS patients when the infectives stay in the I-compartment for 2 and 1 more days, respectively. The peak would be postponed by 4 or 2 days, the numbers at the peak would be much higher.

can be also used in comparing, planning, implementing, evaluating, and optimizing various detection, prevention, therapy, and control programs.

6.2. HIV Transmission Models

AIDS was first identified as a distinct new disease in 1981. In 1983 HIV was identified at the causative agent for AIDS. The mean time from HIV infection to AIDS is approximately 10 years. There is no effective medicine to cure it and the infected individuals do not recover: that is, they continue to be infectious throughout their lives. In this section we give a brief introduction to HIV transmission, and present two HIV transmission models.

6.2.1. *The severity of HIV transmission*

HIV infection is a complex mix of diverse epidemics within and between countries and regions of the world, and is undoubtedly the defining public-health crisis of our time. It is estimated that 38.6 million people worldwide

were living with HIV in 2005, 4.1 million became newly infected with HIV, and 2.8 million lost their lives to AIDS [WHO (2006)]. HIV infections in women is increasing, which has additional implications for mother-to-child transmission. Women now make up about 42% of those infected worldwide. From the global summary of the HIV infections and AIDS epidemic by WHO, the number of people living with HIV in 2006 is 39.5 million, including 17.7 million women and 2.3 million children under 15. The number of people newly infected in 2006 is 4.3 million, and the AIDS death in 2006 is 2.9 million. There are over 11 000 new HIV infections a day in 2006, about 1500 are in children under 15 years of age, almost 50% are among women.

The three known modes of transmission of HIV are sexual contact, direct contact with HIV-infected blood or fluids, and perinatal transmission from an infected mother to child [Hethcote and van Ark (1995)]. South Africa remains the epicenter of the pandemic and continues to have high rates of new HIV infections. Outside of sub-Saharan Africa, a third of all HIV infections are acquired through injecting drug use, most of which are in Eastern Europe and Central and Southeast Asia [Simon *et al.* (2006)].

Chinese Ministry of Health, with support from UNAIDS and WHO, has prepared a updated assessment of the HIV/AIDS epidemic and response in China. The latest estimation results indicate that as of late 2005, people living with HIV/AIDS in China were 650 000, of which 75 000 have developed AIDS. Nationally, HIV prevalence averages 0.05%. In 2005, there were an estimated 70 000 new HIV infections, and 25 000 AIDS deaths. There are approximately 288 000 drug users living with HIV/AIDS, accounting for 44.3% of the total number of estimated HIV cases. Approximately 69 000 former commercial blood and plasma donors and recipients of blood or blood products through transfusions are living with HIV/AIDS, accounting for 10.7% of the total number of estimated HIV cases. Approximately 127 000 sex workers and their clients are living with HIV/AIDS, accounting for 19.6% of the total number of estimated HIV cases. There are approximately 109 000 partners of HIV-positive individuals and members of the general population who are living with HIV/AIDS, accounting for 16.7% of the total number of estimated HIV cases. An estimated 47 000 men who have sex with men (MSM) are living with HIV/AIDS, accounting for 7.3% of the total number of estimated HIV cases. Approximately 9000 cases of mother-to-child transmission have occurred, accounting for 1.4% of the total number of estimated HIV cases [Ministry of Health, China (2006)].

Sentinel surveillance data in China indicate that HIV prevalence among drug users has risen from 1.95% in 1996 to 6.48% in 2004. HIV prevalence

among sex workers has risen from 0.02% in 1996 to 0.93% in 2004. In areas of high transmission, HIV prevalence among pregnant women has risen from 0 in 1997 to 0.26% in 2004. These data indicate that HIV infections continue to increase. HIV/AIDS awareness remains unacceptably low, and many people still do not know enough about how to protect themselves against HIV. National surveillance data indicate that 45.5% of injection drug users are sharing needles and syringes, and 11% of drug users are engaging in high-risk sexual activities, thereby increasing their risk of becoming infected with HIV and accelerating the spread of HIV among drug users, sex workers and their clients. Mobility of people living with HIV is another factor affecting the spread of HIV around China. Other important factors fueling the spread of HIV include increases in risky sexual behavior, and rising sexually transmitted infection rates in many cities.

Typical course of HIV infection is defined by three stages: primary infection and first viremia, asymptomatic stage, and AIDS. The viral load and the CD4 count change as the disease progressing (Fig. 6.18) [Pantaleo *et al.* (1993); Anthony *et al.* (1996)]. The primary infection is characterized by a spike viremia and a migration into lymphatic tissue. The first viremia is characterized by an array of month-long clinical symptoms, including fever,

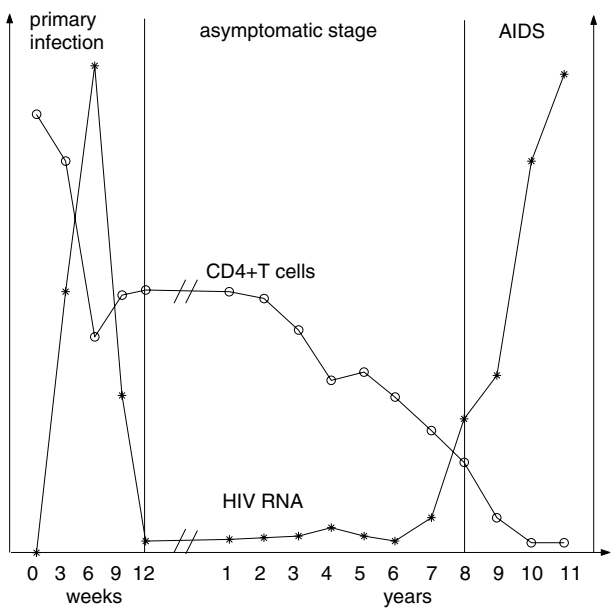


Fig. 6.18. The viral load and the CD4 count during the disease progression.

diarrhea, rash, headache, and lethargy. The immune response reduces HIV replication to a set-point equilibrium that for the most part lasts during the asymptomatic stage until a second viremia induces the onset of AIDS.

Although the relative contribution of cell-free virus compared with cell-associated virus in HIV transmission remains unclear, there is growing evidence that viral load is predictive of transmission risk. The highest levels of viremia are seen during acute infection and advanced HIV disease. There are indications that the transmissibility of HIV infection varies greatly during the multiyear course of infection. Transmission may be more likely just after HIV infection and before the body develops an antibody response. Since the HIV virus level in the blood decreases during the asymptotic period, the transmissibility appears to be lower in this period. Then the transmissibility seems to increase again as the CD4 cell count gets down, the HIV virus level in the blood increases, and symptoms appears.

There are three main approaches to modeling HIV/AIDS transmission. The first and most direct approach to predicting AIDS cases is the extrapolation. This method is to fit an assumed form of AIDS incidence curve to an AIDS incidence data in recent years and then to extent this curve for several years as a prediction of AIDS cases in the future. This method assumed that the current trends will continue at least for a few years in the future. Often separate curves and extrapolations are done for various risk groups. Advantages of extrapolation are its simplicity and ease to use. The second approach is the back calculation. The total number of AIDS cases at time t is the summation up to time t of the product of the HIV incidence at time τ and the probability of developing AIDS within $t-\tau$ years after infection. The third approach is to use HIV transmission dynamic models. Those models often have the population divide into compartments consisting of those who are susceptible, in each of the infectious stages, or in the AIDS phase. In deterministic transmission models, the movements between those compartments are by becoming infected, moving to next stage or AIDS, migrating or dying are specified by systems of difference or differential equations [Hethcote and van Ark (1995)].

In recent years there has been tremendous number of modeling papers. Here we give a few of them to show the applications of dynamic models.

6.2.2. *An age-structured model for the AIDS epidemic*

We consider HIV transmission in a homosexual community. The model and simulation in this section is based on the paper by Griffths *et al.* (2000).

Individuals in the homosexual community are divided into three main categories: the susceptibles, the infected, and AIDS. Each of the categories is divided into high risk and low risk. The numbers of high-risk people in the susceptible, infective, and AIDS categories, at time t, are denoted by $X(t)$, $Y(t)$, and $A(t)$, respectively; and $W(t)$, $V(t)$, and $Z(t)$ are the corresponding numbers in low-risk categories. Under detailed assumptions the HIV transmission model consisting of three systems of differential equations is formulated.

$$\begin{aligned}
\frac{\mathrm{d}X_1(t)}{\mathrm{d}t} &= P\lambda N + \nu_0 W_1(t) - \alpha X_1(t) - (\nu_1 + \theta_1 + \mu_1)X_1(t),\\
\frac{\mathrm{d}W_1(t)}{\mathrm{d}t} &= (1-P)\lambda N + \nu_1 X_1(t) - (\nu_0 + \theta_1 + \mu_1)W_1(t),\\
\frac{\mathrm{d}Y_{1,1}(t)}{\mathrm{d}t} &= a\alpha X_1(t) - (\gamma + \nu_2 + \theta_1 + \mu_1)Y_{1,1}(t),\\
\frac{\mathrm{d}Y_{1,j}(t)}{\mathrm{d}t} &= \gamma Y_{1,j-1}(t) - (\gamma + \nu_2 + \theta_1 + \mu_1)Y_{1,j}(t),\\
\frac{\mathrm{d}V_{1,1}(t)}{\mathrm{d}t} &= (1-a)\alpha X_1(t) + \nu_2 Y_{1,1}(t) - (\gamma + \theta_1 + \mu_1)V_{1,1}(t),\\
\frac{\mathrm{d}V_{1,j}(t)}{\mathrm{d}t} &= \nu_2 Y_{1,j}(t) + \gamma V_{1,j-1}(t) - (\gamma + \theta_1 + \mu_1)V_{1,j}(t),\\
\frac{\mathrm{d}A_1(t)}{\mathrm{d}t} &= b\gamma Y_{1,m}(t) + g\gamma V_{1,m}(t) - (\nu_3 + \theta_1 + \omega + \mu_1)A_1(t),\\
\frac{\mathrm{d}Z_1(t)}{\mathrm{d}t} &= (1-b)\gamma Y_{1,m}(t) + (1-g)\gamma V_{1,m}(t) + \nu_3 A_1(t)\\
&\quad - (\theta_1 + \omega + \mu_1)Z_1(t),
\end{aligned} \tag{6.5}$$

where

$$\alpha = \frac{\beta c \sum_{i=1}^{n-1}(Y_i(t) + A_i(t))}{\sum_{i=1}^{n-1}(X_i(t) + Y_i(t) + A_i(t))},$$

$$Y_i(t) = \sum_{j=1}^{m} Y_{i,j}(t), \quad V_i(t) = \sum_{j=1}^{m} V_{i,j}(t).$$

$$\frac{\mathrm{d}X_i(t)}{\mathrm{d}t} = \theta_{i-1}X_{i-1}(t) + \nu_0 W_i(t) - \alpha X_i(t) - (\nu_1 + \theta_i + \mu_i)X_i(t),$$

$$
\begin{aligned}
\frac{\mathrm{d}W_i(t)}{\mathrm{d}t} &= \theta_{i-1}W_{i-1}(t) + \nu_1 X_i(t) - (\nu_0 + \theta_i + \mu_i)W_i(t),\\
\frac{\mathrm{d}Y_{i,1}(t)}{\mathrm{d}t} &= a\alpha X_i(t) + \theta_{i-1}Y_{i-1,1}(t) - (\gamma + \nu_2 + \theta_i + \mu_i)Y_{i,1}(t),\\
\frac{\mathrm{d}Y_{i,j}(t)}{\mathrm{d}t} &= \gamma Y_{i,j-1}(t) + \theta_{i-1}Y_{i-1,j}(t) - (\gamma + \nu_2 + \theta_i + \mu_i)Y_{i,j}(t),\\
\frac{\mathrm{d}V_{i,1}(t)}{\mathrm{d}t} &= (1-a)\alpha X_i(t) + \nu_2 Y_{i,1}(t) + \theta_{i-1}V_{i-1,1}(t)\\
&\quad - (\gamma + \theta_i + \mu_i)V_{i,1}(t),\\
\frac{\mathrm{d}V_{i,j}(t)}{\mathrm{d}t} &= \nu_2 Y_{i,j}(t) + \gamma V_{i,j-1}(t) + \theta_{i-1}V_{i-1,j}(t)\\
&\quad -(\gamma + \theta_i + \mu_i)V_{i,j}(t),\\
\frac{\mathrm{d}A_i(t)}{\mathrm{d}t} &= b\gamma Y_{i,m}(t) + g\gamma V_{i,m}(t) + \theta_{i-1}A_{i-1}(t)\\
&\quad - (\nu_3 + \theta_i + \omega + \mu_i)A_i(t),\\
\frac{\mathrm{d}Z_i(t)}{dt} &= (1-b)\gamma Y_{i,m}(t) + (1-g)\gamma V_{i,m}(t) + \nu_3 A_i(t)\\
&\quad + \theta_{i-1}Z_{i-1}(t) - (\theta_i + \omega + \mu_i)Z_i(t).
\end{aligned}
\tag{6.6}
$$

$$
\begin{aligned}
\frac{\mathrm{d}W_n(t)}{\mathrm{d}t} &= \theta_{n-1}(X_{n-1}(t) + W_{n-1}(t)) - \nu_n W_n(t),\\
\frac{\mathrm{d}V_{n,1}(t)}{\mathrm{d}t} &= \theta_{n-1}(Y_{n-1,1}(t) + V_{n-1,1}(t)) - (\gamma + \mu_n)V_{n,1}(t),\\
\frac{\mathrm{d}V_{n,j}(t)}{\mathrm{d}t} &= \theta_{n-1}(Y_{n-1,j}(t) + V_{n-1,j}(t)) + \gamma V_{n,j-1}(t)\\
&\quad - (\gamma + \mu_n)V_{n,j}(t),\\
\frac{\mathrm{d}Z_n(t)}{\mathrm{d}t} &= \gamma V_{n,m}(t) + \theta_{n-1}(A_{n-1}(t) + Z_{n-1}(t)) - (\omega + \mu_n)Z_n(t).
\end{aligned}
\tag{6.7}
$$

The explanations of variables and parameters used in the age-dependent model equations (6.5)–(6.7) are given below:

N, initial homosexual population size;
$X_i(t)$, number of high-risk susceptibles in age-group i at time t;

$Y_{i,j}(t)$, number of high-risk infectives in age-group i and at stage of infection j at time t;
$A_i(t)$, number of high-risk AIDS cases in age-group i at time t;
$W_i(t)$, number of low-risk susceptibles in age-group i at time t;
$V_{i,j}(t)$, number of low-risk infectives in age-group i and at stage of infection j at time t;
$Z_i(t)$, number of low-risk AIDS cases in age-group i at time t;
n, number of age-groups;
α, transmission parameter;
β, rate of infection per contact;
c, average number of sexual contacts per annum;
γ, rate of flow from infective to AIDS (incubation period);
ω, death rate from AIDS;
ν_1, ν_2, ν_3, flow rate from high- to low-risk for each category;
ν_0, flow rate from low- to high-risk for susceptibles;
μ_i, death rate from causes other than AIDS for each age-group;
θ_i, transfer rate to next age-group;
λ, entry rate into first age-group;
P, proportion of entry who go straight into high-risk;
a, proportion who transfer from high-risk susceptible directly to high-risk infective;
b, proportion who transfer from high-risk infective directly to high-risk AIDS;
g, proportion who transfer from low-risk infective directly to high-risk AIDS.

The age-structured HIV transmission model has many variables and equations. There are also a large number of parameters to be determined before the application of the model. Most of the parameters in the model have a physical interpretation and so quite narrow limits can be placed on their values. Those parameters related to the age structure of the population can be obtained from national census information, together with death rates for particular age-groups. Estimates for parameters related to sexual behavior can be taken from National Sexual Surveys. The results of the survey indicated that 1.1% of males have exhibited some form of high-risk homosexual tendencies in the past year, and this figure increased to 3.5% in the Greater London area.

The level and type of sexual behavior of the homosexual population is obviously an important input in the model. Originally βc is set to 1 and is

reduced to approximately one fifth in 1985. The movement from the low- to high-risk susceptibles is reduced, and the movement from the high- to low-risk categories increases. The following values for non-age-dependent parameters are used: $N = 140\,000$, $n = 51$, $a = 0.95$, $b = 0.05$, $g = 0.02$, $\nu_3 = 0.5$, $\beta c = 1$ (prior to behavior change), and $\beta c = 0.22$ (after behavior change). The age-dependent parameter values before and after behavior change are given in Table 6.1.

The age-dependent probability density functions of the length of the incubation period are given in Fig. 6.19.

A sensitivity analysis is carried out on the parameters a, b, and g. While very small changes to these parameters result in insignificant changes in results, larger variations in these values resulted in quite substantial changes in AIDS incidence. The actual data by year and age-group for AIDS incidence in Greater London are given in Fig. 6.20, together with the model results in Fig. 6.21.

From the figure we see that the overall picture by the actual data and by the model is very similar. Figure 6.20 provides confidence that the model is functioning correctly. The estimated prevalence for selected years is given in Fig. 6.21. This clearly shows that HIV is far more prevalent among the 20–29 age-group.

Griffths *et al.* (2000) has applied their model to the AIDS incidence in France, and compared the actual data and model prediction. They also discussed the efficiency of the prevention campaigns, and pointed out more attention should be paid to young population.

Table 6.1. Parameter values prior/after the behavior change.

Age	μ	ν_0 (prior/after)	ν_1 (prior/after)	ν_2 (prior/after)
15	0.0007	0.1/0.1	0/0.1	0/0.2
16	0.0007	0.25/0.18	0/0	0/0
17	0.0007	0.25/0.1	0/0	0/0
18	0.0007	0.55/0.3	0/0.03	0/0.03
19	0.0007	0.75/0.35	0/0.1	0/0.1
20–24	0.0007	1/1	0/0	0/0
25–29	0.0013	0.75/0.12	0/0.12	0/0.14
30–34	0.0013	0.35/0.05	0.05/0.35	0.05/0.35
35–39	0.0021	0.15/0	0.15/0.35	0.15/0.35
40–44	0.0021	0.05/0	0.22/0.36	0.22/0.36
45–54	0.0049	0.01/0	0.25/0.5	0.25/0.5
55–59	0.0141	0/0	0.3/0.58	0.3/0.6
60–64	0.0141	0/0	1/1	1/1
$\geq$65	0.04005	0/0	1/1	1/1

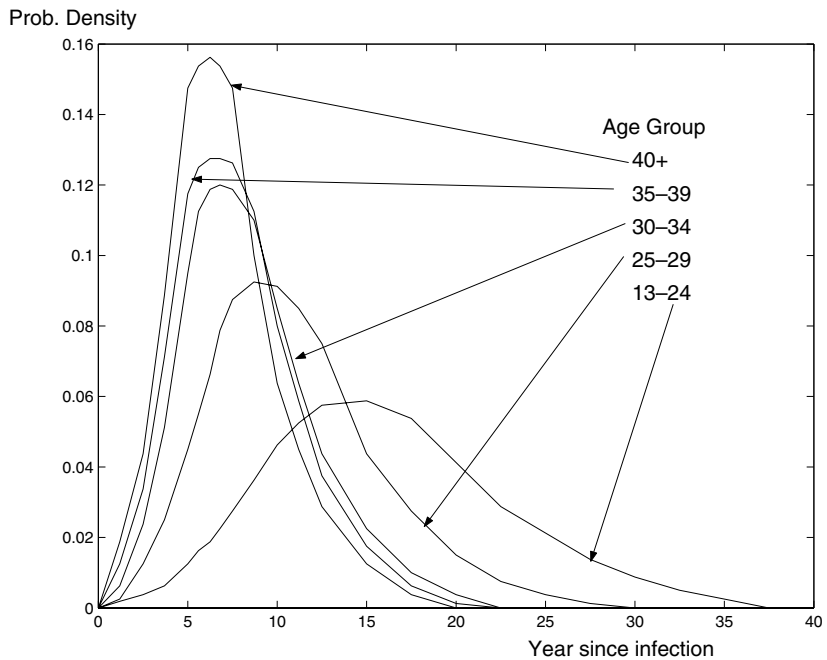


Fig. 6.19. Probability density for age-dependent incubation periods.

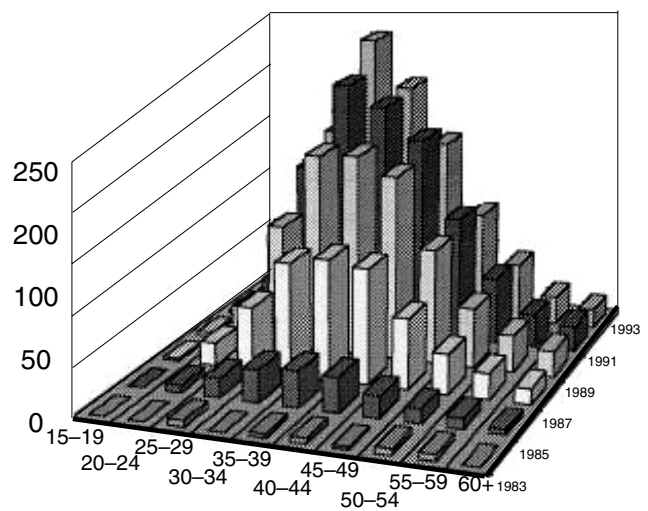


Fig. 6.20. The actual data by year and age-group for AIDS incidence.

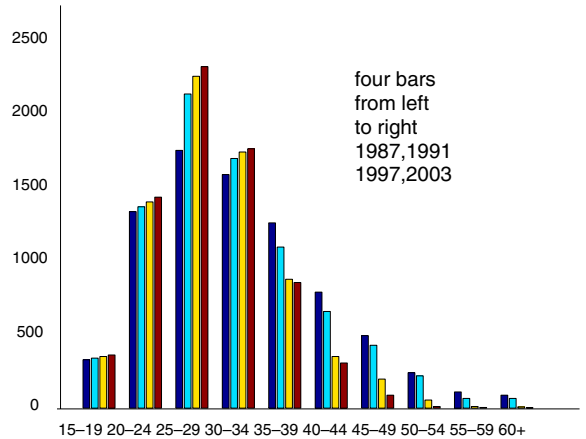


Fig. 6.21. Estimated HIV prevalence for the homosexual population.

6.2.3. *Discrete model with infection age structure*

HIV transmission process involves a long incubation and infection period, and the transmission rate varies greatly with infection stage. During the long incubation period the infectivity of infected people varies depending on the viral loads and the time from infection. Wawer *et al.* estimated that the average rate of HIV transmission is 0.0082, 0.0015, 0.0007, and 0.0028/coital act within roughly 2.5 months after seroconversion of the index partner, 6–15 months after seroconversion of the index partner, among HIV-prevalent index partners, and 6–25 months before the death of the index partner, respectively [Wawer *et al.* (2005)]. Rapatski, Suppe, and Yorke found that the infectivity rates for semen are 0.024, 0.002, and 0.299 for the primary, asymptomatic, and symptomatic stages, respectively [Rapatski *et al.* (2005)].

The other difficulty in modeling HIV transmission is that the annual HIV statistic data available to us involve the number of reported individuals, closely related with the long incubation period. As the infection might occur many years before the reporting, the annual reported number is not the newly effected. Models involving infection-age-dependent transmission rates become necessary to reflect the complicated mechanism of the disease with long infection period. We assume that individuals are in one of the following epidemiologic groups: susceptibles, infected, and AIDS. The infected is further divided into 12 subgroups (indexed by $j, j = 1, 2, \ldots, 12$) according to their infection age. Let $S(t)$ be the number of the susceptibles, $I_j(t)$ the number of the infected with infection age j, and $A(t)$ the number of AIDS

at time t. Let β_j, μ_j, and α_j be the transmission rate, the death rate, and the rate of progressing to AIDS for the infected individuals in the group j, respectively. Let δ be the death rate of AIDS cases. The AIDS progressing rate α_j is introduced to describe the slow and fast progression to AIDS: some HIV infected individuals will enter AIDS stage faster, some may be slow. We assume that $\alpha_1 = 0, \alpha_j \geq 0, j = 2, 3, \ldots, 11$, and $\alpha_{12} = 1 - \mu_{12}$. The transfer among those groups is shown in the schematic diagram (see Fig. 6.22), where the standard incidence rate is used for the transmission rate:

$$\lambda(t) = \sum_{j=1}^{12} \beta_j I_j(t) \frac{S(t)}{N(t)}.$$

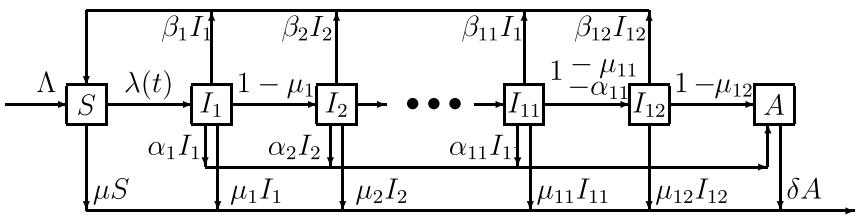


Fig. 6.22. The schematic diagram of the HIV transmission, structured by infection ages.

From the schematic diagram, we formulate the following discrete HIV transmission model with infection-age structure [Zhou *et al.* (2008)]:

$$\begin{aligned}
S(t+1) &= S(t) + \Lambda - \frac{S(t)}{N(t)} \sum_{j=1}^{12} \beta_j I_j(t) - \mu S(t), \\
I_1(t+1) &= \frac{S(t)}{N(t)} \sum_{j=1}^{12} \beta_j I_j(t), \\
I_2(t+1) &= (1-\mu_1) I_1(t), \\
I_{j+1}(t+1) &= (1-\alpha_j-\mu_j) I_j(t), \quad j = 2, 3, \ldots, 11, \\
A(t+1) &= A(t) + \sum_{j=2}^{11} \alpha_j I_j(t) + (1-\mu_{12}) I_{12}(t) - \delta A(t),
\end{aligned} \tag{6.8}$$

where, $N(t)$ is the number of the total population at time t and satisfies,

$$N(t) = S(t) + I_1(t) + I_2(t) + \cdots + I_{12}(t) + A(t),$$

$$N(t+1) = N(t) + \Lambda - \mu S(t) - \sum_{j=1}^{12} \mu_j I_j(t) - \delta A(t).$$

We do not provide the dynamic behavior of the model in more details. The first HIV infected individual in China was reported in 1985, and we have now 20 annually reported data which clearly shows the tendency of exponential growth with time, and thus we use the standard exponential regression to fit these data. There are also different choices to carry out the regression by using data sets during different periods of time. The following three regression curves:

$$\begin{aligned} h_5(t) &= 2552\mathrm{e}^{0.2723(t-1997)}, \\ h_{13}(t) &= 151.5173\mathrm{e}^{0.3740(t-1990)}, \\ h_{20}(t) &= 3.6466\mathrm{e}^{0.4792(t-1984)}, \end{aligned}$$

are based on the data during 1998–2002 ($h_5(t)$), 1990–2002 ($h_{13}(t)$) and 1985–2004 ($h_{20}(t)$). There was very limited knowledge on HIV infection and virtually no surveillance system in 1980s when HIV infection was first reported in China. The surveillance system was then established gradually when more and more attentions to HIV infection were given at various levels of governments. There were local outbreaks due to the contaminated blood during 1995–1997, and then a large scale screening program was launched in 2004 and 2005 to trace and identify the HIV infection status for those with possible contact with the contaminated blood. These factors greatly influence the normal and natural surveillance system and reported data. The annually reported data from 1998 to 2002 are collected in a natural manner that reflects the HIV transmission tendency in China. We therefore will use the regression curve from those 5 years data to estimate the model parameters.

We observed that the percentage of HIV infected in China is quite small even though there are a large number of infected individuals. Therefore, $S(t) \approx N(t)$ and the structured epidemic model (6.8) can be approximated by

$$\begin{aligned} I_1(t+1) &= \sum_{j=1}^{12} \beta_j I_j(t), \\ I_2(t+1) &= (1-\mu_1) I_1(t), \\ I_{j+1}(t+1) &= (1-\mu_j-\alpha_j) I_j(t), \quad j = 2, 3, \ldots, 11, \\ A(t+1) &= A(t) + \sum_{j=2}^{11} \alpha_j I_j(t) + (1-\mu_{12}) I_{12}(t) - \delta A(t). \end{aligned} \tag{6.9}$$

There are 12 transmission rates, $\beta_i, 1 \le i \le 12$, to be estimated. We try to reduce the number of parameters due to the very limited data. We further

regroup these infection ages to five stages according to the viral loads, the CD4 cell counts, and the behavior activity of HIV infected individuals.

We used a data set (Table 6.2) from the State Key Laboratory for Infectious Disease Prevention and Control, that contains information of 433 HIV nontreated infected individuals about their CD4 cell counts and viral loads. We regress the logarithm of the viral load with base 10 on the CD4 cell counts to obtain the following regression model:

$$\log_{10}(\text{viral load}) = 4.790712 - 0.001689 \text{ CD4 counts}.$$

The p-value of the F-test is less than 0.0001, indicating a very significant regression relationship.

Table 6.3 shows that the median value of the CD4 cell counts $(100, 275, 425, 750)$ for each of stages 2 to 5 is close to its corresponding average value. We then substitute the median value of the CD4 count at each stage to the above regression model to obtain the corresponding viral loads, as shown in Table 6.2. We also assume that the transmission rate in each stage is proportional to the viral loads. We can obtain the proportionality coefficient of the transmission rate for each of the stages 2 to 5 when the baseline transmission rate at stage 2 is set to 1.

It is difficult to catch a newly infected within 3 months of the infection, and thus Table 6.3 does not contain relevant information about the viral

Table 6.2. Classification of infection ages by stages.

Stage	Time since infection	Viral load or CD4
1	Within 3 months	Very high viral load
2	4th month to the 3rd year	$\geq$500
3	4th year to the 6th year	499–350
4	7th year to 9th year	349–200
5	10th year to 12th year	$\leq$200

Table 6.3. The CD4 cell count, viral load, and the proportionality coefficient of the transmission rate at each stage.

CD4 cell count	Number	Percentage	Average CD4	Viral load	Proportionality
>500	113	26.1	719.57	3341	1
499–350	108	24.9	413.55	11827	3.54
349–200	99	22.9	275.76	21195	6.34
<200	113	26.1	104.55	41861	12.53

loads. Existing literature does indicate that the viral load is extremely high during this stage [Lang *et al.* (1989)], and it is estimated that the transmission rate in the first 3 months of infection is 30–50 time higher than that in the second stage [Pilcher *et al.* (2004)]. Therefore, if we denote the transmission rate in the second stage by x, then we shall assume the transmission in the first 3 months of the infection as $40x$. On the other hand, since the time scale of our recurrent calculation is one year, we need to spread the very high transmission rate in the first 3 months into the first year with the transmission rate given by $10.7x$.

Behavior analysis shows that there is significant behavior change of the HIV infected due to their illness and the awareness of the others in the last two stages. This behavior change will reduce the transmission rate, and we assume the reduction rates are 0.5 and 0.25, respectively, for the last two stages. Therefore, we obtain the transmission rates used in model (6.9) as follows:

$$\begin{aligned}
&\beta_1 = 10.7x,\\
&\beta_2 = \beta_3 = x,\\
&\beta_4 = \beta_5 = \beta_6 = 3.54x,\\
&\beta_7 = \beta_8 = \beta_9 = 6.34 \times 0.5x = 3.17x,\\
&\beta_{10} = \beta_{11} = \beta_{12} = 12.53 \times 0.25x = 3.13x.
\end{aligned} \tag{6.10}$$

The estimate of 12 transmission rates is now reduced to the determination of the baseline value x.

From the regression function $h_5(t)$, we see that the average yearly increasing rate is 31.3%, the average number that an infected individual can transmit per year is 0.329. Note that the reported number is not the newly infected ones, instead, it is the number of individuals who have been infected in early time and their infection were confirmed that year. We note also that only a part of the HIV infected is reported each year. At the end of 2005, the estimated HIV infected number in China is 650 000, and the cumulative number of the annually reported number from 1985 to 2005 is approximately 17.76% of the estimated number; 17.76% is the ration of the accumulated reported number over the 21 years to the estimated number 650 000.

We assume that the report rate is a constant every year, and we use a simple recursive model to calculate this constant. Let $I(t)$, $H(t)$, and $U(t)$ be the HIV infected number, the reported number, and the unreported number at time t, respectively. The HIV infected increased by 32.9% each year. The unreported number is the remainder of the previous unreported

infected individuals plus the newly infected. The reported is part of the infected who have not been reported that year. The infected, reported, and unreported therefore satisfy the following recursive equations:

$$\begin{aligned} I(t+1) &= 1.329I(t), \\ U(t+1) &= (1-r)U(t) + 0.329I(t), \\ H(t+1) &= rU(t+1), \end{aligned} \tag{6.11}$$

where the parameter r is the report rate. Starting from any initial value, we add all the reported number from the recursive model (6.11), and then calculate the ration of the total reported to the total infected, and finally let the ration be 17.76%. The calculation gives the value of the annually report rate $r = 5.1\%$.

After we understand the feature of the annually reported HIV infected number, we now use the following model to estimate the transmission rate:

$$\begin{aligned} I_1(t+1) &= \sum_{k=1}^{12} \beta_k I_k(t), \\ I_{j+1}(t+1) &= p_j I_j(t) \qquad \text{for } j = 1, 2, \ldots, 11, \\ H_1(t+1) &= rI_1(t+1), \\ H_{j+1}(t+1) &= rp_j U_j(t) \qquad \text{for } j = 1, 2, \ldots, 11, \\ U_1(t+1) &= (1-r)I_1(t+1), \\ U_{j+1}(t+1) &= (1-r)p_j U_j(t) \qquad \text{for } j = 1, 2, \ldots, 11, \\ H(t+1) &= \sum_{k=1}^{12} H_k(t+1), \end{aligned} \tag{6.12}$$

where $p_1 = 1 - \mu_1$, $p_j = 1 - \mu_j - \alpha_j$, $(j = 2, 3, \ldots, 11)$.

The equation for the HIV infected $I_j(t+1)$ is just the simplified model (6.9). The equation for $H_j(t+1)$ calculates the reported number at year $t+1$. The reported number of the new infected in year $t+1$ is the product of the reported rate and the infected. The reported number in other groups are the product of the report rate and the infected who are not reported in year $t+1$. The equation on $U_{j+1}(t+1)$ calculates the unreported number in year $t+1$. The last equation of $H(t+1)$ sums up the total number of the reported HIV infected in year $t+1$.

We do not have the national data for the death rate, μ_j, and the conversion rate, α_j, of the HIV infected. Here we use the survival date of a recent survey in the Anhui province. It is estimated from 159 HIV

infected individuals that the survival time distribution is

$$g(t) = \exp(-0.0006(t-0.5)^{3.099}).$$

The survival rate p_j from the jth infection year to the $(j+1)$th year in the estimate model (6.12) is determined on the basis of the function $g(t)$. In 1985, the reported number of the infected from the regression curve $h_5(t)$ is 97. The initial infected number is chosen to be 1902 such that the reported number in 1985 is 97 under the report rate 5.1%. The expected survival time of the HIV infected with the survival function $g(t)$ is 9.23 year, and 1902 infected individuals in 1985 are distributed into 12 groups by

$$I_1(1985) = \frac{1902}{9.23}, \quad I_2(1985) = \frac{1902p_1}{9.23}, \quad I_j(1985) = \frac{1902p_1p_2\ldots p_{j-1}}{9.23}.$$

After substituting those parameters and the initial values into model (6.12), we observe that the reported number $H(t)$ in year t contains only one unknown parameter x. We thus minimize the following function:

$$\min \phi(x) = \min \sum_{t=1986}^{2005} (H(t) - h_5(t))^2$$

to determine x and estimate the transmission rate, where $h_5(t)$ is the regression curve of the reported number.

The function $\phi(x)$ is a long polynomial. We use Maple to find the expression of $\phi(x)$ and then determine the minimal point x_0. The calculation gives the result $x = 0.0812$. The transmission rates in the five stages are 0.868, 0.0812, 0.287, 0.257, and 0.254, respectively. The basic reproductive number is $R_0 = 2.72$, the average infection period is 9.23 year, and the average number transmitted by an infected individual each year is 0.294.

The prediction from model (6.12) with the estimated transmission rates is shown in the first two rows of Table 6.4, which clearly shows the fast growth of the reported and the total HIV infection. More efforts must be made for the intervention and control. In particular, if more education and effective control measures can be implemented to reduce the HIV transmission rate 50% within 5 years, as the policy makers are hoping, the HIV infection can be substantially reduced. The last two rows of Table 6.4 shows the reported and the total numbers of the HIV infection if the transmission rates are reduced 13% annually from 2006 to 2010.

Table 6.4. The prediction of HIV in China during 2006–2010.

Year	2006	2007	2008	2009	2010
Reported	31 155	41 582	55 499	74 073	98 864
Total	682 440	910 844	1 215 689	1 622 556	2 165 593
Reported	29 897	36 425	42 403	47 557	51 696
Total	657 784	808 494	952 544	1 083 309	1 195 413

6.3. TB Transmission Models

TB is an infectious disease caused by *Mycobacterium tuberculosis*. TB has troubled humankind throughout history. TB has been a leading cause of death throughout the world. The recently increasing prevalence of TB in the developing countries and the high burden of infection in regions of Southeast Asia have sparked renewed interest in TB modeling and analysis. There are abundant publications in literature on TB modeling [Castillo-Chavez and Song (2004)]. We present a few results on TB modeling and applications in this section.

6.3.1. *Global and regional TB transmission*

TB is a contagious disease, and it is transmitted from one person to another when an infectious person coughs, sneezes speaks, or sings and exhales droplets of moisture containing live TB germs. Factors that affect transmission of TB include the number, viability, and virulence of organisms within sputum droplet nuclei, socioeconomic status, family size, crowding, malnutrition, and limited access to health care or effective treatment, and most importantly, time spent in close contact with an infectious person. Left untreated, each person with active TB disease will infect on average between 10 and 15 people every year [WHO Factsheet (2007)]. But people infected with TB bacilli will not necessarily become sick with the disease. The immune system "walls off" the TB bacilli which, protected by a thick waxy coat, can lie dormant for years. When someone's immune system is weakened, the chances of becoming sick are greater. About 5–10% of people who are infected with TB bacilli become sick or infectious at some time during their life [WHO Factsheet (2007)].

It is estimated that TB infected roughly one-third of the world's population resulting in 2–3 million deaths each year [Murphy *et al.* (2002)]. Someone in the world is newly infected with TB bacilli every second. WHO estimates 8.8 million new TB cases in 2005, 7.4 million in Asia and

sub-Saharan Africa. A total of 1.6 million people died of TB, including 195 000 patients infected with HIV [WHO (2007)]. The largest number of new TB cases in 2005 occurred in the Southeast Asia region, which accounted for 34% of incident cases globally. However, the estimated incidence rate in sub-Saharan Africa is nearly twice that of the Southeast Asia region, at nearly 350 cases per 100 000 population. Both the highest number of deaths and the highest mortality per capita are in the Africa Region. The TB epidemic in Africa grew rapidly during the 1990s, but this growth has been slowing each year, and incidence rates now appear to have stabilized or begun to fall. In 2005, estimated per capita TB incidence was stable or falling in all six WHO regions. However, the slow decline in incidence rates per capita is offset by population growth. Consequently, the number of new cases arising each year is still increasing globally and in the WHO regions of Africa, the Eastern Mediterranean, and Southeast Asia.

Let us mention TB transmission in Canada and China. In 2005, 1616 cases of new active and relapsed TB were reported. The three most populous provinces account for 71% of the total number of reported cases. Individuals between the ages for 25 and 34 years made up the largest number of reported cases, accounting for 17% of the total. In 2005, TB among foreign-born individuals accounted for 63% of all reported cases in Canada. Canadian-born non-Aboriginal and Canadian-born Aboriginal cases made up 13% and 19%, respectively [Public Health Agency of Canada (2005)]. China has the world's second largest TB epidemic, behind only India, with more than 1.3 million new cases of TB every year. Among notifiable communicable diseases in China, TB ranks first in terms of cases and deaths [Wang *et al.* (2007)]. The case number and death number are 1 127 571 and 3339 in 2006, 1 259 308, and 3402 in 2005 [Ministry of Health, China (2007)].

The first model for the transmission dynamics of TB was built in 1962 by Waaler. Waaler assumed that the incidence depends only on the number of infectious. Consequently, the latent and infectious classes are uncoupled from the equation for the susceptible class. The central part of this model is

$$\begin{aligned} E(t+1) &= E(t) + aI(t) - eE(t) - d_2E(t) + gI(t), \\ I(t+1) &= I(t) - gI(t) - d_3I(t) + eE(t), \end{aligned}$$

where $E(t)$ and $I(t)$ are the numbers of TB latent and TB infectious individuals at time t, a is the per-capita incidence rate, e is the per-capita progression rate from latent-TB to infectious-TB cases; g is the per-capita treatment rate, and d_2 and d_3 are per-capita death rates of the TB-latent and TB-infectious individuals, respectively. These values of parameters were

estimated $a = 1$, $e = 0.1$, $d_2 = 0.014$, $g = 0.10085$, and $d_3 = 0.07$ on the basis of the model, and the data from a rural area in south India for the period of 1950 to 1955 [Castillo-Chavez and Song (2004)]. These values set useful ranges for the estimation of parameters in developing nations.

There is a lot of research done on TB modeling. Various models are formulated to consider the influence of different factors. We will give a few of TB models in the next three sections.

6.3.2. *A TB model with exogenous reinfection*

Basic TB transmission model has the SEIT compartments structure, where S, E, I, and T refer to the susceptibles, the latent, the infective, and the treated. More realistic models incorporate more factors. Noticing the fact that a small proportion of individuals develop the active TB after the primary infection, and that most people have an effective immune response to the initial infection, Feng *et al.* formulated and studied a TB model with exogenous reinfection. The incorporation of exogenous reinfection into the TB model may lead to a subcritical bifurcation. They found that exogenous reinfection has a drastic effect on the qualitative dynamics of TB [Feng *et al.* (2000)].

Exposed individuals may remain in the latent stage for long and variable periods of time without clinical illness and infectivity. The progression towards active TB may be accelerated with re-exposure to TB bacilli. The exogenous reinfection plays an important role in disease progression. Therefore, we incorporate exogenous reinfections into a TB transmission model. We explore the possible role played by the exogenous infection.

In the model formulation, the host population is divided into four epidemiologic classes: susceptibles (S), exposed (E), infectious (I), and effectively treated (T). We assume that an individual can be infected only through contacts with infectious individuals and the per capita removal rates from infected is constant. The TB transmission model with exogenous reinfection is then given by Feng *et al.* (2000).

$$\begin{aligned}
\frac{\mathrm{d}S}{\mathrm{d}t} &= \Lambda - \frac{\beta c S I}{N} - \mu S, \\
\frac{\mathrm{d}E}{\mathrm{d}t} &= \frac{\beta c S I}{N} - \frac{p\beta c E I}{N} - (\mu + k)E + \frac{\sigma\beta c T I}{N}, \\
\frac{\mathrm{d}I}{\mathrm{d}t} &= \frac{p\beta c E I}{N} + kE - (\mu + \gamma + d)I, \\
\frac{\mathrm{d}T}{\mathrm{d}t} &= \gamma I - \frac{\sigma\beta c T I}{N} - \mu T,
\end{aligned} \tag{6.13}$$

where N is the total population, Λ is the constant recruitment rate, β and $\sigma\beta$ are the average numbers of, respectively, susceptible and treated individuals infected by one infectious individual per contact per unit of time, where $0 \leq \sigma \leq 1$, c is the per-capita contact rate, μ is the per-capita natural death rate, k is the rate at which an individual leaves the latent class by becoming infectious, d is the per-capita disease-induced death rate, and γ is the per-capita treatment rate.

In model (6.13), the term $p\beta cEI/N$ is the exogenous reinfection rate with $p \in (0, 1)$ representing the level of reinfection. The basic reproductive number for model (6.13) is

$$R_0 = \frac{\beta c}{\mu + \gamma + d} \frac{k}{\mu + k}.$$

The basic reproductive number is the product of the average number infected by one infectious individual during his/her effective infectious period and the fraction of the population which survive the latent period.

It is easy to verify that

$$G = \left\{ (S, E, I, T) \mid S \geq 0,\ E \geq 0,\ I \geq 0,\ T \geq 0,\ S + E + I + T \leq \frac{\Lambda}{\mu} \right\}$$

is a positively invariant domain of model (6.13). We consider only solutions of (6.13) in the biological domain $G \in R^4$. We will study the dynamic behavior of model (6.13) theoretically for the special case $d = 0$ and $\sigma = 1$. The general situation will be investigated numericly.

Model (6.13) always has the disease-free equilibrium $P_0(\Lambda/\mu, 0, 0, 0)$. Model (6.13) exhibits a subcritical bifurcation at $R_0 = 1$, and multiple endemic equilibria can occur for $R_0 < 1$. Let

$$p_0 = \frac{(1 + Q)D_e}{1 - D_e}, \quad \text{where } D_e = \frac{k}{\mu + k},\ Q = \frac{k}{\mu + \gamma}.$$

We have the following bifurcation and stability results. The detailed analysis and proof can be found in [Feng *et al.* (2000)].

Theorem 6.1. *If $R_0 > 1$, then model* (6.13) *has exactly one positive equilibrium. If $R_0 < 1$ and $p > p_0$, then for each given p, there exists a positive constant $R_p < 1$ such that model* (6.13) *has exactly two positive equilibria if $R_0 > R_p$, only one positive equilibrium if $R_0 = R_p$, and no positive equilibrium if $R_0 < R_p$.*

Theorem 6.2. *If $R_0 < 1$, then the disease-free equilibrium P_0 is stable. If $p > p_0$ and $R_p < R_0 < 1$, then the large endemic equilibrium P^* is*

stable, and the smaller endemic equilibrium P_* is unstable. If $R_0 > 1$, then the disease-free equilibrium is unstable and the unique endemic equilibrium is stable.

We use the following values in the simulation: $\mu = 0.016$, $d = 0.1$, $p = 0.4$, $\sigma = 0.9$, $\Lambda = 417$, $k = 0.005$, $\gamma = 2$, $c = 2.5$, and $\beta = 3.144$. There are three equilibria: $P_0(26062.5, 0, 0, 0)$, $P_*(3272.09, 15934.6, 411.19, 6444.63)$, and $P^*(3989.27, 15530.3, 320.16, 6222.8)$ of (6.13), as $R_0 < 1$. The disease-free equilibrium P_0 and the larger endemic equilibrium P^* are both stable, while the smaller endemic equilibrium P_* is unstable. Several sets of initial values are used for the simulations. The results are shown in Fig. 6.23.

6.3.3. *TB models with fast and slow progression, case detection, and two treatment stages*

The fast and slow progressions, the case detection of an infected individual, and differentiation of infectiveness of a treated patient during his/her treatment period are considered in our next model, since those factors are recognized important factors for the successful control and management of TB transmission.

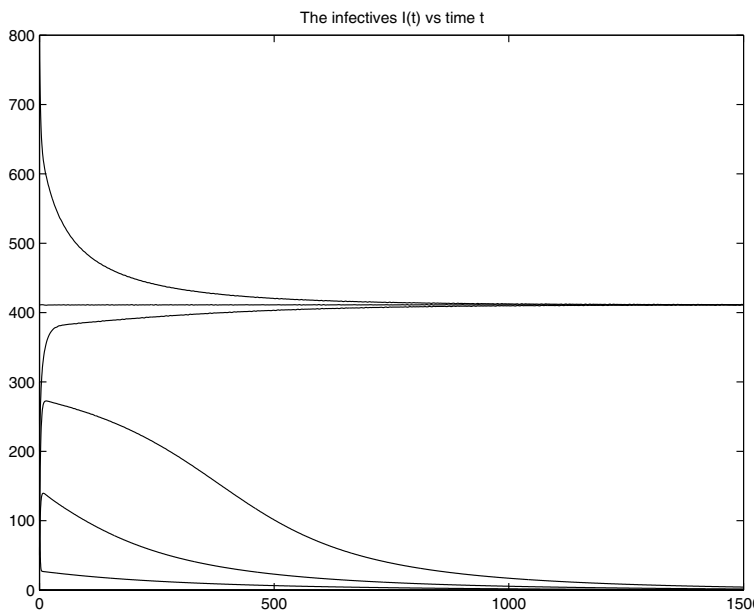


Fig. 6.23. The asymptotic stability of the infectives of model (6.13).

Epidemiologically, the treatment period of an infected individual usually lasts for 6 months, and the period can be separated into two stages: the first two months since the treatment is initiated when the individual is infectious, and the subsequent four months when the individual is no longer infectious. Based on their epidemiologic status and infectivities, the total population is divided into seven classes: the susceptible (S), the early latent (E_1), (with high-risk of developing infectious TB), the later latent (E_2), (with low-risk of developing infectious TB), the infectious and treated (I_1), (TB infectious in the first two month treatment stage), the treated but not infectious (I_2), (TB infected who are in their last 4 month treatment and are no longer infectious), the infectious and untreated (I_n), (not detected and not treated), and the effectively treated (T).

Many parameters are introduced in the model: the recruitment rate (Λ), the per-capita natural death rate (μ), the disease-induced death rate in class I_1 and I_2 (d), the disease-induced death rate (per capita) of class I_n (δ, $\delta > d$), the transfer rate from E_1 class to E_2 or I_1 classes (k_1), the fast progression rate (pk_1), the slow progression rate ($(1-p)k_1$), the lower-risk rate of reactivation to infectious TB in later long-term latency (k_2), the transmission coefficients from class I_1 to S class, (β), the transmission coefficients from class I_n to S class (σ), the transfer rate from class I_1 to I_2 (r_1), the transfer rate from class I_2 to T (r_2), the rate at which treated individuals relapse and move to class I_1 (η), the recovery rate of untreated individuals (γ), the case detection fraction (f), and the fraction that the TB infected not detected and treated ($1-f$).

Using the epidemiologic classes and parameters defined above, the transfer among those classes can be shown in the schematic diagram (Fig. 6.24).

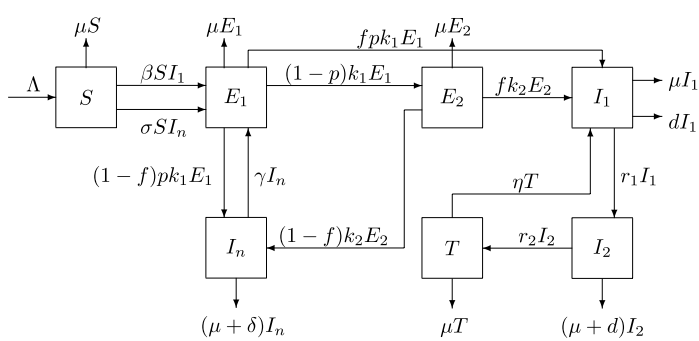


Fig. 6.24. The schematic flow diagram of TB transmission with fast and slow progressions, case detection, and two treatment stages.

The TB transmission model [Liu *et al.* (2008)] is

$$\begin{aligned}
\frac{\mathrm{d}S(t)}{\mathrm{d}t} &= \Lambda - \beta S I_1 - \sigma S I_n - \mu S,\\
\frac{\mathrm{d}E_1(t)}{\mathrm{d}t} &= \beta S I_1 + \sigma S I_n + \gamma I_n - (\mu + k_1) E_1,\\
\frac{\mathrm{d}E_2(t)}{\mathrm{d}t} &= (1-p) k_1 E_1 - (\mu + k_2) E_2,\\
\frac{\mathrm{d}I_1(t)}{\mathrm{d}t} &= f p k_1 E_1 + f k_2 E_2 + \eta T - (\mu + d + r_1) I_1,\\
\frac{\mathrm{d}I_n(t)}{\mathrm{d}t} &= (1-f) p k_1 E_1 + (1-f) k_2 E_2 - (\mu + \delta + \gamma) I_n,\\
\frac{\mathrm{d}I_2(t)}{\mathrm{d}t} &= r_1 I_1 - (\mu + d + r_2) I_2,\\
\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= r_2 I_2 - (\mu + \eta) T.
\end{aligned} \tag{6.14}$$

Let $N = S + E_1 + E_2 + I_1 + I_n + I_2 + T$ be the total number of the population. From the equations in model (6.14), it follows that the domain

$$\Omega = \{(S, E_1, E_2, I_1, I_n, I_2, T) \in \mathbf{R}_7^+ \mid 0 \le N \le \Lambda/\mu\}$$

is positively invariant and attracts all nonnegative solutions of model (6.14). The basic reproductive number R_0 of model (6.14) is defined to be

$$R_0 = \beta \frac{\Lambda}{\mu} \frac{f k_1 A_1}{A_2 A_3} + \sigma \frac{\Lambda}{\mu} \frac{(1-f) k_1 A_1}{A_2 (\mu + \delta + \gamma)},$$

where

$$\begin{aligned}
A_1 &= p + \frac{k_2}{\mu + k_2}(1-p),\\
A_2 &= \mu + k_1 - \frac{(1-f) A_1 \gamma}{\mu + \delta + \gamma} k_1,\\
A_3 &= \mu + d + r_1 - \frac{\eta r_2}{(\mu + \eta)(\mu + d + r_2)} r_1.
\end{aligned}$$

The magnitude of R_0 determines the existence and stability of the equilibria of model (6.14). Model (6.14) always has the disease-free equilibrium $P_0(\Lambda/\mu, 0, 0, 0, 0, 0, 0)$. Simple algebra shows that if $R_0 > 1$, model (6.14)

has exactly one endemic equilibrium $P^* = (S^*, E_1^*, E_2^*, I_1^*, I_n^*, I_2^*, T^*)$, where

$$S^* = \frac{\Lambda}{\mu R_0}, \quad E_1^* = \frac{\Lambda(R_0 - 1)}{A_2 R_0}, \quad E_2^* = \frac{(1-p)k_1}{\mu + k_2} E_1^*,$$
$$I_1^* = \frac{f k_1 A_1}{A_3} E_1^*, \quad I_n^* = \frac{(1-f)k_1 A_1}{\mu + \delta + \gamma} E_1^*, \quad I_2^* = \frac{r_1}{\mu + d + r_2} I_1^*,$$
$$T^* = \frac{r_1 r_2}{(\mu + \eta)(\mu + d + r_2)} I_1^*.$$

The following stability theorem of the equilibria is obtained by Liu *et al.* (2008).

Theorem 6.3. *The disease-free equilibrium P_0 of model* (6.14) *is globally asymptotically stable if $R_0 < 1$, and is unstable, if $R_0 > 1$. When $R_0 > 1$, the unique endemic equilibrium P^* of model* (6.14) *is globally asymptotically stable.*

From the existing literature, the values of parameters in model (6.14) are taken to be $\mu = 1/70$, $\Lambda = 170\,460$, $p = 0.05$, $k_2 = 0.00256$, $d = 0.06$, $\delta = 0.15$, $\eta = 0.001$, $\gamma = 0.2$, $\beta = 1/1\,704\,600$, $\sigma = 1/(7 \times 170\,460)$, $k_1 = 1.5$, $r_1 = 3.6$, and $r_2 = 2.4$. Figure 6.25 demonstrates the global asymptotic stability of the unique endemic equilibrium P^* when $R_0 > 1$. The simulation shows that E_1, E_2, I_1, and I_n all converge to respective values at the endemic equilibrium, despite they start from different initial values.

6.3.4. *TB model with immigration*

The TB transmission models in previous two sections do not consider the influence of the immigration. If we study the TB infection in a country with a lot of immigration from regions with higher TB incidence rate, the immigration should be incorporated in our model. In this section we construct a TB transmission model with immigrants to investigate the impact of immigration on the TB infection. The model incorporates epidemiologic and demographic factors and apply the model to Canada since it has large immigrants every year.

The total population is divided into two classes: Canadian-born population and immigrants, both classes are further divided into four epidemiologic groups: susceptible (S), latent/exposed (E), infectious (I), and recovery/treated (T) class. Let the variables with subscript 0 correspond

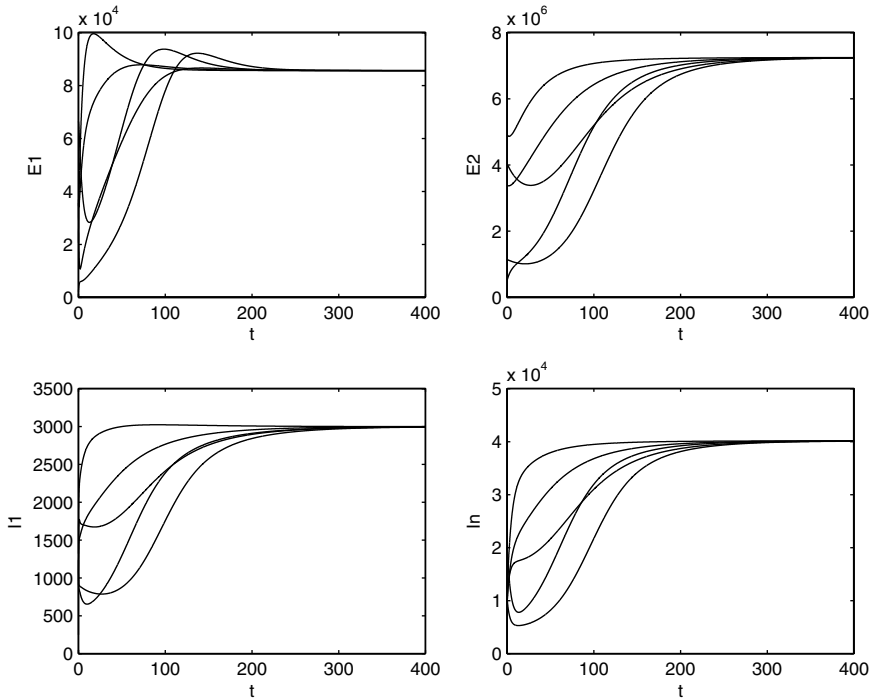


Fig. 6.25. The stability of the endemic equilibrium.

to the Canadian-born population, variables with subscript 1 correspond to the immigrants. The transmission flow diagram is given in Fig. 6.26.

Let $B(t)$ denote the birth function. We use the following system of coupled difference equations to model the TB transmission [Zhou *et al.* (2008)]:

$$\begin{aligned}
S_0(t+1) - S_0(t) &= B(t) - \mu_0 S_0(t) - g_0(t) S_0(t), \\
E_0(t+1) - E_0(t) &= g_0(t) S_0(t) - (\mu_0 + \alpha_0) E_0(t), \\
I_0(t+1) - I_0(t) &= \alpha_0 E_0(t) - (\mu_0 + \delta_0 + \gamma_0) I_0(t), \\
T_0(t+1) - T_0(t) &= \gamma_0 I_0(t) - \mu_0 T_0(t), \\
S_1(t+1) - S_1(t) &= A_s - \mu_1 S_1(t) - g_1(t) S_1(t), \\
E_1(t+1) - E_1(t) &= A_e + g_1(t) S_1(t) - (\mu_1 + \alpha_1) E_1(t), \\
I_1(t+1) - I_1(t) &= \alpha_1 E_1(t) - (\mu_1 + \delta_1 + \gamma_1) I_1(t),
\end{aligned}$$

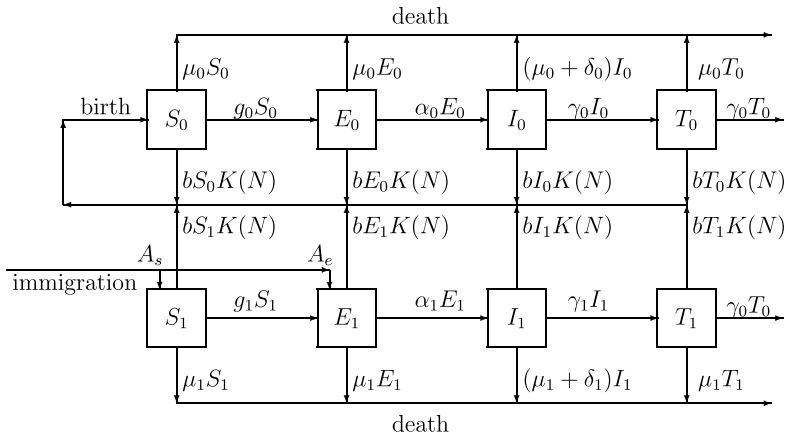


Fig. 6.26. The schematic diagram of TB transmission with immigrants.

$$\begin{aligned} T_1(t+1) - T_1(t) &= \gamma_1 I_1(t) - \mu_1 T_1(t), \\ N_i(t) &= S_i(t) + E_i(t) + I_i(t) + T_i(t), \quad i = 0, 1, \\ N(t) &= N_0(t) + N_1(t), \end{aligned} \tag{6.15}$$

where A_s and A_e are immigration rates of the susceptibles and the latent, respectively, the other parameters and variables have the same meanings as those in previous epidemiologic models, and the forces of infection are given by

$$\begin{aligned} g_0(t) &= \beta_0 I_0(t)/N_0(t) + \beta_{01} I_1(t)/N_1(t), \\ g_1(t) &= \beta_{10} I_0(t)/N_0(t) + \beta_1 I_1(t)/N_1(t). \end{aligned}$$

We use a simplified model of (6.15) to investigate the immigration influence on TB cases in Canada. The simplified model is a linear systems for the exposed and infected compartment given below.

$$\begin{aligned} E_0(t+1) &= E_0(t) - (\mu_0 + \alpha_0)E_0(t) + \beta_0^*(t) I_0(t), \\ I_0(t+1) &= I_0(t) + \alpha_0 E_0(t) - (\mu_0 + \delta_0 + \gamma_0) I_0(t), \\ E_1(t+1) &= A_e + E_1(t) - (\mu_1 + \alpha_1)E_1(t) + \beta_1^*(t) I_1(t), \\ I_1(t+1) &= I_1(t) + \alpha_1 E_1(t) - (\mu_1 + \delta_1 + \gamma_1) I_1(t). \end{aligned} \tag{6.16}$$

We use available data to estimate parameter values, especially, $\beta_0^*(t)$ and $\beta_1^*(t)$. After those parameters and initial values are determined we will give the prediction.

In the recent years, an increasing immigration trend has been observed in Canada. Since 1990, Canada has accepted approximately 230 000 immigrants per year, or about 0.7% of the Canadian population; in 1996, almost 5 million people, or 17.4% of the Canadian population, were foreign-born [Health Canada (2002)]. Details of the immigration data are listed in Table 6.5.

The immigrant number can be well fitted by a cubic curve

$$A_s(t) = 137.5(t-1984)^3 - 5133.4(t-1984)^2 + 59057.8(t-1984) + 15233.$$

A lot of immigrants are from regions with higher TB incidence rates. This trend leads to a dramatic increase in the proportion of foreign-born TB cases. The yearly reported TB case numbers among foreign-born and Canadian-born populations are shown in Table 6.6.

Table 6.5. The annual number of immigrants to Canada.

Year	1985	1986	1987	1988	1989	1990	1991
Number	84 302	99 219	152 098	161 929	192 001	214 230	230 781
Year	1992	1993	1994	1995	1996	1997	1998
Number	252 842	255 819	223 875	212 504	226 773	216 014	174 100
Year	1999	2000	2001	2002	2003	2004	2005
Number	189 816	227 209	250 346	229 091	221 352	235 824	262 236

Table 6.6. The number of TB cases in Canadian-born and foreign-born population.

Year	1985	1986	1987	1988	1989	1990	1991
Canadian total	2 144	2 145	1 972	1 947	2 035	1 997	2 018
Canadian born	1 283	1 290	1 009	1 104	1 056	1 076	1 009
Foreign born	861	855	868	891	959	940	1 009
Year	1992	1993	1994	1995	1996	1997	1998
Canadian total	2 109	2 013	2 074	1 931	1 868	1 976	1 791
Canadian born	975	950	888	780	667	682	626
Foreign born	1 134	1 063	1 186	1 140	1 170	1 273	1 150
Year	1999	2000	2001	2002	2003	2004	2005
Canadian total	1 806	1 695	1 704	1 555	1 628	1 574	1 616
Canadian born	639	568	587	484	476	464	519
Foreign born	1 151	1 103	1 062	1 024	1 111	1 075	1 016

Table 6.7. The number of TB cases by year of arrival in Canada.

Year	-85	-90	91	92	93	94	95	96							XX
1996	110	225	77	71	66	89	113	125							47
Year	-62	-72	-82	-92	93	94	95	96	97						XX
1997	66	73	155	396	67	94	89	118	117						93
Year	-62	-72	-82	-92	93	94	95	96	97	98					XX
1998	65	50	145	329	61	74	65	84	117	93					68
Year	-62	-72	-82	-92	93	94	95	96	97	98	99				XX
1999	59	55	121	314	48	63	59	56	80	74	136				86
Year	-62	-72	-82	-92	93	94	95	96	97	98	99	00			XX
2000	39	33	116	239	52	39	54	50	54	64	124	121			117
Year	-62	-72	-82	-92	93	94	95	96	97	98	99	00	01		XX
2001	44	37	113	240	36	34	32	44	39	45	63	107	120		108
Year	-62	-72	-82	-92	93	94	95	96	97	98	99	00	01	02	XX
2002	38	45	110	200	28	45	32	45	41	33	48	71	152	126	76

XX: The number of TB cases whose arrival time is not clear.

The sum of the Canadian-born and the foreign-born population in Table 6.6 is less than the total number. The reason resulting in the difference is that we are not clear to the origin of some TB cases.

Immigration and reported TB cases are shown in Fig. 6.27.

It is impossible to have the statistics that how many immigrants were infected and in their latent period when they enter Canada. The fact is that the latent period was significantly shorter for Asian immigrants (mean of 9.1 years) compared to immigrants from other countries [Health Canada (2002)]. The reported new active and relapsed foreign-born TB cases by year of arrival in Canada can help us in modeling and simulation. Those data are shown in Table 6.7 [Health Canada (2001, 2000, 1999, 1998, 1997, 1996)].

-85 (-62) in the second column means the arrival time is 1985 (1962) or early than 1985 (1962). -90 means that the arrival time is between 1986 and 1990. The other numbers with a minus sign have the similar meaning.

Let us give the simulation of Canadian-born TB now. The population death rate is 0.71% annually, the TB induced death rate is 6%, the average TB latent period is 5 years, and the TB infectious period is 2 month. Therefore we set $\mu = 0.0071/12$, $\delta = 0.06/12$, $\alpha = 1/60$, $\gamma = 1/2$. The infection rate $\beta_0^*(t)$ is most importance for the simulation. We will use ten year data (1991–2000) to estimate this parameter in our simplified model (6.16), and then use the next 5 year data (2001–2005) to validate the model.

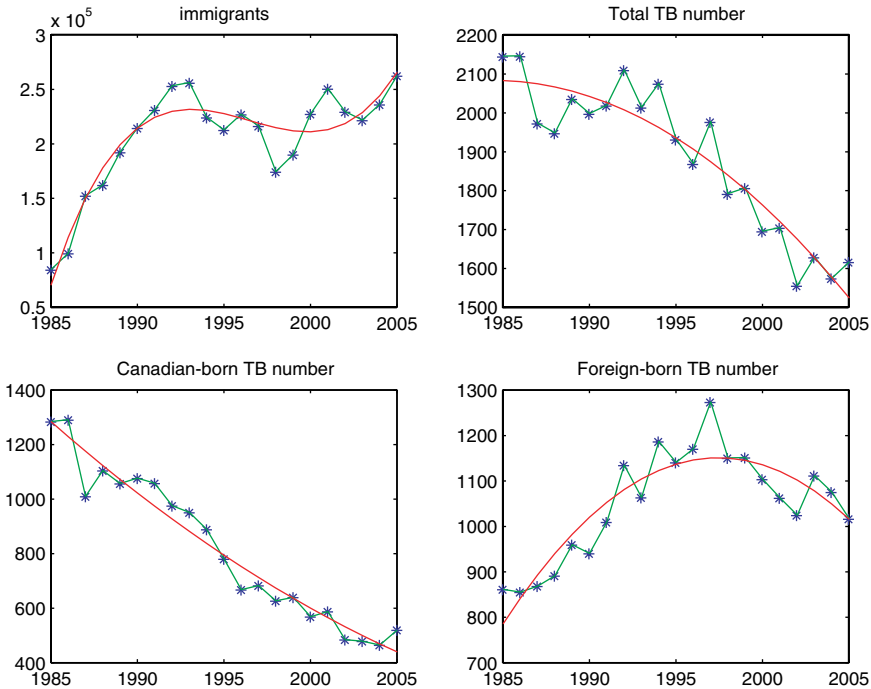


Fig. 6.27. Numbers of immigrants and reported TB from 1985 to 2005, the stars are real data, the curve are their regression.

We first fit the Canadian-born TB case numbers to a quadratic curve, $3.424(t-1990)^2 - 92.842(t-1990) + 1162$. The monthly reported numbers of Canadian-born infectious TB cases can then be computed on the basis of this fitting curve, and these numbers correspond to the item $\alpha E_0(t)$ in the second equation in model (6.16). The monthly number of the infectious TB cases can be obtained from the second equation of (6.16) after the transferring number $\alpha E_0(t)$ and parameters μ, δ, and γ are determined. The estimation of $\beta_0^*(t)$ is obtained from the first equation:

$$\beta_0^*(t) = \frac{E_0(t+1) - (1-\mu-\alpha)E_0(t)}{I_0(t)}.$$

We can average the Canada-born TB infection rate between 1991 and 2000 to have $\bar{\beta}_0 = 0.3435$. The small average infection rate explains why the reported TB cases among Canadian-born population keeps decreasing in the last two decades. The estimation also shows that there is a large pool

of exposed TB which gives the reason that the reported TB in Canadian-born population drops in a slow rate. Substituting those parameters in the first two equations of (6.16), we obtain a linear discrete model for the Canadian-born TB cases as follows:

$$\begin{aligned} E_0(t+1) &= 0.98275E_0(t) + (0.29716 + 0.000766t)I_0(t), \\ I_0(t+1) &= 0.01667E_0(t) + 0.4944I_0(t). \end{aligned} \tag{6.17}$$

We set the initial value of $E_0(t)$ to be 5586, and the initial value for $I_0(t)$ to be 186. The simplified linear model (6.17) then gives the simulation result. The yearly data of our simulation is shown in Fig. 6.28. There are 4 curves in Fig. 6.28. The first is the fitted curve of the Canada-born TB cases from 1991 to 2000, the second one gives the estimated TB infection rate and its fitted curve, the third one shows the number of the exposed TB, and the last one is the simulated result of the Canadian-born TB cases. The stars in the figure are from the statistic data.

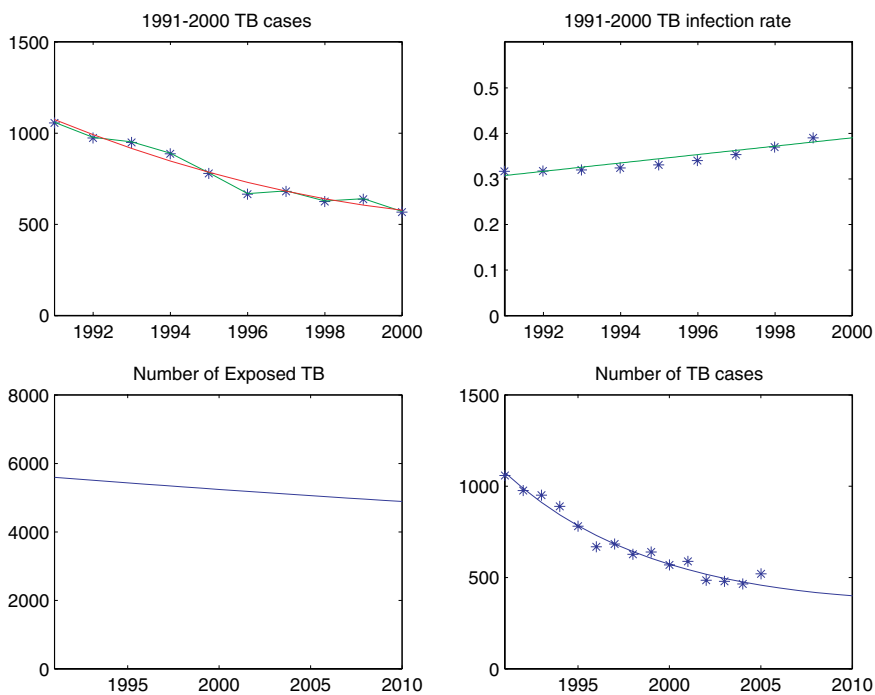


Fig. 6.28. The Canadian-born TB infection.

The similar idea and method can be used to give the simulation of foreign-born TB cases. The fact that the vast majority (95–98%) of all TB infections in immigrants occur in their country of origin should be noticed in the simulation. This fact is supported by the data in Table 6.7. The data of reported new active and relapsed foreign-born TB cases by year of arrival show that new immigrants have more TB cases in their early years of arrival, and the latent TB becomes active some years later. The difference is that we should divide the infected TB number of the new entering $E_1(t)$ into two part, 95% for new immigrants, which gives the latent TB number among immigrants, $A_e(t)$, 5% for the infection after arrival in Canada, which gives the last part of the third equation in (6.16). A similar process gives the estimation of the TB infection rate and the case numbers of the foreign-born population. After we have done the simulation on TB case numbers of Canadian-born and foreign-born populations, we can give the prediction for all the TB case (see Fig. 6.29). In Fig. 6.29, the reported data are the statistic number of active and relapsed TB cases; ITB is the number of the infectious TB cases (62% of the active and relapsed TB), DR TB

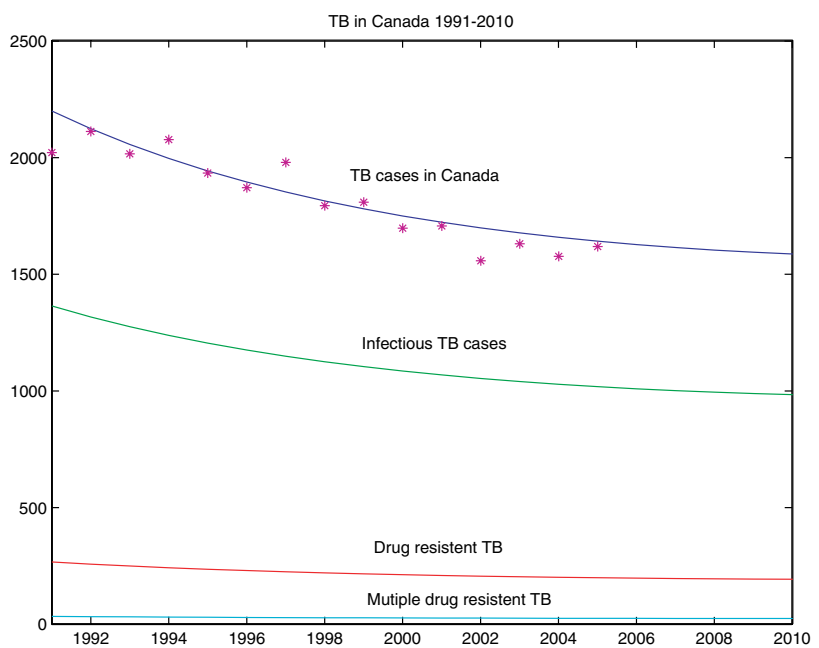


Fig. 6.29. Prediction of all TB cases in Canada 1991–2010.

(drug-resistant TB) is calculated by the formula $0.121 \times prediction$, and MDR TB (multiple-drug-resistant TB) is calculated by the formula $0.015 \times prediction$.

In this chapter, we have applied different models to SARS, HIV/AIDS, and TB transmission. Admittedly, models in this chapter, and other mathematical models in epidemiology, are only an approximation of the corresponding complicated real situation. A model can answer specific questions and give predictions that we are interested in. Those models, even applicable and having nice predictions, have their weak point. We cannot expect a model to be perfect and versatile to incorporate all factors and give very accurate result. In fact, there are a lot of limitations in epidemiologic modeling. There are a lot of flawed mathematical models of disease transmissions, due to lack of systematic data, the underlying mechanics of the diseases, and effective methods. Although epidemiologic modeling is not satisfactory to real applications, those models have a positive and active role in the prediction and control of disease. Epidemiologic modeling will be more useful in disease control in the future.

Bibliography

Agur, Z., Cojocaru, L., Mazor, G., Anderson, R. M., and Danon, Y. L. (1993). Pulse mass measles vaccination across age cohorts. *Proc Nat Acad Sci USA* **90**: 11698–11702.

Aiello, W. G. and Freedman, H. I. (1990). A time delay model of single-species growth with stage structure. *Math Biosci* **101**: 139–153.

Aiello, W. G., Freedman, H. I., and Wu, J. (1992). Analysis of a model representing stage structured population growth with state-dependent time delay. *SIAM J Appl Math* **52**: 855–869.

Alexander, M. E. and Moghadas, S. M. (2004). Periodicity in an epidemic model with a generalized nonlinear incidence. *Math Biosci* **189**: 75–96.

Alexander, M. E. and Moghadas, S. M. (2005). Bifuraction analysis of an SIRS epidemic model with generalized incidence. *SIAM J Appl Math* **65**: 1794–1816.

Allen, L. J. S. (1994). Some discrete-time SI, SIR, and SIS epidemic models. *Math Biol* **124**: 83–105.

Allen, L. J. S. and Thrasher, D. B. (1998). The effects of vaccination in an age-dependent model for varicella and Herpes zoster. *IEEE Trans. Auto. Cont.* **43**(6), 779–789.

Anderson, R. M., Fraser, C., Ghani, A. C., Donnelly, C. A., Riley, S., Ferguson, N. M., Leung, G. M., Lam, T. H. and Hedley, A. J. (2004). Epidemiology, transmission dynamics and control of SARS: The 2002–2003 epidemic. *Philos Trans R Soc Lond B Biol Sci* **359**: 1091–1105.

Anderson, R. M. and May, R. M. (1982). *Population Biology of Infections Disease*. Spring-Verlag, Berlin, Heidelberg, New York.

Anderson, R. M. and May, R. M. (1986). The invasion, persistence, and spread of infectious diseases within animal and plant communities. *Philos Trans R Soc Lond B* **314**: 533–570.

Anderson, R. M. and May, R. M. (1991). *Infectious Diseases of Humans: Dynamics and Control.* Oxford University Press, Oxford.

Anderson, R. M., May, R. M., Boily, M. C., Garnett, G. P., and Rowley, J. T. (1991). The spread of HIV-1 in Africa: Sexual contact patterns and the predicted demographic impact of AIDS. *Nature* **352**: 581–589.

Anthony, S. F., Giuseppe, P., Sharilyn, S., and Drew, W. (1996). Immunopathogenic mechanisms of HIV infection. *Ann Intern Med* **124**: 654–663.

Arino, J., Mccluskey, C. C., and van den Driessche, P. (2003). Global results for an epidemic model with vaccination that exhibits backward bifurcation. *SIAM J Appl Math* **64**: 260–276.

Arino, J. and van den Driessche, P. (2006). Disease spread in metapopulations. In: *Nonlinear Dynamics and Evolution Equations*, Brunner, H., Zhao, Xiaoqiang, and Zou, Xingfu (eds.), Fields Institute Communication, Vol. 48, American Mathematical Society, Providence, RI, pp. 1–12.

Baily, V. T. J. (1975). *The Mathematical Theory of Infectious Disease*, 2nd ed., Hafner, New York.

Bainov, D. D. and Simeonov, P. S. (1995). *Impulsive Differential Equations: Asymptotical Properties of the Solutions.* World Scientific, Singapore.

Bartlett, M. S. (1957). Measles periodicity and community size. *J Roy Stat Soc A* **120**: 48–70.

Begon, M., Hazel, S. M., Baxby, D., Bown, K., Cavanagh, R., Chantrey, J., Jones, T., and Bennett, M. (1999). Transmission dynamics of a zoonotic pathogen within and between wildlife host species. *Proc R Soc Lond B* **266**: 1939–1945.

Bellman, R. E. and Cooke, K. L. (1963). *Differential-Difference Equations.* Academic Press, New York.

Beretta, E. and Kuang, Yang (2002). Geometric stability switch criteria in delay differential systems with delay dependent parameters. *SIAM J Math Anal* **33**: 1144–1165.

Beretta, E. and Takeuchi, Y. (1995). Global stability of an SIR epidemic model with time delays. *J Math Biol* **33**: 250–260.

Berezovsky, F., Karev, G., Song, Baojun, and Castillo-Chavez, C. (2005). A simple epidemic model with surprising dynamics. *Math Biol Eng* **2**: 133–152.

Bernouilli, D. (1760). Essai d'une nouvelle analyse de la mortalite causse par la petite verole et des avantages de l'inoculation pour al prevenir. In: *Memoires de Mathematiques et de physique.* Academie Royale des Science, Paris, pp. 1–45.

Bogdanov, R. (1981). Bifurcations of a limit cycle for a family of vector fields on the plan. *Selecta Math Soviet* **1**: 373–388.

Bogdanov, R. (1981). Versal deformations of a singular point on the plan in the case of zero eigen-values. *Selecta Math Soviet* **1**: 389–421.

Bombardt, J. N. (2006). Congruent epidemic models for unstructured and structured populations: Analytical reconstruction of a 2003 SARS outbreak. *Math Biol* **203**: 171–203.

Bowers, R. G. and Turner, J. (1997). Community structure and the interplay between interspecific infection and competition. *J Theor Biol* **187**: 95–109.

Brauer, F. (2004). Backward bifurcations in simple vaccination models. *J Math Anal Appl* **298**: 418–431.

Brauer, F. and Ma, Zhien (1987). Stability of stage-structured population models. *J Math Anal Appl* **126**: 301–315.

Brauer, F. and Castillo-Chavez, C. (2001). *Mathematical Models in Population Biology and Epidemiology*, Texts in Applied Math. **40**, Springer-Verlag, New York.

Brauer, F. and van den Drissche, P. (2001). Models for transmission of disease with immigration of infectives. *Math Biosci* **171**: 143–154.

Brauer, F., van den Driessche, P., and Wu, Jianhong (eds.) (2008). *Mathematical Epidemiology.* Springer, Berlin.

Britton, N. F. (2003). *Essential Mathematical Biology.* Springer-Verlag, London.

Burnett, M. and White, D. O. (1974). *Natural History of Infectious Disease*, 4th ed. Cambridge University Press, Cambridge.

Busenberg, S. and Castillo-Chavez, C. (1991). A general solution of the problem of mixing of subpopulations and its application to risk- and age-structured epidemic models for the spread of AIDS. *IMA J Math Appl Med Biol* **8**: 1–29.

Busenberg, S. and Cooke, K. (1993). *Vertically Transmitted Diseases, Models and Dynamics.* Biomathematics **23**, Springer-Verlag, Berlin.

Busenberg, S. and Iannelli, M. (1985). Separable models in age-dependent population dynamics. *J Math Biol* **22**: 145–173.

Busenberg, S., Cooke, K., and Iannelli, M. (1988). Endemic thresholds and stability in a class of age-structured epidemic. *SIAM J Appl Math* **48**: 1379–1395.

Busenberg, S. and Hadeler, K. P. (1990). Demograph and epidemics. *Math Biosci* **63**: 63–74.

Busenberg, S., Iannelli, M., and Thieme, H. R. (1991). Global behavior of an age-structured epidemic model. *SIAM J Math Anal* **22**: 1065–1080.

Busenberg, S. and van den Driessche, P. (1990). Analysis of a disease transmission model in a population with varying size. *J Math Biol* **29**: 257–270.

Butler, G., Freedman, H., and Waltman, P. (1986). Unifromly persistent systems. *Proc Amer Math Soc* **96**: 425–430.

Butler, G. and Waltman, P. (1986). Persistence in dynamical systems. *J Diff Eqns* **63**: 255–263.

Cao, Wenjun and Jin, Zhen (2007). The dynamics of the constant and pulse birth in an SIR epidemic model with constant recruitment. *J Biol Sys* **15**: 203–218.

Capasso, V. (1993). *Mathematical Structures of Epidemic Systems*, Lecture Notes in Biomathematics **97**, Springer-Verlag, Berlin.

Capasso, V. and Serio, A. (1978). A generalization of the Kermack-McKendrick deterministic epidemic model. *Math Biosci* **42**: 41–61.

Capasso, V. and Wilson, R. E. (1997). Analysis of a reaction-diffusion modeling man-environment-man epidemics. *SIAM J Appl Math* **57**: 327–346.

Castillo-Chavez, C., Cooke, K. L., Huang, Wenzhang, and Levin, S. A. (1989). On the role of long incubation periods in the dynamics of acquired immunodeficiency syndrome (AIDS). Part 1: Single population models. *J Math Biol* **27**: 373–389.

Castillo-Chavez, C. and Song, Baojun (2004). Dynamical models of tuberculosis and their applications. *Math Biol Eng* **1**: 361–404.

Castillo-Chavez, C. and Thieme, H. R. (1995). Asymptotically autonomous epidemic models. In: *Mathematical Population Dynamics: Analysis of Heterogeneity, Vol. 1, Theory of Epidemics*, Arino, O., Axelrod, D. E., Kimmel, M., and Langlais, M. (eds.), Wuerz, Winnipeg, Canada, pp. 33–50.

Castillo-Chavez, C. and Yakubu, A. (2001). Dispersal, disease and life-history evolution. *Math Biol* **173**: 35–53.

Charlesworth, B. (1994). *Evolution in Age-Structured Populations*, 2nd ed., Cambridge University Press, Cambridge.

Chattopadhyay, J., and Arion, O. (1999). A predator–prey model with disease in the prey. *Nonlinear Anal* **36**: 747–766.

Chattopadhyay, J., Sarkar, R. R., and Ghosal, G. (2002). Removal of infected prevent limit cycle oscillations in an infected prey–predator — a mathematical study. *Ecol Model* **156**: 113–121.

Chen, Lansun, Song, Xinyu, and Lu, Zhengyi (2003). *Mathematical Models and Methods in Ecology.* Sichuan Science and Technology Press, China.

Ministry of Health, China. (2006). *2005 Update on the HIV/AIDS Epidemic and Response in China*, Ministry of Health, People's Republic of China, Joint United Nations Programme on HIV/AIDS World Health Organization, National Center for AIDS/STD Prevention and Control, China CDC.

Ministry of Health, China. (2007). 2006 Notifiable Communicable Disease in China. http://www.moh.gov.cn/newshtml/17829.htm

Chowell, G., Fenimore, P. W., Castillo-Garsow, M. A., and Castillo-Chavez, C. (2003). *SARS Outbreak in Ontario, Hong Kong, and Singapore: The Role of Diagnosis and Isolation as a Control Mechanism*, Los Alamos Unclassified Report, LA-UR-03-2653.

Coddington, E. A. and Levinson, N. (1955). *Theory of Ordinary Differential Equations.* McGraw-Hill, New York.

Cooke, K. L. and van den Driessche, P. (1996). Analysis of an SEIRS epidemic model with two delays. *J Math Biol* **35**: 240–260.

Cooke, K., van den Driessche, P., and Zou, Xingfu (1999). Interaction of maturation delay and nonlinear birth in population and epidemic models. *J Math Biol* **39**: 332–352.

Cooke, K. and Yorke, J. (1973). Some equations modelling growth processes and gonorrhea epidemics. *Math Biosci* **16**: 75–101.

Coppel, W. A. (1965). *Stability and Asymptotic Behavior of Differential Equations.* Health, Boston.

Cull, P. (1981). Global stability for population models. *Bull Math Biol* **43**: 47–58.

Cushing, J. M. (1998). *An Introduction to Structured Population Dynamics.* Society for Industrial and Applied Mathematics, Philadelphia.

Cushing, J. M. and Zhou, Yicang (1994). The net reproductive value and stability in matrix population models. *Nat Res Model* **8**: 297–333.

d'Onofrio A. (2002). Stability properties of pulse vaccination strategy in SEIR epidemic model. *Math Biosci* **179**, 57–72.

Daley, D. J. and Gani, J. (1999). *Epidemic Modeling: An Introduction.* Cambridge University Press, Cambridge.

Diekman, O. and Heesterbeek, J. A. P. (2000). *Mathematical Epidemiology of Infectious Disease*. Wiley, New York.

Diekmann, O., Heesterbeek, J. A. P., and Metz, J. A. J. (1990). On the definition and the computation of the basic reproduction ratio R_0 in the models for infectious disease in heterogeneous populations. *J Math Biol* **28**: 365–382.

Diekmann, O. and Kretzschmar, M. (1991). Patterns in the effects of infectious diseases on population growth. *J Math Biol* **29**: 539–570.

Dietz, K. (1982). Overall population patterns in the transmission cycle of infectious disease agents. In: *Population Biology of Infectious Diseases*, Anderson, R. M. and May, R. M. (eds.), Springer, New York.

Dietz, K. and Schenzle, D. (1985). Proportinate mixing models for age-dependent infection transmission. *J Math Biol* **22**: 117–120.

Donnelly, C. A., *et al.* (2003). Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong. *Lancent* **361**(9371): 1761–1766. http://image.thelacent.com/extras/03art4453web.pdf

Driessche, P. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math Biosci* **180**: 29–48.

Bainov, D. and Simeonov, P. (1993). *Impulsive Differential Equations: Periodic Solutions and Applications.* Longman Scientific and Technical.

Dushoff, J. (1996). Incorporating immunological ideas in epidemiologic models. *J Theoret Biol* **180**: 181–187.

Dushoff, J., Huang, Wenzhang, and Castillo-Chavez, C. (1998). Backward bifurcation and catastrophe in simple models of fatal disease. *J Math Biol* **36**: 227–248.

Elaydi, Saber (1999). *Discrete Chaos.* Chapman & Hall/CRC, Boca Raton.

El-Doma, M. (1999). Analysis of an age-dependent SIS epidemic model with vertical transmission and propotionate mixing assumption. *Math. Comp Model* **29**: 31–43.

Evans, A. S. (1982). *Viral Infections of Humans*, 2nd. ed. Plenum Medical Book Company, New York.

Fan, Meng, Li, M. Y., and Wang, Ke (2001). Global stability of an SEIS epidemic model with recruitment and a varying total population size. *Math Biosci* **170**: 199–208.

Faria, T., Huang, Wenzhang, and Wu, Jianhong (2006). Travelling waves for delayed reaction-diffusion equations with global response. *Proc R Soc A* **62**: 229–261.

Feller, W. (1941). On the integral equation of renewal theory. *Ann Math Stat* **12**: 243–267.

Feng, Zhilan, Castillo-Chavez, C., and Capurro, A. F. (2000). A model for tuberculosis with exogenous reinfection, *Theor Popul Biol* **57**: 235–247.

Feng, Zhilan and Thieme, H. R. (1995). Recurrent outbreaks of childhood disease revisited: The impact of isolation. *Math Biosci* **128**: 93–129.

Feng, Zhilan and Thieme, H. R. (2000a). Endemic models with arbitrarily distributed periods of infection, I: General theory. *SIAM J Appl Math* **61**: 803–833.

Feng, Zhilan and Thieme, H. R. (2000b). Endemic models with arbitrarily distributed periods of infection, I: General theory, *SIAM J Appl Math* **61**: 983–1012.

Fenichel, N. (1979), Geometric singular perturbation theory for ordinary differential equations. *J Diff Eqns* **31**: 53–98.

Ferguson, N. M. (2005). Mathematical prediction in infection. *Medicine* **33**: 1–2.

Fiedler, M. (1974). Additive compound matrices and inequality for eigenvalues of stochastic matrices. *Czech Math J* **99**: 392–402.

Fonda, A. (1988). Uniformly persistent semidynamical systems. *Proc Amer Math Soc* **104**: 111–116.

Frauenthal, J. G. (1980). *Mathematical Modeling in Epidemiology.* Springer-Verlag Universitext, Berlin.

Freedman, H. I. and Moson, P. (1990). Persistence definitions and their connentions. *Proc Amer Math Soc* **109**: 1025–1032.

Fulford, G. R. and Roberts, M. G. (2002). The metapopulation dynamics of an infectious disease: Tuberculosis in possums. *Theor Popul Biol* **61**: 15–29.

Gakkhar, S. and Negi, K. (2008). Pulse vaccination in SIRS epidemic model with non-monotonic incidence rate. *Chaos Solit Fract* **35**: 626–638.

Gao, Shujing, Chen, Lansun, and Sun, Lihua (2005). Dynamic complexities in a seasonal prevention epidemic model with birth pulses. *Chaos Solit Fract* **26**: 1171–1181.

Gao, L. Q. and Hethcote, H. W. (1992). Disease transmission models with density-dependent demographics. *J Math Biol* **30**: 717–731.

Geddes, A. M. (2006). The history of smallpox. *Clin Dermatol* **24**: 152–157.

Gourley, S. A. and So, J. W. H. (2002). Dynamics of a food-limited population model incorporating nonlocal delays on a finite domain. *J Math Biol* **44**: 49–78.

Greenhalgh, D., Diekmann, O., and de Jong, M. C. M. (2000). Subcritical endemic steady states in mathematical models for animal infections with incomplete immunity. *Math Biosci* **165**: 1–25.

Greenhalgh, D. and Moneim, I. A. (2003). SIARS epidemic model and simulations using different types of seasonal contact rate. *Sys Anal Model Simul* **43**: 573–600.

Griffths, J., Lowrie, D., and Williams, J. (2000). An age-structured model for the AIDS epidemic. *Euro J Oper Res* **124**: 1–14.

Gripenberg, G., Londen, S. O., and Staffans, O. (1990). *Volterra Intergral and Functional Equations.* Cambridge University Press, Cambridge.

Guckenheimer, J. and Holmes, P. J. (1996). *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields.* Springer, New York.

Gumel, A. B., Ruan, Shigui, Day, T., Watmough, J., Brauer, F., van den Driessche, P., Gabrielson, D., Bowman, C., Alexander, M. E., Ardal, S., Wu Jianhong, and Sahai, B. M. (2004). Modelling strategies for controlling SARS outbreaks. *Proc R Soc Lond B* **271**: 2223–2232.

Gurtin, M. E. and MacCamy, R. C. (1985). Non-linear age-dependent population dynamics. *Arch Rat Mech Anal* **54**: 281–300.

Hadeler, K. P. and Castillo-Chavez, C. (1995). A core group model for disease transmission. *Math Biosci* **128**: 41–55.

Hadeler, K. P. and Freedman, H. I. (1989). Predator-prey populations with parasitic infection. *J Math Biol* **27**: 609–631.

Hadeler, K. P. and van den Driessche, P. (1997). Backward bifurcation in epidemic control. *Math Biosci* **146**: 15–35.

Hale, J. K. (1977). *Theory of Functional Differential Equations.* Springer Verlag.

Hale, J. K. (1980). *Ordinary Differential Equations.* 2nd ed. Krieger, Basel.

Hale, J. K. and Lunel, S. M. V. (1993). *Introduction to Functional Differential Equations.* Springer-Verlag, New York.

Hale, J. K. and Waltman, P. (1989). Persistence in infinite-dimensional systems. *SIAM J Math Anal* **20**: 388–395.

Hamer, W. H. (1906). Epidemic disease in England. *Lancet*, I, 733.

Han, Litao (2002). *Study on Epidemic Models of Two Interaction Species*, Ph.D. Thesis, Xi'an Jiaotong Univ. Xi'an, China.

Han, Litao, Ma, Zhien, and Hethcote, H. M. (2001). Four predator prey models with infectious diseases. *Math Comp Model* **34**: 849–858.

Han, Litao, Ma, Zhien, and Shi, Tan (2003). An SIRS epidemic model of two competitive species. *Math Comp Model* **37**: 87–108.

Han, Litao, Yuan, Sanling, and Ma, Zhien (2001). An SIS epidemic model of two competitive species [in Chinese], *J Xi'an Jiaotong University* **35**: 864–867.

Health Canada. (2002). http://www.hc-sc.gc.ca/iacb-dgiac/arad-draa/english/rmdd/wpapers/Immigration.pdf

Health Canada. (2001). http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/tbcan01/index.html

Health Canada. (2000). http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/tbcan00/index.html

Health Canada (1999). http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/tbc99/index.html

Health Canada (1998). http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/tbcan98/index.html

Health Canada (1997). http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/tbcan97/index.html

Health Canada (1996). http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/tbcan96/index.html

Heesterbeek, J. A. P. and Metz, J. A. J. (1993). The saturating contact rate in marriage and epidemic models. *J Math Biol* **31**: 529–539.

Hethcote, H. W. (1976). Qualitative analysis for communicable disease models. *Math Biosci* **28**: 335–356.

Hethcote, H. W. (1994). A thousand and one epidemic models. In: *Frontiers in Mathematical Biology*, Levin, S. A. (ed.), Lecture Notes in Biomathematics, Vol. 100, Springer-Verlag, Berlin, pp. 504–515.

Hethcote, H. W. (1997). An age-structured model for pertusis transmission. *Math Biosci* **145**: 89–136.

Hethcote, H. W. (2000). The mathematics of infectious diseases. *SIAM Rev* **42**: 599–653.

Hethcote, H., Ma, Zhien, and Liao, Shengbing (2002). Effects of quarantine in six endemic models for infectious diseases. *Math Biosci* **180**: 141–160.

Hethcote, H. W., Stech, H. W., and van den Driessche, P. (1981). Nonlinear oscillations in epidemic models. *SIAM J Appl Math* **40**: 1–9.

Hethcote, H. W. and van Ark, J. W. (1995). *Modeling HIV Transmission and AIDS in the United States*. Lecture Notes in Biomathematics, Springer-Verlag, Berlin.

Hethcote, H. W. and van den Driessche, P. (1991). Some epidemiologic models with nonlinear incidence. *J Math Biol* **29**: 271–287.

Hethcote, H. W. and van den Driessche, P. (2000). Two SIS epidemiologic models with delays. *J Math Biol* **40**: 3–26.

Hethcote, H. W., and Yorke, J. A. (1984). *Gonorrhea Transmission Dynamics and Control*, Lecture Notes in Biomathematics, Vol. 56, Springer-Verlag, New York.

Hethcote, H. W., Wang, Wendi, Han, Litao, and Ma, Zhien (2004). A predator-prey model with infected prey. *Theor Biol* **66**: 259–268.

Hethcote, H. W., Wang, Wendi, and Li, Yi (2005). Species coexistence and periodicity in host-host-pathogen models. *J Math Biol* **51**: 629–645.

HHS. (2008). *Smallpox Overview*, http://www.smallpox.gov/smallpox/aboutdisease.html

Hirsch, M. W. (1990). Systems of differential equations which are competitive or cooperative. IV: Structural stability in three dimensional systems. *SIAM J Math Anal* **21**: 1225–1234.

Hirsch, M. W. (1991). Systems of differential equations that are competitive or cooperative. VI: A local C^r closing lemma for 3-dimensional systems. *Ergod Th Dynam Sys* **11**: 443–454.

Hirsch, W., Hanisch, H., and Gabriel, J. (1985). Differential equation models for some parastitic infections: Methods for the study of asymptotic behavior. *Comm Pure Appl Math* **38**: 733–753.

Hoppensteadt, F. (1975). *Mathematical Theories of Populations: Demographics, Genetics and Epidemics*. SIAM, Philadelphia.

Hsieh, Y. H., Chen, C. W. S., and Hsu, S. B. (2004). SARS outbreak, Taiwan, 2003 *Emerg Infect Dis* **10**. www.cdc.gov/eid

Hsu, S. B. and Hsieh, Y. H. (2006). Modeling intervention measures and severity-dependent public response during severe acute respiratory syndrome outbreak. *SIAM J Appl Math* **66**: 627–647.

Hudson, P. J., Dobson, A. P., and Newborn, D. (1992). Do parasites make prey more vulnerable to predation? Red grouse and parasites. *J Anim Ecol* **61**: 681–692.

Hui, Jing and Zhu, Deming (2005). Global stability and periodicity on SIS epidemic models with backward bifurcation. *Comp Math Appl* **50**: 1271–1290.

Hyman, J. M. and Stanley, E. A. (1988). Using mathematical models to understand the AIDS epidemic. *Math Biosci* **90**: 415–473.

Hyman, J. M. and Li, Jia (2000). An intuitive formulation for the reproductive number for the spread of diseases in heterogeneous populations. *Math Biosci* **167**: 65–86.

Hyman, J. M. and Li, Jia (2005a). The reproductive number for an HIV model with differential infectivity and staged progression. *Linear Alge Appl* **398**: 101–116.

Hyman, J. M. and Li, Jia (2005b). Differential susceptibility epidemic models. *J Math Biol* **50**: 626–644.

Hyman, J. M. and Li, Jia (2006). Differential susceptibility and infectivity epidemic models. *Math Biosci Eng* **3**: 89–100.

Hyman, J. M. and Li, Jia (2008). Epidemic models with differential susceptibility and staged progression and their dynamics. *Math Biosci Eng* (to appear)

Hyman, J. M., Li, Jia, and Stanley, E. A. (1999). The diffferentiated infectivity and staged progression models for the transmission of HIV. *Math Biosci* **155**: 77–109.

Iannelli, M. (1995). *Mathematical Theory of Age-Structured Population Dynamics*. Applied Mathematical Monographs, C.N.R.

Iannelli, M., Kim, M. I., and Park, J. (1999). Asymptotic behavior for an SIS epidemic model and its approximation. *Nonlinear Anal ATM* **35**: 797–814.

Iannelli, M., Miller, F. A., and Pugliese, A. (1992). Analytic and numeric results for the age-structured SIS epidemic model with mixed inter-intra-cohort transmission. *SIAM J Math Anal* **23**: 662–688.

Inaba, H. (1990). Threshold and stability for an age-structured epidemic model. *J Math Biol* **28**: 411–434.

Inaba, H. and Sekine, H. (2004). A mathematical model for Chagas disease with infection-age-dependent infectivity. *Math Biol* **190**: 36–69.

Ireland, J. M., Mestel, B. D., and Norman, R. A. (2007). The effect of seasonal host birth rates on diseases persistence. *Math Biosci* **206**: 31–45.

Isham, V. and Medley, G. (1996). *Models for Infectious Human Diseases.* Cambridge University Press, Cambridge.

Jin, Zhen (2001). *Study for Ecological and Epidemic Models Influenced by Impulses.* Ph.D. Thesis, Xi'an Jiaotong univ. Xi'an, China.

Jin, Zhen and Ma, Zhien (2006). The stability of an SIR epidemic model with time delays. *Math Biosci Eng* **3**: 101–109.

Jin, Yu, Zhang, Yong, and Wang, Wendi (2003). An epidemic model with stage structutre. *J Southwest China Norm Univ* **28**: 863–868.

Jury, E. I. (1974). *Inners and Stability of Dynamic System.* Wiley, New York.

Kaplan, D. and Glass, L. (1995). *Understanding Nonlinear Dynamics.* Springer-Verlag, New York.

Kao, R. R. (2002). The role of mathematical modelling in the control of the 2001 FMD epidemic in the UK. *Trend Microb* **10**: 279–286.

Kermack, W. O. and McKendrick, A. G. (1927). A contribution to the mathematical theory of epidemics. *Proc Roy Soc Lond* **115**: 700–721.

Kermack, W. O. and McKendrick, A. G. (1932). Contributions to the mathematical theory of epidemics. *Proc Roy Soc Lond* **138**: 55–83.

Korobeinikov, A. (2004). Global properties of basic virus dynamics models. *Bull Math Biol* **66**: 879–883.

Kranz, J. (1990). *Epidemic of Plant Disease: Mathematical Analysis and Modeling.* Springer-Verlag, Berlin.

Kribs-Zaleta, C. M. (1999). Core recruitment effects in SIS models with constant total populations, *Math Biosci* **160**: 109–158.

Kribs-Zaleta, C. M. and Martcheva, M. (2002). Vaccination strategies and backward bifurcation in an age-since-infection structured model. *Math Biol* **177–178**: 317–332.

Kribs-Zaleta, C. M. and Velasco-Hernadez, J. X. (2000). A simple vaccination model with mutiple endemic states. *Math Biosci* **164**: 183–201.

Kuang, Yang (1993). *Delay Differential Equations with Applications in Population Dynamics.* Academic Press, Boston.

Lajmanovich, A. and Yorke, J. A. (1976). A deterministic model for gonorrhea in a nonhomogeneous population. *Math Biosci* **28**: 221–236.

Lakmeeh, A. and Arino, O. (2000). Bifurcation of nontrivial periodic solutions of impulsive differential equations arising chemotherapeutic treatment. *Dyn Cont Disc Impuls Sys* **7**: 265–287.

Lakshmikantham, V., Bainov, D. D., and Simeonov, P. S. (1989). *Theory of Impulsive Differential Equations.* World Scientific Press, London.

Lang, W., Perkins, H., Anderson, R. E., Royce, R., Jewell, N., and Winkelstein, W. Jr. (1989). Patterns of T lymphocyte changes with human immunodeficiency virus infection: From seroconversion to the development of AIDS. *J Acquir Immune Defic Syndr* **2**: 63–69.

Langlais, M. (1995). A mathematical analysis of the SIS intra-cohort model with age-structure. In: *Mathematical Population Dynamics: Analysis of Heterogeneity, Vol. 1, Theory of Epidemics*, Arino, O., Axelrod, D. E., Kimmel, M., and Langlais, M. (eds.), Wuerz, Winnipeg, Canada, pp. 103–117.

LaSalle, J. P. (1976). *The Stability of Dynamical Systems*. Regional Conference Series in Applied Mathematics, SIAM, Philadelphia.

Leslie, P. H. (1945). The use of metrices in certain population mathematics. *Biometrika* **33**: 183–212.

Leslie, P. H. (1948). Some further notes on the use of matrices in population mathematics. *Biometrika* **35**: 213–245.

Li, Jia and Brauer, F. (2008). Continuous-time age-structured models in population dynamics and epidemiology. In: *Mathematical Epidemiology*, Brauer Fred, van den Driessche, Pauline, and Wu, Jianhong, (eds.), Springer, Berlin, pp. 205–227.

Li, Jia and Hallam, T. G., (1988). Survival in continuous structured population models. *J Math Biol* **26**: 421–433.

Li, Jia, Ma, Zhien, Blythe, S. P., and Castillo-Chavez, C. (2003). Coexistence of pathogens in sexually-transmitted disease models. *J Math Biol* **47**: 507–568.

Li, Jia, Zhou, Yican, Ma, Zhien, and Hyman, J. M. (2004). Epidemiological models for mutating pathogens. *SIAM J Appl Math* **65**: 1–23.

Li, Jianquan and Ma, Zhien (2002). Qualitative analyses of SIS epidemic model with vaccination and varying total population size. *Math Comp Model* **35**: 1235–1243.

Li, Jianquan and Ma, Zhien (2003). Qualitative analysis of an epidemic model with vaccination. *Ann Diff Eqns* **19**: 318–324.

Li, Jianquan and Ma, Zhien (2004a). Stability analysis for SIS epidemic model with vaccination and constant population size. *Disc Cont Dyn Sys B* **4**: 637–644.

Li, Jianquan and Ma, Zhien (2004b). Global analysis of SIS epidemic models with variable total population size. *Math Comput Model* **39**: 1231–1242.

Li, Jianquan and Ma, Zhien (2006a). Global stability of an epidemic models with vaccination. *Acta Math Sci* **26A**: 21–30.

Li, Jianquan and Ma, Zhien (2006b). Ultimate stability of a type of characteristic equation with delay dependent parameters. *J Sys Sci Complex* **19**: 137–144.

Li, Jianquan, Ma, Zhien, and Zhang, Fengqin (2008). Stability analysis for an epidemic model with stage structure. *Nonlinear Anal RWA* **9**: 1672–1679.

Li, Jianquan, Ma, Zhien, and Zhou, Yicang (2006). Global analysis of SIS epidmic model with a simple vaccination and mutiple endemic equilibria. *Acta Math Sci* **26B**: 83–93.

Li, Jianquan, Zhang Juan, and Ma, Zhien (2004). Global analysis of some epidemic models with general contact rate and constant immigration. *Appl Math Mech (English Edition)* **25**: 396–404.

Li, Jianquan, Zhou, Yicang, Wu, Jianhong, and Ma, Zhien (2007). Complex dynamics of a simple epidemic model with a nonlinear incidence. *Disc Cont Dyn Sys B* **8**, 161–173.

Li, M. Y. (1996). Dulac criteria for autonomous systems having an invariant affine manifold. *J Math Anal Appl* **199**, 374–390.

Li, M. Y., Graef, J. R., Wang, Liancheng, and Karsai, J. (1999). Global dynamics of a SEIR model with a varying total population size. *Math Biosci* **160**: 191–213.

Li, M. Y. and Muldowney, J. S. (1995a). On R. A. Smith's autonomous convergence theorem. *Rocky M J Math* **25**: 365–379.

Li, M. Y. and Muldowney, J. S. (1995b). Global stability for the SEIR model in epidemiology. *Math Biosci* **125**: 155–164.

Li, M. Y. and Muldowney, J. S. (1996). A geometric approach to the global-stability problems *SIAM J Math Anal* **27**: 1070–1083.

Li, M. Y., Smith, H. L., and Wang, Liancheng (2001). Global stability of an SEIR model with vertical transmission. *SIAM J Appl Math* **62**: 58–69.

Li, M. Y. and Wang, Liancheng (1998). A criterion for stability of matrices. *J Math Anal Appl* **225**: 249–264.

Li, M. Y. and Wang, Liancheng (2002). Global stability in some SEIR epidemic models. In: *Mathematical Approaches for Emerging and Reemerging Infectious Diseases Part II: Models, Methods and Theory*, Castillo-Chavez, C. *et al.* (eds.), IMA Volumes in Mathematics and Its Applications, Vol. 126, Springer-Verlag, pp. 295–311.

Li, Xiuying and Wang, Wendi (2005). A discrete epidemic model with stage structure. *Chaos Solit Fract* **26**: 947–958.

Li, Xuezhi, Gupur, G., and Zhu, Guangtian (2003). *Mathematical Theory of Age-structured Epidemic Dynamics*. Research information Ltd., Hertfordshire.

Lin, Xiaodong (1991). Qualitative analysis of an HIV transmission model. *Math Biosci* **104**: 111–134.

Lin, Xiujuan, Jin, Zhen, and Zhang Juping. (submitted). An SIR epidemic model with birth pulses and standard incidence.

Lipsitch, M. *et al.* (2003). Transmission dynamics and control of severe acute respiratory syndrome. *Science* **300**: 1966–1970.

Liu, Luju, Zhou, Yicang, and Wu, Jianhong (2008). Global dynamics in a TB model incorporating case detection and two treatment stages submitted.

Liu, Rongsong, Feng, Zhilan, and Perelson A. S. (2007). Mathematical analysis of age-structured HIV-1 dynamics with combination antiretroviral therapy. *SIAM J Appl Math* **67**(3): 731–756.

Liu, Wei-min, Hethcote, H. W., and Levin, S. A. (1987). Dynamical behavior of epidemiologic model with nonlinear incidence rates. *J Math Biol* **25**: 359–380.

Liu, Wei-min, Levin, S. A., and Iwasa, Y. (1986). Influence of nonlinear incidence rates upon the behavior of SIRS epidemiologic models. *J Math Biol* **23**: 187–204.

Liu, Xianning and Takeuchi, Y. (2006). Spread of disease with transport-related infection and entry screening. *J Theor Biol* **242**: 517–528.

Lu, Zhengyi and Takeuchi, Y. (1995). Global dynamical behavior for Lotaka-Volterra systems with a reducible interaction matrix. *J Math Anal Appl* **193**: 559–572.

Lu, Zhonghua, Chi, Xuebin, and Chen, Lansun (2002). The effect of constant and pulse vaccination on SIR epidemic model with horizontal and vertical transmission. *Math Comp Model* **36**: 1039–1057.

Lu, Zhonghua, Gao, Shujing, and Chen, Lansun (2003). Analysis of an SI epidemic model with nonlinear transmission and stage structure. *Acta Math Sci* **23B**: 440–446.

Ma, Zhien (1996). *Mathematical Modeling and Studies of Population Ecology*. Anhui Education Press, China.

Ma, Zhien, Liu, Jianping, and Li, Jia (2003). Stability analysis for differential infectivity epidemic models. *Nonlinear Anal RWA* **4**: 841–856.

Ma, Junling and Ma, Zhien (2006). Epidemic threshold conditions for seasonally forced SEIR models. *Math Biol Eng* **3**: 161–172.

Ma, Zhien, Zhou, Yicang, Wang, Wendi, and Jin, Zhen (2004). *The Mathematical Modeling and Analysis of Infectious Diseases.* Chinese Academic Press, Beijing.

Margheri, A. and Rebelo, C. (2003). Some examples of persistence in epidemiologic models. *J Math Biol* **46**: 564–570.

Martin, R. H. Jr. (1974). Logarithmic norms and projections applied to linear differential systems. *J Math Anal Appl* **45**: 432–454.

McCluskey, C. C. (2003). A model of HIV/AIDS with staged progression. *Math Biol* **181**: 1–16.

Mena-Lorca, J. and Hethcote, H. W. (1992). Dynamic models of infectious diseases as regulators of population sizes. *J Math Biol* **30**: 693–716.

Méndez, V. and Fort, J. (2000). Dynamical evolution of discrete epidemic models. *Physica A* **284**: 309–317.

Miller, R. K. (1971). *Nonlinear Volterra Integral Equations*. W.A. Benjamin, Menlo Park.

Ministry of Health, P. R. China. (2003). http://168.160.224.167/sarsmap/

Ministry of Health, P. R. China. (2003) http://www.moh.gov.cn/zhgl/yqfb/1200306130015.htm

Moghadas, S. M. and Gumel, A. B. (2002). Global stability of a two-stage epidemic model with. *Math Comp Sim* **60**: 107–118.

Muldowney, J. S. (1990). Compound matrices and ordinary differential equations. *Rocky M J Math* **20**: 857–872.

Mukherjee, D. (1998) Uniform persistence in a generalized prey–predator system with parasitic infection. *BioSystems* **47**: 149–155.

Muller, J. (1998). Optimal vaccination patterns in age-structured populations. *SIAM J Appl Math* **59**: 222–241.

Mulone, G., Straughan, B., and Wang, Wendi (2007). Stability of epidemic models with evolution. *Stud Appl Math* **118**: 117–132.

Murphy, B. M., Singer, B. H., Anderson, S., and Kirschner, D. (2002). Comparing epidemic tuberculosis in demographically distinct heterogeneous populations. *Math Biol* **180**: 161C185.

Murray, J. D. (1998). *Mathematical Biology*. Springer-Verlag, Berlin.

Nisbet, R. M. and Gurney, W. S. C. (1982). *Modelling Fluctuating Populations*. Wiley-Interscience, New York.

Nowak, M. A., Bonhoeffer, S., Hill, A. M., Boehme, R., and Thomas, H. C. (1996). Viral dynamics in hepatitis B virus infection. *Proc Nat Acad Sci USA* **93**: 4398–4402.

Nuno, M., Feng, Zhilan, Martcheva, M., and Castillo-Chavez, C. (2005). Dynamics of two-strain influenza with isolation and partial cross-immunity. *SIAM J Appl Math* **65**: 964–982.

Packer, C., Holt, R. D., Hudson, P. J., Lafferty, K. D., and Dobson, A. P. (2003). Keeping the herds healthy and alert: Implications of predator control for infectious disease. *Ecol Lett* **6**: 797–802.

Pantaleo, G., Graziosi C., and Fauci, A. S. (1993). New concepts in the immunopathogenesis of human immunodeficiency virus infection. *New Eng J Med* **328**: 327–335.

Pielou, E. C. (1969). *Introduction to Mathematical Ecology.* Wiley-Interscience, New York.

Pugh, C. C. (1967). An improved closing lemma and the general density theorem. *Amer J Math* **89**: 1010–1021.

Pugh, C. C. and Robinson, C. (1983). The C^1 closing lemma including Hamiltonians. *Ergod Th Dynam Sys* **3**: 261–313.

Pilcher, C. D., Tien, H. C., Eron, J. J. Jr., Vernazza, P. L., Leu, S. Y., Stewart, P. W., Goh, L. E., and Cohen, M. S. (2004). Brief but efficient: Acute HIV infection and the sexual transmission of HIV. *J Infect Dis* **189**: 1785–1792.

Public Health Agency of Canada. (2005). Tuberculosis in Canada, Public Health Agency of Canada. http://www.hc-sc.gc.ca/pphb-dgspsp/publicat/tbcan06/pdf/tbcan2006e.pdf

Rabinowitz, P. H. (1971). Some global results for nonlinear eigenvalue problems. *J Func Anal* **7**: 487–513.

Roberts, M. G. and Jowett, J. (1996). An SEI model with density dependent demographics and epidemiology. *IMA J Math Appl Med Biol* **13**: 245–257.

Rapatski, B. L., Suppe, F., and Yorke, J. A. (2005). HIV epidemics driven by late disease stage transmission. *J Acquir Imm Def Syn* **38**(3): 241–253.

Riley, S. *et al.* (2003). Transmission dynamics of the etiological agent of SARS in Hong Kong: Impact of public health Interventions. *Science* **300**: 1961–1966.

Roberts, M. G. and Kao, R. R. (1998). The dynamics of an infectious disease in a population with birth pulses. *Math Biosci* **149**: 23–36.

Rodriguez, D. J. and Torres-Sorando, L. (2001). Models of infectious diseases in spatially heterogenous environments. *Bull Math Biol* **63**: 547–571.

Ross, R. (1911). *The Prevention of Malaria*, 2nd ed. Murray, London.

Ruan, Shigui and Wang, Wendi (2003). Dynamical behavior of an epidemic model with nonlinear incidence rate. *J Diff Eqns* **188**: 135–163.

Ruan, Shigui, Wang, Wendi, and Levin, S. A. (2006). The effect of global travel on the spread of SARS. *Math Biosci Eng* **3**: 205–218.

Saenz, R. A. and Hethcote, H. W. (2006). Competing species models with an infectious. *Math Biosci Eng* **3**: 219–235.

Safan, M., Heesterbeek, H., and Dietz, K. (2006). The minimum effort required to eradicate infections in models with backward bifurcation. *J Math Biol* **53**: 703–718.

Salmani, M. and van den Driessche, P. (2006). A model for disease transmission in a patchy environment. *Disc Cont Dyn Sys B* **6**: 185–202.

Sattenspiel, L. and Dietz, K. (1995). A structured epidemic model incorporating geographic mobility among regions. *Math Biosci* **128**: 71–91.

Sattenspiel, L. and Herring, D. A. (2003). Simulating the effect of quarantine on the spread of the 1918–19 flu in central Canada. *Bull Math Biol* **65**: 1–26.

Shulgin, B., Stone, L., and Agur, Z. (1998). Pulse vaccination strategy in the SIR epidemic model. *Bull Math Biol* **60**: 1123–1148.

Simon, V., Ho, D. D., and Karim, Q. A. (2006). HIV/AIDS epidemiology, pathogenesis, prevention, and treatment. *Lancet* **368**: 489–504.

Smith, R. A. (1986). Some applications of Hausdorff dimension inequalities for ordinary differential equations. *Proc Roy Soc Edin* **104A**: 235–259.

Smith, H. L. (1986). Cooperative systems of differential equations with concave nonlinearities. *Nonlinear Anal* **10**: 1037–1052.

Smith, H. L. (1995). *Monotone Dynamical Systems, An Introduction to the Theory of Competitive and Cooperative Systems,* Math Surveys and Monographs, Vol. 41, American Mathematical Society, Providence.

Smith, H. L. (2001). Competitive exclusion in a discrete-time size-structured chemostat model. *Disc Cont Dyn Sys B* **1**(2): 183–191.

Snell, M. (2008). The Black Death, About.com. http://historymedren.about.com/od/theblackdeath/p/blackdeath.htm

Stone, L., Shulgin, B., and Aguar, Z. (2000). Theoretical examination of the pulse vaccination policy in the SIR epidemic model. *Math Comp Model* **31**: 207–215.

Szmolyan, P. (1991). Transversal heteroclinic and homoclinic orbits in singular perturbation problems. *J Diff Eqns* **92**: 252–281.

Takens, F. (1974). Forced oscillations and bifurcation. In: *Applications of Global Analysis I*, *Comm Mathematical Institute Rijksuniversitat Utrecht*, Vol. 3, pp. 1–59.

Takeuchi, Y., Iwasa, Y., and Sato, K. (2007). *Mathematics for Life Science and Medicine*. Springer-Verlag, pp. 97–119.

Takeuchi, Y., Ma, Wanbiao, and Berreta, E. (2000). Global asymptotic properties of a delay SIR epidemic model with finite incubation times. *Nonlinear Anal* **42**: 931–947

Takeuchi, Y., Wang, Wendi, and Saito, Y. (2006). Global stability of population models with patch structure. *Nonlinear Anal RWA* **7**: 235–247.

Tang, Yilei and Li, Weigu (2007). Global analysis of an epidemic model with a constant removal rate. *Math Comp Model* **45**: 834–843.

Teng, Zhidong, Liu, Yanping, and Zhang, Long (2008). Persistence and extinction of disease in non-autonomous SIRS epidemic models with disease-induced mortality. *Nonlinear Anal* **69**: 2599–2614.

Thieme, H. R. (1992). Convergence results and a Poincaré-Bendixson trichotomy for asymptotically alltonomous differential equations. *J Math Biol* **30**: 755–463.

Thieme, H. R. (1993). Persistence under relaxed point-dissipativity (with application to an emdemic model). *SIAM J Math Anal* **24**: 407–435.

Thieme, H. R. (2000). Uniform persistence and permanence for non-autonomous semiflows in population biology. *Math Biosci* **166**: 173–201.

Tucker, S. L. and Zimmerman, S. O. (1988). A nonlinear model of population dynamics containing an arbitrary number of continuous structure variables. *SIAM J Appl Math* **48**(3): 549–591.

Tudor, D. W. (1985). An age-dependent epidemic model with application to measles. *Math Biosci* **73**: 131–147.

UNTIL. (2008). http://www.until.org/statistics.shtml?gclid=COT9-cLf1-pUCFQGbnAodHg1-WQ

Vainberg, M. M. and Trenogrn, V. A. (1962). The methods of Lyapunov and Schmidt in the theorey of nonlinear equations and further development. *Russian Math Surv* **17**: 1–60.

van den Driessche, P. and Watmough, J. (2000). A simple SIS epidemic model with a backward bifurcation. *J Math Biol* **40**: 525–540.

van den Driessche, P. and Watmough, J. (2002). Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. *Math Biosci* **180**: 29–48.

Venturino, E. (1994). The influence of disease on Lokta Volterra systems. *Rocky Mt. J Math* **24**: 381–402.

Venturino, E. (1995). Epidemics in predator-prey models: Disease in the prey. In: *Mathematical Population Dynamics, Analysis of Heterogeneity, One: Theory of Epidemics*, Arion, O., Axelrod, D., Kimmel, M., and Langlais, M. (eds.), Wuerz Publishing, Winnipeg, Canada, pp. 381–393.

Venturino, E. (2001). The effects of diseases on competing species. *Math Biosci* **174**: 111–131.

Waltman, P. E. (1974). *Deterministic Threshold Models in the Theory of Epidemics*. Lecture Notes in Biomath. I, Spriger-Verlag, Berlin.

Wang, Feng and Ma, Zhien (2004). Persistence and periodic orbits for an SIS model in a polluted environment. *Comp Math Appl* **47**: 779–792.

Wang, Kaifa and Wang, Wendi (2007). Propagation of HBV with spatial dependence. *Math Biosci* **210**: 78–95.

Wang, Ladi and Li, Jianquan (2006). Qualitative analysis of an SEIS epidemic model with nonlinear incidence rate. *Appl Math Mech* **27**: 667–672.

Wang, L., Liu, J., and Chin, D. P. (2007). Progress in tuberculosis control and the evolving public-health system in China. *Lancet* **369**: 691–696.

Wang, Wendi (2002). Global behavior of an SEIRS epidemic model with time delay. *Appl Math Lett* **15**: 423–428.

Wang, Wendi (2004). Population dispersal and disease spread. *Disc Cont Dyn Sys B* **4**: 797–804.

Wang, Wendi (2006). Epidemic models with nonlinear infection forces. *Math Biol Eng* **3**: 267–279.

Wang, Wendi (2006). Backward bifurcation of an epidemic model with treatment. *Math Biosci* **201**: 58–71.

Wang, Wendi (2007), Epidemic models with population dispersal. In: *Mathematics for Life Science and Medicine*, Takeuchi, Y., Iwasa, Y., and Sato, K. (eds.), Springer, Berlin, pp. 67–95.

Wang, Wendi and Chen, Lansun (1997). A predator–prey system with stage-structure for predator. *Comp Math Appl* **33**: 83–91.

Wang, Wendi, Fergola, P., Lombardo, S., and Mulone, G. (2006). Mathematical models of innovation diffusion with stage structure. *Appl Math Model* **30**: 129–146.

Wang, Wendi, Fergola, P., and Tenneriello, C. (1997). Global attractivity of periodic solutions of population models. *J Math Anal Appl* **211**: 498–511.

Wang, Wendi and Mulone, G. (2003). Threshold of disease transmission in a patch environment. *J Math Anal Appl* **285**: 321–335.

Wang, Wendi and Ruan, Shigui (2004). Simulating the SARS outbreak in Beijing with limited data. *J Theor Biol* **227**: 369–379.

Wang, Wendi and Ruan, Shigui (2004). Bifurcation in an epidemic model with constant removal rate of the infectives. *J Math Anal Appl* **291**: 775–793.

Wang, Wendi and Zhao, Xiaoqiang (2004). An epidemic model in a patchy environment. *Math Biosci* **190**: 97–112.

Wang, Wendi and Zhao Xiaoqiang (2005). An age-structured epidemic model in a patchy environment. *SIAM J Appl Math* **65**: 1597–1614.

Wang, Wendi and Zhao, Xiaoqiang (2006). An epidemic model with population dispersal and infection period. *SIAM J Appl. Math* **66**: 1454–1472.

Watts, J. (2003). China takes drastic action over SARS threats. *Lancet* **361**: 1708–1709.

Wawer, M. J., Gray, R. H., Sewankambo, N. K., Serwadda, D., Li, X. B., Laeyendecker, O., Kiwanuka, N., Kigozi, G., Kiddugavu, M., Lutalo, T., Nalugoda, F., Wabwire-Mangen, F., Meehan, M. P., and Quin, T. C. (2005). Rates of HIV-1 transmission per coitalact, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* **191**(9): 1403–1409.

Webb, G. F. (1985). *Theory of Nonlinear Age-Dependent Population Dynamics*. Marcel Dekker, New York.

White, K. A. J., Grenfell, B. T., Hendry, R. J., Lejeune, O., and Murray, J. D. (1996). Effect of seasonal host reproduction on host-macroparasite. *Math Biosci* **137**: 79–99.

WHO. (2004). *WHO Guidelines for the Global Surveillance of Severe Acute Respiratory Syndrome (SARS)*, Department of Communicable Disease Surveillance and Response, WHO/CDS/CSR/ARO/2004.1.

WHO. (2006). *2006 Report on the global AIDS epidemic A UNAIDS 10th anniversary special edition*, A UNAIDS 10th anniversary special edition.

WHO Factsheet. (2007). Tuberculosis, http://www.who.int/mediacentre/factsheets/fs104/en/

WHO. (2007). Global Tuberculosis Control Surveillance, Planning, Financing, *WHO report 2007, Geneva*, http://www.who.int/tb/publications/global_report/2007/pdf/full.pdf

WHO. (2008a). *Leprosy*, http://www.who.int/mediacentre/factsheets/fs101/en/

WHO. (2008b). *Malaria*, http://www.who.int/mediacentre/factsheets/fs094/en/

WHO. (2008c). *Poliomyelitis*, http://www.who.int/topics/poliomyelitis/en/

Wikipedia, the free encyclopedia. (2008). *Antonine Plague*, http://en.wikipedia.org/wiki/AntoninePlague

Williams, B. G. and Dye, C. (1997). Infectious disease persistence when transmission varies seasonally. *Math Biosci* **145**: 77–88.

Wood, S. N., Blythe, S. P., Curney, W. S., and Nisbet, R. M. (1989). Instability in mortality estimation schemes related to stage structure population models. *IMA J Math Appl Med Biol* **6**: 47–68.

Wu, Jianhong (1996). *Theory and Applications of Partial Functional-Differential Equations*, Applied Mathematical Sciences, Vol. 119, Springer-Verlag, New York.

Wu, Jianhong and Zou, Xingfu (2001). Traveling wave front solutions in reaction-diffusion systems with delay. *J Dyn Diff Eqns* **13**: 651–687.

Wu, Lih-Ing and Feng, Zhilan (2000). Homoclinic bifurcation in an SIQR model for childhood diseases. *J Diff Eqns* **168**: 150–167.

Xamxinur, A. and Teng, Zhidong (2006). On the persistence and extinction for a nonautonomous SIRS epidemic model. *J Biomath* **21**: 167–176.

Xiao, Yanni and Chen, Lansun (2001a). Modeling and analysis of a predator–prey model with disease in the prey. *Math Biosci* **171**: 59–82.

Xiao, Yanni and Chen, Lansun (2001b). Analysis of a SIS epidemic model with stage structure and a delay. *Comm Nonlinear Sci Numer Simul* **6**: 35–39.

Xiao, Yanni and Chen, Lansun (2001c). Analysis of a three species eco-epidemiologic model. *J Math Anal Appl* **258**: 733–754.

Xiao, Yanni and Chen, Lansun (2002a). A ratio-dependent predator–prey model with disease in the prey. *Appl Math Comp* **131**: 397–414.

Xiao, Yanni and Chen, Lansun (2002b). A SIS epidemic model with stage structure and a delay. *Acta Math Appl Sinica English Series* **18**: 607–618.

Xiao, Yanni and Chen, Lansun (2003). On an SIS epidemic model with stage stucture. *J Sys Sci Complex* **16**: 275–288.

Xiao, Yanni, Chen, Lansun, and ven den Bosch, F. (2002). Dynamical behavior for a stage-structured SIR infectious disease model. *Nonlinear Anal RWA* **3**: 175–190.

Zeng, Guangzhao, Chen, Lansun, and Sun, Lihua (2003). Complexity of an SIR epidemic dynamics model with impulsive vaccination control. *Chaos Solit Fract* **26**: 495–505.

Zhang, Fang and Zhao, Xiaoqiang (2007). A period epidemic model in a patchy environment. *J Math Anal Appl* **325**: 496–516.

Zhang, Juan, Li, Jianquan, and Ma, Zhien (2006). Global dynamics of an SEIR epidemic model with immigration of different compartments. *Acta Math Sci* **26B**: 551–567.

Zhang, Juan, Lou, Jie, Ma, Zhien, and Wu, Jianhong (2005). A compartmental model for the analysis of SARS transmission patterns and outbreak control measures. *Appl Math Comp* **162**: 909–924.

Zhang, Juan and Ma, Zhien (2003). Global dynamics of an SEIR epidemic model with saturating contact rate. *Math Biosci* **185**: 15–32.

Zhang, Tailei and Teng, Zhidong (2007). On a nonautonomous SEIRS model in epidemiology. *Bull Math Biol*, 2537–2559.

Zhang, Tailei, Teng, Zhidong, and Gao, Shujing (2008). Threshold conditions for a non-autonomous epidemic model with vaccination. *Appl Anal* **87**: 181–199

Zhang, Zhen, Jin, Zhen, and Pan, Jinxiao (2008). An SIR epidemic model with nonlinear birth pulses. Dynamics of continuous. *Disc Impul Sys B: Appl Algor* **15**: 111–128.

Zhang, Zhifen, Ding, Tongren, Huang, Wenzao, and Dong, Zhenxi (1992). *Qualitative Theory of Differential Equations*, Translations of Mathematical Monographs, Vol. 101, American Mathematical Society Providence, Rhode Island.

Zhao, Xiaoqiang (2003). *Dynamical Systems in Population Biology.* CMS Books in Mathematics, Vol. 16. Springer-Verlag, New York.

Zhao, Xiaoqiang and Wang, Wendi (2004). Fisher waves in an epidemic model. *Disc Cont Dyn Sys B* **4**: 1117–1128.

Zhou, Jinshi and Hethcote, H. W. (1994). Population size dependent incidence in models for disease without immunity. *J Math Biol* **32**: 809–834.

Zhou, Yicang and Cushing, J. M. (1998). Stability conditions for equilibria of nonlinear matrix population models. *J Diff Eqns Appl* **4**: 95–126.

Zhou, Yicang and Fergola, P. (2004). Dynamics of a discrete age-structured SIS models. *Disc Cont Dyn Sys B* **4**: 803–852.

Zhou, Yicang, Khan, K., Feng, Zhilan, and Wu, Jianhong (2008). Projection of tuberculosis incidence with increasing immigration trends. *J Theor Biol* **254**: 215–228.

Zhou, Yicang and Liu, Hanwu (2003). Stability of periodic solutions for an SIS model with pulse vaccination. *Math Comp Model* **38**: 299–308.

Zhou, Yicang, Ma, Zhien, and Brauer, F. (2004). A discrete epidemic model for SARS transmission and control in China. *Math Comp Model* **40**: 1491–1506.

Zhou, Yicang, Song, Baojun, and Ma, Zhien (2001). The global stability analysis for a SIS model with age and infection age structures. In: *Mathematical Approaches for Emerging and Reemerging Infectious Diseases*, Castillo-Chavez, C. and Blower, S. (eds.), IMA, Vol. 126, Springer-Verlag, pp. 313–335.

Zhou, Yicang, Shao, Yiming, Ruan, Yuhua, Xu, Jianqing, Ma, Zhien, Mei, Changlin, and Wu, Jianhong (2008). Modeling and prediction of HIV in China: Transmission rates structured by infection ages. *Math Biol Eng* **5**: 403–418.

Zhou, Yugui, Xiao, Dongmei, and Li, Yilong (2007). Bifurcations of an epidemic model with non-monotonic incidence rate of saturated mass action. *Chaos Solit Fract* **32**: 1903–1915.

Index