

Basic Knowledge and Developing Tendencies in Epidemic Dynamics

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Summary. Infectious diseases have been a ferocious enemy since time immemorial. To prevent and control the spread of infectious diseases, epidemic dynamics has played an important role on investigating the transmission of infectious diseases, predicting the developing tendencies, estimating the key parameters from data published by health departments, understanding the transmission characteristics, and implementing the measures for prevention and control. In this chapter, some basic ideas of modelling the spread of infectious diseases, the main concepts of epidemic dynamics, and some developing tendencies in the study of epidemic dynamics are introduced, and some results with respect to the spread of SARS in China are given.

2.1 Introduction

Infectious diseases are those caused by pathogens (such as viruses, bacteria, epiphytes) or parasites (such as protozoans, worms), and which can spread in the population. It is well known that infectious diseases have been a ferocious enemy from time immemorial. The plague spread in Europe in 600 A.C., claiming the lives of about half the population of Europe (Brauer and Castillo-Chavez 2001). Although human beings have been struggling indomitably against various infections, and many brilliant achievements earmarked in the 20th century, the road to conquering infectious diseases is still tortuous and very long. Now, about half the population of the world (6 billion people) suffer the threat of various infectious diseases. For example, in 1995, a report of World Health Organization (WHO) shows that infectious diseases were still the number one of killers for human beings, claiming the lives of 52 million people in the world, of which 17 million died of various infections within that single year (WHO). In the last three decades, some new infectious diseases (such as Lyme diseases, toxic-shock syndrome, hepatitis C, hepatitis E) emerged. Notably, AIDS emerged in 1981 and became a deadly sexually transmitted disease throughout the world, and the newest Severe Acute Respiratory Syndrome (SARS) erupted in China in 2002, spreading to

31 countries in less than 6 months. Both history and reality show that, while human beings are facing menace from various infectious diseases, the importance of investigating the transmission mechanism, the spread rules, and the strategy of prevention and control is increasing rapidly, and such studies are an important mission to be tackled urgently.

Epidemic dynamics is an important method of studying the spread rules of infectious diseases qualitatively and quantitatively. It is based largely on the specific properties of population growth, the spread rules of infectious diseases, and related social factors, serving to construct mathematical models reflecting the dynamical property of infectious diseases, to analyze the dynamical behavior qualitatively or quantitatively, and to carry out simulations. Such research results are helpful to predict the developing tendency of infectious diseases, to determine the key factors of spread of infectious diseases, and to seek the optimum strategy of preventing and controlling the spread of infectious diseases. In contrast with classic biometrics, dynamical methods can show the transmission rules of infectious diseases from the mechanism of transmission of the disease, so that we may learn about the global dynamical behavior of transmission processes. Incorporating statistical methods and computer simulations into epidemic dynamical models could make modelling methods and theoretical analyses more realistic and reliable, enabling us to understand the spread rules of infectious diseases more thoroughly.

The purpose of this article is to introduce the basic ideas of modelling the spread of infectious diseases, the main concepts of epidemic dynamics, some development tendencies of analyzing models of infectious diseases, and some SARS spreading models in China.

2.2 The fundamental forms and the basic concepts of epidemic models

2.2.1 The fundamental forms of the models of epidemic dynamics

Although Bernoulli studied the transmission of smallpox using a mathematical model in 1760 (Anderson and May 1982), research of deterministic models in epidemiology seems to have started only in the early 20th century. In 1906, Hamer constructed and analyzed a discrete model (Hamer 1906) to help understand the repeated occurrence of measles; in 1911, the Public Health Doctor Ross analyzed the dynamical behavior of the transmission of malaria between mosquitos and men by means of differential equation (Ross 1911); in 1927, Kermack and McKendrick constructed the famous compartmental model to analyze the transmitting features of the Great Plague which appeared in London from 1665 to 1666. They introduced a “threshold theory”, which may determine whether the disease is epidemic or not (Kermack and McKendrick 1927, 1932), and laid a foundation for the research of epidemic dynamics. Epidemic dynamics flourished after the mid-20th century, Bailey’s

book being one of the landmark books published in 1957 and reprinted in 1975 (Baily 1975).

Kermack and McKendrick compartment models

In order to formulate the transmission of an epidemic, the population in a region is often divided into different compartments, and the model formulating the relations between these compartments is called **compartmental model**.

In the model proposed by Kermack and McKendrick in 1927, the population is divided into three compartments: a **susceptible compartment** labelled S , in which all individuals are susceptible to the disease; an **infected compartment** labelled I , in which all individuals are infected by the disease and have infectivity; and a **removed compartment** labelled R , in which all individuals are removed from the infected compartment. Let $S(t)$, $I(t)$, and $R(t)$ denote the number of individuals in the compartments S , I , and R at time t , respectively. They made the following three assumptions:

1. The disease spreads in a closed environment (no emigration and immigration), and there is no birth and death in the population, so the total population remains constant, K , i. e., $S(t) + I(t) + R(t) = K$.
2. An infected individual is introduced into the susceptible compartment, and contacts sufficient susceptibles at time t , so the number of new infected individuals per unit time is $\beta S(t)$, where β is the **transmission coefficient**. The total number of newly infected is $\beta S(t)I(t)$ at time t .
3. The number removed (recovered) from the infected compartment per unit time is $\gamma I(t)$ at time t , where γ is the **rate constant for recovery**, corresponding to a mean infection period of $\frac{1}{\gamma}$. The recovered have permanent immunity.

For the assumptions given above, a compartmental diagram is given in Fig. 2.1. The compartmental model corresponding to Fig. 2.1 is the following:

$$\begin{cases} S' = -\beta SI, \\ I' = \beta SI - \gamma I, \\ R' = \gamma I. \end{cases} \tag{1}$$

Since there is no variable R in the first two equations of (1), we only need to consider the following equations

$$\begin{cases} S' = -\beta SI, \\ I' = \beta SI - \gamma I \end{cases} \tag{2}$$

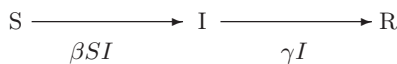


Fig. 2.1. Diagram of the SIR model without vital dynamics

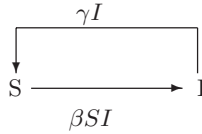


Fig. 2.2. Diagram of the SIS model without vital dynamics

to obtain the dynamic behavior of the susceptible and the infective. After that, the dynamic behavior of the removed R is easy to establish from the third equation of system (1), if necessary.

In general, if the disease comes from a virus (such as flu, measles, chicken pox), the recovered possess a permanent immunity. It is then suitable to use the SIR model (1). If the disease comes from a bacterium (such as cephalitis, gonorrhoea), then the recovered individuals have no immunity, in other words, they can be infected again. This situation may be described using the SIS model, which was proposed by Kermack and McKendrick in 1932 (Kermack and McKendrick 1932). Its compartmental diagram is given in Fig. 2.2.

The model corresponding to Fig. 2.2 is

$$\begin{cases} S' = -\beta SI + \gamma I, \\ I' = \beta SI - \gamma I. \end{cases} \quad (3)$$

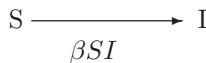
Up to this day, the idea of Kermack and McKendrick in establishing these compartmental models is still used extensively in epidemiological dynamics, and is being developed incessantly. According to the modelling idea, by means of the compartmental diagrams we list the fundamental forms of the model on epidemic dynamics as follows.

Models without vital dynamics

When a disease spreads through a population in a relatively short time, usually the births and deaths (vital dynamics) of the population may be neglected in the epidemic models, since the epidemic occurs relatively quickly, such as influenza, measles, rubella, and chickenpox.

(1) The models without the latent period

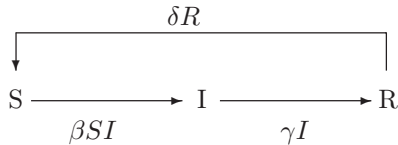
SI model In this model, the infected individuals can not recover from their illness, and the diagram is as follows:



SIS model In this model, the infected individuals can recover from the illness, but have no immunity. The diagram is shown in Fig. 2.2.

SIR model In this model, the removed individuals have permanent immunity after recovery. The diagram is shown in Fig. 2.1.

SIRS model In this model, the removed individuals have temporary immunity after recovery from the illness. Assume that due to the loss of immunity, the number of individuals being moved from the removed compartment to the susceptible compartment per unit time is $\delta R(t)$ at time t , where δ is the **rate constant for loss of immunity**, corresponding to a mean immunity period $\frac{1}{\delta}$. The diagram is as follows:

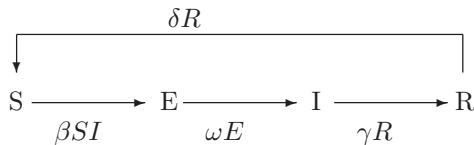


Remark 1. In the SIS model, the infected individuals may be infected again as soon as they recover from the infection. In the SIRS model, the removed individuals can not be infected in a given period of time, and may not be infected until they loose the immunity and become susceptible again.

(2) *The models with the latent period*

Here we introduce a new compartment, E (called **exposed compartment**), in which all individuals are infected but not yet infectious. The exposed compartment is often omitted, because it is not crucial for the susceptible-infective interaction or the latent period is relatively short.

Let $E(t)$ denote the number of individuals in the exposed compartment at time t . Corresponding to the model without the latent period, we can introduce some compartmental models such as SEI, SEIS, SEIR, and SEIRS. For example, the diagram of the SEIRS model is as follows:



where ω is the **transfer rate constant** from the compartment E to the compartment I, corresponding to a mean latent period $\frac{1}{\omega}$.

Models with vital dynamics

(1) *The size of the population is constant*

If we assume that the birth and death rates of a population are equal while the disease actively spreads, and that the disease does not result in the death of the infected individuals, then the number of the total population is a constant, denoted by K . In the following, we give two examples for this case.

SIR model without vertical transmission In this model, we assume that the maternal antibodies can not be inherited by the infants, so all newborn infants are susceptible to the infection. Then, the corresponding compartmental diagram of the SIR model is as follows:

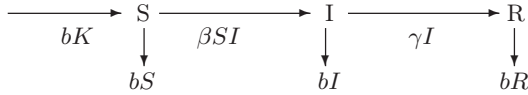
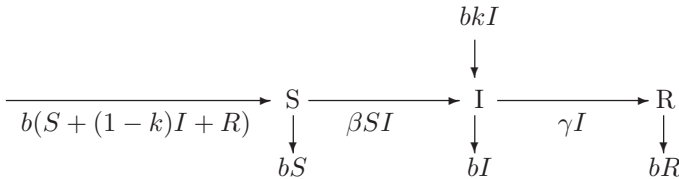


Fig. 2.3. Diagram of the SIR model without vertical transmission

SIR model with vertical transmission For many diseases, some newborn infants of infected parents are to be infected. This effect is called **vertical transmission**, such as AIDS, hepatitis B. We assume that the fraction k of infants born by infected parents is infective, and the rest of the infants are susceptible to the disease. Then, the corresponding compartmental diagram of the SIR model is as follows:



(2) *The size of the population varies*

When the birth and death rates of a population are not equal, or when there is an input and output for the total population, or there is death due to the infection, then the number of the total population varies. The number of the total population at time t is often denoted by $N(t)$.

SIS model with vertical transmission, input, output, and disease-related death The diagram is as follows:

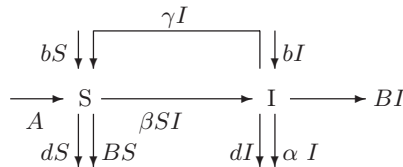
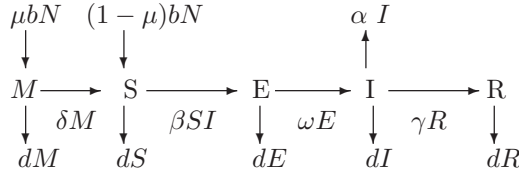


Fig. 2.4. Diagram of the SIS model with vertical transmission

Here, the parameter b represents the birth rate constant, d the natural death rate constant, α the death rate constant due to the disease, A the input rate

of the total population, B the output rate constant of the susceptible and the infective.

MSEIR model with passive immunity Here, we introduce the compartment M in which all individuals are newborn infants with passive immunity. After the maternal antibodies disappear from the body, the infants move to the compartment S . Assume that the fraction of newborn infants with passive immunity is μ , and that the transfer rate constant from the compartment M to the compartment S is δ (corresponding to a mean period of passive immunity $\frac{1}{\delta}$). The diagram is as follows:



According to the diagrams shown above, we can easily write the corresponding compartmental models. For example, the SIR model corresponding to Fig. 2.3 is as follows:

$$\begin{cases} S' = bK - \beta SI - bS, \\ I' = \beta SI - bI - \gamma I, \\ R' = \gamma I - bR. \end{cases} \tag{4}$$

The SIS model corresponding to Fig. 2.4 is as follows:

$$\begin{cases} S' = A + bS - \beta SI - dS - BS + \gamma I, \\ I' = bI + \beta SI - dI - \gamma I - BI - \alpha I. \end{cases}$$

2.2.2 The basic concepts of epidemiological dynamics

Adequate contact rate and incidence

It is well known that infections are transmitted through direct contact. The number of times an infective individual comes into contact with other members per unit time is defined as the **contact rate**, which often depends on the number N of individuals in the total population, and is denoted by a function $U(N)$. If the individuals contacted by an infected individual are susceptible, then they may be infected. Assuming that the probability of infection by every contact is β_0 , then the function $\beta_0 U(N)$, called the **adequate contact rate**, shows the ability of an infected individual infecting others (depending on the environment, the toxicity of the virus or bacterium, etc.). Since, except for the susceptible, the individuals in other compartments of the population can not be infected when they make contact with the infectives, and the fraction of the susceptibles in the total population is $\frac{S}{N}$, then the mean adequate

contact rate of an infective to the susceptible individuals is $\beta_0 U(N) \frac{S}{N}$, which is called the **infective rate**. Further, the number of new infected individuals resulting per unit time at time t is $\beta_0 U(N) \frac{S(t)}{N(t)} I(t)$, which is called the **incidence** of the disease.

When $U(N) = kN$, that is, the contact rate is proportional to the size of the total population, the incidence is $\beta_0 k S(t) I(t) = \beta S(t) I(t)$ (where $\beta = \beta_0 k$ is defined as the **transmission coefficient**), which is described as **bilinear incidence** or **simple mass-action incidence**. When $U(N) = k'$, that is, the contact rate is a constant, the incidence is $\beta_0 k' \frac{S(t)}{N(t)} I(t) = \frac{\beta S(t) I(t)}{N(t)}$ (where $\beta = \beta_0 k'$), which is described as **standard incidence**. For instance, the incidence formulating a sexually transmitted disease is often of standard type. The two types of incidence mentioned above are often used, but they are special for real cases. In recent years, some contact rates with saturation features between them were proposed, such as $U(N) = \frac{\alpha N}{1 + \omega N}$ (Dietz 1982), $U(N) = \frac{\alpha N}{1 + bN + \sqrt{1 + 2bN}}$ (Heesterbeek and Metz 1993). In general, the saturation contact rate $U(N)$ satisfies the following conditions:

$$U(0) = 0, U'(N) \geq 0, \left(\frac{U(N)}{N} \right)' \leq 0, \lim_{N \rightarrow \infty} U(N) = U_0.$$

In addition, some incidences which are much more plausible for some special cases were also introduced, such as $\beta S^p I^q, \frac{\beta S^p I^q}{N}$ (Liu et al. 1986, 1987).

Basic reproduction number and modified reproduction number

In the following, we introduce two examples to understand the two concepts.

Example 1

We consider the SIS model (3) of Kermack and McKendrick. Since $S(t) + I(t) = K(\text{constant})$, (3) can be changed into the equation

$$S' = \beta(K - S) \left(\frac{\gamma}{\beta} - S \right). \quad (5)$$

When $\frac{\gamma}{\beta} \geq K$, (5) has a unique equilibrium $S = K$ on the interval $(0, K]$ which is asymptotically stable, that is, the solution $S(t)$ starting from any $S_0 \in (0, K)$ increases to K as t tends to infinity. Meanwhile, the solution $I(t)$ decreases to zero. This implies that the infection dies out eventually and does not develop to an endemic.

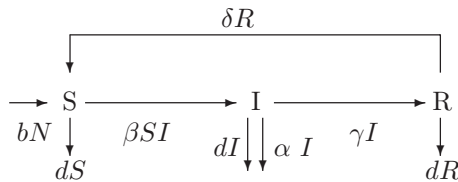
When $\frac{\gamma}{\beta} < K$, (5) has two positive equilibria: $S = K$ and $S = \frac{\gamma}{\beta}$, where $S = K$ is unstable, and $S = \frac{\gamma}{\beta}$ is asymptotically stable. The solution $S(t)$ starting from any $S_0 \in (0, K)$ approaches to $\frac{\gamma}{\beta}$ as t tends to infinity, and $I(t)$ tends to $K - \frac{\gamma}{\beta} > 0$. Thus, point $\left(\frac{\gamma}{\beta}, K - \frac{\gamma}{\beta} \right)$ in S-I plane is called the **endemic equilibrium** of system (3). This case is not expected.

Therefore, $\frac{\gamma}{\beta} = K$, i. e., $R_0 := \frac{\beta K}{\gamma} = 1$ is a threshold which determines whether the disease dies out ultimately. The disease dies out if $R_0 < 1$, is endemic if $R_0 > 1$.

The epidemiological meaning of R_0 as a threshold is intuitively clear. Since $\frac{1}{\gamma}$ is the mean infective period, and βK is the number of new cases infected per unit time by an average infective which is introduced into the susceptible compartment in the case that all the members of the population are susceptible, i. e., the number of individuals in the susceptible compartment is K (this population is called a completely susceptible population), then R_0 represents the average number of secondary infections that occur when an infective is introduced into a completely susceptible population. So, $R_0 < 1$ implies that the number of infectives tends to zero, and $R_0 > 1$ implies that the number of infectives increases. Hence, the threshold R_0 is called the **basic reproduction number**.

Example 2

Consider an SIR model with exponential births and deaths and the standard incidence. The compartmental diagram is as follows:



The differential equations for the diagram are

$$\begin{cases} S' = bN - dS - \frac{\beta SI}{N} + \delta R, \\ I' = \frac{\beta SI}{N} - (\alpha + d + \gamma)I, \\ R' = \gamma I - (d + \delta)R, \end{cases} \tag{6}$$

where b is the birth rate constant, d the natural death rate constant, and α the disease-related death rate constant.

Let $N(t) = S(t) + I(t) + R(t)$, which is the number of individuals of total population, and then from (6), $N(t)$ satisfies the following equation:

$$N' = (b - d)N - \alpha I. \tag{7}$$

The net growth rate constant in a disease-free population is $r = b - d$. In the absence of disease (that is, $\alpha = 0$), the population size $N(t)$ declines exponentially to zero if $r < 0$, remains constant if $r = 0$, and grows exponentially if $r > 0$. If disease is present, the population still declines to zero if $r < 0$. For $r > 0$, the population can go to zero, remain finite or grow exponentially, and the disease can die out or persist.

On the other hand, we may determine whether the disease dies out or not by analyzing the change tendency of the infective fraction $\frac{I(t)}{N(t)}$ in the total population. If $\lim_{t \rightarrow \infty} \frac{I(t)}{N(t)}$ is not equal to zero, then the disease persists; if $\lim_{t \rightarrow \infty} \frac{I(t)}{N(t)}$ is equal to zero, then the disease dies out.

Let

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

then x, y , and z represent the fractions of the susceptible, the infective, and the removed in the total population. From (6) and (7) we have

$$\begin{cases} x' = b - bx - \beta xy + \delta z + \alpha xy, \\ y' = \beta xy - (b + \alpha + \gamma)y + \alpha y^2, \\ z' = \gamma y - (b + \delta)z + \alpha yz, \end{cases} \quad (8)$$

which is actually a two-dimensional system due to $x + y + z = 1$.

Substituting $x = 1 - y - z$ into the middle equation of (8) gives the equations

$$\begin{cases} y' = \beta(1 - y - z)y - (b + \alpha + \gamma)y + \alpha y^2, \\ z' = \gamma y - (b + \delta)z + \alpha yz. \end{cases} \quad (9)$$

Let

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

It is easy to verify that when $R_1 \leq 1$, (9) has only the equilibrium $P_0(0, 0)$ (called **disease-free equilibrium**) in the feasible region which is globally asymptotically stable; when $R_1 > 1$, (9) has the disease-free equilibrium $P_0(0, 0)$ and the positive equilibrium $P^*(y^*, z^*)$ (called the endemic equilibrium), where P_0 is unstable and P^* is globally asymptotically stable (Busenberg and Van den driessche 1990).

The fact that the disease-free equilibrium P_0 is globally asymptotically stable implies $\lim_{t \rightarrow \infty} y(t) = \lim_{t \rightarrow \infty} \frac{I(t)}{N(t)} = 0$, i. e., the infective fraction goes to zero. In this sense, the disease dies out finally no matter what the total population size $N(t)$ keeps finite, goes to zero or grows infinitely. The fact that the endemic equilibrium P^* is globally asymptotically stable implies $\lim_{t \rightarrow \infty} y(t) = \lim_{t \rightarrow \infty} \frac{I(t)}{N(t)} = y^* > 0$, i. e., the infective fraction goes to a positive constant. This shows that the disease persists in population.

It is seen from (6) that the mean infectious period is $\frac{1}{d + \alpha + \gamma}$, the incidence is of standard type, and the adequate contact rate is β , so that the basic reproduction number of model (6) is $R_0 = \frac{\beta}{d + \alpha + \gamma}$.

From the results above we can see that, for this case, the threshold to determine whether the disease dies out is $R_1 = 1$ but not $R_0 = 1$. Therefore, the number R_1 is defined as **modified reproduction number**.

2.3 Some tendencies in the development of epidemic dynamics

2.3.1 Epidemic models described by ordinary differential equations

So far, many results in studying epidemic dynamics have been achieved. Most models involve ordinary equations, such as the models listed in Sect. 2.2.1. When the total population size is a constant, the models SIS, SIR, SIRS and SEIS can be easily reduced to a plane differential system, and the results obtained are often complete. When the birth and death rates of the population are not equal, or the disease is fatal, etc., the total population is not a constant, so that the model can not be reduced in dimensions directly, and the related investigation becomes complex and difficult. Though many results have been obtained by studying epidemic models with bilinear and standard incidences, most of these are confined to local dynamic behavior, global stability is often obtained only for the disease-free equilibrium, and the complete results with respect to the endemic equilibrium are limited.

In the following, we introduce some epidemic models described by ordinary differential equations and present some common analysis methods, and present some related results.

SIRS model with constant input and exponent death rate and bilinear incidence

We first consider the model

$$\begin{cases} S' = A - dS - \beta SI + \delta R, \\ I' = \beta SI - (\alpha + d + \gamma)I, \\ R' = \gamma I - (d + \delta)R. \end{cases} \quad (10)$$

Let $N(t) = S(t) + I(t) + R(t)$, then from (10) we have

$$N'(t) = A - dN - \alpha I, \quad (11)$$

and thus it is easy to see that the set

$$D = \left\{ (S, I, R) \in \mathbb{R}^3 \mid 0 < S + I + R \leq \frac{A}{d}, S > 0, I \geq 0, R \geq 0 \right\}$$

is a positive invariant set of (10).

Theorem 1. (Mena-Lorca and Hethcote 1992) Let $R_0 = \frac{A\beta}{d(\gamma + \alpha + d)}$. The disease-free equilibrium $E_0 \left(\frac{A}{d}, 0, 0 \right)$ is globally asymptotically stable on the set D if $R_0 \leq 1$ and unstable if $R_0 > 1$. The endemic equilibrium $E^*(x^*, y^*, z^*)$ is locally asymptotically stable if $R_0 > 1$. Besides, when $R_0 > 1$, the endemic equilibrium E^* is globally asymptotically stable for the case $\delta = 0$.

Proof

The global stability of the disease-free equilibrium E_0 can be easily proved by using the Liapunov function $V = I$, LaSalle's invariance principle, and the theory of limit system if $R_0 \leq 1$.

In order to prove the stability of the endemic equilibrium E^* for $R_0 > 1$, we make the following variable changes:

$$S = S^*(1 + x), \quad I = I^*(1 + y), \quad R = R^*(1 + z),$$

then (10) becomes

$$\begin{cases} x' = -\beta I^* \left[\left(\frac{\delta}{\beta I^*} + 1 \right) x + y + xy \right], \\ y' = \beta S^* x (1 + y), \\ z' = d(y - z). \end{cases} \quad (12)$$

Noticing that the origin of (12) corresponds to the endemic equilibrium E^* of (10), we define the Liapunov function

$$V = \frac{x^2}{2\beta I^*} + \frac{1}{\beta S^*} [y - \ln(1 + y)],$$

and then the derivative of V along the solution of (12) is

$$V'|_{(12)} = -x^2 \left(\frac{\delta}{\beta I^*} + 1 + y \right) \leq 0.$$

Thus, the global asymptotical stability of the origin of (12) (i. e., the endemic equilibrium E^*) can be obtained by using LaSalle's invariance principle.

Models with latent period

In general, some models with latent period (such as SEIR and SEIRS) may not be reduced to plane differential systems, but they may be competitive systems under some conditions. In this case, the global stability of some of these models can be obtained by means of the orbital stability, the second additive compound matrix, and the method of ruling out the existence of periodic solutions proposed by Muldowney and Li (Li and Muldowney 1995, 1996; Muldowney 1990).

For example, the SEIR model with constant input and bilinear incidence

$$\begin{cases} S' = A - dS - \beta SI, \\ E' = \beta SI - (\epsilon + d)E, \\ I' = \epsilon E - (\gamma + \alpha + d)I, \\ R' = \gamma I - dR \end{cases} \quad (13)$$

has the following results:

Theorem 2. (Li and Wang to appear) Let $R_0 = \frac{A\beta\epsilon}{d(d+\epsilon)(d+\gamma+\alpha)}$. The disease-free equilibrium is globally asymptotically stable if $R_0 \leq 1$ and unstable if $R_0 > 1$; the unique endemic equilibrium is globally asymptotically stable if $R_0 > 1$.

For the SEIR model with exponent input and standard incidence

$$\begin{cases} S' = bN - dS - \frac{\beta SI}{N}, \\ E' = \frac{\beta SI}{N} - (\epsilon + d)E, \\ I' = \epsilon E - (\gamma + \alpha + d)I, \\ R' = \gamma I - dR, \end{cases}$$

Li et al. (1999) introduced the fraction variables: $s = \frac{S}{N}, e = \frac{E}{N}, i = \frac{I}{N}$ and $r = \frac{R}{N}$, and they obtained the following results:

Theorem 3. (Li and et al. 1999) Let $R_0 = \frac{\beta\epsilon}{(d+\epsilon)(d+\gamma+\alpha)}$. The disease-free equilibrium is globally asymptotically stable if $R_0 \leq 1$ and unstable if $R_0 > 1$; the unique endemic equilibrium is locally asymptotically stable if $R_0 > 1$ and globally asymptotically stable if $R_0 > 1$ and $\alpha \leq \epsilon$.

Recently, Zhang and Ma (2003) applied the saturation incidence

$$C(N) = \frac{bN}{1 + bN + \sqrt{1 + 2bN}}$$

instead of the bilinear one in (13), analyzed its global stability completely by using analogous methods, and obtained the basic reproduction number of the corresponding model

$$R_0 = \frac{\beta b \epsilon A}{(d + \gamma + \alpha)(d + \epsilon)(d + bA + \sqrt{d^2 + 2bdA})}.$$

For the SEIS model with constant input, Fan et al. (2001) obtained the complete global behavior with respect to the bilinear incidence. Zhang and Ma (to appear) generalized the incidence to the general form $\beta C(N) \frac{SI}{N}$, where $C(N)$ satisfies the following conditions: (1) $C(N)$ is non-negative, non-decreasing, and continuous differentiable with respect to N ; (2) $\frac{C(N)}{N}$ is non-increasing and continuous differentiable with respect to $N > 0$, and obtained the following results by similar methods for the model

$$\begin{cases} S' = dK - dS - \beta C(N) \frac{SI}{N}, \\ E' = \beta C(N) \frac{SI}{N} - (\epsilon + d)E, \\ I' = \epsilon E - (\gamma + \alpha + d)I, \\ R' = \gamma I - dR, \end{cases}$$

Theorem 4. (Zhang and Ma to appear) Let $R_0 = \frac{\beta\epsilon C(K)}{(d+\epsilon)(d+\gamma+\alpha)}$. The disease-free equilibrium is globally asymptotically stable if $R_0 \leq 1$ and unstable if $R_0 > 1$; the unique endemic equilibrium is globally asymptotically stable if $R_0 > 1$.

The similar method is also used to discuss the global behavior of an SEIR model with bilinear incidence and vertical transmission (Li et al. 2001).

Models with quarantine of the infectives

So far, there are two effective measures to control and prevent the spread of the infection, these being quarantine and vaccination. The earliest studies on the effects of quarantine on the transmission of the infection was achieved by Feng and Thieme (2003a, 2003b), and Wu and Feng (2000). In those papers, they introduced a quarantined compartment, Q , and assumed that all infective individuals must pass through the quarantined compartment before going to the removed compartment or back to the susceptible compartment. Hethcote, Ma, and Liao (2002) considered more realistic cases: a part of the infectives are quarantined, whereas the others are not quarantined and enter into the susceptible compartment or into the removed compartment directly. They analyzed six SIQS and SIQR models with bilinear, standard or quarantine-adjusted incidence, and found that for the SIQR model with quarantine-adjusted incidence, the periodic solutions may arise by Hopf bifurcation, but for the other five models with disease-related death, sufficient and necessary conditions assuring the global stability of the disease-free equilibrium and the endemic equilibrium were obtained.

For instance, for the SIQS model with bilinear incidence

$$\begin{cases} S' = A - \beta SI - dS + \gamma I + \epsilon Q, \\ I' = [\beta S - (d + \alpha + \delta + \gamma)]I, \\ Q' = \delta I - (d + \alpha + \epsilon)Q, \end{cases} \quad (14)$$

the following hold:

Theorem 5. (Hethcote, Ma, and Liao 2002) *Let $R_q = \frac{A\beta}{d(\gamma+\delta+d+\alpha)}$. The disease-free equilibrium is globally asymptotically stable if $R_q \leq 1$ and unstable if $R_q > 1$; the unique endemic equilibrium is globally asymptotically stable if $R_q > 1$.*

To prove the global stability of the endemic equilibrium of system (14), let $N(t) = S(t) + I(t) + Q(t)$, and then system (14) becomes the system

$$\begin{cases} N' = -d(N - N^*) - \alpha(I - I^*) - \alpha(Q - Q^*), \\ I' = \beta[(N - N^*) - (I - I^*) - (Q - Q^*)]I, \\ Q' = \delta(I - I^*) - (d + \alpha + \epsilon)(Q - Q^*), \end{cases}$$

where the point (N^*, I^*, Q^*) is the endemic equilibrium of this last system. Define the Liapunov function

$$\begin{aligned} V(N, I, Q) = & \frac{\delta + \epsilon + 2d + \alpha}{\beta} \left[I - I^* - I^* \ln \frac{I}{I^*} \right] \\ & + \frac{1}{2} \left\{ \frac{(\epsilon + 2d)(N - N^*)^2}{\alpha} + [(N - N^*) - (Q - Q^*)]^2 \right. \\ & \left. + \frac{(\epsilon + 2d)(Q - Q^*)^2}{\delta} \right\}, \end{aligned}$$

then the global stability of the endemic equilibrium can be obtained by computing the derivative of $V(N, I, Q)$ along the solution of the system.

Since the quarantined individuals do not come into contact with the un-quarantined individuals, for the case that the adequate contact rate is constant, the incidence should be $\frac{\beta SI}{N-Q} = \frac{\beta SI}{S+I+R}$, which is called the quarantine-adjusted incidence. Then, the SIQR model with quarantine-adjusted incidence is

$$\begin{cases} S' = A - \frac{\beta SI}{S+I+R} - dS, \\ I' = \frac{\beta SI}{S+I+R} - (\gamma + \delta + d + \alpha)I, \\ Q' = \delta I - (d + \alpha_1 + \epsilon)Q, \\ R' = \gamma I + \epsilon Q - dR. \end{cases} \tag{15}$$

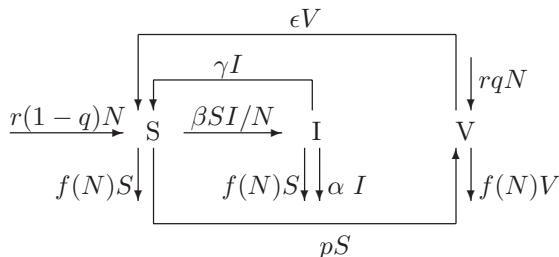
For (15), we have

Theorem 6. (Hethcote, Ma, and Liao 2002) Let $R_q = \frac{\beta}{\gamma + \delta + d + \alpha}$. The disease-free equilibrium is globally asymptotically stable if $R_q \leq 1$ and unstable if $R_q > 1$. If $R_q > 1$, the disease is uniformly persistent, and (15) has a unique endemic equilibrium P^* which is usually locally asymptotically stable, but Hopf bifurcation can occur for some parameters, so that P^* is sometimes an unstable spiral and periodic solutions around P^* can occur.

From Theorem 5 and Theorem 6, we know that the basic reproduction numbers of (14) and (15) include the recovery rate constant γ and the quarantined rate constant δ besides the disease-related death rate constant α , but do not include the recovery rate constant ϵ and the disease-related death rate constant α_1 of the quarantined. This implies that quarantining the infectives and treating the un-quarantined are of the same significance for controlling and preventing the spread of the disease, but this is not related to the behavior of the quarantined.

Models with vaccination Vaccinating the susceptible against the infection is another effective measure to control and prevent the transmission of the infection. To model the transmission of the infection under vaccination, ordinary differential equations, delay differential equations and pulse differential equation (Li and Ma 2002, 2003, 2004a, 2004b, to appear; Li et al. to appear; Jin 2001) are often used. Here, we only introduce some results of ordinary differential equations obtained by Li and Ma (2002, to appear).

The transfer diagram of the SISV model with exponential input and vaccination is



The model corresponding to the diagram is

$$\begin{cases} S' = r(1-q)N - \beta \frac{SI}{N} - [p + f(N)]S + \gamma I + \epsilon V, \\ I' = \beta \frac{SI}{N} - (\gamma + \alpha + f(N))I, \\ V' = rqN + pS - [\epsilon + f(N)]V, \end{cases} \quad (16)$$

where V represents the vaccinated compartment. We assume that the vaccinated individuals have temporary immunity, the mean period of immunity is $\frac{1}{\epsilon}$, and that the natural death rate $f(N)$ depends on the total population N , which satisfies the following conditions:

$$f(N) > 0, \quad f'(N) > 0 \quad \text{for } N > 0 \quad \text{and} \quad f(0) = 0 < r < f(\infty),$$

where q represents the fraction of the vaccinated newborns, and p is the fraction of the vaccinated susceptibles. The other parameters have the same definitions as in the previous sections.

For system (16), by initially making the normalizing transformation to S, I and V , and then using the extensive Bendixson-Dulac Theorem of Ma et al. (2004), we can obtain the following results.

Theorem 7. (*Li and Ma 2002*) Let $R_V = \frac{\beta[q+r(1-q)]}{(p+\epsilon+r)(\alpha+r+\gamma)}$. The disease-free equilibrium is globally asymptotically stable if $R_V \leq 1$ and unstable if $R_V > 1$; the unique endemic equilibrium is globally asymptotically stable if $R_V > 1$.

For the model without vaccination (i. e., $p = q = 0$), the basic reproduction number of (16) is $R_0 = \frac{\beta}{\alpha+r+\gamma}$. By comparing R_V and R_0 , Li and Ma (2002) came to the following conclusion: To control and prevent the spread of the disease, increasing the fraction q of the vaccinated newborns is more efficient when $rR_0 > 1$; increasing the fraction p of the vaccinated susceptibles is more efficient when $rR_0 < 1$.

Model (16) assumed that the vaccine is completely efficient, but, in fact, the efficiency of a vaccine is usually not 100%. Hence, incorporating the efficiency of the vaccine into epidemic models with vaccination is necessary. If we consider an SIS model with the efficiency of vaccine, then the system (16) will be changed into the following:

$$\begin{cases} S' = r(1-q)N - \beta \frac{SI}{N} - [p + f(N)]S + \gamma I + \epsilon V, \\ I' = \beta(S + \sigma V) \frac{I}{N} - (\gamma + \alpha + f(N))I, \\ V' = rqN + pS - \sigma \beta \frac{IV}{N} - [\epsilon + f(N)]V, \end{cases} \quad (17)$$

where the fraction σ ($0 \leq \sigma \leq 1$) reflects the inefficiency of the vaccination. The more effective the vaccine is, the less the value of σ is. Moreover, $\sigma = 0$ implies that the vaccine is completely effective in preventing infection, while $\sigma = 1$ implies that the vaccine is absolutely of no effect.

For model (17), we found the modified reproduction number

$$R_V = \frac{\beta[\epsilon + \sigma p + r(1 - (1 - \sigma)q)]}{(\alpha + r + \gamma)(p + \epsilon + r)}.$$

Theorem 8. (Li, Ma and Zhou to appear) For system (17), the following results are true.

(1) When $R_V > 1$, there exists a unique endemic equilibrium which is globally asymptotically stable.

(2) When $R_V = 1, \alpha < \sigma\beta, B > 0$, there exists a unique endemic equilibrium which is globally asymptotically stable.

(3) When $R_V < 1, \alpha < \sigma\beta, \beta > r + \alpha + \gamma, B > 2\sqrt{AC}$, there exist two endemic equilibria: one is an asymptotically stable node, another is a saddle point.

(4) When $R_V < 1, \alpha < \sigma\beta, \beta > r + \alpha + \gamma, B = 2\sqrt{AC}$, there exists a unique endemic equilibrium, which is a saddle-node.

(5) For all other cases of parameters, the disease-free equilibrium is globally asymptotically stable.

Where

$$A = (\alpha - \sigma\beta)(\beta - \alpha), \quad C = (p + r + \epsilon)(r + \alpha + \gamma)(R_0 - 1),$$

$$B = \alpha(p + \epsilon + \gamma + \alpha + 2r) - \beta[(\alpha + r + \epsilon) - \sigma(\beta - r - \alpha - \gamma - p)].$$

According to Theorem 8, the change of endemic equilibrium of the system (17) can be shown in Fig. 2.5, while the common case is shown in Fig. 2.6. Figure 2.5 shows that, when R_V is less than but close to 1, the system (17) has two endemic equilibria, and has no endemic equilibrium until $R_V < R_c < 1$. One of these two equilibria is an asymptotically stable node, and the other is a saddle point. It implies that, for this case, whether the disease does die out or not depends on the initial condition. This phenomenon is called **backward bifurcation**. Therefore, incorporating the efficiency of vaccine into the epidemic models is important and necessary.

Within this context, the bifurcations with respect to epidemic models were also investigated by many researchers. Liu et al. (1986, 1987) discussed codimension one bifurcation in SEIRS and SIRS models with incidence $\beta I^p S^q$. Lizana and Rivero (1996) considered codimension two bifurcation in the SIRS model. Wu and Feng (2000) analyzed the homoclinic bifurcation in the SIQR model. Watmaough and van den Driessche (2000), Haderler and van den

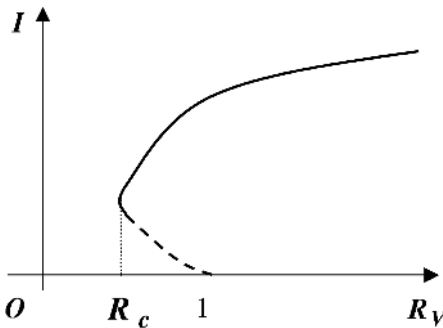


Fig. 2.5. Backward bifurcation

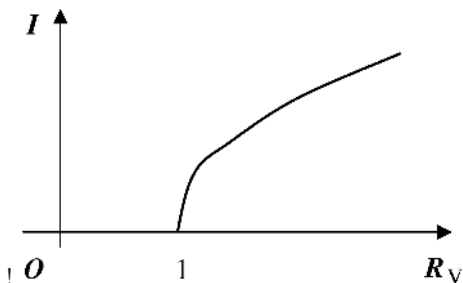


Fig. 2.6. Forward bifurcation

Driessche (1997), and Dushoff et al. (1998) discussed the backward bifurcation in some epidemic models. Ruan and Wang (2003) found the Bogdanov-Takens bifurcation in the SIRS model with incidence $\frac{kI^l S}{1+\alpha I^h}$.

2.3.2 Epidemic models with time delay

The models with time delay reflect the fact: the dynamic behavior of transmission of the disease at time t depends not only on the state at time t but also on the state in some period before time t .

Idea of modelling To formulate the idea of modelling the spread of disease, we show two SIS models with fixed delay (also called discrete delay) and distributed delay (also called continuous delay), respectively.

(1) Models with discrete delay

Assuming that the infective period of all the infectives is constant τ , then the rate at which the infectives recover and return to the susceptible compartment is $\beta S(t - \tau)I(t - \tau)$ if the rate of new infections at time t is $\beta S(t)I(t)$. Corresponding to the system (3), we have the SIS model with delay as follows

$$\begin{cases} S'(t) = -\beta S(t)I(t) + \beta S(t - \tau)I(t - \tau), \\ I'(t) = \beta S(t)I(t) - \beta S(t - \tau)I(t - \tau). \end{cases}$$

If the natural death rate constant d and the disease-related death rate constant α of the infectives are incorporated in the model, then the rate of recovery at time t should be $\beta S(t - \tau)I(t - \tau)e^{-(d+\alpha)\tau}$, where the factor $e^{-(d+\alpha)\tau}$ denotes the fraction of those individuals who were infected at time $t - \tau$ and survive until time t . Thus, we have the model

$$\begin{cases} S'(t) = -\beta S(t)I(t) - dS(t) + \beta S(t - \tau)I(t - \tau)e^{-(d+\alpha)\tau}, \\ I'(t) = \beta S(t)I(t) - (d + \alpha)I(t) - \beta S(t - \tau)I(t - \tau)e^{-(d+\alpha)\tau}. \end{cases}$$

(2) Models with distributed delay

The case that all the infectives have the same period of infection is an extreme one. In fact, the infective period usually depends on the difference of infected

individuals. Assume that $P(\tau)$ is the probability that the individuals, who were infected at time 0, remain in the infected compartment at time τ . It is obvious that $P(0) = 1$. Thus, the number of the infectives at time t is

$$I(t) = \int_0^{+\infty} \beta S(t - \tau) I(t - \tau) P(\tau) d\tau = \int_{-\infty}^t \beta S(u) I(u) P(t - u) du .$$

Assuming that $P(\tau)$ is differentiable, then from the last equation we have

$$I'(t) = \beta S(t) I(t) + \int_{-\infty}^t \beta S(u) I(u) P'(t - u) du .$$

Let $f(\tau) := -P'(\tau)$, then

$$I'(t) = \beta S(t) I(t) - \int_0^{+\infty} \beta S(t - \tau) I(t - \tau) f(\tau) d\tau .$$

It is easy to see that $\int_0^{+\infty} f(\tau) d\tau = \int_0^{+\infty} [-P'(\tau)] d\tau = 1$, and that $\int_0^{+\infty} \tau P(\tau) d\tau$ is the infective period. Therefore, the corresponding SIS model is

$$\begin{cases} S'(t) = -\beta S(t) I(t) + \int_0^{+\infty} \beta S(t - \tau) I(t - \tau) f(\tau) d\tau , \\ I'(t) = \beta S(t) I(t) - \int_0^{+\infty} \beta S(t - \tau) I(t - \tau) f(\tau) d\tau . \end{cases}$$

Similarly to the case with the discrete delay, if the natural death rate constant d and the disease-related death rate constant α of the infectives are incorporated in the model, then the corresponding SIS model becomes

$$\begin{cases} S'(t) = -\beta S(t) I(t) - dS(t) + \int_0^{+\infty} \beta S(t - \tau) I(t - \tau) f(\tau) e^{-(d+\alpha)\tau} d\tau , \\ I'(t) = \beta S(t) I(t) - (d + \alpha) I(t) - \int_0^{+\infty} \beta S(t - \tau) I(t - \tau) f(\tau) e^{-(d+\alpha)\tau} d\tau . \end{cases}$$

In the following, we give some models established according to the idea above.

Example 3

Supposing that the birth and natural death of the population are of exponential type, the disease-related death rate constant is α , the infective period is a constant τ , and that there is no vertical transmission, then the SIS model with standard incidence is

$$\begin{cases} S'(t) = bN(t) - dS(t) - \frac{\beta S(t) I(t)}{N(t)} + \frac{\beta S(t-\tau) I(t-\tau)}{N(t-\tau)} e^{-(d+\alpha)\tau} , \\ I'(t) = \frac{\beta S(t) I(t)}{N(t)} - (d + \alpha) I(t) - \frac{\beta S(t-\tau) I(t-\tau)}{N(t-\tau)} e^{-(d+\alpha)\tau} , \end{cases}$$

where $N(t) = S(t) + I(t)$ satisfies the equation

$$N'(t) = (b - d)N(t) - \alpha I(t) .$$

Example 4

Let A be the birth rate of the population, d the natural death rate constant, α the disease-related death rate constant, ω the latent period, τ the infective period, then the SEIR model with bilinear incidence is

$$\begin{cases} S'(t) = A - dS(t) - \beta S(t)I(t), \\ E'(t) = \beta S(t)I(t) - \beta S(t-\omega)I(t-\omega)e^{-d\omega} - dE(t), \\ I'(t) = \beta S(t-\omega)I(t-\omega)e^{-d\omega} \\ \quad - \beta S(t-\omega-\tau)I(t-\omega-\tau)e^{-d(\omega+\tau)}e^{-\alpha\tau} - (d+\alpha)I(t), \\ R'(t) = \beta S(t-\omega-\tau)I(t-\omega-\tau)e^{-d(\omega+\tau)}e^{-\alpha\tau} - dR(t). \end{cases}$$

Example 5

If we incorporate the vaccination into the SIR model, and assume that the efficient rate constant of the vaccination is p , and that the efficient period of vaccine in the vaccinated body is a constant τ , then the SIR model with vaccination and bilinear incidence is the following:

$$\begin{cases} S'(t) = A - \beta I(t)S(t) - (d+p)S(t) + \gamma I(t) + pS(t-\tau)e^{-d\tau}, \\ I'(t) = \beta I(t)S(t) - (d+\gamma+\alpha)I(t), \\ R'(t) = \gamma I(t) + pS(t) - pS(t-\tau)e^{-d\tau} - dR(t). \end{cases} \quad (18)$$

Note that the term $pS(t-\tau)e^{-d\tau}$ in (18) represents the number of individuals who are vaccinated at time $t-\tau$ and still survive at time t , and the occurrence of delay form is due to the fact that the efficient period of vaccine is a fixed constant τ . If the probability of losing immunity is an exponential distribution $e^{-\mu t}$ ($\frac{1}{\mu}$ is the mean efficient period of vaccine), then the corresponding model is a system of ordinary differential equations (Ma et al. 2004).

For delay differential systems, the local stability of equilibrium is often obtained by discussing the corresponding characteristic equation, which is similar to an ordinary differential equation. Also, the method to obtain the global stability is mainly to construct Liapunov functionals. For example, since the first two equations in (18) do not include the variable R obviously, we can only consider the subsystem consisting of the first two equations to obtain the following results:

Theorem 9. (*Li and Ma to appear*) *Let*

$$R_V = \frac{\beta A}{(d+\alpha+\gamma)[d+p(1-e^{-d\tau})]} = \frac{\beta S_0}{d+\alpha+\gamma}.$$

The disease-free equilibrium is globally asymptotically stable on the positively invariant set $D = \{(S, I) : S > 0, I \geq 0, S + I \leq \frac{A}{d}\}$ if $R_V \leq 1$ and unstable if $R_V > 1$. The unique endemic equilibrium is globally asymptotically stable in the positively invariant set D if $R_V > 1$.

The global stability of the disease-free equilibrium can be proved by constructing the Liapunov functional

$$V = \frac{(S - S_0)^2}{\alpha} + S_0 I + \frac{pe^{-d\tau}}{2} \int_{t-\tau}^t (S(u) - S_0)^2 du;$$

and the global stability of endemic equilibrium can be proved by constructing the Liapunov functional

$$V = \frac{(S - S_0)^2}{2} + \frac{d + \alpha + \gamma}{\beta} \left(I - I^* - I^* \ln \frac{I}{I^*} \right) + \frac{pe^{-d\tau}}{2} \int_{t-\tau}^t (S(u) - S^*)^2 du,$$

where S^* and I^* are the coordinates of the endemic equilibrium of the system (18).

For epidemic dynamical models with delay, many results have been obtained (Hethcote and van den Driessche 1995; Ma et al. 2002; Wang 2002; Wang and Ma 2002; Xiao and Chen 2001a; Yuan and Ma 2001, 2002; Yuan et al. 2003a, 2003b), but few results were achieved with respect to the global stability of the endemic equilibrium. Especially the results about necessary and sufficient conditions like Theorem 9 are rare.

2.3.3 Epidemic models with age structure

Age has been recognized as an important factor in the dynamics of population growth and epidemic transmission, because individuals have usually different dynamic factors (such as birth and death) in different periods of age, and age structure also affects the transmission of disease and the recovery from disease, etc. In general, there are three kinds of epidemic models with age structure: discrete models, continuous models, and stage structure models.

In order to understand epidemic models more easily, we first introduce the age-structured population model.

Population growth model with discrete age structure

We partition the maximum interval in which individuals survive into n equal subintervals, and partition the duration started at time t_0 by the same length as that of the age subinterval as well. Let N_{ij} ($i = 1, 2, 3, \dots, n, j = 1, 2, 3, \dots$) denote the number of individuals whose age is in i th age subinterval at j th time subinterval; let p_i denote the probability that the individual at i th age subinterval still survives at $(i+1)$ th age subinterval, that is, $N_{i+1,j+1} = p_i N_{ij}$; and let B_i denote the number of newborn by an individual at i th age subinterval, then the population growth model with discrete age structure is the

following:

$$\begin{cases} N_{1,j+1} = B_1 N_{1j} + B_2 N_{2j} + B_3 N_{3j} + \cdots + B_n N_{nj}, \\ N_{2,j+1} = p_1 N_{1j}, \\ \vdots \\ N_{n,j+1} = p_{n-1} N_{n-1,j}. \end{cases}$$

The discrete system above can be re-written as the following vector difference equation

$$\mathbf{N}_{j+1} = \mathbf{A}\mathbf{N}_j, \quad (19)$$

where

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

Thus, equation (19) is a population growth model with discrete age structure, which is called the Leslie matrix model.

Population growth model with continuously distributed age structure

When the number of individuals is very large and two generations can coexist, this population may be thought to be continuously distributed in age.

Let $f(a, t)\delta da$ denote the number of individuals whose age is between a and $a + \delta da$ at time t , $\gamma(a - \delta da)$ the death probability of individuals whose age is between $a - \delta da$ and a in unit time, then we have

$$f(a - \delta da, t) - f(a, t + \delta dt) = \gamma(a - \delta da)f(a - \delta da, t)\delta dt,$$

where $\delta da = \delta dt$. Taylor expansion of both sides above yields

$$\frac{\partial f}{\partial t} + \frac{\partial f}{\partial a} + \gamma(a)f = 0.$$

Let $B(a)\delta da$ denote the mean number of offsprings born by an individual with age between a and $a + \delta da$. Note that $f(0, t)\delta da$ is the number of all the newborn of the population at time t , then we have the boundary condition:

$$f(0, t)\delta da = \int_0^{+\infty} B(a)f(a, t)\delta da,$$

where $f(a, t)$ is called the distributed function of age density (or age distribution function). From the inference above, we have the equations

$$\begin{cases} \frac{\partial f}{\partial t} + \frac{\partial f}{\partial a} + \gamma(a)f = 0, \\ f(0, t)\delta da = \int_0^{+\infty} B(a)f(a, t)\delta da, \\ f(a, 0) = f_0(a), \end{cases}$$

where the last equation is the initial condition.

In the following, we introduce epidemic models with age structure.

Epidemic models with continuous age structure

Many results about epidemic models with continuous age structure have been obtained (Busenberg et al. 1988, 1991; Capasso, V. 1993; Castillo-Chavez et al. 2002; Dietz and Schenzle 1985 Hoppensteadt 1974; Iannelli et al. 1992; Iannelli et al. 1999; Langlais 1995; Li et al. 2001, 2003; Liu et al. 2002; Miiller 1998; Pazy 1983; Zhou 1999; Zhou et al. 2002; Zhu and Zhou 2003). The idea of modelling is the same as that in Sect. 2.2, but all individuals in every compartment are of continuous age distribution. For example, in an SIS model with continuous age structure, the total population is divided into the susceptible compartment and the infected compartment. Let $s(a, t)$ and $i(a, t)$ denote their age distributions at time t , respectively, and assume that the disease transmits only between the same age group. According to the ideas of constructing age-structured population growth models and epidemic compartment models, an SIS model with continuous age structure is given as follows:

$$\begin{cases} \frac{\partial s(a,t)}{\partial a} + \frac{\partial s(a,t)}{\partial t} = -\mu(a)s(a,t) - k_0 i(a,t)s(a,t) + \gamma(a)i(a,t), \\ \frac{\partial i(a,t)}{\partial a} + \frac{\partial i(a,t)}{\partial t} = k_0 i(a,t)s(a,t) - (\gamma(a) + \mu(a))i(a,t), \\ s(0, t)\delta da = \int_0^A \beta(a)[s(a,t) + (1 - q)i(a,t)]\delta da, \\ i(0, t) = \int_0^A q\beta(a)i(a,t)\delta da, \\ s(a, 0) = s_0(a), i(a, 0) = i_0(a), \end{cases} \quad (20)$$

where $\mu(a)$ and $\beta(a)$ are the natural death rate and the birth rate of individuals of age a , $\gamma(a)$ is the rate of recovery from infection at age a , A is the length of maximum survival period of individuals, $k_0(a)$ is the transmission coefficient of the infective of age a , and q is the fraction in which the infectives transmit disease vertically. Using the characteristic method and comparison theorem, Busenberg et al. (1988) proved the following results under some common hypotheses.

Theorem 10. (Busenberg et al. 1988) *Let $R_0 = q \int_0^A \beta(a) e^{\int_0^a \alpha(\sigma)\delta d\sigma} \delta da$. The disease-free equilibrium solution $(s^0(a, t), i^0(a, t)) = (p_\infty(a), 0)$ is globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$; The unique endemic equilibrium solution $(s^*(a), i^*(a))$ is globally asymptotically stable if $R_0 > 1$, where $p_\infty(a)$ is the age distribution of total population in the steady state, i. e., $p_\infty(a) = s(a, t) + i(a, t)$ for any $t \geq 0$; $\alpha(\sigma) = -\mu(\sigma) - \gamma(\sigma) + R_0(\sigma)p_\infty(\sigma)$.*

In general, disease can also be transmitted between different age groups. Thus, the term $k_0(a)i(a, t)$ in (20), which reflects the force of the infectivity, should be replaced by term $k_1(a) \int_0^A k_2(a')i(a', t)\delta da'$, which is the sum of infective force of all the infections to the susceptibles of age a .

For some diseases, if the course of disease is longer and the infectivity may have different courses, then besides the age structure we should also consider the structure with the course of disease. Let c denote the course of disease, then the distributed function with age and course of disease should

be denoted by $f(t, a, c)$, and the dimension of the corresponding model will increase and the structure will become more complicated. A few results can be found in references (Hoppensteadt 1974; Zhou et al. 2002; Zhou 1999).

Epidemic models with discrete age structure

Since the unit time of the collection of data about epidemic transmission is usually in days or months, the parameters of the models with discrete age structure can be handled and computed more easily and more conveniently than those with continuous age structure, and these models can sometimes show richer dynamic behaviors. Still, some common methods used for continuous system (such as derivation and integral operation) can not be applied to the discrete system, and so the theoretical analysis of the discrete system will be more difficult. Hence, the results about epidemic models with discrete age structure are few. In order to show the method of constructing models with discrete age structure, we give an SIS model with vertical transmission and death due to disease as follows.

Partition equally the maximum age interval $[0, A]$ into $(m + 1)$ subintervals, and let $\beta_k \lambda_j$ denote the adequate contact rate in which an infected individual whose age belongs to the interval $\left[\frac{kA}{m+1}, \frac{(k+1)A}{m+1}\right]$ ($k = 0, 1, 2, \dots, m$) contacts adequately the individuals with age in the interval $\left[\frac{jA}{m+1}, \frac{(j+1)A}{m+1}\right]$ ($j = 0, 1, 2, \dots, m$), γ_i the recovery rate of the infective with age in the interval $\left[\frac{jA}{m+1}, \frac{(j+1)A}{m+1}\right]$, d_j and b_j the natural death rate constant and birth rate constant respectively, and $p_j = 1 - d_j$. Thus, according to the ideas of constructing population models with discrete age structure and the epidemic compartment model, we form an SIS model with discrete age structure as follows:

$$\begin{cases} S_0(t+1) = \sum_{j=0}^m b_j [S_j(t) + I_j(t)], \\ I_0(t+1) = 0, \\ S_{j+1} = p_j S_j(t) - \lambda_j \sum_{k=0}^m \beta_k I_k(t) \frac{S_j(t)}{N_j(t)} + \gamma_j I_j(t), \quad j = 0, 1, 2, \dots, m-1, \\ I_{j+1} = p_j I_j(t) + \lambda_j \sum_{k=0}^m \beta_k I_k(t) \frac{S_j(t)}{N_j(t)} - \gamma_j I_j(t), \quad j = 0, 1, 2, \dots, m-1, \\ S_j(0) = S_{j0} \geq 0, \quad I_j(0) = I_{j0} \geq 0, S_{j0} + I_{j0} = N_j, \quad j = 0, 1, 2, \dots, m. \end{cases}$$

Allen et al. (1991, 1998) obtained some results for epidemic models with discrete age structure.

Epidemic models with stage structure

In the realistic world, the birth, death, and the infective rate of individuals usually depend on their physiological stage. Thus, investigating the model with stage structure (such as infant, childhood, youth, old age) is significant.

The results (Xiao *et al.* 2002; Xiao and Chen 2002; Xiao and Chen 2003; Lu *et al.* 2003; Zhou *et al.* 2003) in this field are few. In the following, we again introduce an SIS model to show the modelling idea.

We now consider only two stages: larva and adult, and assume that the disease transmits only between larvae. Let $x_1(t)$ denote the number of the susceptibles of the larvae at time t , $x_2(t)$ the number of adults at time t , $y(t)$ the number of the infected larvae of infants at time t , τ the mature period, a_1 the birth rate constant, r the natural death rate constant, b the rate constant for recovery from disease, and c the coefficient of density dependence of the adults.

Since the mature period of the larvae is τ , the number of transfers out of the larva class at time t is the number of the newborn $a_1x_2(t - \tau)$ at time $t - \tau$ multiplied by the probability $e^{-r\tau}$ of these newborn who survive until time t . Thus, an SIS model with stage structure and bilinear incidence can be given as follows (Xiao and Chen 2003):

$$\begin{cases} x_1'(t) = a_1x_2(t) - a_1e^{-r\tau}x_2(t - \tau) - rx_1(t) - \beta x_1(t)y(t) + by(t), \\ y'(t) = \beta x_1(t)y(t) - by(t) - (r + \alpha)y(t), \\ x_2'(t) = a_1e^{-r\tau}x_2(t - \tau) - cx_2^2(t), \end{cases} \quad (21)$$

where the term $cx_2^2(t)$ in the last equation of (21) is the density dependence of the adults.

Xiao and Chen (2003) investigated the model (21), obtained the conditions which determine whether the disease dies out or persists, and compared their results with those obtained by the model without stage structure.

2.3.4 Epidemic model with impulses

Impulses can describe a sudden phenomenon which happens in the process of continuous change, such as the reproduction of some algae being seasonal, and vaccinations being done at fixed times of the year. Thus, it is more realistic to describe the epidemic models with these factors by impulsive differential equations.

Concepts of impulsive differential equations

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

$$\begin{cases} x'(t) = f(t, x), & t \neq \tau_k, k = 1, 2, \dots \\ \Delta x_k = I_k(x(\tau_k)), & t = \tau_k, \\ x(t_0) = x_0, \end{cases} \quad (22)$$

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

$x(t)$ is called a **solution** of (22), if it satisfies

1. $x'(t) = f(t, x(t)), t \in [\tau_k, \tau_{k+1})$;
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 non-automatic, they have no equilibrium. When $\Delta\tau_k = \tau_k - \tau_{k-1}$ is a constant, the existence and stability of the periodic solution with period $\Delta\tau_k$ are often of interest. For further comprehension with respect to impulsive differential equations, see the related references (Lakshmikantham et al. 2003; Bainov and Simeonov 1995; Guo et al. 1995).

Epidemic models with impulsive birth

The study of epidemic models with impulses has started only recently, and related results are scarce (D'Onofri 2002; Jin 2001; Roberts and Kao 1998; Shulgin et al. 1998; Stone et al. 2000; Tang to appear). In the following, we introduce an SIR model with impulsive birth.

Let b denote the birth rate constant, d the natural death rate constant $r = b - d$, and K the carrying capacity of the environment. Assume that there is no vertical transmission and disease-related death, and $\Delta\tau_k = 1$. Note that impulsive birth and the density-dependent term affecting the birth should appear in the impulsive conditions, so the SIS model with impulsive birth is the following:

$$\begin{cases} N'(t) = -dN(t), & t \neq k, \quad k = 1, 2, 3, \dots \\ S'(t) = -dS(t) - \beta S(t)I(t) + \gamma I(t), & t \neq k, \\ I'(t) = \beta S(t)I(t) - (\gamma + d)I(t), & t \neq k, \\ N(t^+) = \left[1 + b - \frac{rN(t)}{K}\right] N(t), & t = k, \\ S(t^+) = S(t) + \left[b - \frac{rN(t)}{K}\right] N(t), & t = k, \\ I(t^+) = I(t), & t = k. \end{cases}$$

Since $N = S + I$, we only need to discuss the following equations:

$$\begin{cases} N'(t) = -dN(t), & t \neq k, \quad k = 1, 2, 3, \dots \\ I'(t) = \beta(N(t) - I(t))I(t) - (\gamma + d)I(t), & t \neq k, \\ N(t^+) = \left[1 + b - \frac{rN(t)}{K}\right] N(t), & t = k, \\ I(t^+) = I(t), & t = k. \end{cases} \quad (23)$$

Theorem 11. (Han 2002) For model (23), there is always the disease-free periodic solution $(N_1^*(t), 0)$; there exists also the endemic periodic solution $(N_2^*(t), I_2^*(t))$ when $\int_0^1 A(t)dt > 0$, where $A(t) = \beta N_1^*(t) - (\gamma + d)$.

Epidemic models with impulsive vaccination

Assume the fraction p of the susceptibles is vaccinated at time $t = k(k = 0, 1, 2, \dots)$ and enters into the removed compartment. Then, we have the SIR epidemic model with impulsive vaccination as follows

$$\begin{cases} S'(t) = bK - bS(t) - \beta S(t)I(t), & t \neq k, \quad k = 0, 1, 2, \dots \\ I'(t) = \beta S(t)I(t) - (\gamma + b + d)I(t), & t \neq k, \\ R'(t) = \gamma I(t) - bR(t), & t \neq k, \\ S(t^+) = (1 - p)S(t), & t = k, \\ I(t^+) = I(t), & t = k, \\ R(t^+) = R(t) + pS(t), & t = k. \end{cases} \quad (24)$$

For the model (24), Jin and Ma (to appear) obtained the following results by means of Liapunov function and impulsive differential inequalities.

Theorem 12. *(Jin and Ma to appear) Model (24) has always the disease-free periodic solution $(S^*(t), 0, R^*(t))$ with period 1, and it is globally asymptotically stable when $\sigma < 1$, where*

$$\begin{aligned} S^*(t) &= K - \frac{Kpe^{-bt}}{1 - (1-p)e^{-b}}, \\ R^*(t) &= \frac{Kpe^{-bt}}{1 - (1-p)e^{-b}}, \\ \sigma &= \frac{\beta K}{\gamma + b + \alpha} \left[1 - \frac{p(e^b - 1)}{b(e^b - 1 + p)} \right]. \end{aligned}$$

2.3.5 Epidemic models with multiple groups

Some diseases may be transmitted between multiple interactive populations, or multiple sub-populations of a population. In models constructed for these cases, the number of variables is increased, such that the structure of the corresponding model is complex, and that analysis becomes difficult, so that some new dynamic behaviors can be found. We introduce some modelling ideas as follows.

DI SIA model with different infectivity

In this section, we introduce an epidemic model with different infectivity (DI). Since the differently infected individuals may have different infectivity and different rate of recovery (removed) from a disease, we may partition the infected compartment into n sub-compartments, denoted by $I_i (i = 1, 2, \dots, n)$, and we let A be the removed compartment in which all the individuals have terminal illness and have no infectivity due to quarantine (for example, the HIV infectives enter into the AIDS period). Assume that all the infectives in compartment I_i can come into contact with the susceptibles, that the infectives in the different sub-compartment I_i have different adequate contact and

recovery rates, and that they do not die out due to disease. Thus, we have a DI SIA model with bilinear incidence (Ma, Liu and Li 2003)

$$\begin{cases} S' = \mu S^0 - \mu S - \sum_{i=1}^n \beta_i S_i I_i, \\ I'_i = p_i \sum_{i=1}^n \beta_i S_i I_i - (\mu + \gamma_i) I_i, \quad i = 1, 2, \dots, n, \\ A' = \sum_{j=1}^n \gamma_j I_j - (\mu + \alpha), \end{cases} \quad (25)$$

where μS^0 denotes a constant input flow, μ the natural death rate constant, α the disease-related death rate constant, γ_i the rate constant of transfer from I_i to A , and β_i the adequate contact number of the infective I_i . p_i is the probability in which the infected individuals enter the compartment I_i , $\sum_{i=1}^n p_i = 1$.

Ma et al. (2003) wrote the first $(n + 1)$ equations of (25) as the following equations of vector form:

$$\begin{cases} S' = \mu(S^0 - S) - B^T I S, \\ I' = S B^T I P - D I, \end{cases}$$

where $I = (I_1, I_2, \dots, I_n)^T$, $B = (\beta_1, \beta_2, \dots, \beta_n)^T$, $D = \text{diag}(\mu + \gamma_1, \mu + \gamma_2, \dots, \mu + \gamma_n)$, $P = (p_1, p_2, \dots, p_n)^T$, and T denotes the transposition. Then, it was obtained that

Theorem 13. (Ma, Liu and Li 2003) *Let $R_0 = S^0 B^T D^{-1} P$. The disease-free equilibrium is globally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$; the unique endemic equilibrium is globally asymptotically stable if $R_0 > 1$.*

For Theorem 13, the global stability of the disease-free equilibrium is proved by using the Liapunov function $V = (D^{-1} B)^T I$. To prove the global stability of the endemic equilibrium, the variable translations $S = S^*(1 + x)$, $I_i = I_i^*(1 + y_i)$ ($i = 1, 2, \dots, n$) are first made, then the Liapunov function $V = \frac{x^2}{2} + \sum_{i=1}^n \frac{\beta_i I_i^*}{\mu + \gamma_i} [y_i - \ln(1 + y_i)]$ is used. At the same time, it is easy to see that R_0 is the basic reproduction number of (25).

DS SIA model with different susceptibility

In this section, we assume that the infected compartment I is homogeneous but the susceptible compartment S is divided into n sub-compartments S_i ($i = 1, 2, \dots, n$) according to their susceptibilities, that the input rate of S_i is μS_i^0 , and then we have a DS SIA model with different susceptibility and standard

incidence

$$\begin{cases} S'_i = \mu(S^0 - S_i) - \frac{\beta k_i S_i I}{N}, \\ I' = \sum_{j=1}^n n \frac{\beta k_j S_j I}{N} - (\mu + \gamma)I, \\ A' = \gamma I - (\mu + \alpha), \end{cases} \quad (26)$$

where k_i reflects the susceptibility of susceptible individuals in sub-compartment S_i , and other parameters are the same as those in the previous section. Since the individuals in A do not come into contact with the susceptible individuals, $N = \sum_{i=1}^n S_i + I$.

Castillo-Chavez et al. (1996) found the basic reproduction number of (26)

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

and proved that the disease-free equilibrium is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$, and that the disease persists if $R_0 > 1$.

Li et al. (2003) investigated a more complex model, which includes different infectivity and different susceptibility and crossing infections, finding the basic reproduction number, and obtaining some conditions assuring the local and global stability of the disease-free equilibrium and the endemic equilibrium.

Epidemic models with different populations

Though Anderson and May (1986) have incorporated the spread of infective disease into predator-prey models in 1986, the study of disease transmission within interactive populations has started only in recent years. For the investigation of combining epidemic dynamics with population biology, the results obtained are still poor so far.

Anderson and May (1986) assume that the disease transmits only within prey species, and that the incidence is bilinear, the model discussed being

$$\begin{cases} H' = rX - (b + \alpha)Y - c[(1 - f)X + Y]P - bX, \\ Y' = \beta XY - (b + \alpha)Y - cYP, \\ P' = \delta HP - dP, \end{cases} \quad (27)$$

where H is the sum of the number of individuals in the prey species, X the number of the susceptible individuals in the prey species, Y the number of the infective individuals in the prey species, $H = X + Y$, P the number of individuals in the predator species, r the birth rate constant of the prey species, b the natural death rate constant of the prey species, α the disease-related death rate constant of the infectives in the prey species, δ reflects the ability of reproduction of the predator from the prey caught, d the natural

death rate constant of the predator, c the catching ability of the predator, and f reflects the difference between catching the susceptible prey and the infected prey. They found that a disease may result in the existence of stable periodic oscillation of two species, which implies that the model (27) has a stable limit cycle.

Some epidemic models of interactive species were discussed (Venturino 1995; Xiao and Chen 2001b; Bowers and Begon 1991; Begon *et al.* 1992; Begon and Bowers 1995; Han et al. 2001). Han et al. (2001) investigated four predator-prey models with infectious disease. Han et al. (2003) analyzed four other SIS and SIRS epidemic models of two competitive species with bilinear or standard incidence and crossing infection, obtaining some complete results where the SIS model with standard incidence is the following

$$\left\{ \begin{array}{l} S'_1 = (b_1 - \frac{a_1 r_1 N_1}{K_1})N_1 - [d_1 + (1 - a_1)\frac{r_1 N_1}{K_1}]S_1 - mN_2 S_1 \\ \quad - \frac{S_1}{N_1}(\beta_{11}I_1 + \beta_{12}I_2) + \gamma_1 I_1, \\ I'_1 = \frac{S_1}{N_1}(\beta_{11}I_1 + \beta_{12}I_2) - \gamma_1 I_1 - [d_1 + (1 - a_1)\frac{r_1 N_1}{K_1}]I_1 - mN_2 I_1, \\ N'_1 = [r_1(1 - \frac{N_1}{K_1}) - mN_2]N_1, \\ S'_2 = (b_2 - \frac{a_2 r_2 N_2}{K_2})N_2 - [d_2 + (1 - a_2)\frac{r_2 N_2}{K_2}]S_2 - nN_1 S_2 \\ \quad - \frac{S_2}{N_2}(\beta_{21}I_1 + \beta_{22}I_2) + \gamma_2 I_2, \\ I'_2 = \frac{S_2}{N_2}(\beta_{21}I_1 + \beta_{22}I_2) - \gamma_2 I_2 - [d_2 + (1 - a_2)\frac{r_2 N_2}{K_2}]I_2 - nN_1 I_2, \\ N'_2 = [r_2(1 - \frac{N_2}{K_2}) - nN_1]N_2, \\ r_i = b_i - d_i > 0, \quad i = 1, 2 \\ 0 \leq a_i \leq 1, \quad i = 1, 2 \end{array} \right. \quad (28)$$

The explanation of parameters in (28) is omitted. Since $N_i = S_i + I_i (i = 1, 2)$, (28) can be simplified as follows:

$$\left\{ \begin{array}{l} I'_1 = \frac{N_1 - I_1}{N_1}(\beta_{11}I_1 + \beta_{12}I_2) - \gamma_1 I_1 \\ \quad - [d_1 + (1 - a_1)\frac{r_1 N_1}{K_1}]I_1 - mN_2 I_1, \\ N'_1 = [r_1(1 - \frac{N_1}{K_1}) - mN_2]N_1, \\ I'_2 = \frac{N_2 - I_2}{N_2}(\beta_{21}I_1 + \beta_{22}I_2) - \gamma_2 I_2 \\ \quad - [d_2 + (1 - a_2)\frac{r_2 N_2}{K_2}]I_2 - nN_1 I_2, \\ N'_2 = [r_2(1 - \frac{N_2}{K_2}) - nN_1]N_2, \\ N_i \geq I_i \geq 0, \quad i = 1, 2 \\ 0 \leq a_i \leq 1, \quad i = 1, 2 \end{array} \right. \quad (29)$$

The model has six boundary equilibria and one positive equilibrium, and the attractive region of all feasible equilibria has been determined. The results obtained show that, under certain conditions, the disease can die out eventually by cutting off the inter-infections between two species or decreasing the inter-transmission coefficients between two species to a fixed value.

2.3.6 Epidemic models with migration

The models in the previous sections do not include the diffusion or migration of individuals in space, and suppose that the distribution of individuals is

uniform. In fact, with the migration of individuals, the influence of individual diffusion on the spread of disease should not be neglected. Here, we introduce two types of diffusions into the epidemic models.

First, we consider the continuous diffusion of individuals in the corresponding compartment. This needs to add the diffusion to the corresponding ordinary differential equations. For example, the SIR model with diffusion corresponding to model (4) is

$$\begin{cases} \frac{\partial S}{\partial t} = \Delta S + bK - \beta SI - bS, \\ \frac{\partial I}{\partial t} = \Delta I + \beta SI - (b + \gamma)S, \\ \frac{\partial R}{\partial t} = \Delta R + \gamma I - bR, \end{cases} \quad (30)$$

where $S = S(t, x, y, z)$, $I = I(t, x, y, z)$ and $R = R(t, x, y, z)$ denote the numbers of the susceptibles, the infectives, and the removed individuals at time t and point (x, y, z) , respectively; $\Delta S = \frac{\partial^2 S}{\partial x^2} + \frac{\partial^2 S}{\partial y^2} + \frac{\partial^2 S}{\partial z^2}$, $\Delta I = \frac{\partial^2 I}{\partial x^2} + \frac{\partial^2 I}{\partial y^2} + \frac{\partial^2 I}{\partial z^2}$ and $\Delta R = \frac{\partial^2 R}{\partial x^2} + \frac{\partial^2 R}{\partial y^2} + \frac{\partial^2 R}{\partial z^2}$ are the diffusion terms of the susceptibles, the infectives, and the removed individuals at time t and point (x, y, z) , respectively. This model is a quasi-linear partial differential system. Model (30), with some boundary conditions, constitutes an SIR epidemic model with diffusion in space.

Second, we consider the migration of individuals among the different patches (or regions). Though Hethcote (1976) established an epidemic model with migration between two patches in 1976, studies dealing with this aspect are rare. Brauer et al. (2001) discussed an epidemic model with migration of the infectives. Recently, Wang (2002) considered an SIS model with migration among n patches. If there is no population migration among patches, that is, the patches are isolated, according to the structure of population dynamics proposed by Cooke et al. (1999), the epidemic model in i th ($i = 1, 2, \dots, n$) patch is given by

$$\begin{cases} S'_i = B_i(N_i)N_i - \mu_i S_i - \beta_i S_i I_i + \gamma_i I_i, \\ I'_i = \beta_i S_i I_i - (\gamma_i + \mu_i) I_i, \end{cases}$$

where the birth rate in i th patch $B_i(N_i)$ for $N_i > 0$ satisfies the following common hypothesis:

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

If n patches are connected with each other, i. e., the individuals between any two patches can migrate, then the SIS epidemic model with migration among n patches is the following:

$$\begin{cases} S'_i = B_i(N_i)N_i - \mu_i S_i - \beta_i S_i I_i + \gamma_i I_i + \sum_{j=1}^n a_{ij} S_j, \\ I'_i = \beta_i S_i I_i - (\gamma_i + \mu_i) I_i + \sum_{j=1}^n b_{ij} I_j, \end{cases} \quad (31)$$

where a_{ii} and b_{ii} ($a_{ii} \leq 0, b_{ii} \leq 0$) denote the migration rates of the susceptibles and the infectives from the i th 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 j th patch to i th patch, respectively. Model (31) assumes that the disease is not fatal, and the death and birth of individuals in the process of migration are neglected. Since the individuals migrating from the i th patch will move dispersedly to the other $(n - 1)$ patches, we have

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

Under the assumptions that the matrices (a_{ij}) and (b_{ij}) are all in-reducible, by means of related theory of matrix, Wang (2002) obtained the conditions of local and global stability of the disease-free equilibrium, and the conditions under which the disease persists in all patches. Particularly, for the case of two patches, the conditions about the disease-free equilibrium obtained by Wang (2002) show the following: when the basic reproduction number R_{12} , which is found when regarding two patches as one patch, is greater than one, the disease persists in two patches; when $R_{12} < 1$ and $R_{12} - \Phi_{12} > 1$ (where Φ_{12} denotes one number minus the other number, the first number is the product of the number of new patients infected by an infected individual within the average infective course in one patch and that in another patch, the second number is the product of the number of migrated patients within the average infective course in one patch and that in another patch), the disease still persists; when $R_{12} < 1$ and $R_{12} - \Phi_{12} < 1$, the disease dies out in two patches. The formulation above indicates: $R_{12} < 1$ can not ensure the extinction of the disease, and the condition $R_{12} - \Phi_{12} < 1$ is also added. This result shows that migration among patches can affect the spread of disease.

Besides those research directions mentioned above, there are some other research directions of epidemic dynamics, such as: using non-autonomous models, where the coefficients of the epidemic model are time dependent, including periodic coefficients and more general time-dependent coefficients (Lu and Chen 1998; Ma 2002); combining epidemic dynamics with eco-toxicology to investigate the effect of pollution on the spread of disease in a polluted environment (Wang and Ma 2004); combining epidemic dynamics with molecular biology to investigate the interaction among viruses, cells and medicines inside the body (De Boer et al. 1998; Lou et al. 2004a, 2004b; Perelson et al. 1993; Wang et al. to appear; Wang et al. 2004); combining epidemic dynamics with optimal control to investigate the control strategy of epidemics (He 2000); considering stochastic factors to investigate the stochastic dynamics of epidemics (Jing 1990); and using some special disease to construct and investigate a specific model (Feng and Castillo-Chavez 2000; Hethcote and Yorke 1984). Because of limited space, we can not discuss these one by one. In the following, we only introduce the modelling and investigation of SARS according to the real situation existing on mainland China in 2003.

2.3.7 Epidemic models for SARS in China

SARS (Severe Acute Respiratory Syndrome) is a newly acute infective disease with high fatality. This infection first appeared and was transmitted within China in November 2002, and spread rapidly to 31 countries within 6 months. In June 2003, the cumulative number of diagnosed SARS cases had reached 8454, of which 793 died in the whole world (WHO; MHC). In China, 5327 cases were diagnosed, and 343 cases died (MHC).

Since SARS had never been recorded before, it was not diagnosed correctly and promptly, and there have been no effective drugs or vaccines for it so far. Therefore, investigating its spread patterns and development tendency, and analyzing the influence of the quarantine and control measures on its spread are significant. In the initial period of onset of SARS, some researchers (Chowell et al. 2003; Donnelly et al. 2003; Lipsitch et al. 2003; Riley et al. 2003) studied its spread rule and predicted its development according to the data published at that time. Based on the data available for China, Zhang et al. (2004) and Zhou et al. (2004) established some continuous and discrete dynamic models, and discovered some transmission features of SARS in China, which matched the real situation quite well.

Continuous model for SARS in China

The difficulties we met in the modelling of SARS are the following: (1) because SARS is a new disease, the infectious probability is unknown, and whether the individuals in the exposed compartment have infectivity is not sure; (2) how to construct the model such that it fits the situation in China? Especially, how to account for those effective control measures carried out by the government, such as various kinds of quarantine, and how to obtain data for those parameters which are difficult to quantify, for example, the intensity of the quarantine?

Based on the general principles of modelling of epidemics, and the special case of the prevention and control measures in China, Zhang et al. (2004) divided the whole 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 could not contact the individuals in the free block. Further, the free block was divided into four compartments: the susceptible compartment (S), the exposed compartment (E), the infectious compartment (I), and the removed compartment (R); the isolated block was divided into three compartments: the quarantined compartment (Q), the diagnosed compartment (D), and the health-care worker compartment (H).

The susceptible compartment (S) consisted of individuals susceptible to the SARS virus; the individuals in the exposed compartment (E) were exposed to the SARS virus, but in the latent period (these were asymptomatic but possibly infective); the individuals in the infectious compartment (I) showed definitive symptoms, and had strong infectivity, but had not yet been isolated; the individuals in the removed compartment (R) were those who had

recovered from SARS, with full immunity against re-infection. The individuals in the quarantined compartment (Q) were either individuals carrying the SARS virus (but not yet diagnosed) or individuals without the SARS virus but misdiagnosed as possible SARS patients; the individuals in the diagnosed compartment (D) were carriers of SARS virus and had been diagnosed; the health-care worker compartment (H) consisted of those who were health-care workers with high susceptibility (since SARS is not known well), and were quarantined due to working with the individuals in the isolated block.

To control and prevent the spread of SARS, the Ministry of Health of China (MHC) decreed the Clinic Diagnostic Standard of SARS, and imposed strict measures of quarantine at that time. According to these measures, any individual who came into contact with a diagnosed patient with SARS directly or indirectly, or had clinical symptoms similar to those of SARS, such as fever, chills, muscular pain, and shortness of breath, would be quarantined as a possible SARS patient. These measures played a very important role in controlling the spread of SARS in China. Inevitably, many individuals were misdiagnosed as SARS suspected, and hence were mistakenly put in the Q -compartment due the to lack of a fast and effective SARS diagnostic test. According to the relations among all compartments, the transfer diagram of SARS should be Fig. 2.7.

Let $S(t)$, $E(t)$, $I(t)$, $R(t)$, $Q(t)$, $D(t)$, and $H(t)$ denote the number of individuals in the compartments S , E , I , R , Q , D , and H at time t , respectively.

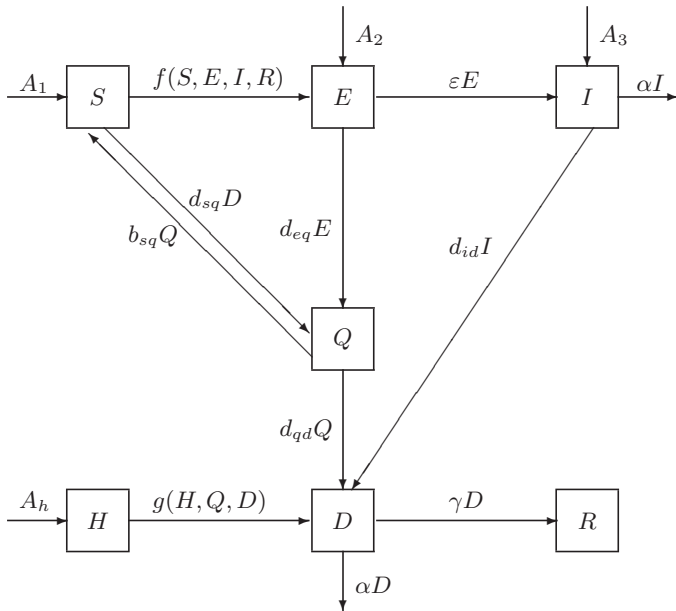


Fig. 2.7. Transfer diagram for the SARS model in China

Thus, corresponding to the transfer diagram in Fig. 2.7, we have the compartment model of SARS as follows:

$$\begin{cases} S' = A_1 - f(S, E, I, R) - d_{sq}D + b_{sq}Q, \\ E' = A_2 + f(S, E, I, R) - \epsilon E - d_{eq}E, \\ I' = A_3 + \epsilon E - d_{id}I - \alpha I, \\ Q' = d_{eq}E + d_{sq}D - b_{sq}Q - d_{qd}Q, \\ D' = g(H, Q, D) + d_{qd}Q + d_{id}I - \alpha D - \gamma D, \\ H' = A_h - g(H, Q, D), \\ R' = \gamma D, \end{cases} \quad (32)$$

where $F(S, E, I, R)$ and $g(H, Q, D)$ are the incidences in the free block and the isolated block, respectively. The general form of the incidences is $\beta C \frac{S}{N} I$, where β is the probability of transmitting the virus per unit time of effective contact (this measures the toxicity of the virus), and C is the adequate contact number of a patient with other individuals (this reflects the strength of control and prevention against SARS). Let C_E and C_I denote the contact rates, and let β_E and β_I denote the probabilities of transmission of exposed individuals and infective individuals in the free block, respectively. Then, the incidence in the free block is given by

$$f(S, E, I, R) = (\beta_E C_E E + \beta_I C_I I) \frac{S}{S + E + I + R}.$$

Here, to be on the safe side, we suppose that the individuals in the exposed compartment have a small infectivity, that is, $0 < \beta_E \ll \beta_I$. Similarly, we can get

$$g(H, Q, D) = (\beta_Q C_Q Q + \beta_D C_D D) \frac{H}{H + Q + D}.$$

For the sake of simplicity, let $k_1 = \frac{\beta_E C_E}{\beta_I C_I}$ denote the ratio of the infectivity between an individual in the E-compartment and an individual in the I-compartment, then we rewrite the incidence terms $f(S, E, I, R)$ as

$$f(S, E, I, R) = \beta(t)(k_1 E + I)$$

where $\beta(t) = \frac{\beta_I C_I S}{S + E + I + R}$ represents the infectious rate.

We took one day as unit time, and assumed that the average latent period is 5 days (WHO; MHC). From the statistical data published by MHC (Rao and Xu 2003), each day 80% of the diagnosed SARS cases come from the Q-compartment, and 20% come from the I-compartment. So, we let

$$\epsilon = \frac{1}{5} \times \frac{20}{100}, \quad d_{eq} = \frac{1}{5} \times \frac{80}{100}$$

Since the average number of days from entering the I-compartment to moving to the D-compartment is 3 days, $d_{id} = \frac{1}{3}$. 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 (those are misdiagnosed) 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, based on the daily reported data from MHC, we get the ratio of non-infected individuals in the Q-compartment, $\frac{q_s}{q_s+q_d} = 0.6341$. Thus,

$$d_{qd} = (1 - 0.6341) \times \frac{1}{3}, \quad b_{sq} = 0.6341 \times \frac{1}{10}.$$

Since the period of recovery for an SARS patient is about 30 days and the statistical analysis from the MHC shows that the ratio of the daily number of new SARS suspected cases to the daily number of new SARS diagnosed cases is 1.3:1, then

$$\gamma = \frac{1}{30}, \quad d_{sd} = 1.3 \times 0.6341 \times \frac{1}{30}.$$

Finally, since the probability of SARS-related death is 14%, $\alpha = \frac{1}{30} \times 0.14$.

The determination of the incidences in the free block and the isolated block is the key to analyzing the SARS model (32). This is difficult because of the poor understanding of the SARS virus toxicities and the difficulty in quantifying these quarantines. Nevertheless, significant amounts of data have been collected during the course of SARS outbreak in China after the middle of April 2003. Here, we use the back-tracking method to estimate the adequate contact rate.

Let $\hat{f}(t)$ denote the number of new diagnosed SARS cases (reported by MHC) 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 (t th day) 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,

$$\beta(t) = \frac{\beta_I C_I S}{S + E + I + R} = \frac{F(t)}{I(t) + k_1 E(t)} = \frac{\hat{f}(t+8)}{\sum_{j=0}^2 \hat{f}(t+j) + k_1 \sum_{j=3}^7 \hat{f}(t+j)}.$$

Analogously, we can obtain the incidence in the isolated block.

By regression analysis of the data published by WHC, we obtain

$$\beta(t) = 0.002 + 0.249e^{-0.1303t}.$$

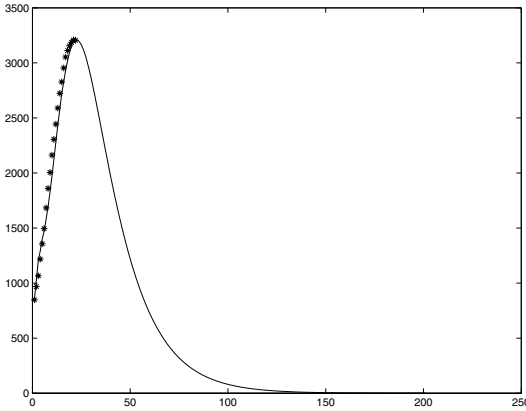


Fig. 2.8. The simulated curve (continuous) and the reported (by MHC, marked in stars) daily number of SARS patients in hospitals

Based on the above approach, Zhang et al. (2004) carried out some numerical simulations to validate the model (32), and discussed the effectiveness of control measures, and to assess the influence of certain measures on the spread of SARS, by varying some parameters to gauge the effectiveness of different control measures. All numerical simulations started on April 21 of 2003, that is, the origin of the time axis (horizontal) corresponds to April 21

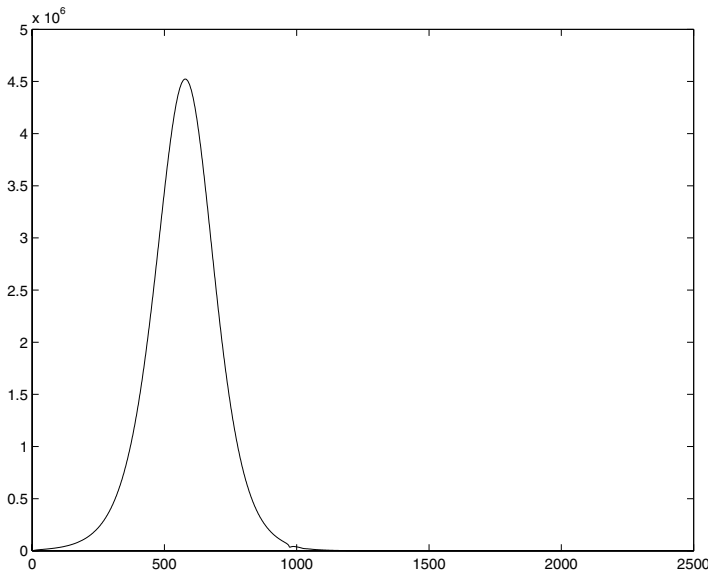


Fig. 2.9. The prediction for the transmission pattern in China without control measures after April of 2003. The outbreak peaks at the end of October of 2004, with over 4.5 million individuals infected, though the SARS toxicity declines exponentially

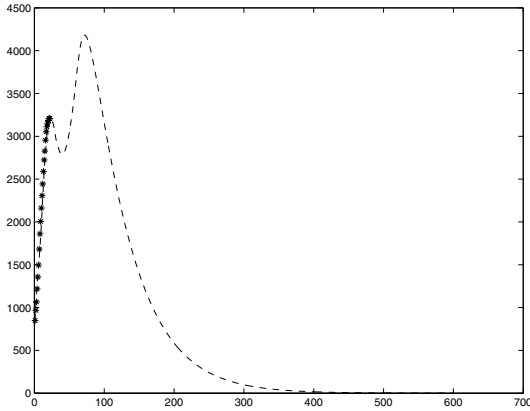


Fig. 2.10. The pattern of SARS transmission if the prevention and control measures were to have been relaxed from May 19 of 2003; though the toxicity of SARS virus naturally declines at a rate of 0.01 per unit time, there would be a second outbreak, with a maximum number of SARS patients higher than that of the first outbreak

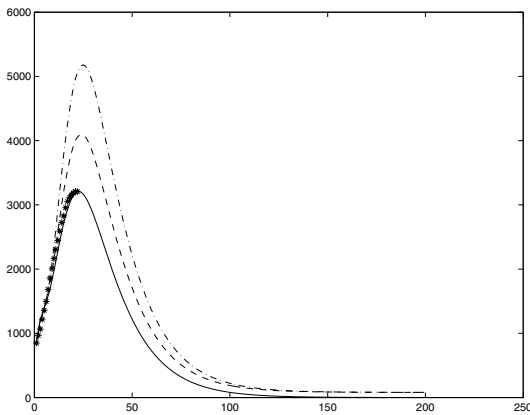


Fig. 2.11. The influence of the slow quarantine speed: the top and bottom lines show the number of daily SARS patients when the infectives stay in the I-compartment for 2 and 1 more days, respectively. The peak would be postponed by 4 or 2 days, but the peak numbers would be much higher

of 2003. Figure 2.8 shows the simulated curve of the daily number of SARS patients in hospitals in reality. Figure 2.9 shows the case with no control measures after April 21 of 2003. Figure 2.10 shows the case under which the prevention and control measures were relaxed from May 19 of 2003 onwards. Figure 2.11 shows the influence of the slow quarantine speed.

From the simulations above, we consider that the rapid decrease of the SARS patients can be 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 necessary and effective.

Discrete model for SARS in China

Zhou et al. (2004) followed the same idea of modelling the transmission of SARS in China as that presented above, and proposed a discrete model for SARS in China. However, the susceptible compartment, which includes the S-compartment and the H-compartment, was omitted in this case, because

the number of susceptible individuals was extremely large compared with the number of individuals in other compartments, and some SARS patient can not contact all the population.

Zhou et al. (2004) made the following assumptions: the new infected exposed is proportional to the sum $kE(t) + I(t)$; individuals in the E-compartment move to the I-compartment and Q-compartment at the rate constant ϵ and λ , respectively; individuals in the Q-compartment move to the D-compartment at the rate constant σ ; individuals in the I-compartment move to the D-compartment at the rate θ ; individuals in the D-compartment move to the R-compartment at rate constant γ ; d and α are the natural death rate constant and the SARS-induced death rate constant, respectively. Then, the model proposed is

$$\begin{cases} E(t+1) = E(t) + \beta(t)[kE(t) + I(t)] - (d + \epsilon + \lambda)E(t), \\ I(t+1) = I(t) + \epsilon E(t) - (d + \alpha + \theta)I(t), \\ Q(t+1) = Q(t) + \lambda E(t) - (d + \sigma)Q(t), \\ D(t+1) = D(t) + \theta I(t) + \sigma Q(t) - (d + \alpha + \gamma)D(t), \\ R(t+1) = R(t) + \gamma D(t) - dR(t). \end{cases} \quad (33)$$

Similarly to the methods used by Zhang et al. (2004), Zhou et al. (2004) determined the parameters in model (33).

Zhang et al. (2004) and Zhou et al. (2004) varied some parameters to analyze the effectiveness of different control and quarantine measures. These new parameters corresponded to the situation when the quarantine measures in the free block were relaxed or when the quarantine time of SARS patients was postponed. The purpose of the introduction of these new parameters was to demonstrate the second outbreak with a maximum number of daily SARS patients and a delayed peak time. They obtained the basic reproduction number, and their results agree quite well with the developing situation of SARS in China.

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