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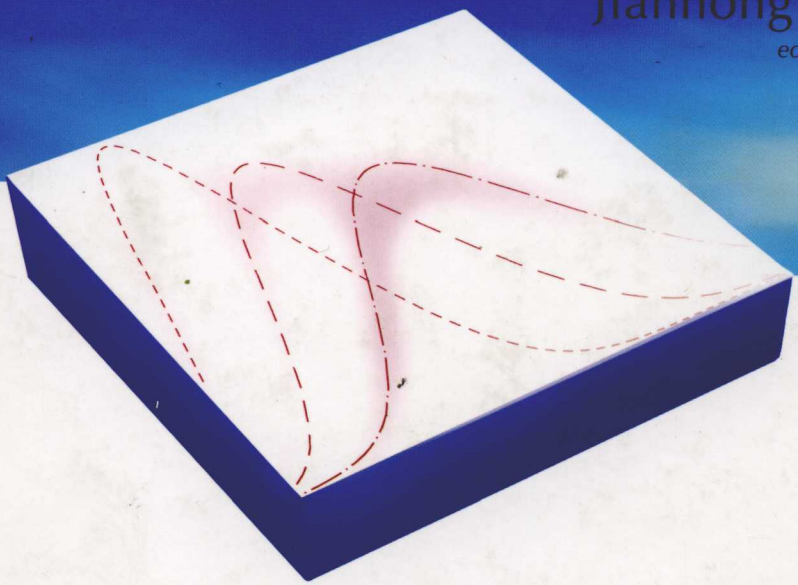
Modeling and Dynamics of Infectious Diseases

传染病的建模与动力学

Zhien Ma
Yicang Zhou
Jianhong Wu
editors



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Preface

This book contains a carefully chosen and coordinated series of lecture notes at the China-Canada Joint Program on Infectious Disease Modeling, held in Xi'an Jiaotong University, May 10-29, 2006. The joint program consists of a summer school attended by over 100 students from a variety of backgrounds, and a workshop participated by invited speakers from both academic institutes and public health agencies such as US Centers for Disease Control and Prevention (CDC) and Public Health Agency of Canada (PHAC).

These contributions are grouped into three categories: lectures notes that briefly introduce the basic concepts and techniques; survey articles that provide reviews on some specific diseases or issues; and research papers dedicating to some important problems of current interest in the epidemiological modeling. There are also two articles describing some recent progresses by a Chinese and a Canadian team.

The aim of this book is to provide fundamental methods and techniques for students who are interested in epidemiological modeling, and to guide junior research scientists to some frontiers in the interface of mathematical modeling and public health. Contributions are provided from different and complementary angles, with the balance between the theory and applications, between mathematical modeling and its applications to public health policy. It is hoped that this book can help in increasing the awareness of the importance of mathematical modeling in the study of infectious disease transmission, and in bridging the gap between mathematical modelers in basic theoretical research and medical scientists and public health policy makers working in health research institutes.

There has been a long history of mathematical epidemiology and there are many successful stories in applying mathematical modeling to optimal design of feasible public health policy for disease prevention, control and management. Some emerging and re-emerging infectious diseases such as HIV, FMD, SARS and pandemic influenza have generated substantial renewed interest, and have been continuing to challenge modelers for effective mathematical and computational models. Covering a comprehensive range of topics, this book hopefully provides an alternative and additional textbook for graduate students in applied mathematics, health informatics, applied statistics and qualitative public health, and a useful resource for researchers in these areas.

The book provides complementary approaches from deterministic, to statistical, to network modeling, and it seeks view points of the same issues from different angles from mathematical modeling, to statistical analysis, to computer simulations, and to concrete applications. For example, we have included a chapter that introduces the network models describing the beginning of a disease outbreak in terms of the degree distribution of a branching process, in comparison with the chapter that introduces the basic deterministic models along with the instructions how to calculate the basic reproduction number and the final size of an epidemic. Other chapters deal with mathematical analysis for disease transmission involving structured population; a chapter develops mathematical approaches for analysis of epidemic models with time delays; a chapter for age structured population models with applications to epidemiology, and age structured epidemic models; and a chapter deals with the uniqueness and global stability of endemic equilibria of multi-group epidemic models of SEIR type.

Disease spread in a heterogeneous environment is an important issue addressed in a chapter which uses metapopulation models consisting of graphs, with systems of differential equations in each vertex, to address the issue of spatial dispersal of diseases. This is further complemented by a chapter that deals with various issues involving stochastic processes for disease spread. A chapter is also included to detail two complimentary mathematical approaches for incorporating evolution into epidemiological models, and a chapter is dedicated to the investigation of the effects of the reservoir on the time course of the disease and on endemic states. The coexistence of a vertically and a horizontally transmitted parasite strain under complete cross protection is addressed as well.

Various chapters deal with the evaluation of different control measures. For instance, there is a chapter that studies the effectiveness of quarantine and isolation as control measures for the spread of infectious diseases, and general integral equation models which assumes an arbitrarily distributed disease stage for both the latent and the infectious stages. Another chapter discusses the pulse vaccination SIR model with periodic infection rate.

Other chapters deal with specific diseases of current interest. One such chapter describes the estimation of congenital rubella syndrome from disease or serological surveillance and demographic, and possible strategies for mitigating the burden of congenital rubella syndrome. Another chapter examines the estimate of turning points and case numbers of the 2003 severe acute respiratory syndrome outbreaks in Taiwan, Beijing, Hong Kong, Toronto, and Singapore. Added to these materials are the chapter that studies HIV transmission and disease progression, and a detailed case study of the West Nile Virus in Southern Ontario Canada. The book also contains a contribution that depicts the man-

ner in which the pandemic develops in a specific community, and the affection of antiviral treatment. This is supplemented by two chapters that briefly summarizes progresses and adventure of the Xi'an Jiatong University group, and a MITACS team for HIV, SARS, West Nile Virus, pandemic influenza and other emerging infectious diseases.

We wish to thank all contributors for their excellent contributions without which this book is impossible, we wish to express our sincere appreciation to the staff members and students of the Xi'an Jiatong University for their hospitality and hard working that made the Canada-China program a successful event and an enjoyable experience. We wish to thank Professor Ta-Tsien Li for encouraging us to include this book in the Series in Contemporary Applied Mathematics by Higher Education Press, and would like to acknowledge the support of Mathematics for Information Technology and Complex Systems (MITACS) for the Canada-China Joint Program.

Zhien Ma and Yicang Zhou, Xi'an Jiaotong University
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Contents

Some Recent Results on Epidemic Dynamics Obtained by Our Group

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Abstract

The goal of this synthetic paper is to introduce a part of research directions on epidemic dynamics investigated by our group and our main results during the past several years. Before this, some basic knowledge on epidemic dynamics will be introduced which may be helpful to those readers who are not familiar with the mathematical modeling on Epidemiology.

1 Basic knowledge on epidemic dynamics

Epidemic dynamics is an important method of studying the spread of infectious disease qualitatively and quantitatively. It is based on the specific property of population growth, the spread rules of infectious diseases, and the related social factors, etc., to construct mathematical models reflecting the dynamic properties of infectious diseases, to analyze the dynamical behavior and to do some simulations. The research results are helpful to predict the developing tendency of the infectious disease, to determine the key factors of the spread of infectious disease and to seek the optimum strategies 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 people may know some global dynamic behavior of the transmission process. Combining statistics methods and computer simulations with dynamic methods could make modeling and the original analysis more realistic and more reliable, make the comprehension for spread rule of infectious diseases more thorough.

Now, the popular epidemic dynamic models are still so called compartmental models which were constructed by Kermack and Mckendrick in 1927[1] and is developed by many other biomathematicians. In the

K-M model, the population is divided into three compartments: susceptible compartment S, in which all individuals are susceptible to the disease; infected compartment I, in which all individuals are infected by the disease and have infectivity; removed compartment R, in which all the individuals recovered from the class I and have permanent immunity. Three assumptions they did as follows:

(1) The disease spread in a closed environment, no emigration and immigration, and is no birth and death in population, so the total population remains a constant k, i.e. $S(t) + I(t) + R(t) \equiv k$.

(2) The infective rate of an infected individual is proportional to the number of susceptible, the coefficient of the proportion is a constant β, so that the total number of new infected at time t is $\beta S(t)I(t)$.

(3) The recovered rate is proportional to the number of infected, and the coefficient of proportion is a constant γ. So that the recovered rate at time t is $\gamma I(t)$.

According to the three assumptions above, it is easy to establish the epidemic model as follows

$$\text{(K-M)} \qquad \begin{cases} \dfrac{dS}{dt} = -\beta SI, \\ \dfrac{dI}{dt} = \beta SI - \gamma I, \qquad S(t) + I(t) + R(t) \equiv k. \\ \dfrac{dR}{dt} = \gamma I, \end{cases}$$

Now, let us explain some basic concepts on epidemilological dynamics.

1.1 Adequate contact rate and incidence

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

rate. Further, the number of new infected individuals yielding in unit time at time t is $\beta_0 U(N)S(t)I(t)/N(t)$, which is called the **incidence of the disease**.

When $U(N) = kN$, that is, the contact rate is proportional to the size of total population, the incidence is $\beta_0 kS(t)I(t) = \beta S(t)I(t)$ (where $\beta = \beta_0 k$ is defined as the transmission coefficient) which is called **bilinear incidence or simple mass-action incidence**. When $U(N) = k'$, that is, the contact rate is a constant, the incidence is $\beta_0 k'S(t)I(t)/N(t) = \beta S(t)I(t)/N(t)$ (where $\beta = \beta_0 k'$) which is called **standard incidence**, for instance, the incidence formulating the sexually transmitted disease is often of standard type. Two types of incidence mentioned above are often used, but they are special for the real cases. In recent years, some contact rates with saturate feature between them are proposed, such as $U(N) = \alpha N/(1+\omega N)$[2], $U(N) = \alpha N/(1+bN+\sqrt{1+2bN})$[3]. In general, the saturate contact rate $U(N)$ satisfies the following conditions:

$$U(0) = 0,\ U'(N) \geqslant 0,\ (U(N)/N)' \leqslant 0,\ \lim_{N\to\infty} U(N) = U_0.$$

Besides, some incidences, which are much more plausible for some special cases, are also introduced, such as $\beta S^p I^q, \beta S^p I^q/N$[4,5].

1.2 Basic reproduction number

Basic reproduction number, denoted by R_0, represents the average number of secondary infectious infected by an individual of infectives during whose whole course of disease in the case that all the members of the population are susceptible. According to this meaning, it is easy to understand that if $R_0 < 1$ then the infectives will decrease so that the disease will go to extinction; if $R_0 > 1$ then the infectives will increase so that the disease can not be eliminated and usually develop into an endemic.

From the mathematical point of view, usually when $R_0 < 1$, the model has only disease free equilibrium $E_0(S_0, 0)$ in the SOI plane, and E_0 is globally asymptotically stable; when $R_0 > 1$, the equilibrium becomes unstable and usually a positive equilibrium $E^*(S^*, I^*)$ appears. E^* is called an endemic equilibrium and in this case it is stable. Hence, if all the members of a population are susceptible in the beginning, then $R_0 = 1$ is usually a threshold whether the disease go to extinction or go to an endemic.

Example Consider the following model:

$$(M_1): \begin{cases} \dfrac{dS}{dt} = \Lambda - \beta SI - bS, \\ \dfrac{dI}{dt} = \beta SI - bI - \gamma I, \\ \dfrac{dR}{dt} = \gamma I - bR, \end{cases}$$

where b is the natural death rate, γ is the recovered rate, Λ is recruitment. Let $\dfrac{\Lambda}{b} = k$, consider the first two equation we have

$$(M_1'): \begin{cases} \dfrac{dS}{dt} = bk - \beta SI - bS, \\ \dfrac{dI}{dt} = \beta SI - (b+\gamma)I. \end{cases}$$

Let $R_0 = \dfrac{\beta k}{b+\gamma}$, it is easy to see that when $R_0 < 1$, the system has only one disease free equilibrium $E_0(k, 0)$ and it is stable; when $R_0 > 1$, besides E_0 there is a positive equilibrium $E^*\left(\dfrac{b+\gamma}{\beta}, \dfrac{b[\beta k - (b+\gamma)]}{\beta(b+\gamma)}\right)$, and, in this case, E_0 is unstable, E^* is stable, the endemic appears. So $R_0 = 1$ is a threshold to distinguish the disease extinction or persistence.

From model (M_1) we can see that

$$\frac{dN}{dt} = b(k - N), \ N(t) = S(t) + I(t) + R(t).$$

Hence, the total number of the population is k, and βk should be the number of secondary infectious infected by an individual of infectives per unit time when the number of susceptible is k. From the second equation of the system M_1' we can see that $1/(b+\gamma)$ is the average course of the disease. Therefore, $R_0 = \beta k/(b+\gamma)$ is the average secondary infectious infected by an individual of the infectives during whose whole course of disease, that is just the reproduction number.

It should be indicated that the reproduction number is not always equivalent to the threshold mentioned above.

2 Epidemic models with vaccination

So far, there are two effective methods to prevent and control the spread of infection, which are vaccination and quarantine. To model the transmission of the infection under vaccination, ordinary differential equations, delay differential equations, and pulse differential equations are often used.

For investigating dynamic behavior of an epidemic model with vaccination, one usually use a SIR compartment model and remove a part of newborns or susceptibles from susceptible class S directly into the removed class R due to vaccination. But if the immunity caused by the vaccination is temporary and the periods of immunity loss from vaccinated and recovered are not the same, then another compartment V should be introduced.

(1) SIS-VS model

The following Figure 2.1 describes an SIS-VS model, where A is newborns per unit time, q is a fraction of vaccinated for the newborns, p is the proportional coefficient of vaccinated for the susceptibles, $Q(t)$ is the probability that an individual remains in the class V at least t time units before returning to the class S, d and α are the natural death rate and death rate due to disease, respectively.

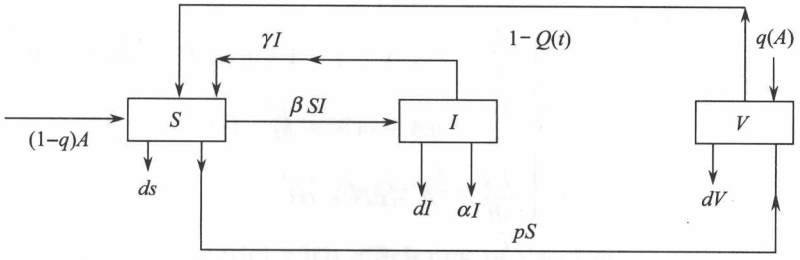

Figure 2.1: The flowchart of an SIS-VS model.

From the flowchart, we may write down the model as follows

$$(M_2): \quad \begin{cases} \dfrac{dI}{dt} = \beta SI - (d+\alpha+\gamma)I, \\ V = V_0(t) + \displaystyle\int_0^t [qA + pS(u)]Q(t-u)e^{-d(t-u)}du, \\ \dfrac{dN}{dt} = A - dN - \alpha I, \end{cases}$$

where $V_0(t)$ is the number of individuals who have already remained in the class V at time $t = 0$.

If the probability Q is exponential distribution, i.e., $Q = e^{-\varepsilon t}$, constant $\varepsilon > 0$ is the immunity loss rate, then the model (M_2) becomes

$$(M_2^1): \quad \begin{cases} \dfrac{dS}{dt} = (1-q)A - \beta SI - (p+d)S + \gamma I + \varepsilon V, \\ \dfrac{dI}{dt} = \beta SI - (d+\alpha+\gamma)I, \\ \dfrac{dV}{dt} = qA + pS - (\varepsilon + d)V. \end{cases}$$

If $Q = \begin{cases} 1, t \in [0, \tau) \\ 0, t \geqslant \tau \end{cases}$, then model (M_2) becomes

$$(M_2^2): \begin{cases} \dfrac{dS}{dt} = (1-q)A - (p+d)S - \beta SI + \gamma I \\ \qquad\qquad +[qA + pS(t-\tau)]e^{-d\tau}, \\ \dfrac{dI}{dt} = \beta SI - (d+\alpha+\gamma)I, \\ \dfrac{dV}{dt} = qA + pS - [qA + pS(t-\tau)]e^{-d\tau} - dV, \end{cases}$$

where τ is the period of immunity.

For model (M_2^1), let $N = S + I + V$, we consider its replacement:

$$(\bar{M}_2^1): \begin{cases} \dfrac{dI}{dt} = I[\beta(N - I - V) - (d + \gamma + \alpha)], \\ \dfrac{dV}{dt} = qA + p(N - I) - (p + d + \varepsilon)V, \\ \dfrac{dN}{dt} = A - dN - \alpha I. \end{cases}$$

The following are the main results of the system (M_2^1).

Theorem 1[6] Let $R_{01} = \dfrac{A\beta[\varepsilon + d(1-q)]}{d(d+\gamma+\alpha)(d+\varepsilon+p)}$.

If $R_{01} \leqslant 1$ then the system $(\bar{M}_2^1)$ has only a disease free equilibrium $E_0\left(0, \dfrac{A(dq+p)}{d(d+\varepsilon+p)}, \dfrac{A}{d}\right)$, and it is globally asymptotically stable; if $R_{01} > 1$, E_0 is unstable, and there is an endemic equilibrium $E^*(I^*, V^*, N^*)$ which is locally stable. Moreover, E^* is globally asymptotically stable if $R_{01} > 1$ and there exist two positive constants m and n such that the matrix M is positive definite, where

$$M = \begin{pmatrix} \beta m & \dfrac{\beta m + n\beta}{2} & \dfrac{\alpha - \beta m}{2} \\ \dfrac{\beta m + n\beta}{2} & n(p+d+\varepsilon) & \dfrac{np}{2} \\ \dfrac{\alpha - \beta m}{2} & -\dfrac{np}{2} & d \end{pmatrix}.$$

For the model (M_2^2), since V does not appear explicitly in the first two equations, we need only to discuss the system consisted of the first two

equations.

$$(\bar{M}_2^2): \begin{cases} \dfrac{dS}{dt} = A(1-q) - \beta SI - (d+p)S + \gamma I \\ \qquad\qquad +[qA + pS(t-\tau)]e^{-d\tau}, \\ \dfrac{dI}{dt} = \beta SI - (d+\gamma+\alpha)I. \end{cases}$$

Theorem 2[7] Let

$$R_{02} = \frac{\beta A[1-q(1-e^{-d\tau})]}{(d+\alpha+\gamma)[d+p(1-e^{-d\tau})]} = \frac{\beta S_{02}}{d+\alpha+\gamma}.$$

If $R_{01} \leqslant 1$, the system $(\bar{M}_2^2)$ has only a disease free equilibrium $E_0(S_{02}, 0)$, it is globally asymptotically stable; if $R_{02} > 1$, E_0 is unstable, and the endemic equilibrium $E^*(S^*, I^*)$ appears, which is globally asymptotically stable, where

$$S_{02} = \frac{A[1-q(1-e^{-d\tau})]}{d+p(1-e^{d\tau})}, \quad S^* = \frac{d+\alpha+\gamma}{\beta},$$

$$I^* = \frac{(d+\alpha+\gamma)[d+p(1-e^{d\tau})]}{\beta(d+\alpha)}(R_{02}-1).$$

(2) SIS-VS model with efficiency of vaccine

In the reality, the efficiency of every type of vaccines may not be 100%, which means that even some of susceptibles have been vaccinated, they still have a certain probability to be infected by the disease. In this case the flowchart of the epidemic may be described by Figure 2.2.

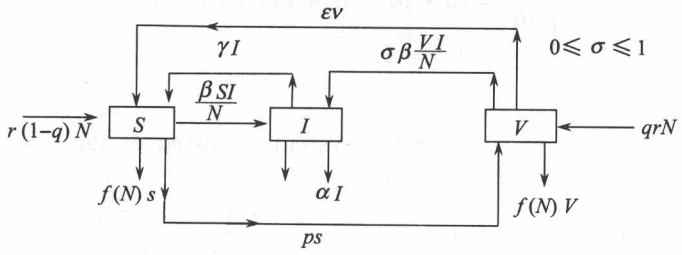

Figure 2.2: The flowchart of an SIS-VS model.

In this model, we assume that the natural death rate is density dependent to the population, i.e., it is a function of N; the disease spreads in the form of standard incidence; the average number of adequate contact of an infective and a vaccinated individual per unit time are β and $\sigma\beta$ respectively, $0 \leqslant \sigma \leqslant 1$, the fraction σ reflects the effect of reducing