

Chapter 2

Simple Compartmental Models for Disease Transmission



Communicable diseases that are endemic (always present in a population) cause many deaths. For example, in 2011 tuberculosis caused an estimated 1,400,000 deaths and HIV/AIDS caused an estimated 1,200,000 deaths worldwide. According to the World Health Organization there were 627,000 deaths caused by malaria, but other estimates put the number of malaria deaths at 1,200,000. Measles, which is easily treated in the developed world, caused 160,000 deaths in 2011, but in 1980 there were 2,600,000 measles deaths. The striking reduction in measles deaths is due to the availability of a measles vaccine. Other diseases such as typhus, cholera, schistosomiasis, and sleeping sickness are endemic in many parts of the world. The effects of high disease mortality on mean life span and of disease debilitation and mortality on the economy in afflicted countries are considerable. Most of these disease deaths are in less developed countries, especially in Africa, where endemic diseases are a huge barrier to development. A reference describing the properties of many endemic diseases is [2].

For diseases that are endemic in some region, public health physicians would like to be able to estimate the number of infectives at a given time as well as the rate at which new infections arise. The effects of quarantine or vaccine in reducing the number of victims are of importance. In addition, the possibility of defeating the endemic nature of the disease and thus controlling or even eradicating the disease in a population is worthy of study.

An epidemic, which acts on a short temporal scale, may be described as a sudden outbreak of a disease that infects a substantial portion of the population in a region before disappearing. Epidemics invariably leave part of the population untouched. Often, epidemic outbreaks recur with intervals of several years between outbreaks, possibly decreasing in severity as populations develop some immunity.

The “Spanish” flu epidemic of 1919–1920 caused an estimated 50,000,000 or more deaths worldwide. The AIDS epidemic, the SARS epidemic of 2002–2003, recurring influenza pandemics such as the H1N1 influenza pandemic of 2009–2010,

and outbreaks of diseases such as the Ebola virus are events of concern and interest to many people.

The essential difference between an endemic disease and an epidemic is that in an endemic disease there is some mechanism for a flow of susceptibles into the population being studied through births of new susceptibles, immigration of susceptibles, recovery from infection without immunity against reinfection, or loss of immunity of recovered individuals. This may result in a level of infection that remains in the population. In an epidemic, there is no flow of new susceptibles into the population and the number of infectives decreases to zero because of the resulting scarcity of susceptibles.

There are many questions of interest to public health physicians confronted with a possible epidemic. For example, how severe will an epidemic be? This question may be interpreted in a variety of ways. For example, how many individuals will be affected and require treatment? What is the maximum number of people needing care at any particular time? How long will the epidemic last? Can an epidemic be averted by vaccination of enough members of the population in advance of the epidemic? How much good would quarantine of victims do in reducing the severity of the epidemic?

The idea of invisible living creatures as agents of disease goes back at least to the writings of Aristotle (384–322 BC) and was developed as a theory in the sixteenth century. The existence of microorganisms was demonstrated by Leeuwenhoek (1632–1723) with the aid of the first microscopes. The first expression of the germ theory of disease by Jacob Henle (1809–1885) came in 1840 and was developed by Robert Koch (1843–1910), Joseph Lister (1827–1912), and Louis Pasteur (1827–1875) in the latter part of the nineteenth century and the early part of the twentieth century.

The mechanism of transmission of infections is now known for most diseases. Generally, diseases transmitted by viral agents, such as influenza, measles, rubella (German measles), and chicken pox, confer immunity against reinfection, while diseases transmitted by bacteria, such as tuberculosis, meningitis, and gonorrhea, confer no immunity against reinfection. Other diseases, such as malaria, are transmitted not directly from human to human but by vectors, agents (usually insects) who are infected by humans and who then transmit the disease to humans. Heterosexual transmission of HIV/AIDS is also a vector process in which transmission goes back and forth between males and females.

In this chapter, our goal is to present and analyze simple compartmental models for disease transmission, both for endemic situations and for epidemics. Here we seek only to introduce the idea of the *basic reproduction number* and how it determines a threshold between two different outcomes. In later chapters we will study models with more detailed structure and will include the effects of different methods to try to control a disease.

2.1 Introduction to Compartmental Models

We formulate our descriptions of disease transmission as *compartmental models*, with the population under study being divided into compartments and with assumptions about the nature and time rate of transfer from one compartment to another. We divide the population being studied into three classes labeled S , I , and R . Let $S(t)$ denote the number of individuals who are susceptible to the disease, that is, who are not (yet) infected at time t . $I(t)$ denotes the number of infected individuals, assumed infective and able to spread the disease by contact with susceptibles. $R(t)$ denotes the number of individuals who have been infected and then removed from the possibility of being infected again or of spreading infection. Removal is carried out either through isolation from the rest of the population, or through immunization against infection, or through recovery from the disease with full immunity against reinfection, or through death caused by the disease. These characterizations of removed members are different from an epidemiological perspective but are often equivalent from a modeling point of view which takes into account only the state of an individual with respect to the disease.

In many diseases, infectives return to the susceptible class on recovery because the disease confers no immunity against reinfection. Such models are appropriate for most diseases transmitted by bacterial agents or helminth agents, and most sexually transmitted diseases (including gonorrhea, but not such diseases as AIDS from which there is no recovery). We use the terminology SIS to describe a disease with no immunity against reinfection, to indicate that the passage of individuals is from the susceptible class to the infective class and then back to the susceptible class.

We will use the terminology SIR to describe a disease which confers immunity against reinfection, to indicate that the passage of individuals is from the susceptible class S to the infective class I to the removed class R . Usually, diseases caused by a virus are of SIR type.

In addition to the basic distinction between diseases for which recovery confers immunity against reinfection and diseases for which recovered members are susceptible to reinfection, and the intermediate possibility of temporary immunity signified by a model of $SIRS$ type, more complicated compartmental structure is possible. For example, there are $SEIR$ and $SEIS$ models, with an exposed period between being infected and becoming infective.

We are assuming that the disease transmission process is *deterministic*, that is, that the behavior of a population is determined completely by its history and by the rules which describe the model. In formulating models in terms of the derivatives of the sizes of each compartment, we are also assuming that the number of members in a compartment is a differentiable function of time. This assumption is plausible in describing an endemic state. However, in Chap. 4 we will describe the modeling of disease outbreaks and epidemics. At the beginning of a disease outbreak, there are only a few infectives and the start of a disease outbreak depends on random contacts with a small number of infectives. This will require a different approach

that we shall study in Sect. 4.1, but for the present we begin with a description of deterministic compartmental models.

The independent variable in our compartmental models is the time t , and the rates of transfer between compartments are expressed mathematically as derivatives with respect to time of the sizes of the compartments, and as a result our models are formulated initially as differential equations. Models in which the rates of transfer depend on the sizes of compartments over the past as well as at the instant of transfer lead to more general types of functional equations, such as differential–difference equations or integral equations. In this chapter, we will always assume that the duration of stay in each compartment is exponentially distributed so that our models will be systems of ordinary differential equations. In Chaps. 3 and 4 we will begin the study of more general classes of models.

In order to formulate a compartmental disease transmission model, we will need to make assumptions on the rates of flow between compartments. In the simplest models we require expressions for the rate of being infected and the rate of recovery from infection. The most common assumption about transmission of infection is *mass action incidence*. It is assumed that in a population of size N on average an individual makes βN contacts sufficient to transmit infection in unit time. Another possible assumption is *standard incidence*, in which it is assumed that on average an individual makes a constant number a of contacts sufficient to transmit infection in unit time. Standard incidence is a common assumption for sexually transmitted diseases. More realistically, one might assume that the parameters β or a are not constants, but are functions of total population size. We will always assume that contacts are *effective*. By this we mean that if there is a contact between an infective individual and a susceptible individual, infection is always passed to the susceptibles. However, it is possible that infectives in one compartment are less infectious than individuals in another compartment. In such situations, we may include a reduction factor in some contacts to model this.

With mass action incidence, (contact rate βN) since the probability that a random contact by an infective is with a susceptible is S/N , the number of new infections in unit time per infective is $(\beta N)(S/N)$, giving a rate of new infections $(\beta N)(S/N)I = \beta SI$. Alternately, we may argue that for a contact by a susceptible the probability that this contact is with an infective is I/N and thus the rate of new infections per susceptible is $(\beta N)(I/N)$, giving a rate of new infections $(\beta N)(I/N)S = \beta SI$. Note that both approaches give the same rate of new infections; in models with more complicated compartmental structure one approach may be more appropriate than the other.

With standard incidence, (contact rate a) similar reasoning leads to the result that the rate of new infections is

$$aS\frac{I}{N}.$$

If the total population size N is constant, we may use a and βN interchangeably. We will most commonly use βN , partly for historical reasons. However, for sexually

transmitted diseases the standard incidence form for contacts is more common. When we study heterogeneous mixing in Chap. 5 it will be more convenient to use the standard incidence form but it would be possible to use the mass action form instead.

A common assumption is that infectives leave the infective class at a constant rate αI per unit time. This assumption requires a fuller mathematical explanation, since the assumption of a recovery rate proportional to the number of infectives has no clear epidemiological meaning. We consider the “cohort” of members who were all infected at one time and let $u(s)$ denote the number of these who are still infective s time units after having been infected. If a fraction α of these leave the infective class in unit time then

$$u' = -\alpha u,$$

and the solution of this elementary differential equation is

$$u(s) = u(0) e^{-\alpha s}.$$

Thus, the fraction of infectives remaining infective s time units after having become infective is $e^{-\alpha s}$, so that the length of the infective period is distributed exponentially with mean $\int_0^\infty e^{-\alpha s} ds = 1/\alpha$, and this is what is really assumed. This assumption is made for simplicity as it leads to ordinary differential equation models, but in a later chapter we will study models with other distributions of the infective period.

To see that the mean infective period is $1/\alpha$, we point out since the fraction of infectives remaining infective s time units after being infected is $e^{-\alpha s}$, the fraction with infective period exactly s is

$$-\frac{d}{ds} e^{-\alpha s}$$

and the mean infective period is

$$\int_0^\infty s \frac{d}{ds} e^{-\alpha s} ds.$$

Integration by parts shows that this is

$$-\int_0^\infty e^{-\alpha s} ds = \frac{1}{\alpha}.$$

In this chapter, we will analyze *SIS* and *SIR* models for disease transmission, both with and without demographics (births and natural deaths). Our goal is to describe both endemic and epidemic situations in the simplest possible contexts. In later chapters, we will analyze more complicated models, including more

compartmental structure, more general distributions of stay in compartments, and heterogeneity of mixing. In this chapter we focus on equilibrium analysis and asymptotic behavior of models for endemic diseases and on final size relations for epidemic models.

A constant solution y_0 of a differential equation

$$y' = f(y), \quad (2.1)$$

meaning a solution of the equation $f(y) = 0$, is called an equilibrium of the differential equation. An equilibrium y_0 is said to be *stable* if every solution $y(t)$ of the differential equation (2.1) with initial value $y(0)$ sufficiently close to y_0 remains close to the equilibrium y_0 for all $t \geq 0$. An equilibrium is said to be *asymptotically stable* if it is stable and if in addition every solution with initial value sufficiently close to y_0 approaches the equilibrium as $t \rightarrow \infty$. We note that in this definition, there is no specification of the meaning of “sufficiently close.” Asymptotic stability is a local concept. An equilibrium y_0 is said to be *globally asymptotically stable* if it is stable and if solutions of (2.1) for all initial values $y(0)$ approach y_0 as $t \rightarrow \infty$. An equilibrium that is not stable is said to be *unstable*. The concepts of asymptotic stability and instability are essential for the qualitative analysis of differential equations. An important basic result is that an equilibrium y_0 of a differential equation (2.1) is asymptotically stable if $f'(y_0) < 0$ and unstable if $f'(y_0) > 0$. The case $f'(y_0) = 0$ is more difficult to analyze.

A central concept in both endemic and epidemic models is the *basic reproduction number*, to be defined in Sect. 2.2.

In the next two sections, we will discuss models for endemic situations, and in the following two sections we will discuss epidemic models.

2.2 The SIS Model

The basic compartmental models to describe the transmission of communicable diseases are contained in a sequence of three papers by W.O. Kermack and A.G. McKendrick in 1927, 1932, and 1933 [17–19].

The simplest SIS model, due to Kermack and McKendrick [18], is

$$\begin{aligned} S' &= -\beta SI + \alpha I \\ I' &= \beta SI - \alpha I. \end{aligned} \quad (2.2)$$

It is based on the following assumptions:

- (i) The rate of new infections is given by mass action incidence.
- (ii) Infectives leave the infective class at rate αI per unit time and return to the susceptible class.

- (iii) There is no entry into or departure from the population.
- (iv) There are no disease deaths, and the total population size is a constant N .

In an SIS model, the total population size N is equal to $S + I$. Later, we will allow the possibility that some infectives recover while others die of the disease to give a more general model. The hypothesis (iii) really says that the time scale of the disease is much faster than the time scale of births and deaths so that demographic effects on the population may be ignored.

Because (2.2) implies $(S + I)' = 0$, the total population $N = S + I$ is a constant. We may reduce the model (2.2) to a single differential equation by replacing S by $N - I$

$$\begin{aligned} I' &= \beta I(N - I) - \alpha I = (\beta N - \alpha)I - \beta I^2 \\ &= (\beta N - \alpha)I \left(1 - \frac{I}{N - \frac{\alpha}{\beta}}\right). \end{aligned} \quad (2.3)$$

Now (2.3) is a logistic differential equation of the form

$$I' = rI \left(1 - \frac{I}{K}\right),$$

with $r = \beta N - \alpha$ and with $K = N - \alpha/\beta$. Let us recall the analysis of the logistic equation.

The logistic equation may be solved explicitly using separation of variables; the solution satisfying the initial condition $x(0) = x_0$ is

$$x(t) = \frac{K x_0 e^{rt}}{K - x_0 + x_0 e^{rt}} = \frac{K x_0}{x_0 + (K - x_0)e^{-rt}}. \quad (2.4)$$

The expression (2.4) for the solution of the logistic initial value problem shows that $x(t)$ approaches the limit K as $t \rightarrow \infty$ if $x_0 > 0$ provided $r > 0$, $K > 0$. If $r < 0$, $K < 0$, $x(t)$ approaches the limit 0 as $t \rightarrow \infty$. This case, $K < 0$ arises in the analysis of the differential equation (2.3), but does not have any biological meaning in itself.

This qualitative result tells us that for the model (2.3), if $\beta N - \alpha < 0$ or $\beta N/\alpha < 1$, then all solutions with non-negative initial values approach the limit zero as $t \rightarrow \infty$, (the constant solution $I = N - \beta/\alpha$ is negative), while if $\beta N/\alpha > 1$, then all solutions with non-negative initial values except the constant solution $I = 0$ approach the limit $N - \alpha/\beta > 0$ as $t \rightarrow \infty$. Thus there is always a single limiting value for I but the value of the quantity $\beta N/\alpha$ determines which limiting value is approached, regardless of the initial state of the disease. In epidemiological terms this says that if the quantity $\beta N/\alpha$ is less than one the infection dies out in the sense that the number of infectives approaches zero. For this reason the constant solution $I = 0$, which corresponds to $S = N$, is called the *disease-free equilibrium*. On the other hand, if the quantity $\beta N/\alpha$ exceeds one,

the infection persists. The constant solution $I = N - \alpha/\beta$, which corresponds to $S = \alpha/\beta$, is called an *endemic equilibrium*.

The value of 1 for the quantity $\beta N/\alpha$ is a tipping point in the sense that the behavior of the solution changes if this quantity passes through 1 because of some change in the parameters of the model.

The quantity $\beta N/\alpha$ also has an epidemiological interpretation. Since βN is the number of contacts made by an average infective per unit time and $1/\alpha$ is the mean infective period, the quantity $\beta N/\alpha$ is the number of secondary infections caused by introducing a single infective into a wholly susceptible population. The basic reproduction number is defined as the number of secondary infections caused by an average infective introduced into a wholly susceptible population over the course of the disease. The basic reproduction number is usually denoted by \mathcal{R}_0 . Here, the basic reproduction number or contact number for the disease is

$$\mathcal{R}_0 = \frac{\beta N}{\alpha}. \quad (2.5)$$

In studying an infectious disease model, the basic reproduction number is a central concept and its determination is invariably an essential first step. The value one for the basic reproduction number defines a threshold at which the course of the infection changes between disappearance and persistence. It is intuitively clear that if $\mathcal{R}_0 < 1$ the infection should die out, while if $\mathcal{R}_0 > 1$ the infection should establish itself. In more highly structured models than the simple one we have developed here, the calculation of the basic reproduction number may be much more complicated, but the essential concept obtains—that of the basic reproduction number as the number of secondary infections caused by an average infective over the course of the disease.

Since an endemic equilibrium corresponds to a long-term situation, it would be more realistic to include demographic processes, that is, births and natural deaths, in our model.

A simple assumption is that there is a birth rate $\Lambda(N)$ depending on total population size, and a proportional death rate μ . Just as for disease recovery rates the assumption of a proportional death rate is equivalent to an assumption of an exponentially distributed life span with mean $1/\mu$. In the absence of disease the total population size N satisfies the differential equation

$$N' = \Lambda(N) - \mu N.$$

At this point, it is necessary to introduce some basic definitions and results to describe the qualitative behavior of solutions of this differential equation, since it is not possible to solve the differential equation analytically.

The *carrying capacity* of the population is the limiting population size K , satisfying

$$\Lambda(K) = \mu K, \quad \Lambda'(K) < \mu.$$

The condition $\Lambda'(K) < \mu$ assures the asymptotic stability of the equilibrium population size K . It is reasonable to assume that K is the only positive equilibrium, so that

$$\Lambda(N) > \mu N$$

for $0 \leq N \leq K$. For most population models,

$$\Lambda(0) = 0, \quad \Lambda''(N) \leq 0.$$

However, if $\Lambda(N)$ represents recruitment into a behavioral class, as would be natural for models of sexually transmitted diseases, it would be plausible to have $\Lambda(0) > 0$, or even to consider $\Lambda(N)$ to be a constant function. If $\Lambda(0) = 0$, we require $\Lambda'(0) > \mu$ because if this requirement is not satisfied there is no positive equilibrium and the population would die out even in the absence of disease.

A model for a disease from which infectives recover with no immunity against reinfection and that includes births and deaths is

$$\begin{aligned} S' &= \Lambda(N) - \beta SI - \mu S + \alpha I \\ I' &= \beta SI - \alpha I - \mu I, \end{aligned} \tag{2.6}$$

describing a population with a density-dependent birth rate $\Lambda(N)$ per unit time, a mass action contact rate, a proportional death rate μ in each class, and a recovery rate α .

If we add the two equations of (2.6) and use $N = S + I$, we obtain

$$N' = \Lambda(N) - \mu N.$$

Thus N approaches K as $t \rightarrow \infty$.

It is easy to verify that

$$\mathcal{R}_0 = \frac{\beta K}{\mu + \alpha}$$

because a single infective introduced into a wholly susceptible population of size K causes βK new infections in unit time and the mean infective period corrected for natural mortality is $1/(\mu + \alpha)$.

It can be shown that the endemic equilibrium of (2.6), which exists if $\mathcal{R}_0 > 1$, is always asymptotically stable. If $\mathcal{R}_0 < 1$, the system has only the disease-free equilibrium and this equilibrium is asymptotically stable. The qualitative behavior of the model (2.6) is the same as the behavior of the model (2.2) without demographics.

We were able to reduce the systems of two differential equations (2.2) to a single equation because of the assumption that the total population $S + I$ is constant or has a constant limit as $t \rightarrow \infty$. If there are deaths due to the disease this assumption is violated, and it would be necessary to use a two-dimensional system as a model.

Let us assume that infectives recover from infection at a rate αI , while infectives die of disease at a rate dI . Then the model (2.6) is replaced by the model

$$\begin{aligned} S' &= \Lambda(N) - \beta SI - \mu S + \alpha I \\ I' &= \beta SI - (\alpha + d)I - \mu I. \end{aligned} \quad (2.7)$$

Now the equation for total population size is

$$N' = \Lambda(N) - \mu N - dI.$$

The model (2.7) involves the three variables S , I , N , and we may reduce it to a two-dimensional system with variables I and N by replacing S by $(N - I)$ to give the model

$$\begin{aligned} I' &= \beta I(N - I) - (\alpha + d + \mu)I \\ N' &= \Lambda(N) - \mu N - dI. \end{aligned}$$

The analysis of this model is more difficult, and rather than going through this analysis now we will shift our attention to SIR models for which the general approach to models involving systems of ordinary differential equations is more readily illustrated.

2.3 The SIR Model with Births and Deaths

The SIR model of Kermack and McKendrick [18] includes births in the susceptible class proportional to total population size and a death rate in each class proportional to the number of members in the class. This model allows the total population size to grow exponentially or die out exponentially if the birth and death rates are unequal. It is applicable to such questions as whether a disease will control the size of a population that would otherwise grow exponentially. We shall return to this topic, which is important in the study of many diseases in less developed countries with high birth rates. To formulate a model in which total population size remains bounded we could follow the approach suggested by Hethcote [12] in which the total population size N is held constant by making birth and death rates equal. Such a model is

$$\begin{aligned} S' &= -\beta SI + \mu(N - S) \\ I' &= \beta SI - \alpha I - \mu I \\ R' &= \alpha I - \mu R. \end{aligned}$$

Because $S+I+R = N$ and $N' = 0$, N is constant and we can view R as determined when S and I are known. Thus we may consider the two-dimensional system

$$\begin{aligned} S' &= -\beta SI + \mu(N - S) \\ I' &= \beta SI - \alpha I - \mu I. \end{aligned} \tag{2.8}$$

We shall examine a more general *SIR* model with births and deaths for a disease that may be fatal to some infectives. For such a disease, the class R of removed members should contain only recovered members, not members removed by death from the disease. It is not possible to assume that the total population size remains constant if there are deaths due to disease; a plausible model for a disease that may be fatal to some infectives must allow the total population to vary in time.

With a mass action contact rate and a density-dependent birth rate we would have a model

$$\begin{aligned} S' &= \Lambda(N) - \beta SI - \mu S \\ I' &= \beta SI - \mu I - dI - \alpha I \\ N' &= \Lambda(N) - dI - \mu N. \end{aligned} \tag{2.9}$$

If $d = 0$, so that there are no disease deaths, the equation for N is

$$N' = \Lambda(N) - \mu N,$$

so that $N(t)$ approaches a limiting population size K provided $\Lambda'(K) < \mu$ so that the equilibrium K of the equation for N is asymptotically stable.

We shall analyze the model (2.9) with $d = 0$ qualitatively. This qualitative analysis depends on the ideas of equilibria and linearization of a system about an equilibrium, a general approach dating back to the early part of the twentieth century. In view of the remark above, our analysis will also apply to the more general model (2.9) if there are no disease deaths. Analysis of the system (2.9) with $d > 0$ is much more difficult. We will confine our study of (2.9) to a description without details.

The first stage of the analysis is to note that the model (2.9) is a properly posed problem. A properly posed problem is a problem that has a unique solution (so that solving the mathematical problem yields an expression that can have epidemiological meaning), and that the solution remains non-negative (so that it has epidemiological meaning). That is, since $S' \geq 0$ if $S = 0$ and $I' \geq 0$ if $I = 0$, we have $S \geq 0$, $I \geq 0$ for $t \geq 0$ and since $N' \leq 0$ if $N = K$ we have $N \leq K$ for $t \geq 0$. Thus the solution always remains in the biologically realistic region $S \geq 0$, $I \geq 0$, $0 \leq N \leq K$ if it starts in this region. By rights, we should verify such conditions whenever we analyze a mathematical model, but in practice this step is frequently overlooked.

Our approach will be to identify equilibria (constant solutions) and then to determine the asymptotic stability of each equilibrium. As we have defined at the

end of Sect. 2.1, asymptotic stability of an equilibrium means that a solution starting sufficiently close to the equilibrium remains close to the equilibrium and approaches the equilibrium as $t \rightarrow \infty$, while instability of the equilibrium means that there are solutions starting arbitrarily close to the equilibrium that do not approach it. Equilibrium analysis of a system of two differential equations requires the idea of linearization of a system of differential equations and some matrix algebra. To find equilibria (S_∞, I_∞) we set the right side of each of the two equations equal to zero. The second of the resulting algebraic equations factors gives two alternatives. The first alternative is $I_\infty = 0$, which will give a disease-free equilibrium, and the second alternative is $\beta S_\infty = \mu + \alpha$, which will give an endemic equilibrium, provided $\beta S_\infty = \mu + \alpha < \beta K$. If $I_\infty = 0$ the other equation gives $S_\infty = K = \Lambda/\mu$. For the endemic equilibrium the first equation gives

$$I_\infty = \frac{\Lambda}{\mu + \alpha} - \frac{\mu}{\beta}.$$

We linearize about an equilibrium (S_∞, I_∞) by letting $y = S - S_\infty$, $z = I - I_\infty$, writing the system in terms of the new variables y and z and retaining only the linear terms in a Taylor expansion. We obtain a system of two linear differential equations,

$$\begin{aligned} y' &= -(\beta I_\infty + \mu)y - \beta S_\infty z \\ z' &= \beta I_\infty y + (\beta S_\infty - \mu - \alpha)z. \end{aligned}$$

The coefficient matrix of this linear system is

$$\begin{bmatrix} -\beta I_\infty - \mu & -\beta S_\infty \\ \beta I_\infty & \beta S_\infty - \mu - \alpha \end{bmatrix}.$$

This matrix is also known as the *Jacobian* matrix. We then look for solutions whose components are constant multiples of $e^{\lambda t}$; this means that λ must be an eigenvalue of the coefficient matrix. The condition that all solutions of the linearization at an equilibrium tend to zero as $t \rightarrow \infty$ is that the real part of every eigenvalue of this coefficient matrix is negative. At the disease-free equilibrium the matrix is

$$\begin{bmatrix} -\mu & -\beta K \\ 0 & \beta K - \mu - \alpha \end{bmatrix},$$

which has eigenvalues $-\mu$ and $\beta K - \mu - \alpha$. Thus, the disease-free equilibrium is asymptotically stable if $\beta K < \mu + \alpha$ and unstable if $\beta K > \mu + \alpha$. Note that this condition for instability of the disease-free equilibrium is the same as the condition for the existence of an endemic equilibrium.

In general, the condition that the eigenvalues of a 2×2 matrix have negative real part is that the determinant be positive and the trace (the sum of the diagonal

elements) be negative. Since $\beta S_\infty = \mu + \alpha$ at an endemic equilibrium, the Jacobian matrix, or matrix of the linearization at an endemic equilibrium is

$$\begin{bmatrix} -\beta I_\infty - \mu & -\beta S_\infty \\ \beta I_\infty & 0 \end{bmatrix}$$

and this matrix has positive determinant and negative trace. Thus, the endemic equilibrium, if there is one, is always asymptotically stable. If the quantity

$$\mathcal{R}_0 = \frac{\beta K}{\mu + \alpha} = \frac{K}{S_\infty}$$

is less than one, then the system has only the disease-free equilibrium and this equilibrium is asymptotically stable. In fact, it is not difficult to prove that this asymptotic stability is *global*, that is, that every solution approaches the disease-free equilibrium. If the quantity \mathcal{R}_0 is greater than one, then the disease-free equilibrium is unstable, but there is an endemic equilibrium that is asymptotically stable. Again, the quantity \mathcal{R}_0 is the basic reproduction number. It depends on the particular disease (determining the parameter α) and on the rate of contacts, which may depend on the population density in the community being studied. The disease model exhibits a *threshold* behavior: If the basic reproduction number is less than one, then the disease will die out, but if the basic reproduction number is greater than one, then the disease will be endemic. Just as for the *SIS* model of the preceding section, the basic reproduction number is the number of secondary infections caused by a single infective introduced into a wholly susceptible population because the number of contacts per infective in unit time is βK , and the mean infective period (corrected for natural mortality) is $1/(\mu + \alpha)$.

There are two aspects of the analysis of the model (2.9) that are more complicated than the analysis of (2.8). The first is in the study of equilibria. Because of the dependence of $\Lambda(N)$ on N , it is necessary to use two of the equilibrium conditions to solve for S and I in terms of N and then substitute this into the third condition to obtain an equation for N . Then by comparing the two sides of this equation for $N = 0$ and $N = K$ it is possible to show that there must be an endemic equilibrium value of N between 0 and K if $\mathcal{R}_0 > 1$.

The second complication is in the stability analysis. Since (2.9) is a three-dimensional system that cannot be reduced to a two-dimensional system, the coefficient matrix of its linearization at an equilibrium is a 3×3 matrix and the resulting characteristic equation is a cubic polynomial equation of the form

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 .$$

The *Routh–Hurwitz* conditions [16, 22]

$$a_1 > 0, \quad a_1 a_2 > a_3 > 0$$

are necessary and sufficient conditions for all roots of the characteristic equation to have negative real part. A technically complicated calculation is needed to verify that these conditions are satisfied at an endemic equilibrium for the model (2.9).

The asymptotic stability of the endemic equilibrium means that the compartment sizes approach a steady state. If the equilibrium had been unstable, there would have been a possibility of sustained oscillations. Oscillations in a disease model mean fluctuations in the number of cases to be expected. If the oscillations have a long period, then this could mean that experimental data for a short period would be quite unreliable as a predictor of the future. Epidemiological models that incorporate additional factors may exhibit oscillations. A variety of such situations is described in [14, 15].

From the third equation of (2.9) we obtain

$$N' = \Lambda - \mu N - \alpha I,$$

where $N = S + I + R$. From this, we see that at the endemic equilibrium $N = \Lambda/\mu - \alpha I/\mu$, and the reduction in the population size from the carrying capacity K is

$$\frac{d}{d\mu} I_{\infty} = \left[\frac{\alpha K}{\mu + \alpha} - \frac{\alpha}{\beta} \right].$$

The parameter α in the *SIR* model may be considered as describing the pathogenicity of the disease. If α is large, it is less likely that $\mathcal{R}_0 > 1$. If α is small, then the total population size at the endemic equilibrium is close to the carrying capacity K of the population. Thus, the maximum population decrease caused by disease will be for diseases of intermediate pathogenicity with α not close to either 0 or 1.

Numerical simulations indicate that the approach to endemic equilibrium for an *SIR* model is like a rapid and severe epidemic if the epidemiological and demographic time scales are very different. The same happens in the *SIS* model. If there are few disease deaths, the number of infectives at endemic equilibrium may be substantial, and there may be damped oscillations of large amplitude about the endemic equilibrium. For both the *SIR* and *SIS* models we may write the differential equation for I as

$$I' = I[\beta(N)S - (\mu + \alpha)] = \beta(N)I[S - S_{\infty}],$$

which implies that whenever S exceeds its endemic equilibrium value S_{∞} , I is increasing and epidemic-like behavior is possible. If $\mathcal{R}_0 < 1$ and $S < K$, it follows that $I' < 0$, and thus I is decreasing. Thus, if $\mathcal{R}_0 < 1$, I cannot increase and no epidemic can occur.

2.4 The Simple Kermack–McKendrick Epidemic Model

One of the early triumphs of mathematical epidemiology was the formulation of a simple model by Kermack and McKendrick in 1927 [17] whose predictions are very similar to the behavior, observed in countless epidemics, of disease that invade a population suddenly, grow in intensity, and then disappear leaving part of the population untouched. The Kermack–McKendrick model is a compartmental model based on relatively simple assumptions on the rates of flow between different classes of members of the population. The SARS epidemic of 2002–2003 revived interest in epidemic models, which had been largely ignored since the time of Kermack and McKendrick, in favor of models for endemic diseases.

The special case of the model proposed by Kermack and McKendrick in 1927 which is the starting point for our study of epidemic models is

$$\begin{aligned} S' &= -\beta SI \\ I' &= \beta SI - \alpha I \\ R' &= \alpha I. \end{aligned} \tag{2.10}$$

A flow chart is shown in Fig. 2.1.

It is based on the same assumptions that were made for the SIS model of Sect. 2.2, except that recovered infectives go to a removed class rather than returning to the susceptible class. We will refer to this model as the simple Kermack–McKendrick epidemic model for convenience, but we remind the reader that it is a very special case of the actual Kermack–McKendrick epidemic model. From (2.10) we see that $N = S + I + R$ is constant.

The assumptions of a constant rate of contacts and of an exponentially distributed recovery rate are unrealistically simple. More general models can be constructed and analyzed, but our goal here is to show what may be deduced from extremely simple models. It will turn out that many more realistic models exhibit very similar qualitative behaviors.

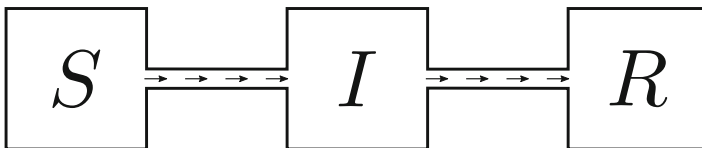


Fig. 2.1 Flow chart for the SIR model (2.10)

In our model, R is determined once S and I are known, and we can drop the R equation from our model, leaving the system of two equations

$$\begin{aligned} S' &= -\beta SI \\ I' &= \beta SI - \alpha I, \end{aligned} \tag{2.11}$$

together with initial conditions

$$S(0) = S_0, \quad I(0) = I_0, \quad S_0 + I_0 = N.$$

We think of introducing a small number of infectious individuals into a population of susceptibles and ask whether there will be an epidemic. We remark that the model makes sense only so long as $S(t)$ and $I(t)$ remain non-negative. Thus if either $S(t)$ or $I(t)$ reaches zero we consider the system to have terminated. We observe that $S' < 0$ for all t and $I' > 0$ if and only if $\beta S/\alpha > 1$. Thus I increases so long as $\beta S/\alpha > 1$ but since S decreases for all t , I ultimately decreases and approaches zero.

The quantity $\mathcal{R}_0 = \beta N/\alpha$ determines whether there is an epidemic. If $\mathcal{R}_0 < 1$, the infection dies out because $I'(t) < 0$ for all t , and there is no epidemic. Ordinarily, $S_0 \approx N$. If the epidemic is started by a member of the population being studied, for example by returning from travel with an infection acquired away from home, we would have $I_0 > 0$, $S_0 + I_0 = N$. A second way would be for an epidemic to be started by a visitor from outside the population. In this case, we would have $S_0 = N$. If $\mathcal{R}_0 > 1$, I increases initially and this is interpreted as saying that there is an epidemic.

Since (2.11) is a two-dimensional autonomous system of differential equations, the natural approach would be to find equilibria and linearize about each equilibrium to determine its stability. However, since every point with $I = 0$ is an equilibrium, the system (2.11) has a line of equilibria and this approach is not applicable (the linearization matrix at each equilibrium has a zero eigenvalue). The standard linearization theory for systems of ordinary differential equations is not applicable, and it is necessary to develop a new mathematical approach.

The sum of the two equations of (2.11) is

$$(S + I)' = -\alpha I.$$

Thus $S + I$ is a non-negative smooth decreasing function and therefore tends to a limit as $t \rightarrow \infty$. Also, it is not difficult to prove that the derivative of a smooth decreasing function which is bounded below must tend to zero, and this shows that

$$I_\infty = \lim_{t \rightarrow \infty} I(t) = 0.$$

Thus $S + I$ has limit S_∞ .

Integration of the sum of the two equations of (2.11) from 0 to ∞ gives

$$-\int_0^{\infty} (S(t) + I(t))' dt = S_0 + I_0 - S_{\infty} = N - S_{\infty} = \alpha \int_0^{\infty} I(t) dt.$$

Division of the first equation of (2.11) by S and integration from 0 to ∞ gives

$$\begin{aligned} \log \frac{S_0}{S_{\infty}} &= \beta \int_0^{\infty} I(t) dt \\ &= \frac{\beta}{\alpha} [N - S_{\infty}] \\ &= \mathcal{R}_0 \left[1 - \frac{S_{\infty}}{N} \right]. \end{aligned} \tag{2.12}$$

Equation (2.12) is called the *final size relation*. It gives a relation between the basic reproduction number and the size of the epidemic. Note that the final size of the epidemic, the number of members of the population who are infected over the course of the epidemic, is $N - S_{\infty}$. This is often described in terms of the *attack rate* ($1 - S_{\infty}/N$). [Technically, the attack rate should be called an attack ratio, since it is dimensionless and is not a rate]. The attack rate is the fraction of the population that becomes infected over the course of the epidemic.

The final size relation (2.12) can be generalized to epidemic models with more complicated compartmental structure than the simple *SIR* model (2.11), including models with exposed periods, treatment models, and models including quarantine of suspected individuals and isolation of diagnosed infectives. The original Kermack–McKendrick model [17] included dependence on the time since becoming infected (age of infection), and this includes such models. We will describe this generalization in Chap. 4.

Integration of the first equation of (2.11) from 0 to t gives

$$\begin{aligned} \log \frac{S_0}{S(t)} &= \beta \int_0^t I(t) dt \\ &= \frac{\beta}{\alpha} [N - S(t) - I(t)], \end{aligned}$$

and this leads to the form

$$I(t) + S(t) - \frac{\alpha}{\beta} \log S(t) = N - \frac{\alpha}{\beta} \log S_0. \tag{2.13}$$

This implicit relation between S and I describes the orbits of solutions of (2.11) in the (S, I) plane.

In addition, since the right side of (2.12) is finite, the left side is also finite, and this shows that $S_{\infty} > 0$. It is not difficult to prove that there is a unique solution of the final size relation (2.12). To see this, we define the function

$$g(x) = \log \frac{S_0}{x} - \mathcal{R}_0 \left[1 - \frac{x}{N} \right].$$

Then

$$g(0+) > 0, \quad g(N) < 0,$$

and $g'(x) < 0$ if and only if

$$0 < x < \frac{N}{\mathcal{R}_0}.$$

If $\mathcal{R}_0 \leq 1$, $g(x)$ is monotone decreasing from a positive value at $x = 0+$ to a negative value at $x = N$. Thus there is a unique zero S_∞ of $g(x)$ with $S_\infty < N$. A graph of the function $g(x)$ is plotted in Fig. 2.2.

If $\mathcal{R}_0 > 1$, $g(x)$ is monotone decreasing from a positive value at $x = 0+$ to a minimum at $x = N/\mathcal{R}_0$ and then increases to a negative value at $x = N$. Thus there is a unique zero S_∞ of $g(x)$ with

$$S_\infty < \frac{N}{\mathcal{R}_0}.$$

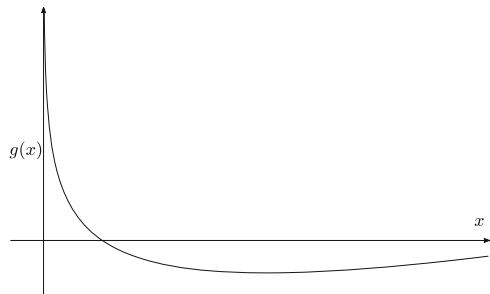
In fact,

$$\begin{aligned} g\left(\frac{S_0}{\mathcal{R}_0}\right) &= \log \mathcal{R}_0 - \mathcal{R}_0 + \frac{S_0}{N} \\ &\leq \log \mathcal{R}_0 - \mathcal{R}_0 + 1. \end{aligned}$$

Since $\log \mathcal{R}_0 < \mathcal{R}_0 - 1$ for $\mathcal{R}_0 > 0$, we actually have

$$g\left(\frac{S_0}{\mathcal{R}_0}\right) < 0,$$

Fig. 2.2 Graph of the function $g(x)$



and

$$S_\infty < \frac{S_0}{\mathcal{R}_0}. \quad (2.14)$$

An important question is how the basic reproduction number changes if a parameter of the model varies. If \mathcal{R}_0 , and therefore S_∞ , is a function of a parameter η , implicit differentiation of the final size relation (2.12) gives

$$\left(\frac{\mathcal{R}_0}{N} - \frac{1}{S_\infty} \right) \frac{dS_\infty}{d\eta} = \frac{d\mathcal{R}_0}{d\eta} \left(1 - \frac{S_\infty}{N} \right).$$

Because of (2.14), if \mathcal{R}_0 increases then S_∞ decreases.

It is generally difficult to estimate the contact rate β which depends on the particular disease being studied but may also depend on social and behavioral factors. The quantities S_0 and S_∞ may be estimated by serological studies (measurements of immune responses in blood samples) before and after an epidemic, and from these data, the basic reproduction number \mathcal{R}_0 may be estimated by using (2.12). This estimate, however, is a retrospective one which can be derived only after the epidemic has run its course.

In order to prevent the occurrence of an epidemic, if infectives are introduced into a population, it is necessary to reduce the basic reproduction number \mathcal{R}_0 below one. This may sometimes be achieved by immunization, which has the effect of transferring members of the population from the susceptible class to the removed class and thus of reducing $S(0)$. Immunization of some members of the population produces a new model. If a fraction p of the population is successfully immunized the effect is to decrease the number of susceptibles from $S(0)$ to $S(0)(1 - p)$. Originally, the basic reproduction number is $\beta N/\alpha$, but in the new situation with a decreased number of susceptibles the basic reproduction number would be $\beta N(1 - p)/\alpha$. This is less than 1 if p satisfies $\beta N(1 - p)/\alpha < 1$. This gives $1 - p < \alpha/\beta N$, or

$$p > 1 - \frac{\alpha}{\beta N} = 1 - \frac{1}{\mathcal{R}_0}.$$

Initially, the number of infectives grows exponentially because the equation for I may be approximated by

$$I' = (\beta N - \alpha)I$$

and the initial growth rate is

$$r = \beta N - \alpha = \alpha(\mathcal{R}_0 - 1).$$

This initial growth rate r may be estimated from incidence data when an epidemic begins. Since N and α may be measured, β may be calculated as

$$\beta = \frac{r + \alpha}{N}.$$

However, because of incomplete data and under-reporting of cases, this estimate may not be very accurate. This inaccuracy is even more pronounced for an outbreak of a previously unknown disease, where early cases are likely to be mis-diagnosed. Because of the final size relation, estimation of β or \mathcal{R}_0 is an important question that has been studied by a variety of approaches. Estimation of the initial growth rate from data can provide an estimate of the contact rate β . However, this relation is valid only for the model (2.11) and does not hold for models with different compartmental structure, such as an exposed period.

If $\beta S_0 > \alpha$, I increases initially to a maximum number of infectives when the derivative of I is zero, that is, when $S = \alpha/\beta$. This maximum is given by

$$I_{max} = S_0 + I_0 - \frac{\alpha}{\beta} \log S_0 - \frac{\alpha}{\beta} + \frac{\alpha}{\beta} \log \frac{\alpha}{\beta}, \quad (2.15)$$

obtained by substituting $S = \alpha/\beta$, $I = I_{max}$ into (2.13).

Example 1 A study of Yale University freshmen [10] reported by Hethcote [13] described an influenza epidemic with $S_0 = 0.911$, $S_\infty = 0.513$. Here we are measuring the number of susceptibles as a fraction of the total population size, or using the population size K as the unit of size. Substitution into the final size relation gives the estimate $\beta N/\alpha = 1.18$ and $\mathcal{R}_0 = 1.18$. Since we know that $1/\alpha$ is approximately 3 days for influenza, we see that βN is approximately 0.39 contacts per day per member of the population.

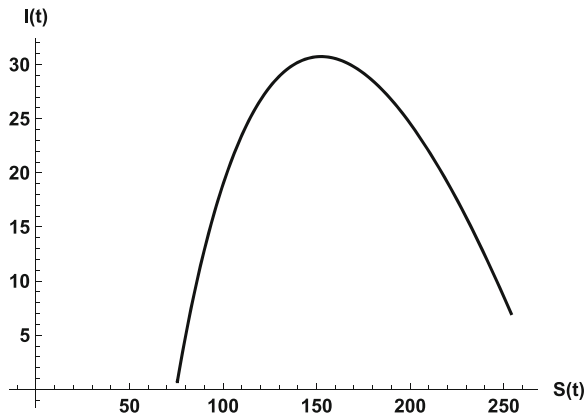
Example 2 (The Great Plague in Eyam) The village of Eyam near Sheffield, England suffered an outbreak of bubonic plague in 1665–1666 the source of which is generally believed to be the Great Plague of London. The Eyam plague was survived by only 83 of an initial population of 350 persons. As detailed records were preserved and as the community was persuaded to quarantine itself to try to prevent the spread of disease to other communities, the disease in Eyam has been used as a case study for modeling [21]. Detailed examination of the data indicates that there were actually two outbreaks of which the first was relatively mild. Thus we shall try to fit the model (2.11) over the period from mid-May to mid-October 1666, measuring time in months with an initial population of 7 infectives and 254 susceptibles, and a final population of 83. Raggett [21] gives values of susceptibles and infectives in Eyam on various dates, beginning with $S(0) = 254$, $I(0) = 7$, shown in Table 2.1.

The final size relation with $S_0 = 254$, $I_0 = 7$, $S_\infty = 83$ gives $\beta/\alpha = 6.54 \times 10^{-3}$, $\alpha/\beta = 153$. The infective period was 11 days, or 0.3667 month, so that $\alpha = 2.73$. Then $\beta = 0.0178$. The relation (2.15) gives an estimate of 30.4 for the maximum

Table 2.1 Eyam Plague data

Date (1666)	Susceptibles	Infectives
July 3/4	235	14.5
July 19	201	22
August 3/4	153.5	29
August 19	121	21
September 3/4	108	8
September 19	97	8
October 4/5	Unknown	Unknown
October 20	83	0

Fig. 2.3 The S – I plane



number of infectives. We use the values obtained here for the parameters β and α in the model (2.11) for simulations of the phase plane, the (S, I) plane, and for graphs of S and I as functions of t (Figs. 2.3 and 2.4). Figure 2.5 plots these data points together with the phase portrait given in Fig. 2.3 for the model (2.11).

The actual data for the Eyam epidemic are remarkably close to the predictions of this very simple model. However, the model is really too good to be true. Our model assumes that infection is transmitted directly between people. While this is possible, bubonic plague is transmitted mainly by rat fleas. When an infected rat is bitten by a flea, the flea becomes extremely hungry and bites the host rat repeatedly, spreading the infection in the rat. When the host rat dies its fleas move on to other rats, spreading the disease further. As the number of available rats decreases the fleas move to human hosts, and this is how plague starts in a human population (although the second phase of the epidemic may have been the pneumonic form of bubonic plague, which can be spread from person to person). One of the main reasons for the spread of plague from Asia into Europe was the passage of many trading ships; in medieval times ships were invariably infested with rats. An accurate model of plague transmission would have to include flea and rat populations, as well as movement in space. Such a model would be extremely complicated and its predictions might well not be any closer to observations than our simple unrealistic model. Raggett

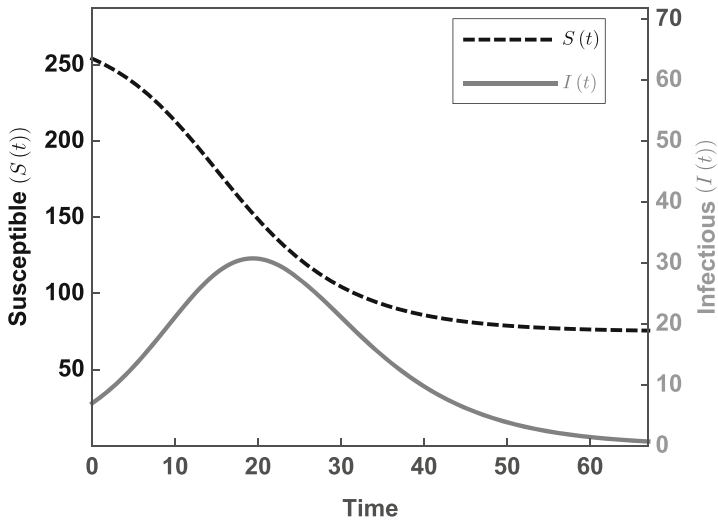


Fig. 2.4 Time plot of S and I

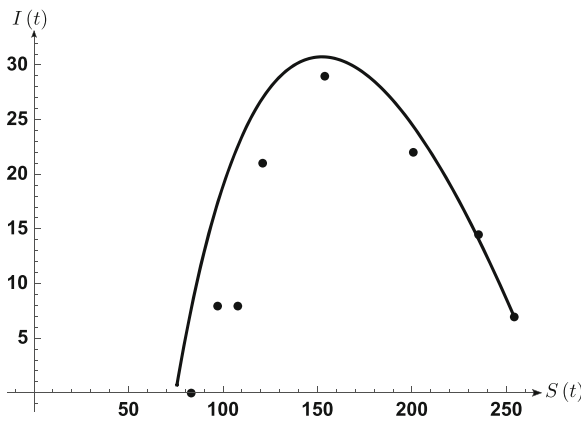


Fig. 2.5 The $S-I$ plane, model and data

also used a stochastic model to fit the data, but the fit was rather poorer than the fit for the simple deterministic model (2.11).

In the village of Eyam the rector persuaded the entire community to quarantine itself to prevent the spread of disease to other communities. One effect of this policy was to increase the infection rate in the village by keeping fleas, rats, and people in close contact with one another, and the mortality rate from bubonic plague was much higher in Eyam than in London. Further, the quarantine could do nothing to prevent the travel of rats and thus did little to prevent the spread of disease to other communities. One message this suggests to mathematical modelers is that control strategies based on false models that do not describe the epidemiological

situation accurately may be harmful, and it is essential to distinguish between assumptions that simplify but do not alter the predicted effects substantially, and wrong assumptions which make an important difference.

2.5 Epidemic Models with Deaths due to Disease

So far, we have analyzed only models with no disease deaths, for which it may be assumed that the total population size is constant.

The assumption in the model (2.11) of a rate of contacts per infective which is proportional to population size N , called *mass action incidence* or bilinear incidence, was used in all the early epidemic models. However, it is quite unrealistic, except possibly in the early stages of an epidemic in a population of moderate size. It is more realistic to assume a contact rate which is a non-increasing function of the total population size. For example, a situation in which the number of contacts per infective in unit time is constant, called *standard incidence*, is a more accurate description for sexually transmitted diseases. If there are no disease deaths, so that the total population size remains constant, such a distinction is unnecessary.

We generalize the model (2.11) by assuming that an average member of the population makes $N\beta(N)$ contacts in unit time [4, 8]. It is reasonable to assume $\beta'(N) \leq 0$ to express the idea of saturation in the number of contacts. Then mass action incidence corresponds to the choice $a(N) = \beta N$, and standard incidence corresponds to the choice $a(N) = a$. The assumptions $a(N) = N\beta(N)$, $a'(N) \geq 0$ imply that

$$\beta(N) + N\beta'(N) \geq 0.$$

Some epidemic models [8] have used a Michaelis–Menten type of interaction of the form

$$\beta(N) = \frac{a}{1 + bN}.$$

Another form based on a mechanistic derivation for pair formation [11] leads to an expression of the form

$$\beta(N) = \frac{a}{1 + bN + \sqrt{1 + 2bN}}.$$

Data for diseases transmitted by contact in cities of moderate size [20] suggests that data fits the assumption of a form

$$\beta(N) = aN^{p-1}$$

with $p = 0.05$ quite well. All of these forms satisfy the conditions $\beta'(N) \leq 0$ and (2.5).

Because the total population size is now present in the model, we must include an equation for total population size in the model. This forces us to make a distinction between members of the population who die of the disease and members of the population who recover with immunity against reinfection. We assume, as in the previous chapter, a recovery rate αI and a disease death rate dI . We use S , I , and N as variables, with $N = S + I + R$. We now obtain a three-dimensional model

$$\begin{aligned} S' &= -\beta(N)SI \\ I' &= \beta(N)SI - (\alpha + d)I \\ N' &= -dI. \end{aligned} \tag{2.16}$$

Since N is now a decreasing function, we define $N(0) = N_0 = S_0 + I_0$. We also have the equation $R' = \alpha I$, but we do not need to include it in the model since R is determined when S , I , and N are known. We should note that if $d = 0$ the total population size remains equal to the constant N , and the model (2.16) reduces to the simpler model (2.11) with $\beta(N)$ replaced by the constant $\beta(N_0)$.

We wish to show that the model (2.16) has the same qualitative behavior as the model (2.11), namely that there is a basic reproduction number which distinguishes between disappearance of the disease and an epidemic outbreak, and that some members of the population are left untouched when the epidemic passes. These two properties are the central features of all epidemic models.

For the model (2.16) the basic reproduction number is given by

$$\mathcal{R}_0 = \frac{N_0\beta(N_0)}{\alpha + d}$$

because a single infective introduced into a wholly susceptible population makes $c(N_0) = N_0\beta(N_0)$ contacts in unit time, all of which are with susceptibles and thus produce new infections, and the mean infective period, corrected for mortality, is $1/(\alpha + d)$.

We assume that $\beta(0)$ is finite, thus ruling out standard incidence (standard incidence does not appear to be realistic if the total population N approaches zero, and it would be more natural to assume that $c(N)$ grows linearly with N for small N). If we let $t \rightarrow \infty$ in the sum of the first two equations of (2.16) we obtain

$$(\alpha + d) \int_0^\infty I(s)ds = S_0 + I_0 - S_\infty = N - S_\infty.$$

The first equation of (2.16) may be written as

$$-\frac{S'(t)}{S(t)} = \beta(N(t))I(t).$$

Since

$$\beta(N) \geq \beta(N_0),$$

integration from 0 to ∞ gives

$$\begin{aligned} \log \frac{S_0}{S_\infty} &= \int_0^\infty \beta(N(t))I(t)dt \\ &\geq \beta(N_0) \int_0^\infty I(t)dt \\ &= \frac{\beta(N_0)(N_0 - S_\infty)}{(\alpha + d)N_0}. \end{aligned}$$

We now obtain a final size inequality

$$\begin{aligned} \log \frac{S_0}{S_\infty} &= \int_0^\infty \beta(N(t))I(t)dt \\ &\geq \beta(N_0) \int_0^\infty I(t)dt = \mathcal{R}_0 \left[1 - \frac{S_\infty}{N_0} \right]. \end{aligned}$$

If the case fatality ratio $d/(d+\alpha)$ is small, the final size inequality is an approximate equality.

It is not difficult to show that $N(t) \geq \alpha N_0/(\alpha + d)$ and then a similar calculation using the inequality $\beta(N) \leq \beta(\alpha N_0/(\alpha + d)) < \infty$ shows that

$$\log \frac{S_0}{S_\infty} \leq \beta(\alpha N_0/(\alpha + d)) \int_0^\infty I(t)dt,$$

from which we may deduce that $S_\infty > 0$.

It is important to be able to estimate the fraction of infectives who die of disease over the course of the epidemic. At every time, the rate of recovery is αI and the rate of disease deaths is dI , and thus the mortality fraction at each time is

$$\frac{d}{d + \alpha}.$$

This is what is sometimes described (incorrectly because it is not a rate) as the epidemic death rate. While the mortality fraction overall is $d/(d+\alpha)$, reports during the epidemic would underestimate the mortality fraction because there may be some infectives who would die later during the epidemic. On the other hand, for a disease like influenza, where many cases are mild enough to go unreported, reports would tend to overestimate the mortality fraction.

2.6 *Project: Discrete Epidemic Models

The discrete analogue of the continuous-time epidemic model (2.11) is

$$\begin{aligned} S_{j+1} &= S_j G_j, \\ I_{j+1} &= S_j(1 - G_j) + \sigma I_j, \\ G_j &= e^{-\beta I_j/N}, \quad j = 1, 2, \dots, \end{aligned} \tag{2.17}$$

where S_j and I_j denote the numbers of susceptible and infective individuals at time j , respectively. Here, G_j is the probability that a susceptible individual at time j will remain susceptible to time $j + 1$, that is, will not be infected between time j and time $j + 1$, and $\sigma = e^{-\alpha}$ is the probability that an infected individual at time j will remain infected to time $j + 1$.

Assume that the initial conditions are $S(0) = S_0 > 0$, $I(0) = I_0 > 0$, and $S_0 + I_0 = N$.

Exercise 1 Consider the system (2.17).

(a) Show that the sequence $\{S_j + I_j\}$ has a limit

$$S_\infty + I_\infty = \lim_{j \rightarrow \infty} (S_j + I_j).$$

(b) Show that

$$I_\infty = \lim_{j \rightarrow \infty} I_j = 0.$$

(c) Show that

$$\log \frac{S_0}{S_\infty} = \beta \sum_{m=0}^{\infty} \frac{I_m}{N}.$$

(d) Show that

$$\log \frac{S_0}{S_\infty} = \mathcal{R}_0 \left[1 - \frac{S_\infty}{N} \right],$$

with $\mathcal{R}_0 = \frac{\beta}{1-\sigma}$.

Next, consider the case that there are k infected stages and there is treatment in some stages, with treatment rates that can be different in different stages. Assume that selection of members for treatment occurs only at the beginning of a stage. Let $I_j^{(i)}$ and $T_j^{(i)}$ denote the numbers of infected and treated individuals, respectively, in stage i ($i = 1, 2, \dots, k$) at time j . Let σ_i^I denote the probability

that an infected individual in the $I^{(i)}$ stage continues on to the next stage, either treated or untreated, and let σ_i^T denote the probability that an individual in the $T^{(i)}$ stage continues on to the next treated stage. In addition, of the members leaving an infected stage $I^{(i)}$, a fraction p_i enters treatment in $T^{(i+1)}$, while the remaining fraction q_i continues to $I^{(i+1)}$. Let m_i denote the fraction of infected members who go through the stage $I^{(i)}$, and n_i the fraction of infected members who go through the stage $T^{(i)}$. Then,

$$\begin{aligned} m_1 &= q_1, \quad m_2 = q_1 q_2, \quad \dots, \quad m_k = q_1 q_2 \cdots q_k, \\ n_1 &= p_1, \quad n_2 = p_1 + q_1 p_2, \quad \dots, \quad n_k = p_1 + q_1 p_2 + \dots + q_1 q_2 \cdots q_{k-1} p_k. \end{aligned}$$

The discrete system with treatment is

$$\begin{aligned} S_{j+1} &= S_j G_j, \\ I_{j+1}^{(1)} &= q_1 S_j (1 - G_j) + \sigma_1^I I_j^{(1)}, \\ T_{j+1}^{(1)} &= p_1 S_j (1 - G_j) + \sigma_1^T T_j^{(1)} \\ I_{j+1}^{(i)} &= q_i (1 - \sigma_{i-1}^I) I_j^{(i-1)} + \sigma_i^I \eta_i I_j^{(i)}, \\ T_{j+1}^{(i)} &= p_i (1 - \sigma_{i-1}^I) I_j^{(i-1)} + (1 - \sigma_{i-1}^T) T_j^{(i-1)} + \sigma_i^T T_j^{(i)}, \end{aligned} \tag{2.18}$$

$[i = 2, \dots, k, j \geq 0]$, with

$$G_j = e^{-\beta \sum_{i=1}^k (\epsilon_i I_j^{(i)} / N + \delta_i T_j^{(i)} / N)},$$

where ϵ_i is the relative infectivity of untreated individuals at stage i and δ_i is the relative infectivity of treated individuals at stage i .

(e) Show that

$$\mathcal{R}_c = \beta N \sum_{i=1}^k \left[\frac{\epsilon_i m_i}{1 - \sigma_i^I} + \frac{\delta_i n_i}{1 - \sigma_i^T} \right]$$

and that

$$\log \frac{S_0}{S_\infty} = \mathcal{R}_c \left[1 - \frac{S_\infty}{N} \right].$$

2.7 *Project: Pulse Vaccination

Consider an SIR model (2.9) with $\Lambda = \mu K$. For measles, typical parameter choices are $\mu = 0.02$, $\beta = 1800$, $\alpha = 100$, $K = 1$ (to normalize carrying capacity to 1) [9].

Question 1 Show that for these parameter choices $\mathcal{R}_0 \approx 18$ and to achieve herd immunity would require vaccination of about 95% of the susceptible population.

In practice, it is not possible to vaccinate 95% of a population because not all members of the population would come to be vaccinated and not all vaccinations are successful. One way to avoid recurring outbreaks of disease is “pulse vaccination” [1, 24, 25]. The basic idea behind pulse vaccination is to vaccinate a given fraction p of the susceptible population at intervals of time T with T (depending on p) chosen to ensure that the number of infectives remains small and approaches zero. In this project we will give two approaches to the calculation of a suitable function $T(p)$.

The first approach depends on the observation that I decreases so long as $S < \Gamma < (\mu + \alpha)/\beta$. We begin by vaccinating $p\Gamma$ members, beginning with $S(0) = (1 - p)\Gamma$. From (8.7),

$$S' = \mu K - \mu S - \beta SI \geq \mu K - \mu S.$$

Then $S(t)$ is greater than the solution of the initial value problem

$$S' = \mu K - \mu S, \quad S(0) = (1 - p)\Gamma.$$

Question 2 Solve this initial value problem and show that the solution obeys

$$S(t) < \Gamma, \quad 0 \leq t < \frac{1}{\mu} \log \frac{K - (1 - p)\Gamma}{K - \Gamma}.$$

Thus a suitable choice for $T(p)$ is

$$T(p) = \frac{1}{\mu} \log \frac{K - (1 - p)\Gamma}{K - \Gamma} = \frac{1}{\mu} \log \left[1 + \frac{p\Gamma}{K - \Gamma} \right].$$

Calculate $T(p)$ for $p = m/10$ ($m = 1, 2, \dots, 10$).

The second approach is more sophisticated. Start with $I = 0$, $S' = \mu K - \mu S$. We let $t_n = nT$ ($n = 0, 1, 2, \dots$) and run the system for $0 \leq t \leq t_1 = T$. Then we let $S_1 = (1 - p)S(t_1)$. We then repeat, i.e. for $t_1 \leq t \leq t_2$, $S(t)$ is the solution of $S' = \mu K - \mu S$, $S(t_1) = S_1$, and $S_2 = (1 - p)S_1$. We obtain a sequence S_n in this way.

Question 3 Show that

$$S_{n+1} = (1 - p)K(1 - e^{-\mu T}) + (1 - p)S_n e^{-\mu T}$$

and for $t_n \leq t \leq t_{n+1}$,

$$S(t) = K \left[1 - e^{-\mu(t-t_n)} \right] + S_n e^{-\mu(t-t_n)}.$$

Question 4 Show that the solution is periodic if

$$S_{n+1} = S_n = S^* \quad (n = 0, 1, 2, \dots)$$

with

$$S^* = K \left[1 - \frac{pe^{\mu T}}{e^{\mu T} - (1-p)} \right]$$

and that the periodic solution is

$$S(t) = \begin{cases} K \left[1 - \frac{pe^{\mu T}}{e^{\mu T} - (1-p)} e^{-\mu(t-t_n)} \right] : & t_n \leq t \leq t_{n+1}, \\ S^* : & t = t_{n+1} \end{cases} \quad I(t) = 0.$$

It is possible to show by linearizing about this periodic solution that the periodic solution is asymptotically stable if

$$\frac{1}{T} \int_0^T S(t) dt < \frac{\mu + \xi}{\beta}.$$

If this condition is satisfied, the infective population will remain close to zero.

Question 5 Show that this stability condition reduces to

$$\frac{K(\mu T - p)(e^{\mu T} - 1) + pK\mu T}{\mu T [e^{\mu} - (1-p)]} < \frac{\mu + \xi}{\beta}.$$

Question 6 Use a computer algebra system to graph $T(p)$, where T is defined implicitly by

$$\frac{K(\mu T - p)(e^{\mu T} - 1) + pK\mu T}{\mu T [e^{\mu} - (1-p)]} = \frac{\mu + \xi}{\beta}.$$

Compare this expression for T with the one obtained earlier in Question 2 in this project. A larger estimate for a safe value of T would save money by allowing less frequent vaccination pulses.

2.8 *Project: A Model with Competing Disease Strains

We model a general discrete-time SIS model with two competing strains in a population with discrete and non-overlapping generations. This model arises from a particular discretization in time of the corresponding SIS continuous-time stochastic model for two competing strains.

State Variables

S_n	Population of susceptible individuals in generation n
I_n^1	Population of infected individuals with strain 1 in generation n
I_n^2	Population of infected individuals with strain 2 in generation n
T_n	Total population in generation n
f	Recruitment function

Parameters

μ	Per capita natural death rate
γ_i	Per capita recovery rate for strain i
α_i	Per capita infection rate for strain i

Construction of the model equations: The model assumes that (i) the disease is not fatal; (ii) all recruits are susceptible and the recruitment function depends only on T_n ; (iii) there are no coinfections; (iv) death, infections, and recoveries are modeled as Poisson processes with rates μ, α_i, γ_i ($i = 1, 2$); (v) the time step is measured in generations; (vi) the populations change only because of “births” (given by the recruitment function), deaths, recovery, and infection of a susceptible individual for each strain; (vii) individuals recover but do not develop permanent or temporary immunity, that is, they immediately become susceptible again.

By assumption we have that the probability of k successful encounters is a Poisson distribution, which in general has the form $p(k) = e^{-\beta} \beta^k / k!$, where β is the parameter of the Poisson distribution. In our context, only one success is necessary. Therefore, when there are no successful encounters, the expression $p(0) = e^{-\beta}$ represents the probability that a given event does not occur. For example, the probability that a susceptible individual does not become infective is $\text{Prob}(\text{not being infected by strain } i) = e^{-\alpha_i I_n^i}$, and, $\text{Prob}(\text{not recovering from strain } i) = e^{-\gamma_i I_n^i}$. Hence, $\text{Prob}(\text{not being infected}) = \text{Prob}(\text{not being infected by strain 1}) \text{Prob}(\text{not being infected by strain 2}) = e^{-\alpha_1 I_n^1} e^{-\alpha_2 I_n^2}$.

Now the probability that a susceptible does become infected is given by $1 - e^{-\alpha_i I_n^i}$. Then, $\text{Prob}(\text{infected by strain } i) = \text{Prob}(\text{infected}) \cdot \text{Prob}(\text{infected by strain } i \mid \text{infected}) = (1 - e^{-(\alpha_1 I_n^1 + \alpha_2 I_n^2)}) \frac{\alpha_i I_n^i}{\alpha_1 I_n^1 + \alpha_2 I_n^2}$.

(a) Using the above discussion, show that the dynamics are governed by the system

$$\begin{aligned}
 S_{n+1} &= f(T_n) + S_n e^{-\mu} e^{-(\alpha_1 I_n^1 + \alpha_2 I_n^2)} + \sum_{j=1}^2 I_n^j e^{-\mu} (1 - e^{-\gamma_j}), \\
 I_{n+1}^1 &= \frac{\alpha_1 S_n I_n^1}{\alpha_1 I_n^1 + \alpha_2 I_n^2} e^{-\mu} (1 - e^{-(\alpha_1 I_n^1 + \alpha_2 I_n^2)}) + I_n^1 e^{-\mu} e^{-\gamma_1}, \\
 I_{n+1}^2 &= \frac{\alpha_2 S_n I_n^2}{\alpha_1 I_n^1 + \alpha_2 I_n^2} e^{-\mu} (1 - e^{-(\alpha_1 I_n^1 + \alpha_2 I_n^2)}) + I_n^2 e^{-\mu} e^{-\gamma_2}.
 \end{aligned} \tag{2.19}$$

(b) Show that

$$T_{n+1} = f(T_n) + T_n e^{-\mu},$$

where

$$T_n = S_n + I_n^1 + I_n^2. \quad (2.20)$$

This equation is called the *demographic equation*. It describes the total population dynamics.

- (c) If we set $I_{n+1}^1 = I_{n+1}^2 = 0$, then model (2.19) reduces to the demographic model

$$S_n = f(S_n) + S_n e^\mu.$$

and

$$T_{n+1} = f(T_n) + T_n e^{-\mu}.$$

Check that this is the case.

- (d) Study the disease dynamics at a demographic equilibrium, that is, at a point where $T_\infty = T_\infty e^{-\mu} + f(T_\infty)$. Substitute $S_n = T_\infty - I_n^1 - I_n^2$ where T_∞ is a stable demographic equilibrium, that is, assume $T_0 = T_\infty$ to get the following equations:

$$\begin{aligned} I_{n+1}^1 &= \frac{\alpha_1 I_n^1}{\alpha_1 I_n^1 + \alpha_2 I_n^2} (T_\infty - I_n^1 - I_n^2) e^{-\mu} \left(1 - e^{-(\alpha_1 I_n^1 + \alpha_2 I_n^2)} \right) + I_n^1 e^{-\mu} e^{-\gamma_1}, \\ I_{n+1}^2 &= \frac{\alpha_2 I_n^2}{\alpha_1 I_n^1 + \alpha_2 I_n^2} (T_\infty - I_n^1 - I_n^2) e^{-\mu} \left(1 - e^{-(\alpha_1 I_n^1 + \alpha_2 I_n^2)} \right) + I_n^2 e^{-\mu} e^{-\gamma_2}. \end{aligned} \quad (2.21)$$

System (2.21) describes the dynamics of a population infected with the two strains at a demographic equilibrium.

Show that in system (2.21), if $R_1 = \frac{e^{-\mu} T_\infty \alpha_1}{1 - e^{-(\mu + \gamma_1)}} < 1$ and $R_2 = \frac{e^{-\mu} T_\infty \alpha_2}{1 - e^{-(\mu + \gamma_2)}} < 1$, then the equilibrium point $(0, 0)$ is asymptotically stable.

- (e) Interpret biologically the numbers R_i , $i = 1, 2$.
 (f) Consider $f(T_n) = \Lambda$, where Λ is a constant. Show that

$$T_{n+1} = \Lambda + T_n e^{-\mu}$$

and that

$$T_\infty = \frac{\Lambda}{1 - e^{-\mu}}.$$

- (g) Consider $f(T_n) = r T_n (1 - T_n) / k$, and show that in this case the total population dynamic is given by

$$T_{n+1} = r T_n \left(1 - \frac{T_n}{k} \right) + T_n e^{-\mu}$$

and that the fixed points are

$$T_n^* = 0, \quad T_n^{**} = \frac{k(r + e^{-\mu} - 1)}{r},$$

whenever $r + e^{-\mu} > 1$.

- (h) Assume that one of the strains is missing, and determine the boundary equilibria, that is, let $I_n^i = 0$ for either $i = 1$ or 2 . Equation (2.21) reduces to

$$I_{n+1} = (T_\infty - I_n)e^{-\mu}(1 - e^{\alpha_1 I_n}) + I_n e^{-(\mu+\gamma)}.$$

Establish necessary and sufficient conditions for the stability and/or instability of boundary equilibria for the system (2.21). Compare your results with simulations of the system (2.21) and of the full system (2.19).

- (i) Does the system (2.21) have endemic ($I_1^* > 0$, $I_2^* > 0$) equilibria?
 (j) Simulate the full system (2.19) when the demographic equation is in the period doubling regime, where there are orbits with periods of double the length of periods for smaller parameter values. What are your conclusions?

References: [5, 6].

2.9 Project: An Epidemic Model in Two Patches

Consider the following SIS model with dispersion between two patches, Patch 1 and Patch 2, where in Patch $i \in \{1, 2\}$ at generation t , $S_i(t)$ denotes the population of susceptible individuals; $I_i(t)$ denotes the population of infected assumed infectious; $T_i(t) \equiv S_i(t) + I_i(t)$ denotes the total population size. The constant dispersion coefficients D_S and D_I measure the probability of dispersion by the susceptible and infective individuals, respectively. Observe that we are using a different notation from what we have used elsewhere, writing variables as a function of t rather than using a subscript for the independent variable in order to avoid needing double subscripts:

$$\begin{aligned} S_1(t+1) &= (1 - D_S)\tilde{S}_1(t) + D_S\tilde{S}_2(t), \\ I_1(t+1) &= (1 - D_I)\tilde{I}_1(t) + D_I\tilde{I}_2(t), \\ S_2(t+1) &= D_S\tilde{S}_1(t) + (1 - D_S)\tilde{S}_2(t), \\ I_2(t+1) &= D_I\tilde{I}_1(t) + (1 - D_I)\tilde{I}_2(t), \end{aligned}$$

where

$$\tilde{S}_i(t) = f_i(T_i(t)) + \gamma_i S_i(t) \exp\left(\frac{-\alpha_i I_i(t)}{T_i(t)}\right) + \gamma_i I_i(t)(1 - \sigma_i),$$

$$\tilde{I}_i(t) = \gamma_i(1 - \exp\left(\frac{-\alpha_i I_i(t)}{T_i(t)}\right)) S_i(t) + \gamma_i \sigma_i I_i(t)$$

and

$$0 \leq \gamma_i, \sigma_i, \alpha_i, D_S, D_I \leq 1.$$

Let

$$f_i(T_i(t)) = T_i(t) \exp(r_i - T_i(t)),$$

where r_i is a positive constant.

- (a) Using computer explorations, determine whether it is possible to have a globally stable disease-free equilibrium on a patch (without dispersal) where the full system with dispersal has a stable endemic equilibrium. Do you have a conjecture?
- (b) Using computer explorations determine whether it is possible to have a globally stable endemic equilibrium on a patch (without dispersal) where the full system with dispersal has a stable disease-free equilibrium. Do you have a conjecture?

References:[3, 7, 23].

2.10 Project: Fitting Data for an Influenza Model

Consider an SIR model (2.11) with basic reproduction number 1.5.

1. Describe the qualitative changes in (S, I, R) as a function of time for different values of β and α with $\beta \in \{0.0001, 0.0002, \dots, 0.0009\}$, for the initial condition $(S, I, R) = (10^6, 1, 0)$.
2. Discuss the result of part (a) in terms of the basic reproduction number (what is β/γ ?). Use a specific disease such as influenza to provide simple interpretations for the different time courses of the disease for the different choices of β and γ .
3. Repeat the steps in part (a) for values of $\mathcal{R}_0 \in \{1.75, 2, 2.5\}$, and for each value of \mathcal{R}_0 , choose the best pair of values (β, α) that fits the slope before the first peak in the data found in Table 2.2 for reported H1N1 influenza cases in México. (Hint: normalize the data so that the peak is 1, and then multiply the data by the size of the peak in the simulations.)

Table 2.2 Reported cases for H1N1-pandemic in Mexico

Day	Cases	Day	Cases	Day	Cases	Day	Cases	Day	Cases	Day	Cases
75	2	95	4	115	318	135	83	155	152	175	328
76	1	96	11	116	399	136	75	156	138	176	298
77	3	97	5	117	412	137	87	157	159	177	335
78	2	98	7	118	305	138	98	158	186	178	330
79	3	99	4	119	282	139	71	159	222	179	375
80	3	100	4	120	227	140	73	160	204	180	366
81	4	101	4	121	212	141	78	161	257	181	291
82	4	102	11	122	187	142	67	162	208	182	251
83	5	103	17	123	212	143	68	163	198	183	215
84	7	104	26	124	237	144	69	164	193	184	242
85	3	105	20	125	231	145	65	165	243	185	223
86	1	106	12	126	237	146	85	166	231	186	317
87	2	107	26	127	176	147	55	167	225	187	305
88	5	108	33	128	167	148	67	168	239	188	228
89	7	109	44	129	139	149	75	169	219	189	251
90	4	110	107	130	142	150	71	170	199	190	207
91	10	111	114	131	162	151	97	171	215	191	159
92	11	112	155	132	138	152	168	172	309	192	155
93	13	113	227	133	117	153	126	173	346	193	214
94	4	114	280	134	100	154	148	174	332	194	237

2.11 Project: Social Interactions

Suppose we have a system with multiple classes of mathematical biology teachers (MBT) at time t . The classes roughly capture the MBT individual attitudes toward learning new stuff. “Reluctant” means the class of MBTs that come into the door as new hires without a disposition to learn new stuff; the positive class corresponds to those who join the MBTs with the right attitude; and the rest of the classes should be self-explanatory. The total population is divided into five classes of MBT individuals: positive (P), reluctant (R), masterful (M), unchangeable (that is, negative) (U), and inactive (I). Assume that $N(t) = R(t) + P(t) + M(t) + U(t) + I(t)$ and that the total number of MBTs is constant, that is, $N(t) = \frac{K}{\mu}$ for all t , where K is a constant. The model is

$$P' = qK - \beta P \frac{M}{K} + \delta R - \mu P$$

$$R' = (1 - q)K - (\delta + \mu)R - \alpha R$$

$$M' = \beta P \frac{M}{K} - (\gamma + \mu)M$$

$$U' = -\mu U + \alpha R$$

$$I' = \gamma M - \mu I,$$

where $q, \beta, \delta, \mu, \gamma$, and α are constants and $0 \leq q \leq 1$.

1. Interpret the parameters.
2. Look at the stability of the simplest equilibrium (your choice).
3. From \mathcal{R}_0 , discuss what would be the impact of changing parameters q, γ , and δ .
4. What are your conclusions from this model?

2.12 Exercises

1. Find the basic reproduction number and the endemic equilibrium for the *SIS* model

$$S' = -\beta SI + \alpha I$$

$$I' = \beta SI - (\alpha + d)I,$$

with a death rate dI due to disease.

2. Find the basic reproduction number for the *SIS* model (2.7) that includes births, natural deaths, and disease deaths. Show that the disease-free equilibrium is asymptotically stable if and only if $\mathcal{R}_0 < 1$, and that if $\mathcal{R}_0 > 1$ there is an asymptotically stable endemic equilibrium.
3. Modify the *SIS* model (2.2) to the situation in which there are two competing strains of the same disease, generating two infective classes I_1, I_2 under the assumption that coinfections are not possible. Does the model predict coexistence of the two strains or competitive exclusion?
- 4.* A communicable disease from which infectives do not recover may be modeled by the pair of differential equations

$$S' = -\beta SI, \quad I' = \beta SI.$$

Show that in a population of fixed size K such a disease will eventually spread to the entire population.

- 5.* Consider a disease spread by carriers who transmit the disease without exhibiting symptoms themselves. Let $C(t)$ be the number of carriers and suppose that carriers are identified and isolated from contact with others at a constant per capita rate α , so that $C' = -\alpha C$. The rate at which susceptibles become infected is proportional to the number of carriers and to the number of susceptibles, so that $S' = -\beta SC$. Let C_0 and S_0 be the numbers of carriers and susceptibles, respectively, at time $t = 0$.

- (a) Determine the number of carriers at time t from the equation for C .
- (b) Substitute the solution to part (a) into the equation for S and determine the number of susceptibles at time t .
- (c) Find $\lim_{t \rightarrow \infty} S(t)$, the number of members of the population who escape the disease.
- 6.* Consider a population of fixed size K in which a rumor is being spread by word of mouth. Let $y(t)$ be the number of people who have heard the rumor at time t and assume that everyone who has heard the rumor passes it on to r others in unit time. Thus, from time t to time $(t+h)$ the rumor is passed on $hry(t)$ times, but a fraction $y(t)/K$ of the people who hear it have already heard it, and thus there are only $hry(t) \left(\frac{K-y(t)}{K} \right)$ people who hear the rumor for the first time. Use these assumptions to obtain an expression for $y(t+h) - y(t)$, divide by h , and take the limit as $h \rightarrow 0$ to obtain a differential equation satisfied by $y(t)$.
7. At 9 AM one person in a village of 100 inhabitants starts a rumor. Suppose that everyone who hears the rumor tells one other person per hour. Using the model of the previous exercise, determine how long it will take until half the village has heard the rumor.
- 8.* If a fraction λ of the population susceptible to a disease that provides immunity against reinfection moves out of the region of an epidemic, the situation may be modeled by a system

$$S' = -\beta SI - \lambda S, \quad I' = \beta SI - \alpha I.$$

Show that both S and I approach zero as $t \rightarrow \infty$.

9. Consider the basic SIR model. We now consider a vaccination class in place of recovery:

$$\begin{aligned} S'(t) &= \mu N - \beta S \frac{I}{N} - (\mu + \phi)S \\ I'(t) &= \beta S \frac{I}{N} - (\mu + \gamma)I \\ V'(t) &= \gamma I + \phi S - \mu V. \end{aligned} \tag{2.22}$$

- (a) Show that $\frac{dN}{dt} = 0$. What does this result imply?
- (b) Discuss why it is enough to study the first two equations.
- (c) Let $\mathcal{R}_0(\phi)$ be \mathcal{R}_0 when $\phi \neq 0$, and $\mathcal{R}_0(0)$ be \mathcal{R}_0 when $\phi = 0$. Compute $\mathcal{R}_0(\phi)$. What is the value of $\mathcal{R}_0(0)$? Compare $\mathcal{R}_0(\phi)$ with $\mathcal{R}_0(0)$.
- (d) Compute the equilibria.
- (e) Do the local stability analysis of the disease-free equilibrium state and the endemic state.
10. In cases of constant recruitment, the limiting system as $t \rightarrow \infty$ and the original system usually have the same qualitative dynamics. We thus consider our previous SIR model with vaccination (refer to problem 9) changing the recruitment rate from the constant μN to the constant Λ . This means that a

certain fixed number of individuals join or arrive into the susceptible class per unit time. The model becomes

$$\begin{aligned} S'(t) &= \Lambda - \beta S \frac{I}{N} - \mu S \\ I'(t) &= \beta S \frac{I}{N} - (\mu + \gamma)I \\ V'(t) &= \gamma I - \mu V, \end{aligned} \quad (2.23)$$

where, again, $N(t) = S(t) + I(t) + V(t)$.

- What are the units of Λ , $\beta S \frac{I}{N}$, μ , γ , β , and μS ?
- Find the equation for $N'(t)$ where $N = S + I + V$, and solve this equation for $N(t)$. Observe that the population size for this model is not constant.
- Show that $N(t) \rightarrow \frac{\Lambda}{\mu}$ as $t \rightarrow \infty$.
- Consider the limiting system

$$\begin{aligned} S'(t) &= \mu N - \beta SI - \mu S \\ I'(t) &= \beta SI - (\mu + \gamma)I \\ V'(t) &= \gamma I - \mu V. \end{aligned} \quad (2.24)$$

Explain why it is enough to consider the first two equations as $V(t) = N - S(t) - I(t)$ when studying the dynamics of this limiting system, find \mathcal{R}_0 , and do the local stability analysis of the equilibria.

- An epidemic model with two latent classes is described by the following system of ODE's:

$$\begin{aligned} S' &= \Lambda - \beta S \frac{I}{N} - \mu S \\ L_1' &= p\beta S \frac{I}{N} - (\mu + k_1 + r_1)L_1 \\ L_2' &= (1-p)\beta S \frac{I}{N} - (\mu + k_2 + r_2)L_2 \\ I' &= k_1 L_1 + k_2 L_2 - (\mu + r_3)I, \end{aligned}$$

where $N = S + L_1 + L_2 + I$. A fraction p , $0 < p < 1$, goes into the first latent class and a fraction $1 - p$ goes into the second latent class. The two classes have different rates of progression to the infectious stage. Compute the basic reproduction number \mathcal{R}_0 .

- If vaccination strategies are incorporated for newborns, we assume that not every new birth is susceptible. Suppose that the per capita vaccination rate is p ; a newborn is vaccinated with probability p . The modified model is

$$\begin{aligned} S'(t) &= (1-p)\mu N - \beta S \frac{I}{N} - \mu S \\ I'(t) &= \beta S \frac{I}{N} - (\mu + \gamma)I \\ V'(t) &= \gamma I - \mu V + p\mu N. \end{aligned} \quad (2.25)$$

- (a) Calculate the Jacobian matrix of (2.25) at the disease-free equilibrium points?
 - (b) Find the corresponding eigenvalues of the above matrix.
 - (c) Find the basic reproduction numbers (\mathcal{R}_0).
 - (d) Study the stability of the disease-free equilibrium points of model (2.25). Although N is constant and we could reduce this to a 2-D system, derive the stability of the full 3×3 system by using the Routh–Hurwitz criteria.
13. The same survey of Yale students described in Example 1, Sect. 2.4 reported that 91.1% were susceptible to influenza at the beginning of the year and 51.4% were susceptible at the end of the year. Estimate the basic reproduction number and decide whether there was an epidemic.
 14. What fraction of Yale students in Exercise 13 would have had to be immunized to prevent an epidemic?
 15. What was the maximum number of Yale students in Exercises 13 and 14 suffering from influenza at any time?
 16. An influenza epidemic was reported at an English boarding school in 1978 that spread to 512 of the 763 students. Estimate the basic reproduction number.
 17. What fraction of the boarding school students in Exercise 16 would have had to be immunized to prevent an epidemic?
 18. What was the maximum number of boarding school students in Exercises 16 and 17 suffering from influenza at any time?
 19. A disease is introduced by two visitors into a town with 1200 inhabitants. An average infective is in contact with 0.4 inhabitants per day. The average duration of the infective period is 6 days, and recovered infectives are immune against reinfection. How many inhabitants would have to be immunized to avoid an epidemic?
 20. Consider a disease with $\beta N = 0.4$, $1/\alpha = 6$ days in a population of 1200 members. Suppose the disease conferred immunity on recovered infectives. How many members would have to be immunized to avoid an epidemic?
 21. A disease begins to spread in a population of 800. The infective period has an average duration of 14 days and the average infective is in contact with 0.1 persons per day. What is the basic reproduction number? To what level must the average rate of contact be reduced so that the disease will die out?
 22. European fox rabies is estimated to have a transmission coefficient β of 80 km² years/fox (assuming mass action incidence), and an average infective period of 5 days. There is a critical carrying capacity K_c measured in foxes per km², such that in regions with fox density less than K_c , rabies tends to die out, while in regions with fox density greater than K_c , rabies tends to persist. Use a simple Kermack–McKendrick epidemic model to estimate K_c . [Remark: It has been suggested in Great Britain that hunting to reduce the density of foxes below the critical carrying capacity would be a way to control the spread of rabies.]
 23. A large English estate has a population of foxes with a density of 1.3 foxes/km². A large fox hunt is planned to reduce the fox population enough to prevent an outbreak of rabies. Assuming that the contact number β/α is 1 km²/fox, find what fraction of the fox population must be caught.

24. Following a complaint from the SPCA, organizers decide to replace the fox hunt of Exercise 23 by a mass inoculation of foxes for rabies. What fraction of the fox population must be inoculated to prevent a rabies outbreak?
25. What actually occurs on the estate of these exercises is that 10% of the foxes are killed and 15% are inoculated. Is there danger of a rabies outbreak?
26. Let S , I , and R represent the densities of susceptible, infected, and recovered individuals. Suppose that recovered individuals can become susceptible again after some time. The model equations are

$$\frac{dS}{dt} = -\beta SI + \theta R$$

$$\frac{dI}{dt} = \beta SI - \alpha I$$

$$\frac{dR}{dt} = \alpha I - \theta R$$

where $N = S + I + R$ and β , θ , and α are the infection, loss of immunity, and recovery rates, respectively.

- (a) Reduce this model to a two-dimensional system of equations. Don't forget to show that N is constant.
- (b) Find the equilibrium points. Is there a disease-free equilibria ($I = 0$)? Is there an endemic equilibria ($I \neq 0$)? If so, when does it exist?
- (c) Determine the local stability of each of the equilibrium points you found in (b).
27. Here is another approach to the analysis of the SIR model (2.11).

- (a) Divide the two equations of the model to give

$$\frac{I'}{S'} = \frac{dI}{dS} = \frac{(\beta S - \alpha)I}{-\beta SI} = -1 + \frac{\alpha}{\beta S}.$$

- (b) Integrate to find the orbits in the (S, I) -plane,

$$I = -S + \frac{\alpha}{\beta} \log S + c,$$

with c an arbitrary constant of integration.

- (c) Define the function

$$V(S, I) = S + I - \frac{\alpha}{\beta} \log S$$

and show that each orbit is given implicitly by the equation $V(S, I) = c$ for some choice of the constant c .

- (d) Show that no orbit reaches the I -axis and deduce that $S_\infty = \lim_{t \rightarrow \infty} S(t) > 0$, which implies that part of the population escapes infection.

28. For the model (2.16) show that the final total population size is given by

$$N_\infty = \frac{\alpha}{\alpha + d} N_0 + \frac{d}{\alpha + d} S_\infty.$$

29. Consider the basic SIR model with disease deaths, but we now consider a vaccination class in place of recovery:

$$\begin{aligned} S'(t) &= \mu N - \beta S \frac{I}{N} - (\mu + \phi) S \\ I'(t) &= \beta S \frac{I}{N} - (\mu + \gamma + \delta) I \\ V'(t) &= \gamma I + \phi S - \mu V. \end{aligned} \tag{2.26}$$

- (a) Let $\mathcal{R}_0(\phi)$ be \mathcal{R}_0 when $\phi \neq 0$, and $\mathcal{R}_0(0)$ be \mathcal{R}_0 when $\phi = 0$. Compute $\mathcal{R}_0(\phi)$. What is the value of $\mathcal{R}_0(0)$? Compare $\mathcal{R}_0(\phi)$ with $\mathcal{R}_0(0)$.
- (b) Compute the equilibria.
- (c) Do the local stability analysis of the disease-free equilibrium state and the endemic state.

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