Chapter 3
Endemic Disease Models

In this chapter, we consider models for disease that may be endemic. In the preceding chapter we studied SIS models with and without demographics and SIR models with demographics. In each model, the basic reproduction number $\mathscr{R}_0$ determined a threshold. If $\mathscr{R}_0 < 1$ the disease dies out, while if $\mathscr{R}_0 > 1$ the disease becomes endemic. The analysis in each case involves determination of equilibria and determining the asymptotic stability of each equilibrium by linearization about the equilibrium. In each of the cases studied in the preceding chapter the disease-free equilibrium was asymptotically stable if and only if $\mathscr{R}_0 < 1$ and if $\mathscr{R}_0 > 1$ there was a unique endemic equilibrium that was asymptotically stable. In this chapter, we will see that these properties continue to hold for many more general models, but there are situations in which there may be an asymptotically stable endemic equilibrium when $\mathscr{R}_0 < 1$, and other situations in which there is an endemic equilibrium that is unstable for some values of $\mathscr{R}_0 > 1$.

In Sect. 2.3 we analyzed the SIR model for diseases from which infectives recover with immunity against reinfection:

$$\begin{aligned} S' &= \Lambda(N) - \beta SI - \mu S \\ I' &= \beta SI - \mu I - \alpha I - dI \\ N' &= \Lambda(N) - dI - \mu N. \end{aligned} \tag{3.1}$$

The following basic result holds for (3.1).

Theorem 3.1 *The basic reproduction number for the model* (3.1) *is given by*

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

If $\mathscr{R}_0 < 1$*, the system has only the disease-free equilibrium and this equilibrium is asymptotically stable.*

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Here, K is the population carrying capacity and S_∞ is the susceptible population size at the endemic equilibrium. The theorem says that the disease-free equilibrium is locally asymptotically stable. We recall that this means that solutions with initial values close to this equilibrium remain close to the equilibrium and approach the equilibrium as $t \to \infty$. 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 $\mathscr{R}_0$ is greater than one, then the disease-free equilibrium is unstable, but there is an endemic equilibrium that is (locally) asymptotically stable.

In fact, these properties hold for some endemic disease models with more complicated compartmental structure . We will describe some examples.

3.1 More Complicated Endemic Disease Models

3.1.1 Exposed Periods

In many infectious diseases there is an exposed period after the transmission of infection from susceptibles to potentially infective members but before these potential infectives develop symptoms and can transmit infection. To incorporate an exposed compartment with mean exposed period $1/\kappa$ we add an exposed class E and use compartments S, E, I, R and total population size $N = S + E + I + R$ to give a generalization of the epidemic model (3.1)

$$\begin{aligned} S' &= \Lambda(N) - \beta SI - \mu S \\ E' &= \beta SI - (\kappa + \mu)E \\ I' &= \kappa E - (\alpha + \mu)I. \end{aligned} \tag{3.2}$$

A flow chart is shown in Fig. 3.1.

The analysis of this model is similar to the analysis of (3.1), but with I replaced by $E + I$. That is, instead of using the number of infectives as one of the variables we use the total number of infected members, whether or not they are capable of transmitting infection.

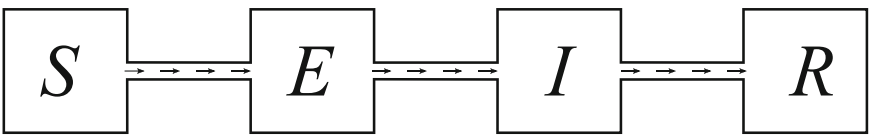


Fig. 3.1 Flow chart for the $SEIR$ endemic model (3.2)

3.1.2 A Treatment Model

One form of treatment that is possible for some diseases is vaccination to protect against infection before the beginning of an epidemic. For example, this approach is commonly used for protection against annual influenza outbreaks. A simple way to model this would be to reduce the total population size by the fraction of the population protected against infection.

In reality, such inoculations are only partly effective, decreasing the rate of infection and also decreasing infectivity if a vaccinated person does become infected. This may be modeled by dividing the population into two groups with different model parameters which would require some assumptions about the mixing between the two groups. This is not difficult but we will not explore this direction until Chap. 5 on heterogeneous mixing.

If there is a treatment for infection once a person has been infected, this may be modeled by supposing that there is a rate γ proportional to the number of infectives at which infectives are selected for treatment, and that treatment reduces infectivity by a fraction δ. Suppose that the rate of removal from the treated class is η. This leads to the $SITR$ model, where T is the treatment class, given by

$$\begin{aligned} S' &= \mu N - \beta S[I + \delta T] - \mu S \\ I' &= \beta S[I + \delta T] - (\alpha + \gamma + \mu)I \\ T' &= \gamma I - (\eta + \mu)T. \end{aligned} \tag{3.3}$$

A flow chart is shown in Fig. 3.2. In this model, we assume that the natural birth and death rates are equal so that the total population size remains constant.

In order to calculate the basic reproduction number, we observe that an infective in a totally susceptible population causes βN new infections in unit time, and the

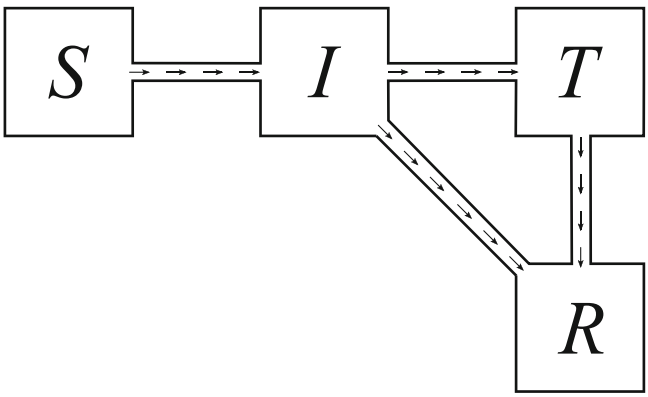


Fig. 3.2 Flow chart for the $SITR$ endemic model (3.3)

mean time spent in the infective compartment is $1/(\alpha+\gamma+\mu)$. In addition, a fraction $\gamma/(\alpha+\gamma+\mu)$ of infectives are treated because $(\gamma+\alpha+\mu)$ is the rate at which the number of infectives decreases overall while γ is the rate at which these infectives are selected for treatment. While in the treatment stage the number of new infections caused in unit time is $\delta\beta N$, and the mean time in the treatment class is $1/(\eta+\mu)$. Thus

$$\mathscr{R}_0 = \frac{\beta N}{\alpha+\gamma+\mu} + \frac{\gamma}{\alpha+\gamma+\mu}\frac{\delta\beta N}{\eta+\mu}. \tag{3.4}$$

It is possible that if $\delta < 1$ and $\alpha > \eta$ the treatment may increase the reproduction number. However, since $\alpha > \eta$ would mean that treatment prolongs the infection, this is quite unlikely.

The equilibrium conditions for the model (3.3) are

$$\begin{aligned} \mu N &= \beta S[I+\delta T] + \mu S \\ \beta S[I+\delta T] &= (\alpha+\gamma+\mu)I \\ \gamma I &= (\eta+\mu)T. \end{aligned} \tag{3.5}$$

Substitution of the last of these equilibrium conditions into the second gives

$$\beta S\frac{\delta\gamma+\eta+\mu}{\eta+\mu}I = (\alpha+\gamma+\mu)I,$$

and this implies that either $I = 0$ (disease-free equilibrium) or

$$\beta S = \frac{(\alpha+\gamma+\mu)(\eta+\mu)}{\delta\gamma+\eta+\mu}$$

(endemic equilibrium). An endemic equilibrium exists if and only if the value of S given by this condition is less than N, and this is equivalent to $\mathscr{R}_0 > 1$.

The Jacobian matrix or matrix of the linearization of (3.3) at an equilibrium (S, I, T) is

$$\begin{bmatrix} -\beta(I+\delta T)-\mu & -\beta S & -\delta\beta S \\ \beta(I+\delta T) & \beta S-(\alpha+\gamma+\mu) & \delta\beta S \\ 0 & \gamma & -(\eta+\mu) \end{bmatrix},$$

and at the disease-free equilibrium $(N, 0, 0)$ this is

$$\begin{bmatrix} -\mu & -\beta N & -\delta\beta N \\ 0 & \beta N-(\alpha+\gamma+\mu) & \delta\beta N \\ 0 & \gamma & -(\eta+\mu) \end{bmatrix}.$$

The eigenvalues of this matrix are $-\mu$ and the eigenvalues of the 2×2 matrix

$$\begin{bmatrix} \beta N - (\alpha + \gamma + \mu) & \delta\beta N \\ \gamma & -(\eta + \mu) \end{bmatrix}.$$

The eigenvalues of a 2×2 matrix have negative real part if and only if the matrix has negative trace and positive determinant. The condition that the determinant is positive is

$$\beta N < \frac{(\eta + \mu)(\alpha + \gamma + \mu)}{\eta + \mu + \delta\gamma}, \tag{3.6}$$

and the condition that the trace is negative is

$$\beta N < (\alpha + \gamma + \mu) + (\eta + \mu). \tag{3.7}$$

Then, since

$$(\eta + \mu)(\alpha + \gamma + \mu) < (\alpha + \gamma + \mu)(\eta + \mu + \delta\gamma) + (\eta + \mu + \delta\gamma)(\eta + \mu),$$

if (3.6) is satisfied (3.7) is also satisfied. Thus the condition $\mathscr{R}_0 < 1$ is equivalent to (3.6) and the asymptotic stability of the disease-free equilibrium.

To show that the endemic equilibrium is asymptotically stable if it exists, that is, if $\mathscr{R}_0 > 1$, we must make use of the four conditions [26, 37] introduced in Chap. 2. A somewhat complicated calculation shows that this is indeed the case.

3.1.3 *Vertical Transmission*

In some diseases, notably Chagas' disease, HIV/AIDS, hepatitis B, and rinderpest (in cattle), infection may be transferred not only horizontally (by contact between individuals) but also vertically (from an infected parent to a newly born offspring) [8]. We formulate an SIR model with vertical transmission by assuming that a fraction q of the offspring of infective members of the population are infective at birth. For simplicity, we assume that there are no disease deaths so that the total population size N is constant, and our model is based on (3.1). The birth rate in this model is $\Lambda = \mu N$, and we assume that births are distributed proportionally among compartments. Thus the rate of births to infectives is μI, the rate of newborn infectives is $q\mu I$, and the rate of newborn susceptibles is $\mu N - q\mu I$. This leads to the model

$$\begin{aligned} S' &= \mu N - q\mu I - \beta SI - \mu S \\ I' &= q\mu I + \beta SI - \mu I - \alpha I. \end{aligned} \tag{3.8}$$

From the second equation, we see that equilibrium requires either $I = 0$ (disease-free) or $\beta S = \mu(1-q) + \alpha$. At the disease-free equilibrium, $S = N$, $I = 0$, and the matrix of the linearization is

$$\begin{bmatrix} -\mu & -q\mu - \beta N \\ 0 & \beta N - \mu(1-q) - \alpha \end{bmatrix}.$$

Thus the disease-free equilibrium is asymptotically stable if and only if

$$\beta N < \mu(1-q) + \alpha.$$

This suggests that

$$\mathscr{R}_0 = \frac{\beta N + \mu q}{\mu + \alpha}.$$

To see that this is indeed correct, we note that the term $\beta N/(\mu + \alpha)$ represents horizontally transmitted infections at rate βN over a death-adjusted infective period $1/(\mu + \alpha)$, and the term $\frac{\mu q}{\mu+\alpha}$ represents vertically transmitted infections per infective. It is not difficult to verify that the endemic equilibrium, which exists if and only if $\mathscr{R}_0 > 1$ is asymptotically stable.

3.2 Some Applications of the *SIR* Model

3.2.1 Herd Immunity

In order to prevent a disease from becoming endemic, it is necessary to reduce the basic reproduction number $\mathscr{R}_0$ below one. This may sometimes be achieved by immunization. If a fraction p of the $\Lambda(N)$ newborn members per unit time of the population is successfully immunized, the effect is to replace N by $N(1-p)$, and thus to reduce the basic reproduction number to $\mathscr{R}_0(1-p)$. The requirement $\mathscr{R}_0(1-p) < 1$ gives $1 - p < 1/\mathscr{R}_0$, or

$$p > 1 - \frac{1}{\mathscr{R}_0}.$$

A population is said to have *herd immunity* if a large enough fraction has been immunized to assure that the disease cannot become endemic. The only disease for which this has actually been achieved worldwide is smallpox for which $\mathscr{R}_0$ is approximately 5, so that 80% immunization does provide herd immunity, and rinderpest, a cattle disease.

For measles, epidemiological data in the USA indicate that $\mathscr{R}_0$ for rural populations ranges from 5.4 to 6.3, requiring vaccination of 81.5–84.1% of the

population. In urban areas $\mathscr{R}_0$ ranges from 8.3 to 13.0, requiring vaccination of 88.0–92.3% of the population. In Great Britain, $\mathscr{R}_0$ ranges from 12.5 to 16.3, requiring vaccination of 92–94% of the population. The measles vaccine is not always effective, and vaccination campaigns are never able to reach everyone. As a result, herd immunity against measles has not been achieved (and probably never can be). An additional issue is that an anti-vaccination movement has developed, partly because of a fallacious belief that there is a link between the measles-mumps-rubella vaccine and the development of autism and partly because of a general opposition to vaccines.

Since smallpox is viewed as more serious and requires a lower percentage of the population be immunized, herd immunity was attainable for smallpox. In fact, smallpox has been eliminated; the last known case was in Somalia in 1977, and the virus is maintained now only in laboratories. The eradication of smallpox was actually more difficult than expected because high vaccination rates were achieved in some countries but not everywhere, and the disease persisted in some countries. The eradication of smallpox was possible only after an intensive campaign for worldwide vaccination [22].

3.2.2 Age at Infection

In order to calculate the basic reproduction number $\mathscr{R}_0$ for a disease modeled by a system (3.1), we need to know the values of the contact rate β and the parameters μ, K, and α. The parameters μ, K, and α can usually be measured experimentally but the contact rate β is difficult to determine directly. There is an indirect method of estimating $\mathscr{R}_0$ in terms of the life expectancy and the mean age at infection which enables us to avoid having to estimate the contact rate. In this calculation, we will assume that β is constant, but we will also indicate the modifications needed when β is a function of total population size N. The calculation assumes exponentially distributed life spans and infective periods. The result is valid so long as the life span is exponentially distributed, but if the life span is not exponentially distributed the result could be quite different.

Consider the "age cohort" of members of a population born at some time t_0 and let a be the age of members of this cohort. If $y(a)$ represents the fraction of members of the cohort who survive to age (at least) a, then the assumption that a fraction μ of the population dies per unit time means that $y'(a) = -\mu y(a)$. Since $y(t_0) = 1$, we may solve this first order initial value problem to obtain $y(a) = e^{-\mu a}$. The fraction dying at (exactly) age a is $-y'(a) = \mu y(a)$. The mean life span is the average age at death, which is $\int_0^\infty a[-y'(a)]da$, and if we integrate by parts we find that this life expectancy is

$$\int_{t_0}^{\infty} [-ay'(a)]\,da = [-ay(a)]_{t_0}^{\infty} + \int_{t_0}^{\infty} y(a)\,da = \int_{t_0}^{\infty} y(a)\,da.$$

Since $y(a) = e^{-\mu a}$, this reduces to $1/\mu$. The life expectancy is often denoted by L, so that we may write

$$L = \frac{1}{\mu}.$$

The rate at which surviving susceptible members of this cohort become infected at age a and time $t_0 + a$ is $\beta I(t_0 + a)$. Thus, if $z(a)$ is the fraction of the age cohort alive and still susceptible at age a, $z'(a) = -[\mu + \beta I(t_0 + a)]z(a)$. Solution of this first linear order differential equation gives

$$z(a) = e^{-[\mu a + \int_0^a \beta I(t_0+b)\,db]} = y(a)e^{-\int_0^a \beta I(t_0+b)\,db}.$$

The mean length of time in the susceptible class for members who may become infected, as opposed to dying while still susceptible, is

$$\int_0^\infty e^{-\int_0^a \beta I(t_0+b)db} da,$$

and this is the mean age at which members become infected. If the system is at an equilibrium I_∞, this integral may be evaluated, and the mean age at infection, denoted by A, is given by

$$A = \int_0^\infty e^{-\beta I_\infty a}\, da = \frac{1}{\beta I_\infty}.$$

For our model the endemic equilibrium is

$$I_\infty = \frac{\mu K}{\mu + \alpha} - \frac{\mu}{\beta},$$

and this implies

$$\frac{L}{A} = \frac{\beta I_\infty}{\mu} = \mathscr{R}_0 - 1. \tag{3.9}$$

This relation is very useful in estimating basic reproduction numbers. For example, in some urban communities in England and Wales between 1956 and 1969 the average age of contracting measles was 4.8 years. If life expectancy is assumed to be 70 years, this indicates $\mathscr{R}_0 = 15.6$.

If β is a function $\beta(N)$ of total population size and K is the carrying capacity, the relation (3.9) becomes

$$\mathscr{R}_0 = \frac{\beta(K)}{\beta(N_0)}\left[1 + \frac{L}{A}\right].$$

If disease mortality does not have a large effect on total population size, in particular if there is no disease mortality, this relation is very close to (3.9).

The relation between age at infection and basic reproduction number indicates that measures such as inoculations, which reduce $\mathscr{R}_0$, will increase the average age at infection. For diseases such as rubella (German measles), whose effects may be much more serious in adults than in children, this indicates a danger that must be taken into account: While inoculation of children will decrease the number of cases of illness, it will tend to increase the danger to those who are not inoculated or for whom the inoculation is not successful. Nevertheless, the number of infections in older people will be reduced, although the fraction of cases which are in older people will increase.

3.2.3 The Inter-Epidemic Period

Many common childhood diseases, such as measles, whooping cough, chicken pox, diphtheria, and rubella, exhibit variations from year to year in the number of cases. These fluctuations are frequently regular oscillations, suggesting that the solutions of a model might be periodic. This does not agree with the predictions of the model we have been using in this section; however, it would not be inconsistent with solutions of the characteristic equation, which are complex conjugate with small negative real part corresponding to lightly damped oscillations approaching the endemic equilibrium. Such behavior would look like recurring epidemics. If the eigenvalues of the matrix of the linearization at an endemic equilibrium are $-u \pm iv$, where $i^2 = -1$, then the solutions of the linearization are of the form $Be^{-ut}\cos(vt + c)$, with decreasing "amplitude" Be^{-ut} and "period" $\frac{2\pi}{v}$.

For the model (3.1) we recall that at the endemic equilibrium we have

$$\beta I_\infty + \mu = \mu\mathscr{R}_0, \qquad \beta S_\infty = \mu + \alpha$$

and the matrix of the linearization is

$$\begin{bmatrix} -\mu\mathscr{R}_0 & -(\mu+\alpha) \\ \mu(\mathscr{R}_0 - 1) & 0 \end{bmatrix}.$$

The eigenvalues are the roots of the quadratic equation

$$\lambda^2 + \mu\mathscr{R}_0\lambda + \mu(\mathscr{R}_0 - 1)(\mu + \alpha) = 0,$$

which are

$$\lambda = \frac{-\mu\mathscr{R}_0 \pm \sqrt{\mu^2\mathscr{R}_0{}^2 - 4\mu(\mathscr{R}_0 - 1)(\mu+\alpha)}}{2}.$$

If the mean infective period $1/\alpha$ is much shorter than the mean life span $1/\mu$, we may neglect the terms that are quadratic in μ. Thus, the eigenvalues are approximately

$$\frac{-\mu\mathscr{R}_0 \pm \sqrt{-4\mu(\mathscr{R}_0 - 1)\alpha}}{2},$$

and these are complex with imaginary part $\sqrt{\mu(\mathscr{R}_0 - 1)\alpha}$. This indicates oscillations with period approximately

$$\frac{2\pi}{\sqrt{\mu(\mathscr{R}_0 - 1)\alpha}}.$$

We use the relation $\mu(\mathscr{R}_0 - 1) = \mu L/A$ and the mean infective period $\tau = 1/\alpha$ to see that the interepidemic period T is approximately $2\pi\sqrt{A\tau}$. Thus, for example, for recurring outbreaks of measles with an infective period of 2 weeks or 1/26 year in a population with a life expectancy of 70 years with R_0 estimated as 15, we would expect outbreaks spaced 2.76 years apart. Also, as the "amplitude" at time t is $e^{-\mu R_0 t/2}$, the maximum displacement from equilibrium is multiplied by a factor $e^{-(15)(2.76)/140} = 0.744$ over each cycle. In fact, many observations of measles outbreaks indicate less damping of the oscillations, suggesting that there may be additional influences that are not included in our simple model. To explain oscillations about the endemic equilibrium a more complicated model is needed. One possible generalization would be to assume seasonal variations in the contact rate [13, 27]. This is a reasonable supposition for a childhood disease most commonly transmitted through school contacts, especially in winter in cold climates. Note, however, that data from observations are never as smooth as model predictions and models are inevitably gross simplifications of reality which cannot account for random variations in the variables. It may be difficult to judge from experimental data whether an oscillation is damped or persistent.

3.2.4 "Epidemic" Approach to Endemic Equilibrium

In the model (3.1) the demographic time scale described by the birth and natural death rates μK and μ and the epidemiological time scale described by the rate α of departure from the infective class may differ substantially. Think, for example, of a natural death rate $\mu = 1/75$, corresponding to a human life expectancy of 75 years, and epidemiological parameter $\alpha = 25$, describing a disease from which all infectives recover after a mean infective period of $1/25$ year, or 2 weeks. Suppose we consider a carrying capacity $K = 1000$ and take $\beta = 0.1$, indicating that an average infective makes (0.1)(1000)= 100 contacts per year. Then $\mathscr{R}_0 = 4.00$, and at the endemic equilibrium we have $S_\infty = 250.13$, $I_\infty = 0.40$, $R_\infty = 749.47$. This

equilibrium is globally asymptotically stable and is approached from every initial state.

However, if we take $S(0) = 999$, $I(0) = 1$, $R(0) = 0$, simulating the introduction of a single infective into a susceptible population and solve the system numerically we find that the number of infectives rises sharply to a maximum of 400 and then decreases to almost zero in a period of 0.4 year, or about 5 months. In this time interval the susceptible population decreases to 22 and then begins to increase, while the removed (recovered and immune against reinfection) population increases to almost 1000 and then begins a gradual decrease. The size of this initial "epidemic" could not have been predicted from our qualitative analysis of the system (3.1). On the other hand, since μ is so small compared to the other parameters of the model, we might consider neglecting μ, replacing it by zero in the model. If we do this, the model reduces to the simple Kermack–McKendrick epidemic model (without births and deaths) of Sect. 2.4.

If we follow the model (3.1) over a longer time interval we find that the susceptible population grows to 450 after 46 years, then drops to 120 during a small epidemic with a maximum of 18 infectives, and exhibits widely spaced epidemics decreasing in size. It takes a very long time before the system comes close to the endemic equilibrium and remains close to it. The large initial epidemic conforms to what has often been observed in practice when an infection is introduced into a population with no immunity, such as the smallpox inflicted on the Aztecs by the invasion of Cortez.

If we use the model (3.1) with the same values of β, K, and μ, but take $\alpha = 0$, $d = 25$ to describe a disease fatal to all infectives, we obtain very similar results. Now the total population is $S + I$, which decreases from an initial size of 1000 to a minimum of 22 and then gradually increases and eventually approaches its equilibrium size of 250.53. Thus, the disease reduces the total population size to one-fourth of its original value, suggesting that infectious diseases may have large effects on population size. This is true even for populations which would grow rapidly in the absence of infection, as we shall see in a later section (Sect. 3.7).

3.3 Temporary Immunity

In the SIR models that we have studied, it has been assumed that the immunity received by recovery from the disease is permanent. This is not always true, as there may be a gradual loss of immunity with time. In addition, there are often mutations in a virus, and as a result the active disease strain is sufficiently different from the strain from which an individual has recovered and the immunity received may wane.

Temporary immunity may be described by an $SIRS$ model in which a rate of transfer from R to S is added to an SIR model. For simplicity, we confine our attention to epidemic models, without including births, natural deaths, and disease deaths, but the analysis of models including births and deaths would lead to the same conclusions. Thus we begin with a model

$$S' = -\beta SI + \theta R$$
$$I' = \beta SI - \alpha I$$
$$R' = \alpha I - \theta R,$$

with a proportional rate θ of loss of immunity.

Since $N' = (S + I + R)' = 0$, the total population size N is constant, and we may replace R by $N - S - I$ and reduce the model to a two-dimensional system

$$\begin{aligned} S' &= -\beta SI + \theta(N - S - I) \\ I' &= \beta SI - \alpha I. \end{aligned} \tag{3.10}$$

Equilibria are solutions of the system

$$\beta SI + \theta S + \theta I = \theta N$$
$$\alpha I + \theta S + \theta I = \theta N,$$

and there is a disease-free equilibrium $S = \alpha/\beta$, $I = 0$. If $\mathscr{R}_0 = \beta N/\alpha > 1$, there is also an endemic equilibrium with

$$\beta S = \alpha, \quad (\alpha + \theta)I = \theta(N - S).$$

The matrix of the linearization of (3.10) at an equilibrium (S, I) is

$$A = \begin{bmatrix} -(\beta I + \theta) & -(\beta S + \theta) \\ \beta I & \beta S - \alpha \end{bmatrix}.$$

At the disease-free equilibrium A has the sign structure

$$\begin{bmatrix} - & - \\ 0 & \beta N - \alpha \end{bmatrix}.$$

This matrix has negative trace and positive determinant if and only if $\beta N < \alpha$, or $\mathscr{R}_0 < 1$. At an endemic equilibrium, the matrix has sign structure

$$\begin{bmatrix} - & - \\ + & 0 \end{bmatrix}.$$

and thus always has negative trace and positive determinant. We see from this that, as in other models studied in this chapter, the disease-free equilibrium is asymptotically stable if and only if the basic reproduction number is less than 1 and the endemic equilibrium, which exists if and only if the basic reproduction number

exceeds 1, is always asymptotically stable. However, it is possible for a different $SIRS$ model to have quite different behavior.

3.3.1 *Delay in an $SIRS$ Model

We consider an $SIRS$ model, which assumes a constant period of temporary immunity following recovery from the infection in place of an exponentially distributed period of temporary immunity [24]. We assume that there is a temporary immunity period of fixed length ω, after which recovered infectives revert to the susceptible class. The resulting model is described by the system of differential–difference equations

$$\begin{aligned} S'(t) &= -\beta S(t)I(t) + \alpha I(t-\omega) \\ I'(t) &= \beta S(t)I(t) - \alpha I(t) \\ R'(t) &= \alpha I(t) - \alpha I(t-\omega). \end{aligned} \tag{3.11}$$

The equilibrium analysis of a system of differential–difference equations with a delay ω is analogous to the equilibrium analysis of a system of ordinary differential equations, but there are important variations. Instead of assigning an initial condition at $t = 0$ it is necessary to assign initial data on the interval $-\omega \leq t \leq 0$. Equilibria of a system of differential–difference equations are constant solutions, just as for systems of differential equations, and the process of linearization about an equilibrium is the same.

The characteristic equation at an equilibrium is the condition that the linearization at the equilibrium has a solution whose components are constant multiples of $e^{\lambda t}$. In the ordinary differential equation case, this is just the equation that determines the eigenvalues of the coefficient matrix, a polynomial equation, but in the general case, it is a transcendental equation. The result on which our analysis depends, which we state without proof, is that an equilibrium is asymptotically stable if all roots of the characteristic equation have negative real part, or equivalently that the characteristic equation have no roots with real part greater than or equal to zero [5].

In (3.11), since $N = S + I + R$ is constant, we may discard the equation for R and use a two-dimensional model

$$\begin{aligned} S'(t) &= -\beta S(t)I(t) + \alpha I(t-\omega) \\ I'(t) &= \beta S(t)I(t) - \alpha I(t). \end{aligned} \tag{3.12}$$

Equilibria are given by $I = 0$ or $\beta S = \alpha$. There is a disease-free equilibrium $S = N$, $I = 0$. There is also an endemic equilibrium for which $\beta S = \alpha$. However, the two equations for S and I give only a single equilibrium condition. To determine the

endemic equilibrium (S_∞, I_∞), we must write the equation for R in the integrated form

$$R(t) = \int_{t-\omega}^{t} \alpha I(x)dx$$

to give $R_\infty = \omega\alpha I_\infty$. We also have $\beta S_\infty = \alpha$, and from $S_\infty + I_\infty + R_\infty = N$ we obtain

$$\beta I_\infty = \frac{(\beta N - \alpha)}{1 + \omega\alpha}.$$

To linearize about an equilibrium (S_∞, I_∞) of (3.12) we substitute

$$S(t) = S_\infty + u(t), \quad I(t) = I_\infty + v(t),$$

and neglect the quadratic term, giving the linearization

$$\begin{aligned} u'(t) &= -\beta I_\infty u(t) - \beta S_\infty v(t) + \alpha v(t-\omega) \\ v'(t) &= \beta I_\infty u(t) + \beta S_\infty v(t) - \alpha v(t). \end{aligned}$$

The characteristic equation is the condition on λ that this linearization has a solution

$$u(t) = u_0 e^{\lambda t}, \quad v(t) = v_0 e^{\lambda t},$$

and this is

$$\begin{aligned} (\beta I_\infty + \lambda)u_0 + (\beta S_\infty - \alpha e^{-\lambda\omega})v_0 &= 0 \\ \beta I_\infty u_0 + (\beta S_\infty - \alpha - \lambda)v_0 &= 0, \end{aligned}$$

or

$$det \begin{bmatrix} \lambda + \beta I_\infty & \beta S_\infty - \alpha e^{\lambda\omega} \\ \beta I_\infty & \beta S_\infty - \alpha - \lambda \end{bmatrix}.$$

This reduces to

$$\alpha\beta I_\infty \frac{1 - e^{-\omega\lambda}}{\lambda} = -[\lambda + \alpha + \beta S_\infty + \beta I_\infty]. \tag{3.13}$$

At the disease-free equilibrium $S_\infty = N$, $I_\infty = 0$, this reduces to a linear equation with a single root $\lambda = -\beta N - \alpha$, which is negative if and only if $\mathscr{R}_0 = \beta N/\alpha < 1$.

We think of ω and N as fixed and consider β and α as parameters. If $\alpha = 0$ the Eq. (3.13) is linear and its only root is $-\beta S_\infty - \beta I_\infty < 0$. Thus, there is a region in

the (α, β) parameter space containing the β-axis, in which all roots of (3.13) have negative real part. In order to find how large this stability region is, we make use of the fact that the roots of (3.13) depend continuously on β and α. A root can move into the right half-plane only by passing through the value zero or by crossing the imaginary axis as βN and α vary. Thus, the stability region contains the β-axis and extends into the plane until there is a root $\lambda = 0$ or until there is a pair of pure imaginary roots $\lambda = \pm iy$ with $y > 0$. Since the left side and right side of (3.13) have opposite sign for real $\lambda \geq 0$, there cannot be a root $\lambda = 0$.

The condition that there is a root $\lambda = iy$ is

$$\alpha\beta I_\infty \frac{1 - e^{-i\omega\alpha}}{iy} = -(iy + \alpha + \beta S_\infty + \beta I_\infty) \tag{3.14}$$

and separation into real and imaginary parts gives the pair of equations

$$\alpha\beta \frac{\sin \omega y}{y} = -[\alpha + \beta S_\infty + \beta I_\infty], \quad \alpha\beta I_\infty \frac{1 - \cos \omega y}{y} = y. \tag{3.15}$$

To satisfy the first condition, it is necessary to have $\omega\alpha > 1$ since $|\sin \omega y| \leq |\omega y|$ for all y. This implies, in particular, that the endemic equilibrium is asymptotically stable if $\omega\alpha < 1$. In addition, it is necessary to have $\sin \omega y < 0$. There is an infinite sequence of intervals on which $\sin \omega y < 0$, the first being $\pi < \omega y < 2\pi$. For each of these intervals, the equations (3.15) define a curve in the (β, α) plane parametrically with y as parameter. The region in the plane below the first of these curves is the region of asymptotic stability, that is, the set of values of β and α for which the endemic equilibrium is asymptotically stable. This curve is shown for $\omega = 1$, $N = 1$ in Fig. 3.3. Since $\mathscr{R}_0 = \beta N/\alpha > 1$, only the portion of the (β, α) plane below the line $\alpha = \beta N$ is relevant.

The new feature of the model of this section is that the endemic equilibrium is not asymptotically stable for all parameter values. What is the behavior of the model if the parameters are such that the endemic equilibrium is unstable? A plausible suggestion is that since the loss of stability corresponds to a root $\lambda = iy$ of the characteristic equation there are solutions of the model behaving like the real part of e^{iyt}, that is, that there are periodic solutions. This is exactly what does happen according to a very general result called the Hopf bifurcation theorem [25], which says that when roots of the characteristic equation cross the imaginary axis a stable periodic orbit arises.

From an epidemiological point of view periodic behavior is unpleasant. It implies fluctuations in the number of infectives which makes it difficult to allocate resources for treatment. It is also possible for oscillations to have a long period. This means that if data are measured over only a small time interval the actual behavior may not be displayed. Thus, the identification of situations in which an endemic equilibrium is unstable is an important problem.

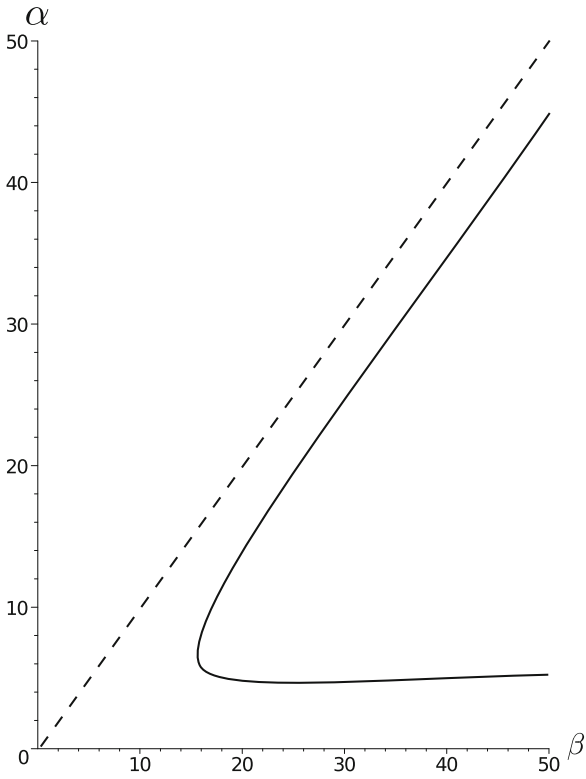


Fig. 3.3 Region of asymptotic stability for endemic equilibria ($\omega = 1$, $N = 1$)

3.4 A Simple Model with Multiple Endemic Equilibria

In compartmental models for the transmission of communicable diseases there is usually a basic reproduction number $\mathscr{R}_0$, representing the mean number of secondary infections caused by a single infective introduced into a susceptible population. If $\mathscr{R}_0 < 1$ there is a disease-free equilibrium which is asymptotically stable, and the infection dies out. If $\mathscr{R}_0 > 1$ the usual situation is that there is a unique endemic equilibrium which is asymptotically stable, and the infection persists. Even if the endemic equilibrium is unstable, the instability commonly arises from a Hopf bifurcation [25], described in Sect. 3.3, and the infection still persists but in an oscillatory manner. More precisely, as $\mathscr{R}_0$ increases through 1 there is an exchange of stability between the disease-free equilibrium and the endemic equilibrium (which is negative as well as unstable and thus biologically meaningless if $\mathscr{R}_0 < 1$).

There are, however, situations in which there may be more than one endemic equilibrium even in very simple epidemic models, and we describe such a model suggested in [42, 43]. We consider an SIS model in a population of constant total size N with treatment of infectives, assuming that the treatment cures the infection but that there is a maximum capacity for treatment. Thus we assume a model

$$\begin{aligned} S' &= -\beta SI + h(I) \\ I' &= \beta SI - \alpha I - h(I), \end{aligned} \tag{3.16}$$

assuming a treatment function $h(I)$ of the form

$$h(I) = \begin{cases} rI, & (I < I^*) \\ rI^*, & (I \geq I^*), \end{cases}$$

in which r is a constant representing the treatment rate up to a maximum capacity rI^*. Since the total population size $S + I$ is a constant N, we may replace S by $N - I$ and reduce the model to a single equation

$$I' = \beta I(N - I) - \alpha I - h(I) = g(I). \tag{3.17}$$

There is a disease-free equilibrium $I = 0$, and it is easily verified that the disease-free equilibrium is asymptotically stable if and only if $\mathscr{R}_0 = \beta N/(\alpha + r) < 1$.

For $I \leq I^*$,

$$g(I) = \beta I(N - I) - (\alpha + r)I,$$

and an endemic equilibrium with $I \leq I^*$ is a positive solution I_∞ of $g(I) = 0$, namely

$$I_\infty = N - \frac{\alpha + r}{\beta} = N\left(1 - \frac{1}{\mathscr{R}_0}\right),$$

and there is such an equilibrium if and only if

$$I^* \geq N - \frac{\alpha + r}{\beta} = N\left(1 - \frac{1}{\mathscr{R}_0}\right). \tag{3.18}$$

For $I \leq I^*$,

$$g'(I) = \beta(N - 2\beta I - (\alpha + r),$$

and $g'(I_\infty) < 0$ if and only if

$$N - \frac{\alpha + r}{\beta} < 2I_\infty = 2\left(N - \frac{\alpha + r}{\beta}\right),$$

and this is equivalent to $\mathscr{R}_0 > 1$. Thus, the equilibrium $I_\infty \leq I^*$ exists and is asymptotically stable if and only if (3.18) is satisfied.

Equilibria $I > I^*$ are solutions of the quadratic equation

$$g(I) = -\beta I^2 + (\beta N - \alpha)I - rI^* = 0,$$

which are

$$I = \frac{(\beta N - \alpha) + \sqrt{(\beta N - \alpha)^2 - 4r\beta I^*}}{2\beta}, \quad J = \frac{(\beta N - \alpha) - \sqrt{(\beta N - \alpha)^2 - 4\beta r I^*}}{2\beta}.$$

Then $J < (\beta N - \alpha)/2\beta$ and $I > (\beta N - \alpha)/2\beta$. For these to qualify as equilibria, they must also be greater than I^* and less than N, but it is possible to choose parameter values such that the model (3.16) has more than one endemic equilibrium. For example, the choices

$$\alpha = 0.5, \quad r = 0.5, \quad N = 1, \quad I^* = 0.05,$$

so that $\mathscr{R}_0 = \beta$, give two equilibria I, J for some values of β, including some values with $\mathscr{R}_0 < 1$. With these parameter values, $I = J = 0.279$ when $\beta = 0.779$.

An equilibrium I_∞ of the differential equation $I' = g(I)$ is asymptotically stable if $g'(I_\infty) < 0$, and unstable if $g'(I_\infty) > 0$. From this, it is easy to deduce that the equilibrium J is unstable, while the equilibrium I is asymptotically stable. If we plot the equilibrium values as functions of β, the curve I begins at the point $(0.779, 0.279)$ and goes upwards to the right, while the curve J goes downward to the right from the same starting point. Because of the choice $I^* = 0.05$, only the portion of the J curve above the line $I = 0.05$ is relevant. For $0.779 \le \mathscr{R}_0 \le 1$ there are two asymptotically stable equilibria, namely 0 and I separated by an unstable equilibrium J. For this reason, we have drawn the J curve as a dotted curve in Fig. 3.4.

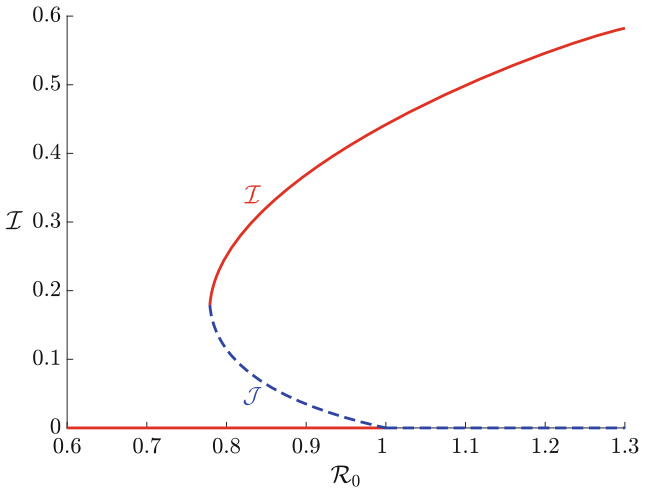


Fig. 3.4 Multiple endemic equilibria

A *bifurcation curve*, a graph of equilibria as a function of the basic reproduction number, as in Fig. 3.4, gives a good deal of information about the behavior of endemic equilibria. We observe, for example, that in Fig. 3.4, there are endemic equilibria for some values of the basic reproduction number less than 1, and that there is a discontinuity in the endemic equilibria at $\mathscr{R}_0 = 1$.

3.5 A Vaccination Model: Backward Bifurcations

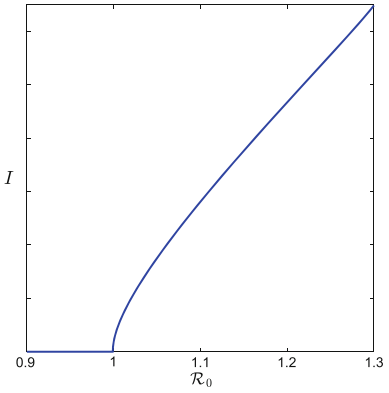
In a compartmental model, there is a bifurcation, or change in equilibrium behavior, at $\mathscr{R}_0 = 1$ but the equilibrium infective population size depends continuously on $\mathscr{R}_0$. Such a transition is called a forward, or transcritical, bifurcation.

The behavior at a bifurcation may be described graphically by the bifurcation curve, which is the graph of equilibrium infective population size I as a function of the basic reproduction number $\mathscr{R}_0$. For a forward bifurcation, the bifurcation curve is as shown in Fig. 3.5.

It has been noted [14, 20, 21, 29] that in epidemic models with multiple groups and asymmetry between groups or multiple interaction mechanisms it is possible to have a very different bifurcation behavior at $\mathscr{R}_0 = 1$. There may be multiple positive endemic equilibria for values of $\mathscr{R}_0 < 1$ and a backward bifurcation at $\mathscr{R}_0 = 1$. This means that the bifurcation curve has the form shown in Fig. 3.4 with a broken curve denoting an unstable endemic equilibrium that separates the domains of attraction of asymptotically stable equilibria.

The qualitative behavior of an epidemic system with a backward bifurcation differs from that of a system with a forward bifurcation in at least three important ways. If there is a forward bifurcation at $\mathscr{R}_0 = 1$ it is not possible for a disease to invade a population if $\mathscr{R}_0 < 1$ because the system will return to the disease-free equilibrium $I = 0$ if some infectives are introduced into the population. On the other hand, if there is a backward bifurcation at $\mathscr{R}_0 = 1$ and enough infectives are

Fig. 3.5 Forward bifurcation



introduced into the population to put the initial state of the system above the unstable endemic equilibrium with $\mathscr{R}_0 < 1$, the system will approach the asymptotically stable endemic equilibrium.

Other differences are observed if the parameters of the system change to produce a change in $\mathscr{R}_0$. With a forward bifurcation at $\mathscr{R}_0 = 1$ the equilibrium infective population remains zero so long as $\mathscr{R}_0 < 1$ and then increases continuously as $\mathscr{R}_0$ increases. With a backward bifurcation at $\mathscr{R}_0 = 1$, there is an asymptotically stable disease-free equilibrium so long as $\mathscr{R}_0 < 1$ but there is also an asymptotically stable endemic equilibrium for some values of $\mathscr{R}_0 < 1$ and as $\mathscr{R}_0$ increases through 1 the infective population size jumps to the positive endemic equilibrium. In the other direction, if a disease is being controlled by means that decrease $\mathscr{R}_0$ it is sufficient to decrease $\mathscr{R}_0$ to 1 if there is a forward bifurcation at $\mathscr{R}_0 = 1$ but it is necessary to bring $\mathscr{R}_0$ well below 1 if there is a backward bifurcation.

These behavior differences are important in planning how to control a disease; a backward bifurcation at $\mathscr{R}_0 = 1$ makes control more difficult. One control measure often used is the reduction of susceptibility to infection produced by vaccination. By vaccination, we mean either an inoculation that reduces susceptibility to infection or an education program such as encouragement of better hygiene or avoidance of risky behavior for sexually transmitted diseases. Whether vaccination is inoculation or education, typically it reaches only a fraction of the susceptible population and is not perfectly effective. In an apparent paradox, models with vaccination may exhibit backward bifurcations, making the behavior of the model more complicated than the corresponding model without vaccination. It has been argued [6] that a partially effective vaccination program applied to only part of the population at risk may increase the severity of outbreaks of such diseases as HIV/AIDS.

We will give a qualitative analysis of a model which may have a variable total population size $N \leq K$ for which there is a possibility of a backward bifurcation. The model we will study adds vaccination to the simple SIS model with births and natural deaths but with no disease deaths studied in Sect. 2.2. We have considered the model

$$\begin{aligned} S' &= \Lambda(N) - \beta(N)SI - \mu S + \alpha I \\ I' &= \beta SI - (\mu + \alpha)I, \end{aligned} \tag{3.19}$$

where the population carrying capacity K is defined by $\Lambda(K) = \mu K$, $\Lambda'(K) < \mu$ and the contact rate $\beta(N)$ is a function of total population size with $N\beta(N)$ non-decreasing and $\beta(N)$ non-increasing. We have seen that there is a disease-free equilibrium $I = 0$ that is asymptotically stable if

$$\mathscr{R}_0 = \frac{K\beta(K)}{\mu + \alpha} < 1.$$

If $\mathscr{R}_0 > 1$ the disease-free equilibrium is unstable but there is an endemic equilibrium that is asymptotically stable.

To the model (3.19) we add the assumption that in unit time a fraction φ of the susceptible class is vaccinated. The vaccination may reduce but not completely eliminate susceptibility to infection. We model this by including a factor σ, $0 \leq \sigma \leq 1$, in the infection rate of vaccinated members with $\sigma = 0$ meaning that the vaccine is perfectly effective and $\sigma = 1$ meaning that the vaccine has no effect. We describe the new model by including a vaccinated class V, with

$$\begin{aligned} S' &= \mu N - \beta(N)SI - (\mu + \varphi)S + \alpha I \\ I' &= \beta(N)SI + \sigma\beta(N)VI - (\mu + \alpha)I \\ V' &= \varphi S - \sigma\beta(N)VI - \mu V \end{aligned} \tag{3.20}$$

and $N = S + I + V$. Since N is constant, we can replace S by $N - I - V$ to give the equivalent system

$$\begin{aligned} I' &= \beta\,[N - I - (1 - \sigma)V]\,I - (\mu + \alpha)I \\ V' &= \varphi[N - I] - \sigma\beta VI - (\mu + \varphi)V \end{aligned} \tag{3.21}$$

with $\beta = \beta(N)$. The system (3.21) is the basic vaccination model which we will analyze. We remark that if the vaccine is completely ineffective, $\sigma = 1$, then (3.21) is equivalent to an SIS model. If all susceptibles are vaccinated immediately (formally, $\varphi \to \infty$), the model (3.21) is equivalent to

$$I' = \sigma\beta I(K - I) - (\mu + \alpha)I$$

which is an SIS model with basic reproduction number

$$\mathscr{R}_0^* = \frac{\sigma\beta K}{\mu + \alpha} = \sigma\mathscr{R}_0 \leq \mathscr{R}_0.$$

We will think of the parameters μ, α, φ, and σ as fixed and will view β as variable. In practice, the parameter φ is the one most easily controlled, and later we will express our results in terms of an uncontrolled model with parameters β, μ, α, and σ fixed and examine the effect of varying φ. With this interpretation in mind, we will use $\mathscr{R}(\varphi)$to denote the basic reproduction number of the model (3.21), and we will see that

$$\mathscr{R}_0^* \leq \mathscr{R}(\varphi) \leq \mathscr{R}_0.$$

Equilibria of the model (3.21) are solutions of

$$\begin{aligned} \beta I\,[K - I - (1 - \sigma)V] &= (\mu + \alpha)I \\ \varphi[K - I] &= \sigma\beta VI + (\mu + \varphi)V. \end{aligned} \tag{3.22}$$

If $I = 0$, then the first of these equations is satisfied and the second leads to

$$V = \frac{\varphi}{\mu + \varphi} K.$$

This is the disease-free equilibrium.

The matrix of the linearization of (3.21) at an equilibrium (I, V) is

$$\begin{bmatrix} -2\beta I - (1-\sigma)\beta V - (\mu+\alpha) + \beta K & -(1-\sigma)\beta I \\ -(\varphi + \sigma\beta V) & -(\mu + \varphi + \sigma\beta I) \end{bmatrix}.$$

At the disease-free equilibrium this matrix is

$$\begin{bmatrix} -(1-\sigma)\beta V - (\mu+\alpha) + \beta K & 0 \\ -(\varphi + \sigma\beta V) & -(\mu+\varphi) \end{bmatrix}$$

which has negative eigenvalues, implying the asymptotic stability of the disease-free equilibrium, if and only if

$$-(1-\sigma)\beta V - (\mu+\alpha) + \beta K < 0.$$

Using the value of V at the disease-free equilibrium this condition is equivalent to

$$\mathscr{R}(\varphi) = \frac{\beta K}{\mu+\alpha} \cdot \frac{\mu + \sigma\varphi}{\mu+\varphi} = \mathscr{R}_0 \frac{\mu+\sigma\varphi}{\mu+\varphi} < 1.$$

The case $\varphi = 0$ is that of no vaccination with $\mathscr{R}(0) = \mathscr{R}_0$, and $\mathscr{R}(\varphi) < \mathscr{R}_0$ if $\varphi > 0$. We note that $\mathscr{R}_0^* = \sigma\mathscr{R}_0 = \lim_{\varphi\to\infty} \mathscr{R}(\varphi) < \mathscr{R}_0$.

If $0 \le \sigma < 1$ endemic equilibria are solutions of the pair of equations

$$\begin{aligned} \beta\,[K - I - (1-\sigma)V] &= \mu + \alpha \\ \varphi[K - I] &= \sigma\beta V I + (\mu+\varphi)V. \end{aligned} \tag{3.23}$$

We eliminate V using the first equation of (3.23) and substitute into the second equation to give an equation of the form

$$AI^2 + BI + C = 0 \tag{3.24}$$

with

$$\begin{aligned} A &= \sigma\beta \\ B &= (\mu + \theta + \sigma\varphi) + \sigma(\mu+\alpha) - \sigma\beta K \\ C &= \frac{(\mu+\alpha)(\mu+\theta+\varphi)}{\beta} - (\mu+\theta+\sigma\varphi)K. \end{aligned} \tag{3.25}$$

If $\sigma = 0$ (3.24) is a linear equation with unique solution.

$$I = K - \frac{(\mu+\alpha)(\mu+\varphi)}{\beta\mu} = K\left[1 - \frac{1}{\mathscr{R}(\varphi)}\right]$$

which is positive if and only if $\mathscr{R}(\varphi) > 1$. Thus if $\sigma = 0$ there is a unique endemic equilibrium if $\mathscr{R}(\varphi) > 1$ that approaches zero as $\mathscr{R}(\varphi) \to 1+$ and there cannot be an endemic equilibrium if $\mathscr{R}(\varphi) < 1$. In this case, it is not possible to have a backward bifurcation at $\mathscr{R}(\varphi) = 1$.

We note that $C < 0$ if $\mathscr{R}(\varphi) > 1$, $C = 0$ if $\mathscr{R}(\varphi) = 1$, and $C > 0$ if $\mathscr{R}(\varphi) < 1$. If $\sigma > 0$, so that (3.24) is quadratic and if $\mathscr{R}(\varphi) > 1$ then there is a unique positive root of (3.24) and thus there is a unique endemic equilibrium. If $\mathscr{R}(\varphi) = 1$, then $C = 0$ and there is a unique non-zero solution of (3.24) $I = -B/A$ which is positive if and only if $B < 0$. If $B < 0$ when $C = 0$ there is a positive endemic equilibrium for $\mathscr{R}(\varphi) = 1$. Since equilibria depend continuously on φ there must then be an interval to the left of $\mathscr{R}(\varphi) = 1$ on which there are two positive equilibria

$$I = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A}.$$

This establishes that the system (3.21) has a backward bifurcation at $\mathscr{R}(\varphi) = 1$ if and only if $B < 0$ when β is chosen to make $C = 0$.

We can give an explicit criterion in terms of the parameters μ, φ, σ for the existence of a backward bifurcation at $\mathscr{R}(\varphi) = 1$. When $\mathscr{R}(\varphi) = 1$, $C = 0$ so that

$$(\mu + \sigma\varphi)\beta K = (\mu+\alpha)(\mu+\varphi). \tag{3.26}$$

The condition $B < 0$ is

$$(\mu + \sigma\varphi) + \sigma(\mu+\alpha) < \sigma\beta K$$

with βK determined by (3.26), or

$$\sigma(\mu+\alpha)(\mu+\varphi) > (\mu+\sigma\varphi)\left[(\mu+\sigma\varphi) + \sigma(\mu+\alpha)\right]$$

which reduces to

$$\sigma(1-\sigma)(\mu+\alpha)\varphi > (\mu+\sigma\varphi)^2. \tag{3.27}$$

A backward bifurcation occurs at $\mathscr{R}(\varphi) = 1$, with βK given by (3.26) if and only if (3.27) is satisfied. We point out that for an SI model, where $\alpha = 0$, the condition (3.27) becomes

$$\sigma(1-\sigma)\mu\varphi > (\mu+\sigma\varphi)^2.$$

But

$$(\mu+\sigma\varphi)^2 = \mu^2+\sigma^2\varphi^2+2\mu\sigma\varphi$$
$$> 2\mu\sigma\varphi > \sigma(1-\sigma)\mu\varphi$$

because $\sigma < 1$. Thus a backward bifurcation is not possible if $\alpha = 0$, that is, for an SI model. Likewise, (3.27) cannot be satisfied if $\sigma = 0$.

If $C > 0$ and either $B \geq 0$ or $B^2 < 4AC$, there are no positive solutions of (3.24)and thus there are no endemic equilibria. Equation (3.24) has two positive solutions, corresponding to two endemic equilibria, if and only if $C > 0$, or $\mathscr{R}(\varphi) < 1$, and $B < 0$, $B^2 > 4AC$, or $B < -2\sqrt{AC} < 0$. If $B = -2\sqrt{AC}$, there is one positive solution $I = -B/2A$ of (3.24).

If (3.27) is satisfied, so that there is a backward bifurcation at $\mathscr{R}(\varphi) = 1$, there are two endemic equilibria for an interval of values of β from

$$\beta K = \frac{(\mu+\alpha)(\mu+\varphi)}{\mu+\sigma\varphi}$$

corresponding to $\mathscr{R}(\varphi) = 1$ to a value β_c defined by $B = -2\sqrt{AC}$. To calculate β_c, we let $x = \mu+\alpha-\beta K$, $U = \mu+\sigma\varphi$ to give $B = \sigma x + U$, $\beta C = \beta K U + (\mu+\alpha)(\mu+\varphi)$. Then $B^2 = 4AC$ becomes

$$(\sigma x+U)^2 + 4\beta\sigma K U - 4\sigma(\mu+\alpha)(\mu+\varphi) = 0$$

which reduces to

$$(\sigma x)^2 - 2U(\sigma x) + \left[U^2 + 4\sigma(1-\sigma)(\mu+\alpha)\varphi\right] = 0$$

with roots

$$\sigma x = U \pm 2\sqrt{\sigma(1-\sigma)(\mu+\alpha)\varphi}.$$

For the positive root $B = \sigma x + U > 0$, and since we require $B < 0$ as well as $B^2 - 4AC = 0$, we obtain β_c from $\sigma x = U - 2\sqrt{\sigma(1-\sigma)(\mu+\alpha)\varphi}$ so that

$$\sigma\beta_c K = \sigma(\mu+\alpha) + 2\sqrt{\sigma(1-\sigma)(\mu+\alpha)\varphi} - (\mu+\sigma\varphi). \tag{3.28}$$

Then the critical basic reproduction number $\mathscr{R}_c$ is given by

$$\mathscr{R}_c = \frac{\mu+\sigma\varphi}{\mu+\varphi}\cdot\frac{\sigma(\mu+\alpha)+2\sqrt{\sigma(1-\sigma)(\mu+\alpha)\varphi}-(\mu+\sigma\varphi)}{\sigma(\mu+\alpha)\varphi}$$

and it is possible to verify with the aid of (3.28) that $\mathscr{R}_c < 1$.

3.5.1 The Bifurcation Curve

In drawing the bifurcation curve (the graph of I as a function of $\mathscr{R}(\varphi)$), we think of β as variable with the other parameters $\mu, \alpha, \sigma, Q, \varphi$ as constant. Then $\mathscr{R}(\varphi)$ is a constant multiple of β and we can think of β as the independent variable in the bifurcation curve.

Implicit differentiation of the equilibrium condition (3.24) with respect to β gives

$$(2AI + B)\frac{dI}{d\beta} = \sigma I(K - I) + \frac{(\mu + \alpha)(\mu + \varphi)}{\beta^2}.$$

It is clear from the first equilibrium condition in (3.23) that $I \leq K$ and this implies that the bifurcation curve has positive slope at equilibrium values with $2AI + B > 0$ and negative slope at equilibrium values with $2AI + B < 0$. If there is not a backward bifurcation at $\mathscr{R}(\varphi) = 1$, then the unique endemic equilibrium for $\mathscr{R}(\varphi) > 1$ satisfies

$$2AI + B = \sqrt{B^2 - 4AC} > 0$$

and the bifurcation curve has positive slope at all points where $I > 0$. Thus the bifurcation curve is as shown in Fig. 3.5.

If there is a backward bifurcation at $\mathscr{R}(\varphi) = 1$, then there is an interval on which there are two endemic equilibria given by

$$2AI + B = \pm\sqrt{B^2 - 4AC}.$$

The bifurcation curve has negative slope at the smaller of these and positive slope at the larger of these. Thus the bifurcation curve is as shown in Fig. 3.4.

The condition $2AI + B > 0$ is also significant in the local stability analysis of endemic equilibria. An endemic equilibrium of (3.21) is (locally) asymptotically stable if and only if it corresponds to a point on the bifurcation curve at which the curve is increasing. To prove this, we observe that the matrix of the linearization of (3.21) at an equilibrium (I, V) is

$$\begin{bmatrix} -2\beta I - (1-\sigma)\beta V - (\mu + \alpha) + \beta K & -(1-\sigma)\beta I \\ -(\varphi + \sigma\beta V) & -(\mu + \varphi + \sigma\beta I) \end{bmatrix}.$$

Because of the equilibrium conditions (3.23), the matrix at an endemic equilibrium (I, V) is

$$\begin{bmatrix} -\beta I & -(1-\sigma)\beta I \\ -(\varphi + \sigma\beta V) & -(\mu + \varphi + \sigma\beta I) \end{bmatrix}.$$

This has negative trace, and its determinant is

$$\begin{aligned}&\sigma(\beta I)^2+\beta I(\mu+\varphi)-(1-\sigma)\varphi\beta I-(1-\sigma)\beta V\cdot\sigma\beta I\\&=\beta I\big[2\sigma\beta I+(\mu+\sigma\varphi)+\sigma(\mu+\alpha)-\sigma\beta K\big]\\&=\beta I[2AI+B].\end{aligned}$$

If $2AI + B > 0$, that is, if the bifurcation curve has positive slope, then the determinant is positive and the equilibrium is asymptotically stable. If $2AI+B < 0$ the determinant is negative and the equilibrium is unstable. In fact, it is a saddle point. A saddle point in the plane is an equilibrium at which the linearization has one positive eigenvalue and one negative eigenvalue. This means that there are two orbits approaching the saddle point called stable separatrices and two orbits going out from the saddle point, called unstable separatrices. Because orbits cannot cross the separatrices, the stable separatrices divide the plane into two regions and divide the plane into two domains of attraction. The stable separatrices in the (I, V) plane separate the domains of attraction of the other (asymptotically stable) endemic equilibrium and the disease-free equilibrium.

3.6 *An *SEIR* Model with General Disease Stage Distributions

The ODE models considered in earlier parts of the chapter, except the SIRS model in Sect. 3.3, assume exclusively that the durations of disease stages (e.g., latent and infectious stages) are exponentially distributed. This assumption, while making the models and their analyses easier, is not biologically realistic for most infectious diseases. A more appropriate distribution is the gamma distribution, for which the probability of remaining in the stage is given by

$$p_n(s)=\sum_{k=0}^{n-1}\frac{(n\theta s)^k s^{-n\theta s}}{k!} \tag{3.29}$$

where $1/\theta$ is the mean of the distribution and n is the shape parameter. The exponential distribution is the special case when $n = 1$. The other extreme case is when $n \to \infty$, which corresponds to a fixed duration. Figure 3.6 illustrates the gamma distribution for various n values. Let $1/\kappa$ and $1/\alpha$ denote the mean latent and infectious periods, and let m and n denote the shape parameter for the latent and infectious stages, respectively. It has been reported [44] that for measles

$$1/\kappa = 8,\quad 1/\alpha = 5,\quad m = n = 20,$$

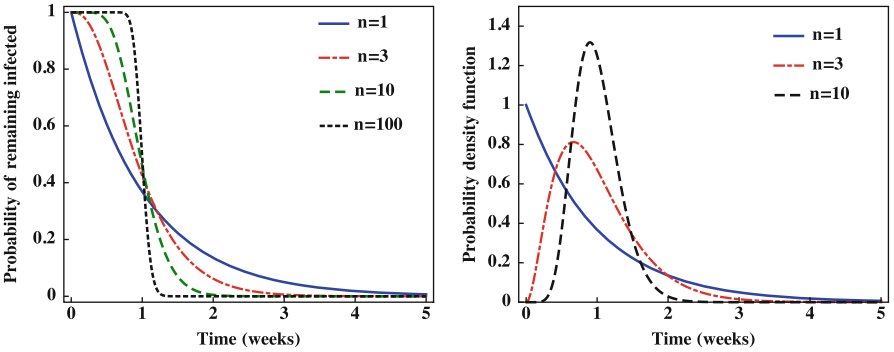


Fig. 3.6 Depictions of the survival probability (3.29) for the infectious period (left) and the probability density function (right) with different shape parameter values (n). The special case of $n = 1$ gives the exponential distribution. The mean infectious period ($1/\theta$) is chosen to be 1 week

and for smallpox

$$1/\kappa = 14, \quad 1/\alpha = 8.6, \quad m = 40, \quad n = 4.$$

There are other cases where the disease stage durations do not fit well by the standard family distributions. Epidemiological models with non-exponential distributions such as the gamma distribution have been previously studied (see, for example, [23, 30, 31]. In these studies, the authors discussed various drawbacks associated with the exponential distribution assumption. For example, it is pointed out that constant recovery is a poor description of real-world infections, and they show that in models with more realistic distributions of disease stages less stable behavior may be expected and disease persistence may be diminished [23, 30]. In [18] it was demonstrated that when control measures such as quarantine and isolation are considered, models with exponential and gamma distributions may generate contradictory evaluations on control strategies. Thus, it will be helpful to have mathematical results for models that allow arbitrary distributions. This is the goal of this section.

Let $P_E, P_I : [0, \infty) \to [0, 1]$ describe the durations of the exposed (latent) and infective stages, respectively. That is, $P_i(s)$ $(i = E, I)$ gives the probability that the disease stage i lasts longer than s time units (or the probability of being still in the same stage at stage age s). Then, the derivative $-\dot{P}_i(s)$ $(i = E, I)$ gives the rate of removal from the stage i at stage age s by the natural progression of the disease. These duration functions have the following properties:

$$P_i(0) = 1, \quad \dot{P}_i(s) \le 0, \quad \int_0^\infty P_i(s)ds < \infty, \quad i = E, I.$$

For the vital dynamics, we use the simplest function $e^{-\mu t}$ for the probability of survival (because our focus is on the effect of arbitrary distribution for disease stages). Let the numbers of initial susceptible and removed individuals be $S_0 > 0$ and $R_0 > 0$ respectively. Let $E_0(t)e^{-\mu t}$ and $I_0(t)e^{-\mu t}$ be the non-increasing functions that represent the numbers of individuals that were initially exposed and infective, respectively, and are still alive and in the respective classes at time t. $E(0)$ and $I(0)$ are constants representing the number of individuals in the E and I classes, respectively, at time $t = 0$. Let $\tilde{I}_0(t)$ denote those initially infected who have moved into the I, and are still alive at time t. Consider the force of infection $\lambda(t)$ that takes the form

$$\lambda(t) = c\frac{I(t)}{N}. \tag{3.30}$$

Then the number of individuals who became exposed at some time $s \in (0, t)$ and are still alive and in the E class at time t is

$$E(t) = \int_0^t \lambda(s)S(s)P_E(t-s)e^{-\mu(t-s)}ds + E_0(t)e^{-\mu t},$$

and the number of infectious individuals at time t is

$$I(t) = \int_0^t \int_0^\tau \lambda(s)S(s)[-\dot{P}_E(\tau - s)]P_I(t-\tau)e^{-\mu(t-s)}dsd\tau + I_0(t)e^{-\mu t} + \tilde{I}_0(t).$$

Assume that the recruitment rate is μN and they all enter the S class. Then the $SEIR$ model reads

$$\begin{aligned} S(t) &= \int_0^t \mu N e^{-\mu(t-s)}ds - \int_0^t \lambda(s)S(s)e^{-\mu(t-s)}ds + S_0e^{-\mu t}, \\ E(t) &= \int_0^t \lambda(s)S(s)P_E(t-s)e^{-\mu(t-s)}ds + E_0(t)e^{-\mu t}, \\ I(t) &= \int_0^t \int_0^\tau \lambda(s)S(s)[-\dot{P}_E(\tau - s)]P_I(t-\tau)e^{-\mu(t-s)}dsd\tau + \tilde{I}(t), \end{aligned} \tag{3.31}$$

where $\lambda(t)$ is given in (3.30), and $\tilde{X}(t) = X_0(t)e^{-\mu t} + \tilde{X}_0(t)$ $(X = Q, I, H, R)$. It can be shown that under standard assumptions on initial data and parameter functions the system (3.31) has a unique non-negative solution defined for all positive time.

When specific distributions are assumed for functions P_E and P_I the system (3.31) might be simplified. In particular, under the exponential distribution assumption (EDA) and gamma distribution assumption (GDA) the system can be reduced to be ODE systems, which will be referred to as the exponential distribution model (EDM) and gamma distribution model (GDM), respectively. This allows the examination of how the distribution assumptions may affect the model predictions.

Let

$$a(\tau) = e^{-\mu\tau} \int_0^\tau [-\dot{P}_E(\tau - u)] P_I(u) du. \tag{3.32}$$

The reproduction number is given by

$$\mathscr{R}_c = \int_0^\infty c a(\tau) d\tau. \tag{3.33}$$

To see the biological meaning of the expression (3.33) and to simplify the notation in later sections we introduce the following quantities:

$$\begin{aligned} \mathscr{T}_E &= \int_0^\infty [-\dot{P}_E(s)] e^{-\mu s} ds, \quad \mathscr{T}_I = \int_0^\infty [-\dot{P}_I(s)] e^{-\mu s} ds, \\ \mathscr{D}_E &= \int_0^\infty P_E(s) e^{-\mu s} ds, \qquad \mathscr{D}_I = \int_0^\infty P_I(s) e^{-\mu s} ds. \end{aligned} \tag{3.34}$$

$\mathscr{T}_E$, $\mathscr{T}_I$ represent, respectively, the probability that exposed individuals survive and become infectious, and the probability that infectious individuals survive and become recovered. $\mathscr{D}_E$ represents the mean sojourn time (death-adjusted) in the exposed stage, and $\mathscr{D}_I$ represents the mean sojourn time (death-adjusted) in the infectious stage. Using (3.34) we can rewrite $\mathscr{R}_c$ in (3.33) as

$$\mathscr{R}_c = c \int_0^\infty a(\tau) d\tau = c \mathscr{T}_{E_k} \mathscr{D}_{I_l}. \tag{3.35}$$

System (3.31) always has the disease-free equilibrium (DFE), and an endemic equilibrium may exist depending on the value of $\mathscr{R}_0$ as described below. The proof of the result can be found in [18].

Result *For System (3.31), the DFE is a global attractor if $\mathscr{R}_c < 1$ and unstable if $\mathscr{R}_c > 1$, in which case an endemic equilibrium exists and is stable.*

To compare the model behavior under different stage distributions, let P_E and P_I be the gamma distributions with the duration functions $P_E(s) = p_m(s, \kappa)$ and $P_I(s) = p_n(s, \alpha)$, with mean $1/\kappa$ and $1/\alpha$, respectively. When $m = n = 1$, where m and n are the shape parameters, P_E and P_I are exponential distributions the general model (3.31) has the usual form of the standard SEIR model:

$$\begin{aligned} S' &= \mu N - cS\tfrac{I}{N} - \mu S, \\ E' &= cS\tfrac{I}{N} - (\kappa + \mu)E, \\ I' &= \kappa E - (\alpha + \mu)I. \end{aligned} \tag{3.36}$$

For other integers m and n, then the integral equation model (3.31) can be reduced to an ordinary differential equation model. It has been noted that the use

of the gamma distribution $p_n(s,\theta)$ for a disease stage, e.g., the exposed stage, is equivalent to assuming that the entire stage is replaced by a series of n sub-stages, and each of the sub-stages is exponentially distributed with the removal rate $n\theta$ and the mean sojourn time T/n, where $T = 1/\theta$ is the mean sojourn time of the entire stage (see, for example, [23, 30, 32]). This approach of converting a gamma distribution to a sequence of exponential distributions is known as the "linear chain trick". In this case, the general model (3.31) reduces to the following ODEs:

$$\begin{aligned}
&S' = \mu N - cS\tfrac{I}{N} - \mu S,\\
&E_1' = cS\tfrac{I}{N} - (m\kappa + \mu)E_1,\\
&E_j' = m\kappa E_{j-1} - (m\kappa + \mu)E_j, \quad j = 2, \cdots, m,\\
&I_1' = m\kappa E_m - (n\alpha + \mu)I_1,\\
&I_j' = n\alpha I_{j-1} - (n\alpha + \mu)I_j, \quad j = 2, \cdots, n,\\
&\text{with } I = \textstyle\sum_{j=1}^{n} I_j.
\end{aligned} \tag{3.37}$$

From the formula (3.35) we get the reproduction number for system (3.37):

$$\mathscr{R}_c = \frac{(m\kappa)^m}{(\mu + m\kappa)^m} \frac{c}{\mu + n\alpha} \sum_{j=0}^{n-1} \frac{(n\alpha)^j}{(\mu + n\alpha)^j}. \tag{3.38}$$

The qualitative behavior of the two systems (3.36) and (3.37) is the same due to the results stated above. For the quantitative behavior, some differences exist. For example, Fig. 3.7 illustrates that the model with gamma distributions tend to generate a lower frequency in oscillations than the model with exponential

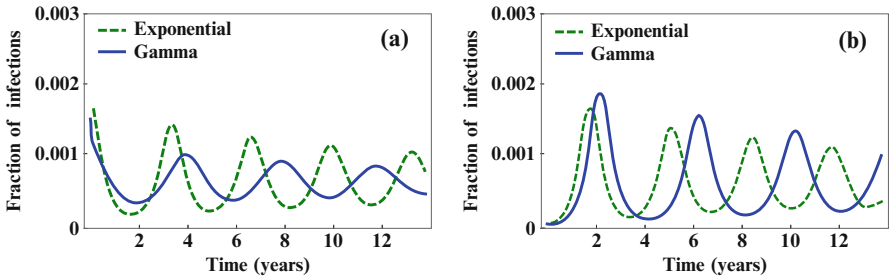


Fig. 3.7 Comparison of simulations of the SEIR model with exponential and gamma distributions (3.36) and (3.37). Plot in (**a**) is for the case when the initial fraction of infectious individuals is higher (0.0015) while in (**b**) it is lower (0.0001). We observe in (**a**) that the solution of the model with gamma distribution has much lower magnitude in the oscillation than the solution of the model with exponential distribution, whereas in (**b**) it is opposite. However, in both (**a**) and (**b**) the frequency of the oscillation is lower for the gamma distribution model than for the exponential distribution model. The parameter values used are $1/\kappa = 2$ (day), $1/\alpha = 7$ (day), $1/\mu = 15$ (year). This is more appropriate for modeling school entry and exit. The values of c is chosen so that $\mathscr{R}_0 = 2$

distributions. As for the magnitude of oscillations, either model can have a higher magnitude than the other depending on the initial conditions.

3.6.1 *Incorporation of Quarantine and Isolation

As pointed out earlier, the model with gamma distributions for disease stages (3.37) has similar qualitative behavior as the model with exponential distributions (3.36). As will be shown in this section, when control measures with quarantine and isolation are considered, models with exponential and gamma distributions can generate very different quantitative outcomes, including contradictory evaluations regarding control strategies.

Let ρ denote the isolation efficiency with $\rho = 1$ representing complete effectiveness. Thus, when $\rho < 1$ the isolated individuals can transmit the infection with a reduced infectivity $1 - \rho$. The force of infection is

$$\lambda(t) = c\frac{I(t) + (1-\rho)H(t)}{N}. \tag{3.39}$$

Let $k(s), l(s): [0, \infty) \to [0, 1]$ denote, respectively, the probabilities that exposed, infective individuals have not been quarantined, isolated at stage age s. Hence, $1 - k(s) =: \bar{k}(s)$, $1 - l(s) =: \bar{l}(s)$ give the respective probabilities of being quarantined, isolated before reaching stage age s. Assume that $k(0) = l(0) = 1$, $\dot{k}(s) \le 0$ and $\dot{l}(s) \le 0$. Consider the simpler case when the survivals from quarantine and isolation are described by the exponential functions

$$k(s) = e^{-\chi s}, \qquad l(s) = e^{-\phi s} \tag{3.40}$$

with χ and ϕ being constants, we have

$$E_0(t) = E(0)e^{-(\chi+\alpha)t}, \quad I_0(t) = I(0)e^{-(\phi+\delta)t}, \quad \text{etc.} \tag{3.41}$$

The model with general distributions as well as quarantine and isolation is

$$S(t) = \int_0^t \mu N e^{-\mu(t-s)}ds - \int_0^t \lambda(s)S(s)e^{-\mu(t-s)}ds + S_0 e^{-\mu t},$$

$$E(t) = \int_0^t \lambda(s)S(s)P_E(t-s)k(t-s)e^{-\mu(t-s)}ds + E_0(t)e^{-\mu t},$$

$$Q(t) = \int_0^t \int_0^\tau \lambda(s)S(s)[-P_E(\tau-s)\dot{k}(\tau-s)]P_E\big(t-\tau\big|\tau-s\big)e^{-\mu(t-s)}dsd\tau + \tilde{Q}(t),$$

$$I(t) = \int_0^t \int_0^\tau \lambda(s)S(s)[-\dot{P}_E(\tau-s)k(\tau-s)]P_I(t-\tau)l(t-\tau)e^{-\mu(t-s)}dsd\tau + \tilde{I}(t),$$

$$
\begin{aligned}
H(t) = &\int_0^t \int_0^u \int_0^\tau \lambda(s)S(s)[-\dot{P}_E(\tau - s)k(\tau - s)][-P_I(u - \tau)\dot{l}(u - \tau)] \\
&\qquad \times P_I\big(t - u\big|u - \tau\big)e^{-\mu(t-s)}dsd\tau du \\
&+\int_0^t \int_0^\tau \lambda(s)S(s)[-\dot{P}_E(\tau - s)\bar{k}(\tau - s)]P_I(t - \tau)e^{-\mu(t-s)}dsd\tau + \tilde{H}(t), \\
R(t) = &\int_0^t \int_0^\tau \lambda(s)S(s)[-\dot{P}_E(\tau - s)][1 - P_I(t - \tau)]e^{-\mu(t-s)}dsd\tau + \tilde{R}(t),
\end{aligned}
\tag{3.42}
$$

where $\lambda(t)$ is given in (3.39) and $\tilde{X}(t) = X_0(t)e^{-\mu t} + \tilde{X}_0(t)$ $(X = Q, I, H, R)$. Again $\tilde{X}(t) \to 0$ as $t \to \infty$.

Let

$$
\begin{aligned}
a_1(\tau) &= e^{-\mu\tau}\int_0^\tau [-\dot{P}_E(\tau - u)k(\tau - u)]P_I(u)l(u)du, \\
a_2(\tau) &= e^{-\mu\tau}\int_0^\tau [-\dot{P}_E(\tau - u)k(\tau - u)]P_I(u)\bar{l}(u)du, \\
a_3(\tau) &= e^{-\mu\tau}\int_0^\tau [-\dot{P}_E(\tau - u)\bar{k}(\tau - u)]P_I(u)du,
\end{aligned}
\tag{3.43}
$$

where $\bar{k}(s) = 1 - k(s)$, $\bar{l}(s) = 1 - l(s)$. Let

$$
A(\tau) = a_1(\tau) + (1 - \rho)\Big[a_2(\tau) + a_3(\tau)\Big].
$$

Then, the reproduction number is

$$
\mathscr{R}_c = c\int_0^\infty A(\tau)d\tau. \tag{3.44}
$$

We can also rewrite $\mathscr{R}_0$ in the following form:

$$
\mathscr{R}_c = \mathscr{R}_I + \mathscr{R}_{IH} + \mathscr{R}_{QH}, \tag{3.45}
$$

where

$$
\begin{aligned}
\mathscr{R}_I &= c\int_0^\infty a_1(\tau)d\tau = c\mathscr{T}_{E_k}\mathscr{D}_{I_l}, \\
\mathscr{R}_{IH} &= (1 - \rho)c\int_0^\infty a_2(\tau)d\tau = (1 - \rho)c\mathscr{T}_{E_k}(\mathscr{D}_I - \mathscr{D}_{I_l}), \\
\mathscr{R}_{QH} &= (1 - \rho)c\int_0^\infty a_3(\tau)d\tau = (1 - \rho)c(\mathscr{T}_E - \mathscr{T}_{E_k})\mathscr{D}_I.
\end{aligned}
$$

and

$$\begin{aligned}
\mathscr{T}_E &= \int_0^\infty [-\dot{P}_E(s)]e^{-\mu s}ds, & \mathscr{T}_{E_k} &= \int_0^\infty [-\dot{P}_E(s)k(s)]e^{-\mu s}ds,\\
\mathscr{T}_I &= \int_0^\infty [-\dot{P}_I(s)]e^{-\mu s}ds, & \mathscr{T}_{I_l} &= \int_0^\infty [-\dot{P}_I(s)l(s)]e^{-\mu s}ds,\\
\mathscr{D}_E &= \int_0^\infty P_E(s)e^{-\mu s}ds, & \mathscr{D}_{E_k} &= \int_0^\infty P_E(s)k(s)e^{-\mu s}ds,\\
\mathscr{D}_I &= \int_0^\infty P_I(s)e^{-\mu s}ds, & \mathscr{D}_{I_l} &= \int_0^\infty P_I(s)l(s)e^{-\mu s}ds.
\end{aligned} \tag{3.46}$$

The three components, $\mathscr{R}_I, \mathscr{R}_{IH}, \mathscr{R}_{QH}$ in $\mathscr{R}_c$ represent contributions from the I class and from the H class through isolation and quarantine, respectively. $\mathscr{T}_E$ and $\mathscr{T}_{E_k}$ represent, respectively, the probability and the "quarantine-adjusted" probability that exposed individuals survive and become infectious. $\mathscr{T}_I$ and $\mathscr{T}_{I_l}$ represent, respectively, the probability and the "isolation-adjusted" probability that infectious individuals survive and become recovered. $\mathscr{D}_E$ and $\mathscr{D}_{E_k}$ represent, respectively, the mean sojourn time (death-adjusted) and the "quarantine-adjusted" mean sojourn time (death-adjusted as well) in the exposed stage. $\mathscr{D}_I$ and $\mathscr{D}_{I_l}$ represent, respectively, the mean sojourn time (death-adjusted) and the "isolation-adjusted" mean sojourn time (death-adjusted as well) in the infectious stage.

For system (3.42), the same results as for system (3.31) holds, i.e., the DFE is a global attractor if $\mathscr{R}_c < 1$ and unstable if $\mathscr{R}_c > 1$, in which case an endemic equilibrium exists and is stable.

3.6.2 *The Reduced Model of (3.42) Under GDA

Again let P_E and P_I be the gamma distributions with the duration functions $P_E(s) = p_m(s,\kappa)$ and $P_I(s) = p_n(s,\alpha)$, with mean $1/\kappa$ and $1/\alpha$, respectively. Then using the functions $k(s)$ and $l(s)$ given in (3.40) we can differentiate the equations in system (3.42) and obtain the following system of ordinary differential equations

$$\begin{aligned}
S' &= \mu N - cS\frac{I+(1-\rho)H}{N} - \mu S,\\
E_1' &= cS\frac{I+(1-\rho)H}{N} - (\chi + m\kappa + \mu)E_1,\\
E_j' &= m\kappa E_{j-1} - (\chi + m\kappa + \mu)E_j, \qquad j = 2,\cdots,m,\\
Q_1' &= \chi E_1 - (m\kappa + \mu)Q_1,\\
Q_j' &= \chi E_j + m\kappa Q_{j-1} - (m\kappa + \mu)Q_j, \qquad j = 2,\cdots,m,\\
I_1' &= m\kappa E_m - (\phi + n\alpha + \mu)I_1,
\end{aligned} \tag{3.47}$$

$$
\begin{aligned}
&I_j' = n\alpha I_{j-1} - (\phi + n\alpha + \mu)I_j, \qquad j = 2, \cdots, n,\\
&H_1' = m\kappa Q_m + \phi I_1 - (n\alpha + \mu)H_1,\\
&H_j' = n\alpha H_{j-1} + \phi I_j - (n\alpha + \mu)H_j, \qquad j = 2, \cdots, n,\\
&R' = n\alpha I_n + n\alpha H_n - \mu R,\\
&\text{with } I = \sum_{j=1}^{n} I_j,\ H = \sum_{j=1}^{n} H_j.
\end{aligned}
$$

In the special case when $m = n = 1$, the system (3.47) reduces to:

$$
\begin{aligned}
S' &= \mu N - cS\tfrac{I+(1-\rho)H}{N} - \mu S,\\
E' &= cS\tfrac{I+(1-\rho)H}{N} - (\chi + \kappa + \mu)E,\\
Q' &= \chi E - (\kappa + \mu)Q,\\
I' &= \kappa E - (\phi + \alpha + \mu)I,\\
H' &= \kappa Q + \phi I - (\alpha + \mu)H.
\end{aligned}
\tag{3.48}
$$

From the formula (3.45) we get the reproduction number for system (3.47):

$$
\begin{aligned}
\mathscr{R}_c = &\frac{(m\kappa)^m}{(\mu + m\kappa)^m}\frac{c}{\mu + n\delta}\sum_{j=0}^{n-1}\frac{(n\alpha)^j}{(\mu + n\alpha)^j}\\
&\left[1 - \rho\left(1 - \frac{(\mu + m\kappa)^m}{(\mu + m\kappa + \chi)^m}\frac{\mu + n\alpha}{\mu + n\alpha + \phi}\frac{\sum_{j=0}^{n-1}\frac{(n\alpha)^j}{(\mu+n\alpha+\phi)^j}}{\sum_{j=0}^{n-1}\frac{(n\alpha)^j}{(\mu+n\alpha)^j}}\right)\right],
\end{aligned}
\tag{3.49}
$$

with the derivatives

$$
\frac{\partial \mathscr{R}_c}{\partial \chi} = -c\rho\frac{m(m\kappa)^m}{(\mu + m\kappa + \chi)^{m+1}}\sum_{j=0}^{n-1}\frac{(n\alpha)^j}{(\mu + n\alpha + \phi)^{j+1}} < 0, \tag{3.50}
$$

$$
\frac{\partial \mathscr{R}_c}{\partial \phi} = -c\rho\frac{(m\kappa)^m}{(\mu + m\kappa + \chi)^m}\sum_{j=0}^{n-1}\frac{(j+1)(n\alpha)^j}{(\mu + n\alpha + \phi)^{j+2}} < 0. \tag{3.51}
$$

3.6.3 *Comparison of EDM and GDM

In this section, we show that when the GDA is used to replace the EDA, model predictions regarding the effectiveness of disease intervention policies may be different both quantitatively and qualitatively. We illustrate this by comparing the two models, GDM (3.47) and EDM (3.48). Two criteria are used in the comparison.

One is the impact of control measures described by χ and ϕ on the reduction in the magnitude of $\mathscr{R}_c$ and the other one is the reduction in the number of cumulative infections C at the end of an epidemic (the final epidemic size).

From (3.49) to (3.51) we know that the reproduction number $\mathscr{R}_c$ for GDM decreases with increasing χ and ϕ. Similarly, using the formula (3.45) we get the reproduction number for the EDM, $\mathscr{R}_c = \mathscr{R}_I + \mathscr{R}_{IH} + \mathscr{R}_{QH}$, where

$$\mathscr{R}_I = \frac{c\kappa}{(\mu+\kappa+\chi)(\mu+\alpha+\phi)},$$

$$\mathscr{R}_{IH} = \frac{(1-\rho)c\kappa}{\mu+\kappa+\chi}\left(\frac{1}{\mu+\alpha} - \frac{1}{\mu+\alpha+\phi}\right),$$

$$\mathscr{R}_{QH} = (1-\rho)c\left(\frac{\kappa}{\mu+\kappa} - \frac{\kappa}{\mu+\kappa+\chi}\right)\frac{1}{\mu+\alpha},$$

which can be written in a simpler form as:

$$\mathscr{R}_c = \frac{\kappa}{\mu+\kappa}\frac{c}{\mu+\alpha}\left[1-\rho\left(1-\frac{\mu+\kappa}{\mu+\kappa+\chi}\frac{\mu+\alpha}{\mu+\alpha+\phi}\right)\right]. \tag{3.52}$$

The derivatives of $\mathscr{R}_c$ with respect to the control parameters are

$$\frac{\partial \mathscr{R}_c}{\partial \chi} = -c\rho\frac{\kappa}{(\mu+\kappa+\chi)^2}\frac{1}{\mu+\alpha+\phi} < 0,$$
$$\frac{\partial \mathscr{R}_c}{\partial \phi} = -c\rho\frac{\kappa}{\mu+\kappa+\chi}\frac{1}{(\mu+\alpha+\phi)^2} < 0.$$

Hence, the reproduction number $\mathscr{R}_c$ for EDM also decreases as the control parameters χ and ϕ increase. Therefore, both models seem to work well when the impact of each individual control measure is considered. When we try to compare model predictions of combined control strategies, however, inconsistent predictions by the two models are observed. For example, in Fig. 3.8a, b, $\mathscr{R}_c$ for both models is plotted either as a function of ϕ for a fixed value of $\chi = 0.05$, or as a function of χ for a fixed value $\phi = 0.05$, or as a function of both χ and ϕ with $\chi = \phi$. For any vertical line except the one at 0.1, the three curves intersect the vertical line at three points that represent three control strategies. The order of these points (from top to bottom) determines the order of effectiveness (from low to high) of the corresponding control strategies since a larger $\mathscr{R}_c$ value will most likely lead to a higher disease prevalence. The order of these three points (labeled by a circle, a triangle, and a square) predicted by the EDM and the GDM is clearly different for the selected parameter sets, suggesting conflict assessments of interventions between the two models. These conflict assessments are also shown when we compare the C values. For example, Fig. 3.8a shows that the strategy corresponding to $\chi = 0.3, \phi = 0.05$ (indicated by the triangle) is more effective

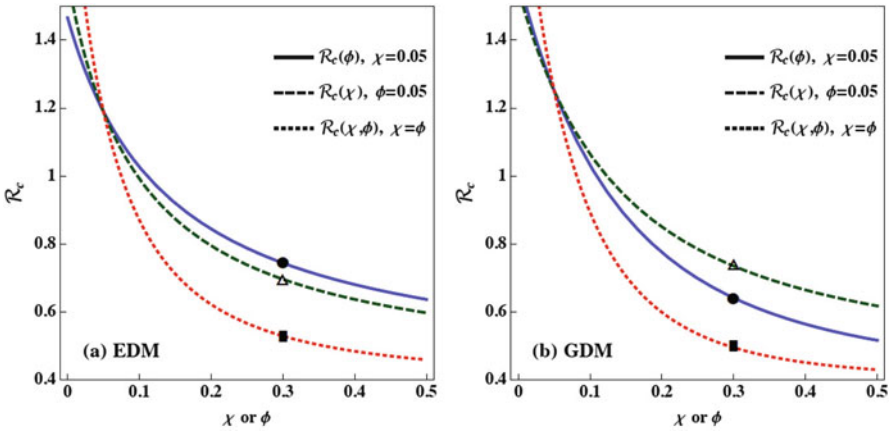


Fig. 3.8 Comparison of the EDM and the GDM on the impact of various control measures. (**a**) and (**b**) are plots of the reproduction number $\mathscr{R}_c$ as functions of control measures (χ and ϕ) for the EDM and GDM, respectively

than the strategy corresponding to $\chi = 0.05, \phi = 0.3$ (indicated by the solid circle). However, Fig. 3.8b shows the opposite, i.e., the strategy corresponding to $\chi = 0.3, \phi = 0.05$ (indicated by the triangle) is less effective than the strategy corresponding to $\chi = 0.05, \phi = 0.3$ (indicated by the solid circle). The parameter values used in Fig. 3.8 are $c = 0.2$, $\rho = 0.8$, $\kappa = 1/7$, and $\alpha = 1/10$, corresponding to a disease with a latency period of $1/\kappa = 7$ days and an infectious period of $1/\alpha = 10$ days (e.g., SARS).

To examine in more detail the quantitative differences between the two models we conducted intensive simulations of the EDM and the GDM for various control measures, some of which are illustrated in Fig. 3.9. In this figure, the parameters for gamma distributions are $m = n = 3$, E and I represent the fraction of latent and infectious fractions $E = (E_1 + E_2 + E_3)/N$ and $I = (I_1 + I_2 + I_3)/N$, respectively. The latent and infectious periods are $\kappa = 1/7$ and $\alpha = 1/10$. The cumulative infection is calculated by integrating the incidence function, i.e.,

$$C(t) = \int_0^t cS(s)\big[I(s) + (1-\rho)H(s)\big]/N ds$$

where $H = H_1 + H_2 + H_3$. Figure 3.9a, b is for Strategy I which implements quarantine alone with $\chi = 0.07$, and Fig. 3.9c, d is for Strategy II which implements isolation alone with $\phi = 0.06$. The effectiveness of these control measures is reflected by the corresponding $C(t)$ values. According to Fig. 3.9a, c, the EDM predicts that Strategy II is *more* effective than Strategy I as the number C of cumulative infections (fractions) under Strategy II is 30% lower than the C value under Strategy I (notice that $C \approx 0.3$ and $C \approx 0.2$ under strategies I and II, respectively). However, according to Fig. 3.9b, d, the GDM predicts that Strategy

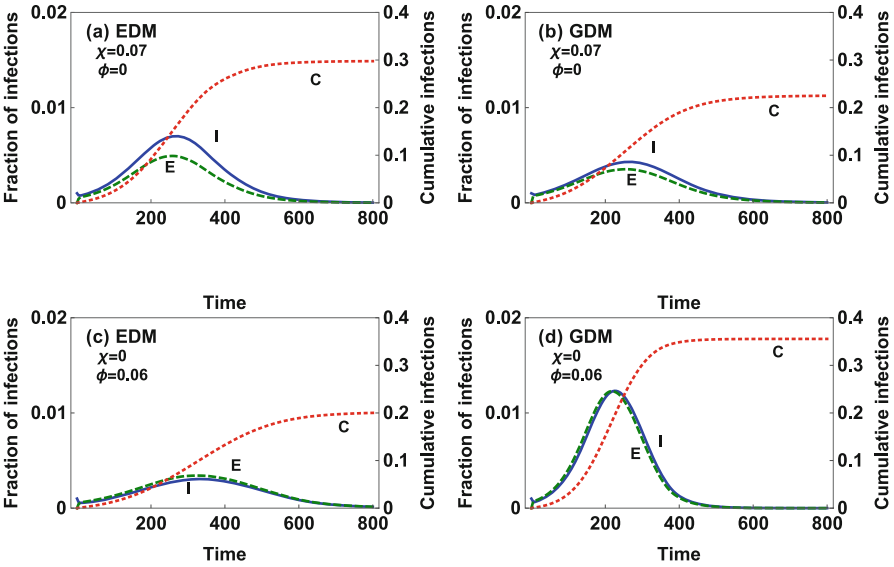


Fig. 3.9 Comparison of control strategies and evaluations given by the exponential distribution model (EDM) and the gamma distribution model (GDM) with $m = n = 3$. Two strategies represented by χ and ϕ are compared: Strategy I involves quarantine alone ($\chi = 0.07$ and $\phi = 0$) while Strategy II involves isolation alone ($\chi = 0$ and $\phi = 0.06$). Other parameter values used are $1/\kappa = 7$ (day), $1/\alpha = 10$ (day), $1/\mu = 75$ (year), and $c = 0.2$. The time unit is day

II is *less* effective than Strategy II as the number C of cumulative infections under Strategy I is 30% lower than the C value under Strategy II (notice that $C \approx 0.23$ and $C \approx 0.36$ under strategies I and II, respectively). Obviously, in this example, the predictions by the EDM and by the GDM are inconsistent.

One of the main reasons for the discrepancy between models with exponential and gamma distributions is the memoryless property of the exponential distribution. This can be made more transparent by examining the expected remaining sojourns from the distributions. Under the gamma distribution $p_n(s, \theta)$ (or simply denoted by $p_n(s)$) with $n \geq 2$, the expected remaining sojourn at stage age s is

$$\mathscr{M}_n(s) = \int_0^\infty \frac{p_n(t+s)}{p_n(s)} dt = \frac{1}{p_n(s)} \int_s^\infty p_n(t) dt = \frac{1}{n\theta} \frac{\sum_{k=0}^{n-1} \sum_{j=0}^{k} \frac{(n\theta s)^j}{j!}}{\sum_{k=0}^{n-1} \frac{(n\theta s)^k}{k!}}.$$

After checking $\mathscr{M}_n'(s) < 0$ and $\lim_{s\to\infty} \mathscr{M}_n(s) \to T/n$ where $T = 1/\theta$, we know that $\mathscr{M}_n(s)$ strictly decreases with stage age s, and that when s is large the expected remaining sojourn can be as small as T/n. Hence, the expected remaining sojourn in a stage is indeed dependent on the time already spent in the stage. Therefore, the gamma distribution $p_n(s)$ for $n \geq 2$ provides a more realistic description than the exponential distribution $p_1(s)$ for which $\mathscr{M}_1(s) = T$ for all s.

3.7 Diseases in Exponentially Growing Populations

Many parts of the world experienced very rapid population growth in the eighteenth century. The population of Europe increased from 118 million in 1700 to 187 million in 1800. In the same time period the population of Great Britain increased from 5.8 to 9.15 million, and the population of China increased from 150 to 313 million [33]. The population of English colonies in North America grew much more rapidly than this, aided by substantial immigration from England, but the native population, which had been reduced to one tenth of their previous size by disease following the early encounters with Europeans and European diseases, grew even more rapidly. While some of these population increases may be explained by improvements in agriculture and food production, it appears that an even more important factor was the decrease in the death rate due to diseases. Disease death rates dropped sharply in the eighteenth century, partly from better understanding of the links between illness and sanitation and partly because the recurring invasions of bubonic plague subsided, perhaps due to reduced susceptibility. One plausible explanation for these population increases is that the bubonic plague invasions served to control the population size, and when this control was removed the population size increased rapidly.

In developing countries it is quite common to have high birth rates and high disease death rates. In fact, when disease death rates are reduced by improvements in health care and sanitation it is common for birth rates to decline as well, since families no longer need to have as many children to ensure that enough children survive to take care of the older generations. Again, it is plausible to assume that population size would grow exponentially in the absence of disease but is controlled by disease mortality.

The SIR model with births and deaths of Kermack and McKendrick [28] includes births in the susceptible class proportional to population size and a natural death rate in each class proportional to the size of the class. Let us analyze a model of this type with birth rate r and a natural death rate $\mu < r$. For simplicity we assume the disease is fatal to all infectives with disease death rate α, so that there is no removed class and the total population size is $N = S + I$. Our model is

$$\begin{aligned} S' &= r(S+I) - \beta SI - \mu S \\ I' &= \beta SI - (\mu+\alpha)I. \end{aligned} \tag{3.53}$$

From the second equation we see that equilibria are given by either $I = 0$ or $\beta S = \mu + \alpha$. If $I = 0$, the first equilibrium equation is $rS = \mu S$, which implies $S = 0$ since $r > \mu$. It is easy to see that the equilibrium (0,0) is unstable. What actually would happen if $I = 0$ is that the susceptible population would grow exponentially with exponent $r - \mu > 0$. If $\beta S = \mu + \alpha$, the first equilibrium condition gives

$$r\frac{\mu+\alpha}{\beta} + rI - (\mu+\alpha)I - \frac{\mu(\mu+\alpha)}{\beta} = 0\,,$$

which leads to

$$(\alpha + \mu - r)I = \frac{(r - \mu)(\mu + \alpha)}{\beta} .$$

Thus, there is an endemic equilibrium provided $r < \alpha + \mu$, and it is possible to show by linearizing about this equilibrium that it is asymptotically stable. On the other hand, if $r > \alpha + \mu$ there is no positive equilibrium value for I. In this case we may add the two differential equations of the model to give

$$N' = (r - \mu)N - \alpha I \geq (r - \mu)N - \alpha N = (r - \mu - \alpha)N$$

and from this we may deduce that N grows exponentially. For this model, either we have an asymptotically stable endemic equilibrium or population size grows exponentially. In the case of exponential population growth we may have either vanishing of the infection or an exponentially growing number of infectives.

If only susceptibles contribute to the birth rate, as may be expected if the disease is sufficiently debilitating, the behavior of the model is quite different. Let us consider the model

$$\begin{aligned} S' &= rS - \beta SI - \mu S = S(r - \mu - \beta I) \\ I' &= \beta SI - (\mu + \alpha)I = I(\beta S - \mu - \alpha) \end{aligned} \tag{3.54}$$

which has the same form as the Lotka–Volterra predator–prey model of population dynamics. This system has two equilibria, obtained by setting the right sides of each of the equations equal to zero, namely (0, 0) and an endemic equilibrium $((\mu + \alpha)/\beta, (r - \mu)/\beta)$. It turns out that the qualitative analysis approach we have been using is not helpful as the equilibrium (0, 0) is unstable and the eigenvalues of the coefficient matrix at the endemic equilibrium have real part zero. In this case the behavior of the linearization does not necessarily carry over to the full system. However, we can obtain information about the behavior of the system by a method that begins with the elementary approach of separation of variables for first order differential equations. We begin by taking the quotient of the two differential equations and using the relation

$$\frac{I'}{S'} = \frac{dI}{dS}$$

to obtain the separable first order differential equation

$$\frac{dI}{dS} = \frac{I(\beta S - \mu - \alpha)}{S(r - \beta I)} .$$

Separation of variables gives

$$\int \left(\frac{r}{I} - \beta\right) dI = \int \left(\beta - \frac{\mu + \alpha}{S}\right) dS .$$

Integration gives the relation

$$\beta(S + I) - r \log I - (\mu + \alpha) \log S = c$$

where c is a constant of integration. This relation shows that the quantity

$$V(S, I) = \beta(S + I) - r \log I - (\mu + \alpha) \log S$$

is constant on each orbit (path of a solution in the (S, I) plane). Each of these orbits is a closed curve corresponding to a periodic solution.

We may view the model as describing an epidemic initially, leaving a susceptible population small enough that infection cannot establish itself. Then there is a steady population growth until the number of susceptibles is large enough for an epidemic to recur. During this growth stage the infective population is very small and random effects may wipe out the infection, but the immigration of a small number of infectives will eventually restart the process. As a result, we would expect recurrent epidemics. In fact, bubonic plague epidemics did recur in Europe for several hundred years. If we modify the demographic part of the model to assume limited population growth rather than exponential growth in the absence of disease, the effect would be to give behavior like that of the model studied in the previous section, with an endemic equilibrium that is approached slowly in an oscillatory manner if $\mathscr{R}_0 > 1$.

3.8 Project: Population Growth and Epidemics

When one tries to fit epidemiological data over a long time interval to a model, it is necessary to include births and deaths in the population. Throughout the book we have considered population models with birth and death rates that are constant in time. However, population growth often may be fit better by assuming a linear population model with a time-dependent growth rate, even though this does not have a model-based interpretation. There could be many reasons for variations in birth and death rates; we could not quantify the variations even if we knew all of the reasons. Let $r(t) = \frac{dN}{dt}/N$ denote the time-dependent per capita growth rate. To estimate $r(t)$ from linear interpolation of census data, proceed as follows:

1. Let N_i and N_{i+1} be the consecutive census measurements of population size taken at times t_i and t_{i+1}, respectively. Let $\Delta N = N_{i+1} - N_i$, $\Delta t = t_{i+1} - t_i$, and $\delta N = N(t + \delta t) - N(t)$.
2. If $t_i \le t \le t_{i+1}$, $\frac{\Delta N}{\Delta t} = \frac{\delta N}{\delta t}$, then we make the estimate $r(t) \approx \frac{\Delta N}{\Delta t N(t)}$.
3. A better approximation is obtained by replacing $N(t)$ by $N(t + \delta t/2)$. Why? Show that in this case, $r(t) \approx (\frac{\delta t}{2} + \frac{N(t)\Delta t}{\Delta N})^{-1}$.

Table 3.1 Population data growth for the USA

Year	Population size	Year	Population size	Year	Population size
1700	250,888	1800	5,308,483	1900	75,994,575
1710	331,711	1810	7,239,881	1910	91,972,266
1720	466,185	1820	9,638,453	1920	105,710,620
1730	629,445	1830	12,866,020	1930	122,775,046
1740	905,563	1840	17,069,453	1940	131,669,275
1750	1,170,760	1850	23,192,876	1950	151,325,798
1760	1,593,625	1860	31,443,321	1960	179,323,175
1770	2,148,076	1870	39,818,449	1970	203,302,031
1780	2,780,369	1880	50,155,783	1980	226,542,199
1790	3,929,214	1890	62,947,714	1990	248,718,301
–	–	–	–	2000	274,634,000

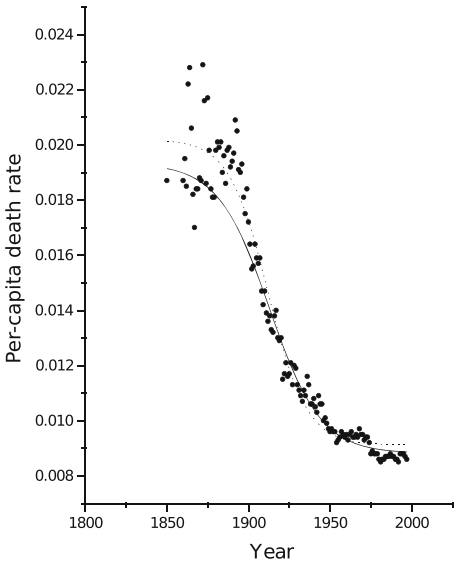


Fig. 3.10 Observed death rate (filled circle) and the best fit obtained with the function (3.55)

Question 1 Use the data of Table 3.1 to estimate the growth rate $r(t)$ for the population of the USA.

Figure 3.10 shows the time evolution of the USA mortality rate. This mortality rate is fit well by

$$\mu = \mu_0 + \frac{\mu_0 - \mu_f}{1 + e^{(t - t'_{1/2})/\Delta'}} \tag{3.55}$$

with $\mu_0 = 0.01948$, $\mu_f = 0.008771$, $t'_{1/2} = 1912$, and $\Delta' = 16.61$. Then the "effective birth rate" $b(t)$ is defined as the real birth rate plus the immigration rate.

Question 2 Estimate $b(t)$ using $r(t) = b(t) - \mu(t)$, with $r(t)$ found in Question 1.

Consider an SEIR disease transmission model. We assume that:

(a) An average infective individual produces β new infections per unit of time when all contacts are with susceptibles but that otherwise, this rate is reduced by the ratio S/N.
(b) Individuals in the exposed class E progress to the infective class at the per capita rate k.
(c) There is no disease-induced mortality or permanent immunity, and there is a mean infective period of $1/\gamma$.

We define $\gamma = r + \mu$. The model becomes:

$$\begin{aligned} \frac{dS}{dt} &= bN - \mu S - \beta S\frac{I}{N}, \\ \frac{dE}{dt} &= \beta S\frac{I}{N} - (k+\mu)E, \\ \frac{dI}{dt} &= kE - (r+\mu)I, \\ \frac{dR}{dt} &= rI - \mu R. \end{aligned} \tag{3.56}$$

Question 3

(a) Show that the mean number of secondary infections (belonging to the exposed class) produced by one infective individual in a population of susceptibles is $Q_0 = \beta/\gamma$.
(b) Assuming that k and μ are time-independent, show that $\mathscr{R}_0$ is given by $Q_0 f$, where $f = k/(k+\mu)$. What is the epidemiological interpretation of $Q_0 f$?

The usual measure of the severity of an epidemic is the incidence of infective cases. The incidence of infective cases is defined as the number of new infective individuals per year. If we take 1 year as the unit of time, the incidence of infective cases is given approximately by kE. The incidence rate of infective cases per 100,000 population is given approximately by $10^5\, kE/N$.

Tuberculosis (TB) is an example of a disease with an exposed (noninfective) stage. Infective individuals are called active TB cases. Estimated incidence of active TB in the USA was in a growing phase until around 1900 and then experienced a subsequent decline. The incidence rate of active TB exhibited a declining trend from 1850 (see Table 3.2 and Fig. 3.11). The proportion of exposed individuals who survive the latency period and become infective is $f = \frac{k}{k+\mu}$. The number f will be used as a measure of the risk of developing active TB by exposed individuals.

Question 4 Assume that the mortality rate varies according to the expression (3.55), and that the value of b found in Question 2 is used. Set $\gamma = 1$ years^{-1} and $\beta = 10$ years $^{-1}$, both constant through time. Simulate TB epidemics starting in 1700 assuming constant values for f. Can you reproduce the observed trends (Table 3.2)?

Table 3.2 Reported incidence and incidence rate (per 100,000 population) of active TB

Year	Incidence rate	Incidence	Year	Incidence rate	Incidence
1953	53	84,304	1976	15	32,105
1954	49.3	79,775	1977	13.9	30,145
1955	46.9	77,368	1978	13.1	28,521
1956	41.6	69,895	1979	12.6	27,769
1957	39.2	67,149	1980	12.3	27,749
1958	36.5	63,534	1981	11.9	27,337
1959	32.5	57,535	1982	11	25,520
1960	30.8	55,494	1983	10.2	23,846
1961	29.4	53,726	1984	9.4	22,255
1962	28.7	53,315	1985	9.3	22,201
1963	28.7	54,042	1986	9.4	22,768
1964	26.6	50,874	1987	9.3	22,517
1965	25.3	49,016	1988	9.1	22,436
1966	24.4	47,767	1989	9.5	23,495
1967	23.1	45,647	1990	10.3	25,701
1969	19.4	39,120	1992	10.5	26,673
1970	18.3	37,137	1993	9.8	25,287
1971	17.1	35,217	1994	9.4	24,361
1972	15.8	32,882	1995	8.7	22,860
1973	14.8	30,998	1996	8	21,337
1974	14.2	30,122	1997	7.4	19,885
1975	15.9	33,989	1998	6.8	18,361

It is not possible to obtain a good fit of the data of Table 3.2 to the model (3.56). It is necessary to use a refinement of the model that includes time-dependence in the parameters, and the next step is to describe such a model. The risk of progression to active TB depends strongly on the standard of living. An indirect measure of the standard of living can be obtained from the life expectancy at birth. The observed life expectancy for the USA is approximated well by the sigmoid shape function

$$\tau = \tau_f + \frac{(\tau_0 - \tau_f)}{1 + exp[(t - t_{1/2})/\Delta]}, \tag{3.57}$$

shown in Fig. 3.12. Here τ_0 and τ_f are asymptotic values for life expectancy; $t_{1/2} = 1921.3$ is the time by which life expectancy reaches the value $(\tau_0 + \tau_f)/2$; and $\Delta = 18.445$ determines the width of the sigmoid.

Assume that the risk f varies exactly like life expectancy, that is, assume that f is given by

$$f(t) = f_f + \frac{(f_i - f_f)}{1 + exp[(t - t_{1/2})/\Delta]}. \tag{3.58}$$

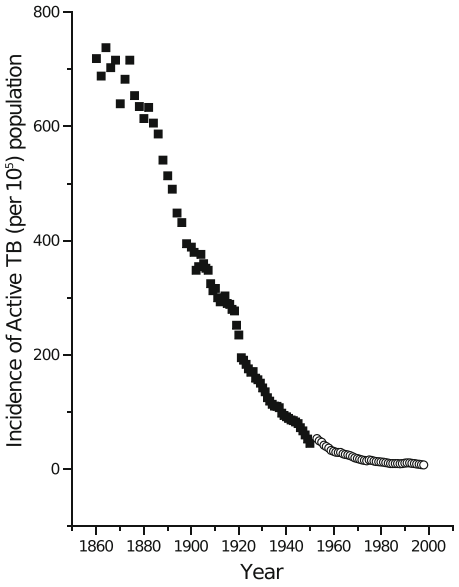


Fig. 3.11 Incidence of active TB

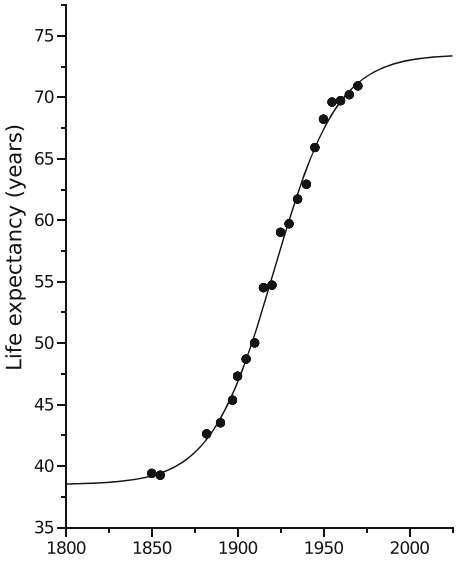


Fig. 3.12 Observed average life expectancy at birth (filled circle) and its best fit (continuous line) using expression (3.57)

We refine the model (3.56) by replacing the parameter k by the variable expression $\mu f(t)/(1 - f(t))$ and $k + \mu$ by $\mu/(1 - f(t))$, obtained from the relation $f = k/(k + \mu)$. Since the time scale of the disease is much faster than the demographic time scale, the recovery rate r is approximately equal to γ. This gives the model

$$\begin{aligned}
\frac{dS}{dt} &= b(t)N - \mu(t)S - \beta S\frac{I}{N},\\
\frac{dE}{dt} &= \beta S\frac{I}{N} - \frac{\mu(t)}{1-f(t)}E,\\
\frac{dI}{dt} &= \frac{\mu(t)f(t)}{1-f(t)}E - \gamma I,\\
\frac{dR}{dt} &= \gamma I - \mu(t)R.
\end{aligned} \tag{3.59}$$

Question 5 Simulate TB epidemics starting in 1700 using the model (3.59) with $\gamma = 1$ years^{-1} and $\beta = 10$ years^{-1}, both constant, and with $\mu(t)$ given by (3.55) and $f(t)$ given by (3.58). Find values of f_0 and f_f for which an accurate reproduction of the observed TB trends (Table 3.2) is achieved.

References: [1–4, 9–11, 15, 16, 38–41].

3.9 *Project: An Environmentally Driven Infectious Disease

Consider an environmentally driven infectious disease such as cholera and toxoplasmosis (a parasite disease caused by *T. gondii*). For this type of disease, the transmission occurs when susceptible hosts have contacts with a contaminated environment, and the rate of environment contamination is dependent on both the number of infected hosts and the average pathogen load within an infected host. One way to model the transmission dynamics for such a disease is to consider both the disease transmission at the population level and the infection process within the hosts. The following model couples a simple within-host system for cell–parasite interactions (e.g., see [34–36]) and an endemic SI model with an interaction with a contaminated environment:

$$\begin{aligned}
\dot{T} &= \Lambda - kVT - mT,\\
\dot{T^*} &= kVT - (m+d)T^*,\\
\dot{V} &= g(E) + pT^* - cV,\\
\dot{S} &= \mu(S+I) - \lambda ES - \mu S,\\
\dot{I} &= \lambda ES - \mu I,\\
\dot{E} &= \theta(V)I(1-E) - \gamma E.
\end{aligned} \tag{3.60}$$

Here, the variables for the within-host system $T = T(t)$, $T^* = T^*(t)$, and $V = V(t)$ are the densities of healthy cells, infected cells, and parasite load, respectively. $S = S(t)$ and $I = I(t)$ denote the numbers of susceptible and infective individuals at time t, respectively. Λ denotes the recruitment rate of cells; k is the per-capita infection rate of cells; m and d are the per-capita background and infection-induced

cell mortalities, respectively; p denotes the parasite production rate by an infected cell and c is the within-host clearance rate of pathogens.

The variables $S(t)$ and $I(t)$ denote the numbers of susceptible and infective hosts at time t, and $E(t)$ ($0 \leq E \leq 1$) represents the level of environmental contamination at time t, or the concentration of the pathogen per unit area of a region being considered. The parameter λ denotes the per-capita infection rate of hosts in a contaminated environment; μ denotes per-capita birth and natural death rate of hosts; and γ denotes the rate of pathogen clearance in the environment.

The function $g(E)$ in the V equation represents an added rate in the change of parasite load due to the continuous ingestion of parasites by the host from a contaminated environment, and is assumed to have the following properties:

$$g(0) = 0, \quad g(E) \geq 0, \quad g'(E) > 0, \quad g''(E) \leq 0. \tag{3.61}$$

One of the simplest forms for $g(E)$ is the linear function $g(E) = aE$, where a is a positive constant. Other forms of $g(E)$ include $g_1(E) = aE/(1 + bE)$ with a and b being positive constants and $g_2(E) = aE^q$ ($q < 1$).

For the analysis of the coupled model (3.60), a commonly used approach is to consider that the within-host system (consisting of the T, T^*, and V equations) occurs on a much faster time scale than the between-host system (consisting of S, I, and E equations), which allows the substitution of a stable equilibrium of the fast-system (treating the slow-variables as constant) into the slow-system and study the lower-dimensional slow system (see, e.g., [7, 12, 17, 19]). The system for the fast variables is

$$\begin{aligned} \dot{T} &= \Lambda - kVT - mT \\ \dot{T^*} &= kVT - (m + d)T^* \\ \dot{V} &= g(E) + pT^* - cV, \end{aligned} \tag{3.62}$$

and the system for the slow variables is

$$\begin{aligned} \dot{S} &= \mu(S + I) - \lambda ES - \mu S, \\ \dot{I} &= \lambda ES - \mu I, \\ \dot{E} &= \theta IV(1 - E) - \gamma E. \end{aligned} \tag{3.63}$$

Question 1 Consider the fast system (3.62). The within-host reproduction number $\mathscr{R}_w$ (w for within) is given by

$$\mathscr{R}_w = \frac{kpT_0}{c(m + d)} \tag{3.64}$$

where $T_0 = \Lambda/\mu$.

(a) Let $E > 0$ be a constant. Show that (3.62) has a unique biologically feasible equilibrium (which depends on E) $\tilde{U}(E) = (\tilde{T}(E), \tilde{T}^*(E), \tilde{V}(E))$.
(b) Show that the unique equilibrium $\tilde{U}(E) = (\tilde{T}(E), \tilde{T}^*(E), \tilde{V}(E))$ of (3.62) is globally, asymptotically stable.
Hint: Consider the following Lyapunov function

$$\mathscr{L}(T, T^*, V) = \tilde{T}\left(\frac{T}{\tilde{T}} - \log\frac{T}{\tilde{T}} - 1\right) + \tilde{T}^*\left(\frac{T^*}{\tilde{T}^*} - \log\frac{T^*}{\tilde{T}^*} - 1\right) + \frac{m+d}{p}\tilde{V}\left(\frac{V}{\tilde{V}} - \log\frac{V}{\tilde{V}} - 1\right).$$

Consider the case when $\mathscr{R}_w > 1$. It can be verified that $\tilde{V}(0) = \lim_{E\to 0}\tilde{V}(E) > 0$. Note that the total population of hosts $N = S + I$ remains constant for all $t > 0$. Thus, the fast system (3.62) can be reduced to a two-dimensional system (by ignoring the S equations). Note also that $\tilde{U}$ is g.a.s. in the fast system. We can replace the fast variable V in (3.62) by $\tilde{V}(E)$ and study the following fast system

$$\begin{aligned} \dot{I} &= \lambda E(N - I) - \mu I, \\ \dot{E} &= \theta I\tilde{V}(E)(1 - E) - \gamma E. \end{aligned} \tag{3.65}$$

The reproduction number for the between-host system, which is denoted by $\mathscr{R}_b$ (b for between) and defined as

$$\mathscr{R}_b = \frac{\theta\tilde{V}(0)}{\mu}\,\frac{\lambda N}{\gamma}. \tag{3.66}$$

Therefore, $\mathscr{R}_b$ represents the number of secondary infections through the environment by one infected individual during the entire infectious period in a completely susceptible host population and environment.

Let $\hat{W} = (\hat{I}, \hat{E})$ denote a biologically feasible equilibrium for (3.65). Show that $\hat{I} = \lambda\hat{E}N/(\lambda\hat{E}+\mu)$ and $\hat{E}$ is a solution of the equation $F(E) = G(E)$, $0 < E < 1$, where

$$\begin{aligned} F(E) &= \frac{1-E}{c}\left[g(E) + \frac{pm}{m+d}\left(T_0 - \tilde{T}(E)\right)\right], \\ G(E) &= \frac{\gamma E}{\theta N} + \frac{\mu\gamma}{\theta\lambda N}. \end{aligned} \tag{3.67}$$

Equivalently, $\hat{E}$ is a zero of the function $H(E) = F(E) - G(E)$ with $0 < E < 1$.

(a) Let $\hat{W}_0 = (0, 0)$ denote the infection-free equilibrium of (3.65). Show that $\hat{W}_0$ locally asymptotically stable when $\mathscr{R}_b < 1$ and unstable when $\mathscr{R}_b > 1$.

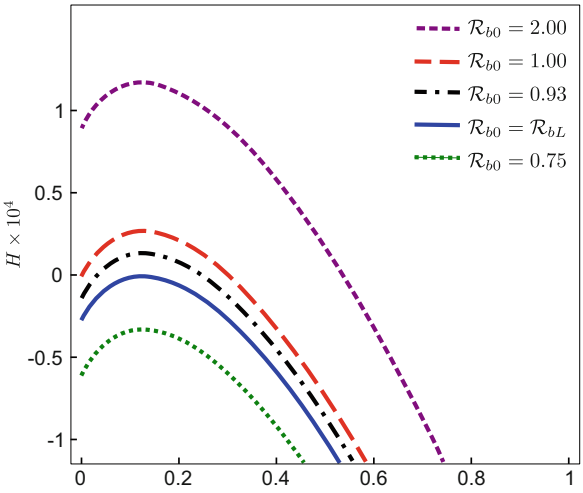


Fig. 3.13 Plot of the function $H(E)$ for different $\mathscr{R}_b$ value between 0.75 and 2. A zero of $H(E)$ in (0, 1) corresponds to positive equilibrium of the slow system (3.65)

(b) Show that it is possible for the equation $H(E) = F(E) - G(E) = 0$ to have 0, 1, or 2 solutions in (0, 1).
Hint: Show first that $H''(E) > 0$ for $0 < E < 1$.

(c) Figure 3.13 illustrates a numerical plot of the function $H(E)$ for various $\mathscr{R}_b$ (by varying λ) values between 0.75 and 2. Other parameter values used are: $\Lambda = 6 \times 10^3$, $k = 1.5 \times 10^{-6}$, $m = 0.3$, $d = 0.2$, $a = 4 \times 10^5$, $c = 50$, $\mathscr{R}_{w0} = 1.09$ ($p = 908$), $N = 10^4$, $\mu = 4 \times 10^{-4}$, $\theta = 1 \times 10^{-10}$, and $\gamma = 0.02$. What do you observe? How does the number of solutions of $H(E) = 0$ depend on $\mathscr{R}_b$?

(d) From the plot in part (c) we can observe that there exists a lower bound $\mathscr{R}_{bL} \in (0, 1)$ such that for all $\mathscr{R}_b \in (\mathscr{R}_{bL}, 1)$, the equation $H(E) = F(E) - G(E) = 0$ has two solutions in (0, 1), which correspond to two positive equilibria $\hat{W}_i = (\hat{I}_i, \hat{E}_i)$ $(i = 1, 2)$ with $\hat{I}_2 > \hat{I}_1$. In this case, prove analytically that $\hat{W}_2$ is locally asymptotically stable and $\hat{W}_1$ is unstable. (**Hint:** Check the sign of the eigenvalues of the Jacobian matrix at $\hat{W}$).

(e) For the full system (3.60), conduct numerical simulations to confirm the results stated in parts (a)–(d), which are obtained by separating the fast and slow systems.

(i) Reproduce the Fig. 3.14 (left) by plotting the fraction of infected $I(t)/N$ vs. time with several sets of initial conditions. Use the same parameter values as in Part (c) except that $p = 850$ (corresponding to $\mathscr{R}_b = 0.37 < 1$), $a = 5 \times 10^5$, $\lambda = 5.5 \times 10^{-4}$, and $\gamma = 0.015$.

(ii) Reproduce the phase portrait shown in Fig. 3.14 (right), which illustrates one fast variable (V) and one slow variable (E). Use the same parameter values as in Part (c) except that $p = 10^3$ (corresponding to $\mathscr{R}_b > 1$) and $a = 4 \times 10^4$.

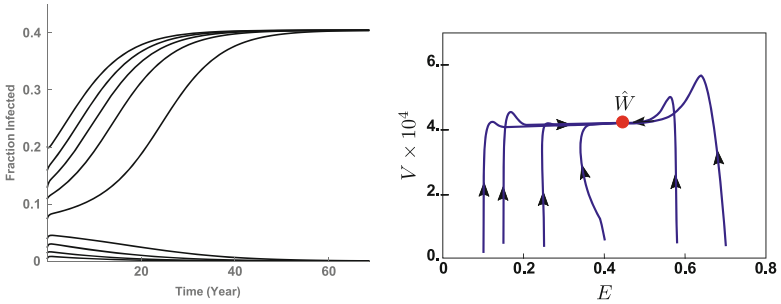


Fig. 3.14 Left: Time plot of the full system (3.60) for $\mathscr{R}_b \in (\mathscr{R}_{bL}, 1)$, in which case there are two stable equilibria, one with the infection-free and one with positive infection level. Right: Phase portrait of the full system (3.60) for $\mathscr{R}_b > 1$, in which case there is a unique stable equilibrium

3.10 *Project: A Two-Strain Model with Cross Immunity

This project concerns a two-strain model with cross immunity. Divide the population into ten different classes: susceptibles (S), infected with strain i (I_i), primary infection), isolated with strain i (Q_i), recovered from strain i (R_i, as a result of primary infection), infected with strain i (V_i, secondary infection), given that the population had recovered from strains $j \neq i$, and recovered from both strains (W). Let A denote the population of non-isolated individuals and let $\frac{\beta_i S(I_i+V_i)}{A}$ be the rate at which susceptibles become infected with strain i. That is, the ith ($i \neq j$) incidence rate is assumed to be proportional to both the number of susceptibles and the available modified proportion of i-infectious individuals, $\frac{(I_i+V_i)}{A}$. Let σ_{ij} denote a measure of the cross-immunity provided by a prior infection with strain i to exposure with strain j ($i \neq j$). Consider the following model

$$
\begin{aligned}
\frac{dS}{dt} &= \Lambda - \sum_{i=1}^{2} \beta_i S \frac{(I_i + V_i)}{A} - \mu S, \\
\frac{dI_i}{dt} &= \beta_i S \frac{(I_i + V_i)}{A} - (\mu + \gamma_i + \delta_i) I_i, \\
\frac{dQ_i}{dt} &= \delta_i I_i - (\mu + \alpha_i) Q_i, \\
\frac{dR_i}{dt} &= \gamma_i I_i + \alpha_i Q_i - \beta_j \sigma_{ij} R_i \frac{(I_j + V_j)}{A} - \mu R_i, \qquad j \neq i \\
\frac{dV_i}{dt} &= \beta_i \sigma_{ij} R_j \frac{(I_i + V_i)}{A} - (\mu + \gamma_i) V_i, \qquad j \neq i \\
\frac{dW}{dt} &= \textstyle\sum_{i=1}^{2} \gamma_i V_i - \mu W, \\
A &= S + W + \textstyle\sum_{i=1}^{2} (I_i + V_i + R_i).
\end{aligned}
\tag{3.68}
$$

The basic reproduction number for strain i is

$$\mathscr{R}_i = \frac{\beta_i}{\mu + \gamma_i + \delta_i}, \quad i = 1, 2.$$

Assume that $\sigma_{12} = \sigma_{21} = \sigma$. The values of reproduction numbers $\mathscr{R}_i$ and the cross-immunity levels σ determine the existence and stability of equilibrium points of the system (3.68). Let E_i denote the boundary equilibria where only strain i is present ($i = 1, 2$).

Question 1 Consider the case when changes in $\mathscr{R}_i$ are due to changes in β_i. Let $f(\mathscr{R}_1)$ and $g(\mathscr{R}_2)$ be the two functions given by

$$f(\mathscr{R}_1) = \frac{\mathscr{R}_1}{1 + \sigma(\mathscr{R}_1 - 1)\left(1 + \frac{\delta_2}{\mu+\gamma_2}\right)\left(1 - \frac{\mu(\mu+\alpha_1)}{(\mu+\gamma_1)(\mu+\alpha_1)+\alpha_1\delta_1}\right)} \tag{3.69}$$

and

$$g(\mathscr{R}_2) = \frac{\mathscr{R}_2}{1 + \sigma(\mathscr{R}_2 - 1)\left(1 + \frac{\delta_1}{\mu+\gamma_1}\right)\left(1 - \frac{\mu(\mu+\alpha_2)}{(\mu+\gamma_2)(\mu+\alpha_1)+\alpha_2\delta_2}\right)}, \tag{3.70}$$

and let σ_1^* and σ_2^* be the critical values such that

$$f'(\mathscr{R}_1) \equiv \frac{\partial f(\mathscr{R}_1, \sigma)}{\partial \mathscr{R}_1}\Big|_{\sigma_1^*} = 0, \quad g'(\mathscr{R}_2) \equiv \frac{\partial g(\mathscr{R}_2, \sigma)}{\partial \mathscr{R}_2}\Big|_{\sigma_2^*} = 0. \tag{3.71}$$

Determine the properties of f and g and sketch these functions in the $\mathscr{R}_1 - \mathscr{R}_2$ plane.

Question 2

(a) Determine the region(s) in the $\mathscr{R}_1 - \mathscr{R}_2$ plane for the existence of E_1 and E_2.
(b) Determine the conditions for the stabilities of E_1 and E_2.

3.11 Exercises

1. Consider the following SEIR model with disease-induced mortality:

$$\frac{dS}{dt} = \mu N - \beta S\frac{I}{N} - \mu S,$$
$$\frac{dE}{dt} = \beta S\frac{I}{N} - (\kappa + \mu)E,$$

$$\begin{aligned}\frac{dI}{dt} &= \kappa E - (\gamma + \mu + \delta)I,\\ \frac{dR}{dt} &= \gamma I - \mu R,\\ N &= S + E + I + R,\end{aligned}$$

where δ denotes the per capita rate of disease related death.

(a) Compute the basic reproduction number $\mathscr{R}_0$.
(b) Does the system have an endemic equilibrium? If yes, find the condition in terms of $\mathscr{R}_0$.
(c) Show that the endemic equilibrium is locally asymptotically stable whenever it exists.
(d) Reduce the system to a three-dimensional system by introducing fractions $u = S/N$, $x = E/N$, $y = I/N$, $z = R/N$.

2. Show that the endemic equilibrium of (3.3) is asymptotically stable if $\mathscr{R}_0 > 1$.
3. Consider a population in which a fraction $p \in (0, 1)$ of newborns are successfully vaccinated and assume permanent immunity after infection and vaccination. Assume that infectious individuals are treated at a per capita rate r. Let $\mathscr{R}_c$ denote the control reproduction number such that the disease-free equilibrium is locally asymptotically stable when $\mathscr{R}_c < 1$. Consider a disease for which $\beta = 0.86$, $\gamma = 1/14\ days^{-1}$, $\mu = 1/75\ years^{-1}$. Use the following SIR model to calculate the threshold immunity level p_c such that $\mathscr{R}_c < 1$ for $p > p_c$.

$$\begin{aligned}\frac{dS}{dt} &= \mu N(1-p) - \beta S\frac{I}{N} - \mu S,\\ \frac{dI}{dt} &= \beta S\frac{I}{N} - (\gamma + \mu + r)I,\\ \frac{dR}{dt} &= \mu N p + (\gamma + r)I - \mu R,\\ N &= S + I + R.\end{aligned}$$

(a) Find p_c in the absent of treatment (i.e., $r = 0$).
(b) Find p_c when $r = 0.2$.
(c) Plot p_c as a function of r.
(d) Plot $\mathscr{R}_c$ as a function of p and r
(e) Plot several contour curves of $\mathscr{R}_c$ in the (p, r) plane including the curve for $\mathscr{R}_c = 1$.

4. Consider the SIRS model (3.10).

(a) Find the expression for the fraction I^*/N of the infected individuals at the endemic equilibrium.
(b) Explore the dependence of I^*/N on the immunity loss (θ), particularly in the two extreme cases when the immunity period is very short or very long.

5.* Consider the SIR model with delay (3.12).

(a) Find the endemic equilibrium.
(b) Let $\beta = 0.86$ and $\alpha = 1/14$. Determine the threshold value ω_c such that the stability of the endemic equilibrium switches its stability.

6. Consider the vaccination model (3.21).

(a) Verify that $\mathscr{R}_c < 1$ whenever there is a backward bifurcation.
(b) Show how to choose φ to make $\mathscr{R}_c < \mathscr{R}_0$, assuming that all parameters other than φ are kept fixed.
(c) Is it possible to improve the vaccine (decrease σ) enough to make $\mathscr{R}_c < \mathscr{R}_0$, assuming all parameters other than σ are kept fixed?

7.* Consider the model with a gamma distribution (3.47) and the exponential distribution (3.48). Compare the behavior of the two models under the scenarios specified below. Assume that all parameters have the same values as in Fig. 3.10 except the control parameters χ and φ.

(a) $\chi = \varphi = 0$. Do you observe any differences in the disease prevalence between the two models? Explain why or why not.
(b) Compare the two models under two strategies. Strategy I: $\chi = 0.08$ and $\varphi = 0$, Strategy II: $\chi = 0$ and $\varphi = 0.08$. Do you observe any differences in the disease prevalence between the two models? Explain why or why not.

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