Chapter 13
Class-Age Structured Epidemic Models

13.1 Variability of Infectivity with Time-Since-Infection

Many diseases progress quickly. Once infected, an individual goes through a short incubation period and becomes infectious. In a matter of days, this individual has either recovered or is dead. That is the case with influenza, which many have experienced. Other diseases with short span are SARS, meningitis, plague, and many of the childhood diseases. We will call such diseases *quickly progressive diseases*. See Table 13.1 for a more extensive list of quickly progressive diseases. In modeling such diseases, it is acceptable to ignore host vital dynamics and to assume that the infectivity of infectious individuals is constant throughout their infectious period.

Other diseases infect their hosts for a long time, sometimes for the duration of the lifespan of the host. Examples of such diseases include HIV/AIDS, tuberculosis, and hepatitis C. These diseases necessarily include a long-term latent or chronic stage. Such diseases are called *slowly progressive diseases*. Table 13.1 contains a list of slowly progressive diseases. Models of slowly progressive diseases should include host demography.

Evidence exists that the infectivity, that is, the probability of infection, given a contact, may vary in time since the moment at which the infectious individual has become infected. This variability exists with fast diseases but is far more important with slow diseases. Infectivity for several common diseases is plotted in Fig. 13.1. The problem of variability of infectivity with time-since-infection has been studied most extensively in HIV. The *California Partners' Study* examined 212 females having regular sexual contacts with their HIV-infected male partners. Couples were followed for different durations (duration of exposure) up to 100 months. All partners were already infected before the contact began. Only about 20% of the females were eventually infected. Shiboski and Jewell [145] use the data to estimate a time-since-infection-dependent infectivity. No explicit form of the function is given. Generally, it is accepted that the viral load in HIV-infected patients is correlated with their infectivity. Since the viral load is high right after infection, and then during the time when AIDS develops, the infectivity is assumed to be higher for those two periods,

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Table 13.1 Slow and fast diseases

Slow diseases	Length of infection	Fast diseases	Length of infection
HIV/AIDS	Lifelong	Influenza	2–10 days
Hepatitis C	Lifelong[a]	Measles	10–12 days
Tuberculosis	Lifelong[a]	Mumps	12–25 days
Genital herpes	Lifelong	Rubella	3–4 weeks
Hepatitis B	Lifelong	Chicken pox	17–30 days
Cervical cancer (HPV)	Lifelong	Dengue fever	10–30 days
Malaria	200[a] days	Ebola	3–6 weeks

[a]If not treated

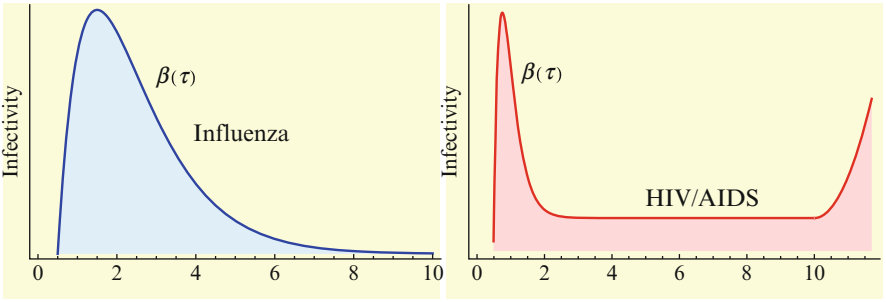

Fig. 13.1 Infectivity for the fast disease influenza [35] and the slow disease HIV [42]

and generally lower during the latent stage of the infection. Shiboski and Jewell's functions do not possess these properties, presumably because infected individuals were already past their acute stage when they were enrolled in the study. Shiboski and Jewell's functions first increase from 0 to 40 months after infection, and then rapidly decrease, so that they are nearly zero at 90 months after infection.

In fact, the very first epidemic model developed by Kermack and McKendrick [84] structures the infected individuals by the time-since-infection (also called *age of infection*). Kermack and McKendrick's motivation for inclusion of infection-age was not only that infectivity may change with infection-age but also that the possibility of recovery or death may depend on the time elapsed since infection. In modeling with ODEs, it is implicitly assumed that the time to recovery or death is exponentially distributed. This assumption may be weakened if infection-age is incorporated into the model. Although Kermack-McKendrick's age-since-infection model did not include birth and natural death in the population, more recent age-since-infection models of slowly progressive diseases include demography.

13.2 Time-Since-Infection Structured SIR Model

In this section, we consider a continuous version of the Kermack–McKendrick time-since-infection structured model. Because mass action incidence is used, the model can be used to describe diseases such as influenza and childhood diseases, but it is not suitable for HIV.

13.2.1 Derivation of the Time-Since-Infection Structured Model

Since infectivity for infectious individuals varies with the time since infection (see Fig. 13.1), we must keep track of the time that has elapsed since infection for each infected individual. Let τ denote the time-since-infection. The time-since-infection begins when an individual becomes infected and progresses with the chronological time t. Let $i(0,t)$ denote the number of individuals who have just become infected at time t. All individuals who become simultaneously infected make up one disease "cohort," that is, they have experienced the same life event together, namely getting infected with the disease. As time progresses, this group of people has the same time-since-infection τ. Let $i(\tau,t)$ be the density of infected individuals with time-since-infection τ at time t. The fact that $i(\tau,t)$ is a density means that $i(\tau,t)\Delta\tau$ is the number of individuals with time-since-infection in the interval $(\tau,\tau+\Delta\tau)$. Suppose that time Δt elapses. Then the same group of individuals who at time t had time-since-infection in the interval $(\tau,\tau+\Delta\tau)$, now at time $t+\Delta t$ have time-since infection in the interval $(\tau+\Delta t,\tau+\Delta\tau+\Delta t)$. The number of those individuals is given by $i(\tau+\Delta t,t+\Delta t)\Delta\tau$. Adding all individuals in all infection-age classes gives the total infected population:

$$I(t)=\int_0^\infty i(\tau,t)\,d\tau.$$

Since this is the same group of individuals, their numbers might have changed in the interval $(t,t+\Delta t)$ as a result of two possible events: some of them might have recovered, and other might have left the system due to natural causes (e.g., death). We assume that the lifespan of individuals in the system is exponentially distributed, and equal for susceptible, infected, and recovered individuals. Thus, susceptible, infected, and recovered individuals leave the system at a constant rate. Denote by μ the per capita rate at which individuals leave the system. The number of infected individuals who leave the system in the time interval $(t,t+\Delta t)$ is given by

$$\mu\Delta t i(\tau,t)\Delta\tau,$$

where $i(\tau,t)\Delta\tau$ is the number of people in the age interval $(\tau,\tau+\Delta\tau)$, and $\mu i(\tau,t)\Delta\tau$ is the number of people in that age interval who leave the system at time t. To model the number of individuals who recover in the time interval $(t,t+\Delta t)$, we denote the per capita recovery rate by γ. We will assume that the recovery rate

depends on the time-since-infection τ: $\gamma(\tau)$. Following a similar line of reasoning as in the case with the number of individuals who leave the system, the number of individuals who recover from this cohort of infecteds is given by

$$\gamma(\tau)\Delta t i(\tau,t)\Delta\tau.$$

The balance equation for the change in the number of infected individuals in this cohort is given by

$$i(\tau+\Delta t,t+\Delta t)\Delta\tau - i(\tau,t)\Delta\tau = -\gamma(\tau)\Delta t i(\tau,t)\Delta\tau - \mu\Delta t i(\tau,t)\Delta\tau.$$

Dividing by $\Delta\tau\Delta t$, we obtain

$$\frac{i(\tau+\Delta t,t+\Delta t)-i(\tau,t)}{\Delta t} = -\gamma(\tau)i(\tau,t) - \mu i(\tau,t). \tag{13.1}$$

We rewrite the left-hand side above as

$$\frac{i(\tau+\Delta t,t+\Delta t)-i(\tau,t+\Delta t)}{\Delta t} + \frac{i(\tau,t+\Delta t)-i(\tau,t)}{\Delta t} = -\gamma(\tau)i(\tau,t) - \mu i(\tau,t). \tag{13.2}$$

We take the limit as $\Delta t \to 0$. If the partial derivatives of the function i exist and are continuous, we can rewrite the equation above in the form

$$i_\tau(\tau,t) + i_t(\tau,t) = -\gamma(\tau)i(\tau,t) - \mu i(\tau,t). \tag{13.3}$$

This is a first-order partial differential equation. It is linear. It is defined on the domain

$$\mathscr{D} = \{(\tau,t) : \tau \geq 0, t \geq 0\}.$$

To complete the partial differential equation, we must derive a boundary condition along the boundary $\tau = 0$ and an initial condition.

To derive the boundary condition, let $S(t)$ be the number of susceptible individuals at time t, $R(t)$ the number of recovered individuals, and $N(t)$ the total population size:

$$N(t) = S(t) + \int_0^\infty i(\tau,t)\,d\tau + R(t).$$

The newly infected individuals have time-since-infection equal to zero and their number is given by $i(0,t)$. To derive the expression for newly infected individuals, we let $\beta(\tau)N$ be the infectivity of the infectious individuals, where N is the total population. The infectivity depends on the time-since-infection τ that has elapsed for the infecting individual. It is assumed that infectious individuals have different infectivities at different times-since-infection. This is the case with most infectious diseases. The probability that an infectious individual with time-since-infection equal to τ will come in a contact with a susceptible individual, given that the individual makes a contact, is $\frac{S}{N}$. Thus, this infectious individual with time-since-infection equal to τ will transmit the disease to

$$\beta(\tau)N\frac{S}{N} = \beta(\tau)S$$

individuals. Since there are $i(\tau,t)\Delta\tau$ infectious individuals with time-since-infection in the interval $(\tau, \tau+\Delta\tau)$, the total number of infections generated by such infectious individuals will be

$$\beta(\tau)Si(\tau,t)\Delta\tau.$$

Adding all newly infected individuals generated by all infected individuals in all time-since-infection classes, we get

$$i(0,t) = S\int_0^\infty \beta(\tau)i(\tau,t)\,d\tau.$$

This incidence is the equivalent of mass action incidence in the ODE case. This equation gives the *boundary condition* of the partial differential equation. To derive the equation that gives the dynamics of the susceptible individuals, we assume that the recruitment into the population occurs at a constant rate Λ. Thus, the equation becomes

$$S'(t) = \Lambda - S\int_0^\infty \beta(\tau)i(\tau,t)\,d\tau - \mu S(t).$$

Finally, the equation for the recovered individuals has as an inflow the total number of recovered individuals summed by all age-since-infection classes:

$$R'(t) = \int_0^\infty \gamma(\tau)i(\tau,t)d\tau - \mu R(t).$$

The susceptible, infected, and recovered populations make up the total population. The equations for the susceptible, infected, and recovered populations define a closed system of equations, which we will consider in itself:

$$\begin{cases} S'(t) = \Lambda - S(t)\displaystyle\int_0^\infty \beta(\tau)i(\tau,t)\,d\tau - \mu S(t), \\ i_\tau(\tau,t) + i_t(\tau,t) = -\gamma(\tau)i(\tau,t) - \mu i(\tau,t), \\ i(0,t) = S(t)\displaystyle\int_0^\infty \beta(\tau)i(\tau,t)\,d\tau, \\ R'(t) = \displaystyle\int_0^\infty \gamma(\tau)i(\tau,t)d\tau - \mu R(t). \end{cases} \tag{13.4}$$

The model is equipped with the following initial conditions:

$$\begin{aligned} S(0) &= S_0, \\ i(\tau,0) &= i_0(\tau), \\ R(0) &= R_0, \end{aligned} \tag{13.5}$$

where S_0 and R_0 are given numbers, and $i_0(\tau)$ is a given function that is assumed integrable. We note that

$$N_0 = S_0 + \int_0^\infty i_0(\tau)d\tau + R_0.$$

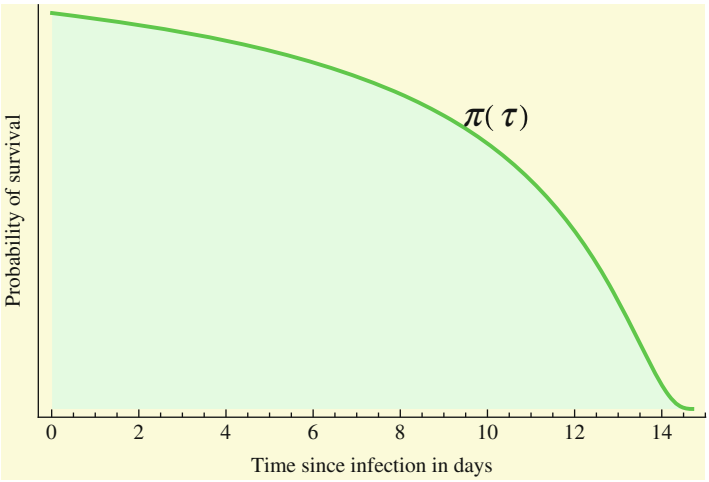

Fig. 13.2 A typical probability of survival in a class

Model (13.4) together with the initial conditions (13.5) is the time-since-infection structured Kermack–McKendrick SIR epidemic model.

Remark 13.1. Typically, the infectivity $\beta(\tau)$ is assumed to be a bounded function:

$$\bar{\beta} = \sup_\tau \beta(\tau).$$

A key quantity related to the survival of infectious individuals in a given class is $\pi(\tau)$, the probability of still being infectious τ time units after becoming infected. Then, if $\hat{I}$ individuals become infected at some moment of time, the number of those who are still infectious after τ time units is $\hat{I}\pi(\tau)$. Those numbers change in a small interval of time-since-infection $\Delta\tau$ by those who have stopped being infectious or those who have left the system:

$$\hat{I}\pi(\tau+\Delta\tau) - \hat{I}\pi(\tau) = -\mu\hat{I}\pi(\tau)\Delta\tau - \gamma(\tau)\hat{I}\pi(\tau)\Delta\tau.$$

The probability of still being infectious τ time units after becoming infected/infectious, $\pi(\tau)$, satisfies the following differential equation:

$$\pi'(\tau) = -\mu\pi(\tau) - \gamma(\tau)\pi(\tau),$$

whose solution is

$$\pi(\tau) = e^{-\mu\tau - \int_0^\tau \gamma(s)\,ds}.$$

Different assumptions on $\gamma(\tau)$ correspond to different real-life scenarios. If all infected individuals are assumed to recover or leave the infectious class by certain age-since-infection $\bar{\tau}$, their probability $\pi(\tau)$ of still being infectious, that is, of being in the class i, τ time units after becoming infected/infectious must tend to zero as $\tau \to \bar{\tau}^-$. This will occur if the function $\gamma(\tau)$ tends to ∞ as $\tau \to \bar{\tau}^-$. Thus, we may assume that

$$\gamma(\tau) \to \infty \qquad \text{as} \qquad \tau \to \bar{\tau}^-; \qquad\qquad \gamma(\tau) = 0 \qquad \text{for} \qquad \tau > \bar{\tau}.$$

A simple example of a possible function $\gamma(\tau)$ that tends to infinity is given by

$$\gamma(\tau) = \frac{0.2\bar{\tau}}{(\bar{\tau} - \tau)^2}.$$

The corresponding probability of survival in the infectious class when $\mu = 0$ is given by

$$\pi(\tau) = e^{-\dfrac{0.2\tau}{\bar{\tau} - \tau}}.$$

This probability of survival is graphed in Fig. 13.2 with $\bar{\tau} = 15$. The coefficient 0.2 is used to give the typical shape of the graph characterized by slow decrease for small τ and fast decrease for $\tau \approx \bar{\tau}$.

13.2.2 Equilibria and Reproduction Number of the Time-Since-Infection SIR Model

The model (13.4) is a first-order integrodifferential equation model. We would like to be able to say something about the solutions. Could a reproduction number $\mathscr{R}_0$ be defined such that the disease dies out if $\mathscr{R}_0 < 1$ and persists otherwise? First, one has to show that for each nonnegative and integrable initial condition (13.5), the model has a unique nonnegative solution. This result is not obvious, but the derivation is somewhat technical and will not be included. Next, we would like to see that the solutions are bounded. To see this, we must obtain the differential equation satisfied by the total population size. Integrating with respect to τ the PDE in system (13.4), we obtain

$$i(\tau,t)|_0^\infty + I' = -\int_0^\infty \gamma(\tau) i(\tau,t) d\tau - \mu I(t),$$

where I' above is the derivative of the total infected population size I with respect to t. If we assume $\lim_{\tau\to\infty} i(\tau,t) = 0$, the above equality leads to

$$I'(t) = S(t)\int_0^\infty \beta(\tau) i(\tau,t)\,d\tau - \int_0^\infty \gamma(\tau) i(\tau,t) d\tau - \mu I(t).$$

Adding the equation above to the equations for S' and R' from (13.4), we obtain

$$S' + I' + R' = \Lambda - \mu(S + I + R).$$

Thus, the total population size satisfies the usual equation, whose solution we know. In particular, we know that

$$\max N(t) \leq \max\left\{N_0, \frac{\Lambda}{\mu}\right\}.$$

Now we consider equilibria of the model. As before, to find the equilibria, we look for time-independent solutions $(S, i(\tau))$ that satisfy the system (13.4) with the time derivatives equal to zero. The system for the equilibria takes the form

$$\begin{cases} \Lambda - S\displaystyle\int_0^\infty \beta(\tau) i(\tau)\, d\tau - \mu S = 0, \\ i_\tau(\tau) = -\gamma(\tau) i(\tau) - \mu i(\tau), \\ i(0) = S\displaystyle\int_0^\infty \beta(\tau) i(\tau)\, d\tau, \\ \displaystyle\int_0^\infty \gamma(\tau) i(\tau) d\tau - \mu R = 0. \end{cases} \tag{13.6}$$

This system consists of one first-order ODE with initial condition that depends on the solution, and two algebraic equations. Clearly, $\mathscr{E}_0 = (\frac{\Lambda}{\mu}, 0, 0)$ is one solution of that system. This solution gives the *disease-free equilibrium*, where the age-since-infection distribution of infectious individuals is identically zero. The disease-free equilibrium always exists. An *endemic equilibrium* will be given by a nontrivial solution $\mathscr{E}^* = (S, i(\tau), R)$.

There is a typical approach for solving such systems. We first solve the differential equation whose solution is

$$i(\tau) = i(0)\pi(\tau). \tag{13.7}$$

This is not an explicit solution, since $i(0)$ depends on $i(\tau)$. The following notation is useful:

$$P = \int_0^\infty \pi(\theta)\, d\theta.$$

This notation occurs when we compute the total infectious population:

$$I = i(0)P.$$

The usual approach to solving the system (13.6) is to substitute the expression for $i(\tau)$ from (13.7) in the boundary condition and the total population size. We typically obtain a system for $i(0)$ and S. However, in this case, when we substitute $i(\tau)$ in the boundary condition, we obtain an explicit expression for the susceptible individuals in the endemic equilibrium:

$$S = \frac{1}{\int_0^\infty \beta(\tau)\pi(\tau)\,d\tau}. \tag{13.8}$$

From the third equation in (13.6), we can express R in terms of $i(0)$:

$$R = \frac{i(0)}{\mu}\int_0^\infty \gamma(\tau)\pi(\tau)d\tau = \frac{i(0)}{\mu}\Gamma. \tag{13.9}$$

We note that Γ is a given number. To find $i(0)$, we use the first equation in (13.6), which becomes

$$\Lambda - i(0) - \mu S = 0.$$

Substituting S, we obtain

$$i(0) = \Lambda\left(1 - \frac{1}{\mathscr{R}_0}\right), \tag{13.10}$$

where we have defined the basic reproduction number as

$$\mathscr{R}_0 = \frac{\Lambda}{\mu}\int_0^\infty \beta(\tau)\pi(\tau)\,d\tau.$$

From the above expressions, we see that the endemic equilibrium is unique and exists if and only if $\mathscr{R}_0 > 1$.

Remark 13.2. We notice that integration by parts gives the following identity:

$$\int_0^\infty \gamma(\tau)\pi(\tau)\,d\tau + \mu\int_0^\infty \pi(\tau)\,d\tau = 1,$$

which makes each term on the left-hand side less than one. The equation above says that the probability of leaving the infectious class i through leaving the system (dying), $\mu\int_0^\infty \pi(\tau)\,d\tau$, or through recovery, $\int_0^\infty \gamma(\tau)\pi(\tau)\,d\tau$, is equal to 1. Indeed, all individuals leave the infectious class through one of those two routes.

13.2.3 Local Stability of Equilibria

To investigate the local stability of the equilibria, we need to linearize the system. For a PDE model, that is done directly following the underlying linearization procedure. In particular, let $S(t) = S^* + x(t)$, $i(\tau,t) = i^*(\tau) + y(\tau,t)$ and $R(t) = R^* + z(t)$, where $x(t)$, $y(\tau,t)$, and $z(t)$ are the perturbations, and $(S^*, i^*(\tau), R^*)$ denotes a generic equilibrium. We substitute the expressions for S, $i(\tau,t)$, and R in the system (13.4):

$$\begin{cases} (S^*+x(t))' = \Lambda - (S^*+x(t))\displaystyle\int_0^\infty \beta(\tau)(i^*(\tau)+y(\tau,t))\,d\tau - \mu(S^*+x(t)), \\ (i^*(\tau)+y(\tau,t))_\tau + (i^*(\tau)+y(\tau,t))_t = -\gamma(\tau)(i^*(\tau)+y(\tau,t)) - \mu(i^*(\tau)+y(\tau,t)), \\ i^*(0)+y(0,t) = (S^*+x(t))\displaystyle\int_0^\infty \beta(\tau)(i^*(\tau)+y(\tau,t))\,d\tau, \\ (R^*+z(t))' = \displaystyle\int_0^\infty \gamma(\tau)(i^*(\tau)+y(\tau,t))d\tau - \mu(R^*+z(t)). \end{cases} \tag{13.11}$$

Multiplying out the expressions, we have

$$\begin{cases} x'(t) = \Lambda - S^*\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)d\tau - \mu S^* - x(t)\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau \\ \qquad\qquad -S^*\displaystyle\int_0^\infty \beta(\tau)y(\tau,t)\,d\tau - x(t)\int_0^\infty \beta(\tau)y(\tau,t)\,d\tau - \mu x(t), \\ i^*_\tau(\tau)+y_\tau(\tau,t)+y_t(\tau,t) = -\gamma(\tau)i^*(\tau) - \gamma(\tau)y(\tau,t) - \mu i^*(\tau) - \mu y(\tau,t), \\ i^*(0)+y(0,t) = S^*\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau + x(t)\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau \\ \qquad\qquad +S^*\displaystyle\int_0^\infty \beta(\tau)y(\tau,t))\,d\tau + x(t)\int_0^\infty \beta(\tau)y(\tau,t)\,d\tau. \\ z'(t) = \displaystyle\int_0^\infty \gamma(\tau)i^*(\tau)d\tau + \int_0^\infty \gamma(\tau)y(\tau,t)d\tau - \mu R^* - \mu z(t). \end{cases} \tag{13.12}$$

This system can be simplified further by the use of two techniques. First, we use the equations for the equilibria (13.6). This approach simplifies the system to

$$\begin{cases} x'(t) = -x(t)\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau \\ \qquad -S^*\displaystyle\int_0^\infty \beta(\tau)y(\tau,t)\,d\tau - x(t)\int_0^\infty \beta(\tau)y(\tau,t)\,d\tau - \mu x(t), \\ y_\tau(\tau,t)+y_t(\tau,t) = -\gamma(\tau)y(\tau,t) - \mu y(\tau,t), \\ y(0,t) = x(t)\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau \\ \qquad\qquad +S^*\displaystyle\int_0^\infty \beta(\tau)y(\tau,t))\,d\tau + x(t)\int_0^\infty \beta(\tau)y(\tau,t)\,d\tau, \\ z'(t) = \displaystyle\int_0^\infty \gamma(\tau)y(\tau,t)d\tau - \mu z(t). \end{cases} \tag{13.13}$$

Notice that after this transformation, system (13.13) contains only terms that include a perturbation. However, system (13.13) is not linear. Terms such as $x(t)\int_0^\infty \beta(\tau)$ $y(\tau,t)\,d\tau$ are quadratic in the perturbations. Since we assume that the perturbations are small, the quadratic terms must be much smaller. Therefore, the second technique that we use to simplify the system is to neglect the quadratic terms. After disregarding the quadratic terms, we obtain the following linear system in the perturbations:

$$\begin{cases} x'(t) = -x(t)\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau - S^*\int_0^\infty \beta(\tau)y(\tau,t)\,d\tau - \mu x(t), \\ y_\tau(\tau,t) + y_t(\tau,t) = -\gamma(\tau)y(\tau,t) - \mu y(\tau,t), \\ y(0,t) = x(t)\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau + S^*\int_0^\infty \beta(\tau)y(\tau,t))\,d\tau, \\ z'(t) = \displaystyle\int_0^\infty \gamma(\tau)y(\tau,t)d\tau - \mu z(t). \end{cases} \tag{13.14}$$

System (13.14) is a linear system for $x(t)$, $y(\tau,t)$, and $z(t)$. Just like linear systems of ODEs, the above system also has exponential solutions. Therefore, it is sensible to look for solutions of the form $x(t) = \bar{x}e^{\lambda t}$, $y(\tau,t) = \bar{y}(\tau)e^{\lambda t}$, $z(t) = \bar{z}e^{\lambda t}$, where $\bar{x}$, $\bar{y}(\tau)$, $\bar{z}$, and λ have to be determined in such a way that $\bar{x}$, $\bar{y}(\tau)$, $\bar{z}$ are not all zero. Substituting the constitutive form of the solutions in the system (13.14), we obtain the following problem for $\bar{x}$, $\bar{y}(\tau)$, $\bar{z}$, and λ (the bars have been omitted):

$$\begin{cases} \lambda x = -x\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau - S^*\int_0^\infty \beta(\tau)y(\tau)\,d\tau - \mu x, \\ y_\tau(\tau) + \lambda y(\tau) = -\gamma(\tau)y(\tau) - \mu y(\tau), \\ y(0) = x\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau + S^*\int_0^\infty \beta(\tau)y(\tau)\,d\tau, \\ \lambda z = \displaystyle\int_0^\infty \gamma(\tau)y(\tau)d\tau - \mu z. \end{cases} \tag{13.15}$$

Remark 13.3. Solutions of system (13.15) give the eigenvectors and eigenvalues λ of the differential operator. Eigenvalues are the only points in the spectrum of operators generated by ODEs. However, operators that originate from PDEs may have other points in the spectrum besides eigenvalues, which also contribute to the stability or instability of an equilibrium. It can be shown [112] that for the problems of type (13.4), knowing the distribution of the eigenvalues is sufficient to determine the stability of a given equilibrium. In other words, we have the same rules that are used in ODEs. In particular, if all eigenvalues have negative real parts, the corresponding equilibrium is locally stable; if there is an eigenvalue with a positive real part, then the equilibrium is unstable. Because of that, we will concentrate on investigating eigenvalues.

The next step will be to eliminate x, $y(\tau)$, and z so that an equation in λ is obtained. This process is different for the different equilibria, so we have to consider two cases. The first case is that of the disease-free equilibrium. Then $S^* = \frac{\Lambda}{\mu}$, $i^* = 0$, and $R^* = 0$. System (13.15) simplifies to the following system:

$$\begin{cases} \lambda x = -S^*\displaystyle\int_0^\infty \beta(\tau)y(\tau)\,d\tau - \mu x, \\ y_\tau(\tau) + \lambda y(\tau) = -\gamma(\tau)y(\tau) - \mu y(\tau), \\ y(0) = S^*\displaystyle\int_0^\infty \beta(\tau)y(\tau)\,d\tau, \\ \lambda z = \displaystyle\int_0^\infty \gamma(\tau)y(\tau)d\tau - \mu z. \end{cases} \tag{13.16}$$

It is easy to see that the equation for $y(\tau)$ is independent of x and z. Solving the differential equation, we have

$$y(\tau) = y(0)e^{-\lambda\tau}\pi(\tau).$$

Substituting this solution in the boundary condition and canceling $y(0)$ (assumed nonzero), we obtain the following *characteristic equation* for λ:

$$S^* \int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau = 1. \tag{13.17}$$

The above equation is a *transcendental equation*, and it may have many solutions. To show stability of the disease-free equilibrium, we need to show that all solutions λ of the above equation have negative real parts. If there is a solution λ with positive real part, then the disease-free equilibrium will be unstable. To investigate this, we define

$$\mathscr{G}(\lambda) = S^* \int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau.$$

We first notice that $\mathscr{G}(0) = \mathscr{R}_0$. Hence, if $\mathscr{R}_0 > 1$, and if $\beta(\tau)$ is strictly positive on a positive interval, then the function $\mathscr{G}(\lambda)$ as a function of the real variable λ is a decreasing function. Since $\mathscr{G}(0) > 1$ and $\lim_{\lambda\to\infty} G(\lambda) = 0$, there exists $\lambda^* > 0$ such that $\mathscr{G}(\lambda^*) = 1$. Consequently, the disease-free equilibrium is unstable. If, alternatively, $\mathscr{R}_0 < 1$, then for all $\lambda = a + bi$ with $a \geq 0$, we have

$$|\mathscr{G}(\lambda)| \leq S^* \int_0^\infty \beta(\tau)|e^{-\lambda\tau}|\pi(\tau)\,d\tau = S^* \int_0^\infty \beta(\tau)e^{-a\tau}\pi(\tau)\,d\tau \leq \mathscr{R}_0 < 1.$$

We conclude that those λ whose real part is nonnegative cannot satisfy the equation $\mathscr{G}(\lambda) = 1$. Therefore, the disease-free equilibrium is locally asymptotically stable in this case. We summarize these results in the following proposition:

Proposition 13.1. *If $\mathscr{R}_0 < 1$, the disease-free equilibrium is locally stable. If $\mathscr{R}_0 > 1$, then the disease-free equilibrium is unstable.*

We see that we obtain similar results as for ODE epidemiological models.

Now we turn to the stability of the endemic equilibrium. We consider system (13.15), where the equilibrium is the endemic equilibrium. The goal again is to eliminate x, $y(\tau)$, and z, but this time the first and the second equations are coupled. We can neglect the equation for z, since z does not participate in the first two equations. Because the differential equation depends on y and λ only, we can solve it and replace $y(\tau)$ by its expression in the boundary condition and in the equation for x. That will produce a linear system for the numbers $y(0)$ and x (assuming that λ is given). Namely, solving the differential equation, we get

$$y(\tau) = y(0)e^{-\lambda\tau}\pi(\tau).$$

From the first equation and the boundary equation, we obtain the system

$$\begin{cases} \lambda x = -x\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau - S^*y(0)\int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau - \mu x, \\ y(0) = x\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau + S^*y(0)\int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau. \end{cases} \tag{13.18}$$

There are many ways to solve this system in order to find a nontrivial solution. One way is to require that the determinant be zero:

$$\begin{vmatrix} \lambda+\mu+\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau & S^*\displaystyle\int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau \\ -\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau & 1-S^*\displaystyle\int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau \end{vmatrix} = 0. \tag{13.19}$$

Adding the second row to the first, we obtain

$$\begin{vmatrix} \lambda+\mu & 1 \\ -\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau & 1-S^*\displaystyle\int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau \end{vmatrix} = 0. \tag{13.20}$$

We notice that $\displaystyle\int_0^\infty \beta(\tau)i^*(\tau)\,d\tau$ is just a positive number. We denote that positive number by B. Expanding the determinant, we have

$$(\lambda+\mu)(1-S^*\int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau)+B=0.$$

The general idea is to rewrite this equation so that there are positive terms on both sides of the equation. In this case, a useful form for the characteristic equation of the endemic equilibrium is

$$\frac{\lambda+\mu+B}{\lambda+\mu} = S^*\int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau. \tag{13.21}$$

Now we will show that this equation cannot have solutions λ with positive real part. Let $\lambda = a+bi$, and assume $a \geq 0$. Taking the absolute value of both sides of the above equality, we have

$$\left|\frac{\lambda+\mu+B}{\lambda+\mu}\right| = \frac{\sqrt{(a+\mu+B)^2+b^2}}{\sqrt{(a+\mu)^2+b^2}} > 1.$$

On the other hand, for $a \geq 0$ we have

$$\begin{aligned} |S^*\int_0^\infty \beta(\tau)e^{-\lambda\tau}\pi(\tau)\,d\tau| &\leq S^*\int_0^\infty \beta(\tau)|e^{-\lambda\tau}|\pi(\tau)\,d\tau \\ &\leq S^*\int_0^\infty \beta(\tau)e^{-a\tau}\pi(\tau)\,d\tau \\ &\leq S^*\int_0^\infty \beta(\tau)\pi(\tau)\,d\tau = 1. \end{aligned} \tag{13.22}$$

This means that for λ with nonnegative real part, the left-hand side remains strictly greater than one, while the right-hand side is strictly less than one. Thus, such λ's cannot satisfy the characteristic equation (13.21). We conclude that the endemic equilibrium is locally asymptotically stable.

Stability for the endemic equilibrium in age-since-infection structured models is a rare event. It has been established that infection-age can destabilize the endemic equilibrium in a simple SI model of HIV [153]. The main differences of the HIV model from model (13.4) is that there is no recovery and that the incidence must be a standard incidence, since sexual contacts do not increase linearly with the population size.

13.3 Influenza Model Structured with Time-Since-Recovery

Besides the infectious class, other classes could be structured by the duration of residence in the class or *class-age*. This is necessary particularly when parameters describing the class may vary with the time individuals spend in the class.

13.3.1 Equilibria of the Time-Since-Recovery Model

To be more specific, let us consider again influenza. Instead of structuring the infectious class with time-since-infection, it may be more realistic to consider structuring the recovered class with time-since-recovery. Influenza strains are believed to impart permanent immunity to themselves and partial immunity to related influenza strains. Because the makeup of influenza strains that circulate in the population continuously changes, a recovered individual has an increasing probability of contracting influenza again. Our goal with this model is to present an example of a different class structure, as well as the fact that the endemic equilibrium does not necessarily needs to be locally stable.

To introduce the model, we have classes of susceptible individuals $S(t)$ who have never had influenza, infected individuals $I(t)$, and recovered individuals whose density is structured with time-since-recovery, $r(\tau,t)$. The model, first introduced in [154], is given below:

$$\begin{aligned} S'(t) &= \Lambda - \beta SI - \mu S, \\ I'(t) &= \beta SI + I\int_0^\infty \gamma(\tau) r(\tau,t)\, d\tau - (\mu+\alpha)I, \\ r_\tau + r_t &= -\gamma(\tau) I r(\tau,t) - \mu r(\tau,t), \\ r(0,t) &= \alpha I. \end{aligned} \tag{13.23}$$

This model is structured by time-since-recovery. The newly recovered individuals αI move into the recovery class with age-since-recovery equal to zero, that is, they

give the boundary condition of the PDE. Recovered individuals can become infected at a rate $\gamma(\tau)$. Realistically, we may expect that $\gamma(\tau)$ is an increasing function of τ. The model is augmented with the following initial conditions:

$$\begin{aligned} S(0) &= S_0, \\ I(0) &= I_0, \\ r(\tau,0) &= \phi(\tau). \end{aligned} \tag{13.24}$$

We define the probability of survival in the recovered class:

$$\pi(\tau) = e^{-I\int_0^\tau \gamma(\sigma)d\sigma} e^{-\mu\tau}.$$

To determine the equilibria, we set the time derivatives equal to zero. We have to solve the following system:

$$\begin{aligned} \Lambda - \beta SI - \mu S &= 0, \\ \beta SI + I\int_0^\infty \gamma(\tau) r(\tau)\, d\tau - (\mu+\alpha)I &= 0, \\ r_\tau &= -\gamma(\tau) I r(\tau) - \mu r(\tau), \\ r(0) &= \alpha I. \end{aligned} \tag{13.25}$$

Solving the differential equation, we obtain an expression for $r(\tau)$ in terms of the number of infected I:

$$r(\tau) = \alpha I \pi(\tau).$$

In addition, we express S in terms of I from the first equation:

$$S = \frac{\Lambda}{\beta I + \mu}.$$

Substituting in the second equation, we obtain an equation for I:

$$\frac{\beta\Lambda I}{\beta I+\mu} + \alpha I^2 \int_0^\infty \gamma(\tau)\pi(\tau)\, d\tau - (\mu+\alpha)I = 0. \tag{13.26}$$

This equation clearly has the disease-free equilibrium $\mathscr{E}_0 = (\frac{\Lambda}{\mu}, 0, 0)$. To find the endemic equilibria, we can cancel one I and obtain the following equation for $I \neq 0$:

$$\frac{\beta\Lambda}{\beta I+\mu} + \alpha I \int_0^\infty \gamma(\tau)\pi(\tau)\, d\tau = (\mu+\alpha). \tag{13.27}$$

We define the basic reproduction number

$$\mathscr{R}_0 = \frac{\beta\Lambda}{\mu(\alpha+\mu)}. \tag{13.28}$$

Proposition 13.2. *Assume $\mathscr{R}_0 > 1$. Then Eq. (13.27) has at least one positive solution.*

Proof. Integration by parts shows that

$$I\int_0^\infty \gamma(\tau)\pi(\tau)\,d\tau = 1-\mu\int_0^\infty \pi(\tau)\,d\tau.$$

Hence,

$$\lim_{I\to\infty} I\int_0^\infty \gamma(\tau)\pi(\tau)\,d\tau = 1.$$

We denote the left-hand side of (13.27) by $f(I)$. We have $f(0)=\frac{\beta\Lambda}{\mu}$. Hence, since $\mathscr{R}_0>1$, we have $f(0)>\mu+\alpha$. On the other hand, we have $\lim_{I\to\infty} f(I)=\alpha<\alpha+\mu$. This shows that the equation $f(I)=\alpha+\mu$ has at least one solution. □

It is biologically reasonable to assume that the reinfection rate $\gamma(\tau)$ is a bounded function and that its supremum does not exceed β:

$$\sup_\tau \gamma(\tau)\le\beta. \tag{13.29}$$

Under this condition, Thieme and Yang [154] showed that the endemic equilibrium $\mathscr{E}^*=(S^*,I^*,r^*(\tau))$ is unique. This equilibrium cannot be explicitly computed. If condition (13.29) is not satisfied, then backward bifurcation may occur, and multiple endemic equilibria are possible (see Problem 13.2).

13.3.2 Stability of Equilibria

In this subsection, we investigate the stability of the equilibria. We will concentrate primarily on the unique endemic equilibrium in the case that condition (13.29) holds. As before, we start from linearizing system (13.23). Let (S^*,I^*,r^*) denote a generic equilibrium. We set $S=S^*+x(t)$, $I=I^*+y(t)$, and $r(\tau,t)=r^*(\tau)+z(\tau,t)$. Substituting in the equations of (13.23), we obtain

$$\begin{aligned}
(S^*+x)'(t) &= \Lambda-\beta(S^*+x)(I^*+y)-\mu(S^*+x),\\
(I^*+y)'(t) &= \beta(S^*+x)(I^*+y)+(I^*+y)\int_0^\infty \gamma(\tau)(r^*+z(\tau,t))\,d\tau-(\mu+\alpha)(I^*+y),\\
(r^*+z)_\tau+z_t &= -\gamma(\tau)(I^*+y)(r^*(\tau)+z(\tau,t))-\mu(r^*+z(\tau,t)),\\
r^*(0)+z(0,t) &= \alpha(I^*+y).
\end{aligned} \tag{13.30}$$

Multiplying out and using the equations for the equilibria (13.25), we obtain the following system:

$$
\begin{aligned}
x'(t) &= -\beta S^* y - \beta I^* x - \beta xy - \mu x,\\
y'(t) &= \beta S^* y + \beta I^* x + \beta xy + I^* \int_0^\infty \gamma(\tau) z(\tau,t)\, d\tau + y \int_0^\infty \gamma(\tau) r^*(\tau)\, d\tau\\
&\quad + y \int_0^\infty \gamma(\tau) z(\tau,t)\, d\tau - (\mu+\alpha) y,\\
z_\tau + z_t &= -\gamma(\tau) y r^*(\tau) - \gamma(\tau) I^* z(\tau,t) - \gamma(\tau) y z(\tau,t), -\mu z(\tau,t),\\
z(0,t) &= \alpha y.
\end{aligned}
\tag{13.31}
$$

We also neglect the quadratic terms in the perturbations x, y, and z to obtain the following linear system in the perturbations:

$$
\begin{aligned}
x'(t) &= -\beta S^* y - \beta I^* x - \mu x,\\
y'(t) &= \beta S^* y + \beta I^* x + I^* \int_0^\infty \gamma(\tau) z(\tau,t)\, d\tau + y \int_0^\infty \gamma(\tau) r^*(\tau)\, d\tau - (\mu+\alpha) y,\\
z_\tau + z_t &= -\gamma(\tau) y r^*(\tau) - \gamma(\tau) I^* z(\tau,t) - \mu z(\tau,t),\\
z(0,t) &= \alpha y.
\end{aligned}
\tag{13.32}
$$

This is our linear system for the perturbations. To investigate the local stability of the equilibria, we have to study the solutions of this system. As before, we expect that the solutions are exponential. Therefore, we look for solutions of the form $x(t) = \bar{x}e^{\lambda t}$, $y(t) = \bar{y}e^{\lambda t}$, $z(\tau,t) = \bar{z}(\tau)e^{\lambda t}$. We obtain the following linear eigenvalue problem for $\bar{x}$, $\bar{y}$, and $\bar{z}(\tau)$, and the eigenvalue λ:

$$
\begin{aligned}
\lambda x &= -\beta S^* y - \beta I^* x - \mu x,\\
\lambda y &= \beta S^* y + \beta I^* x + I^* \int_0^\infty \gamma(\tau) z(\tau)\, d\tau + y \int_0^\infty \gamma(\tau) r^*(\tau)\, d\tau - (\mu+\alpha) y,\\
z_\tau + \lambda z &= -\gamma(\tau) y r^*(\tau) - \gamma(\tau) I^* z(\tau) - \mu z(\tau),\\
z(0) &= \alpha y,
\end{aligned}
\tag{13.33}
$$

where in the above, we have dropped the bars. To investigate the stability of the disease-free equilibrium, we have to write the above system for that equilibrium. This will simplify that system significantly:

$$
\begin{aligned}
\lambda x &= -\beta S^* y - \mu x,\\
\lambda y &= \beta S^* y - (\mu+\alpha) y,\\
z_\tau + \lambda z &= -\mu z(\tau,t),\\
z(0) &= \alpha y.
\end{aligned}
\tag{13.34}
$$

Problem 13.3 asks you to determine the stability of the disease-free equilibrium. Use the above system to answer Problem 13.3.

Here, we assume that condition (13.29) holds, and we continue with the investigation of the unique endemic equilibrium. The next step will be to solve system (13.33) and derive the characteristic equation. A typical way in which this can be done is to solve an ordinary differential equation and express z in terms of y. Then from the first equation, we can express x in terms of y. Then we may substitute the expressions for z and x in the second equation. We will obtain an equation in y only.

Since we are looking for a nontrivial eigenvector, we assume that y is not zero and we cancel it. We obtain an equation in λ that constitutes the characteristic equation.

To carry out this plan, we begin by solving the differential equation. The ODE is a first-order linear ODE with nonzero right-hand side. We move the terms that depend on z to the left-hand side and the terms that do not depend on z to the right-hand side. We multiply by the integrating factor $e^{(\lambda+\mu)\tau+I\int_0^\tau \gamma(\sigma)d\sigma}$. The differential equation becomes

$$\left[e^{(\lambda+\mu)\tau+I^*\int_0^\tau \gamma(\sigma)d\sigma}z\right]' = -\gamma(\tau)yr^*(\tau)e^{(\lambda+\mu)\tau+I^*\int_0^\tau \gamma(\sigma)d\sigma}.$$

Integrating both sides of this equation from 0 to τ and recalling that $z(0)=\alpha y$, we have

$$z(\tau) = \alpha y e^{-(\lambda+\mu)\tau-I^*\int_0^\tau \gamma(\sigma)d\sigma} - y\int_0^\tau \gamma(s)r^*(s)e^{-(\lambda+\mu)(\tau-s)-I^*\int_s^\tau \gamma(\sigma)d\sigma}ds.$$

This gives an expression for z in terms of y. This equation can be rewritten also in the form

$$z(\tau) = \alpha y e^{-(\lambda+\mu)\tau-I^*\int_0^\tau \gamma(\sigma)d\sigma} - yr^*(\tau)\int_0^\tau \gamma(s)e^{-\lambda(\tau-s)}ds.$$

From the first equation in system (13.33), we have

$$x = -\frac{\beta S^* y}{\lambda+\beta I^*+\mu}.$$

From the second equation in system (13.33), after substituting z and x and canceling y, we obtain the characteristic equation:

$$\begin{aligned}(\lambda+\mu+\alpha) &= \beta S^* - \frac{\beta I^*\beta S^*}{\lambda+\beta I^*+\mu} + \int_0^\infty \gamma(\tau)r^*(\tau)e^{-\lambda\tau}d\tau \\ &\quad - I\int_0^\infty \gamma(\tau)r^*(\tau)\int_0^\tau \gamma(s)e^{-\lambda(\tau-s)}dsd\tau + \int_0^\infty \gamma(\tau)r^*(\tau)d\tau.\end{aligned} \tag{13.35}$$

Integrating the double integral by parts, thinking of $I\gamma(\tau)e^{-I\int_0^\tau \gamma(\sigma)d\sigma}$ as u' and the rest as v, we can obtain the following simplified characteristic equation:

$$\begin{aligned}\lambda+\mu+\alpha = \frac{\beta S(\lambda+\mu)}{\lambda+\beta I^*+\mu} &+ \int_0^\infty \gamma(\tau)r^*(\tau)e^{-\lambda\tau}d\tau \\ &+(\lambda+\mu)\int_0^\infty r^*(\tau)\int_0^\tau \gamma(s)e^{-\lambda(\tau-s)}dsd\tau.\end{aligned} \tag{13.36}$$

This characteristic equation does not always have only roots with negative real parts. One can pose additional conditions that would imply stability. However, here we would like to show that instability and oscillations may occur in this model. To show this, we need to exhibit a specific example in which Hopf bifurcation can occur and sustained oscillations are possible. To demonstrate this, we consider the following special case:

Assumption: Assume

$$\gamma(\tau) = \begin{cases} 0 & 0 \le \tau \le A, \\ \beta & \tau > A, \end{cases} \tag{13.37}$$

where A is an arbitrary constant. This form of $\gamma(\tau)$ suggests that recovered individuals are completely protected for a period of time A and then completely susceptible again. This is a reasonable assumption in influenza modeling. With this $\gamma(\tau)$, the recovered individuals are given by the following expression:

$$r^*(\tau) = \begin{cases} \alpha I^* e^{-\mu\tau} & 0 \le \tau \le A, \\ \alpha I^* e^{-\mu\tau} e^{-\beta I^*(\tau - A)} & \tau > A. \end{cases} \tag{13.38}$$

When the class-age structured function is a step function, the class-age model becomes equivalent to a delay model. As a result, the characteristic equation (13.36) can be significantly simplified. We compute the integrals:

$$\begin{aligned} \int_0^\infty \gamma(\tau) r^*(\tau) e^{-\lambda\tau} d\tau &= \alpha\beta I^* \int_A^\infty e^{-\mu\tau} e^{-\beta I^*(\tau - A)} e^{-\lambda\tau} d\tau \\ &= \frac{\alpha\beta I^*}{\lambda + \mu + \beta I^*} e^{-(\lambda+\mu)A}. \end{aligned} \tag{13.39}$$

Given the value of the integral above with $\lambda = 0$, the equation for the equilibria becomes

$$\beta S^* + \frac{\alpha\beta I^*}{\mu + \beta I^*} e^{-\mu A} = (\mu + \alpha). \tag{13.40}$$

Recalling that $S^* = \Lambda/(\beta I^* + \mu)$, we can solve the resulting equation for I^* to obtain

$$I^* = \frac{\beta\Lambda - \mu(\mu + \alpha)}{\beta(\mu + \alpha + \alpha e^{-\mu A})}. \tag{13.41}$$

The double integral in (13.36) can also be computed:

$$\begin{aligned} \int_0^\infty r^*(\tau) \int_0^\tau \gamma(s) e^{-\lambda(\tau - s)} ds d\tau &= \int_A^\infty r^*(\tau) \int_A^\tau \gamma(s) e^{-\lambda(\tau - s)} ds d\tau \\ &= \beta\alpha I^* \int_A^\infty e^{-\mu\tau} e^{-\beta I^*(\tau - A)} \int_A^\tau e^{-\lambda(\tau - s)} ds d\tau \\ &= \frac{\alpha\beta I^* e^{\beta I^* A}}{\lambda} \int_A^\infty e^{-\mu\tau} e^{-\beta I^*\tau} e^{-\lambda\tau} (e^{\lambda\tau} - e^{\lambda A}) d\tau \\ &= \frac{\alpha\beta I^* e^{\beta I^* A}}{\lambda} \int_A^\infty e^{-\mu\tau} e^{-\beta I^*\tau} d\tau \\ &\quad - \frac{\alpha\beta I^* e^{\beta I^* A + \lambda A}}{\lambda} \int_A^\infty e^{-\mu\tau} e^{-\beta I^*\tau} e^{-\lambda\tau} d\tau \\ &= \frac{\alpha\beta I^* e^{-\mu A}}{\lambda(\mu + \beta I^*)} - \frac{\alpha\beta I^* e^{-\mu A}}{\lambda(\lambda + \mu + \beta I^*)} \\ &= \frac{\alpha\beta I^* e^{-\mu A}}{(\mu + \beta I^*)(\lambda + \mu + \beta I^*)}. \end{aligned} \tag{13.42}$$

Using the equation for the equilibria (13.40), the characteristic equation (13.36) can be simplified as follows:

$$\lambda+\mu+\alpha=\frac{\beta S^*(\lambda+\mu)}{\lambda+\beta I^*+\mu}+\frac{\alpha\beta I^* e^{-(\lambda+\mu)A}}{\lambda+\beta I^*+\mu}+\frac{\alpha\beta I^*(\lambda+\mu)e^{-\mu A}}{(\lambda+\beta I^*+\mu)(\beta I^*+\mu)}. \quad (13.43)$$

Collecting terms gives us

$$(\lambda+\mu+\alpha)(\lambda+\beta I^*+\mu)=(\lambda+\mu)\left[\beta S^*+\frac{\alpha\beta I^* e^{-\mu A}}{\mu+\beta I^*}\right]+\alpha\beta I^* e^{-(\lambda+\mu)A}. \quad (13.44)$$

Using (13.40) and simplifying, we obtain

$$(\lambda+\mu+\alpha)(\lambda+\beta I^*+\mu)-(\lambda+\mu)(\alpha+\mu)=\alpha\beta I^* e^{-(\lambda+\mu)A}. \quad (13.45)$$

Hence, the characteristic equation simplifies to the following transcendental equation:

$$\lambda^2+(\beta I^*+\mu)\lambda+\beta I^*(\mu+\alpha)=\alpha\beta I^* e^{-(\lambda+\mu)A}. \quad (13.46)$$

Let $\lambda=\xi+i\eta$. We can use the methodology first introduced in Chap. 4 to find eigenvalues with positive real part. We separate the real and the imaginary part in the equation above. We obtain the following system:

$$\begin{cases}\xi^2-\eta^2+(\beta I^*+\mu)\xi+\beta I^*(\mu+\alpha)=\alpha\beta I^* e^{-(\xi+\mu)A}\cos\eta A,\\ 2\xi\eta+(\beta I^*+\mu)\eta=-\alpha\beta I^* e^{-(\xi+\mu)A}\sin\eta A.\end{cases} \quad (13.47)$$

To find parameters that will give us oscillations, we proceed in the following way. We notice that the system above is linear in βI^* and $\alpha\beta I^*$. Hence, we can solve for these parameters. That cannot be done by hand, but a computer algebra system such as Mathematica can do it. The expressions we obtain are rather large, and we will not include them here. We view $\beta I^*=f(\eta)$ and $\alpha\beta I^*=g(\eta)$. We plot parametrically the points $(f(\eta),g(\eta))$ in the $(\beta I^*,\alpha\beta I^*)$-plane. We obtain the left figure in Fig. 13.3. Before plotting, we fix the other parameters as follows. Since the current worldwide lifespan of humans is 70 years, we define $\mu=1/(70*365)$ days^{-1}. The worldwide human population is 7 billion. So we compute $\Lambda=1000/365$ births per day (in units of 10^5). In this way, at equilibrium, where the population is Λ/μ, we would have 70,000 individuals (in units 10^5), that is, 7 billion individuals. We will compute the infectious period so that oscillations occur. We take $A=30$ days. That is, prior exposure to influenza protects a person completely for 30 days, after which one becomes completely susceptible again. That value for A will give too small a period of oscillations for influenza. If we want a more realistic period, we need to take $A=365$. We fix $\xi=0.01$. From the left figure of Fig. 13.3, we see that for some η's, the point in the $(\beta I^*,\alpha\beta I^*)$-plane is in the positive quadrant. Hence, it gives a viable point. We guess a value of η that gives positive $\beta I^*=f(\eta)$ and $\alpha\beta I^*=g(\eta)$. In the simulations, we took $\eta=0.19$. That gives $\beta I^*=0.172187$ and $\alpha\beta I^*=0.0896313$. Dividing the second of these numbers by the first, we get $\alpha=0.520548$, which gives an infectious period of less than two days. We determine β from the formula for I^*:

$$\beta I^* = \frac{\beta\Lambda - \mu(\mu+\alpha)}{(\mu+\alpha-\alpha e^{-\mu A})} = f(0.19) = 0.172187.$$

This gives $\beta = 0.0000482876$. To observe the principal eigenvalue, we plot the equations in system (13.47) as contour plots in the (ξ, η)-plane. The eigenvalues of Eq. (13.46) are given from the intersection of the two types of level curves. The right-hand picture of Figure 13.3 shows that Eq. (13.46) exhibits Hopf bifurcation and has a principal eigenvalue with positive real part.

To illustrate the oscillations, one needs to simulate the solution of system (13.23). As an integrodifferential PDE system with nonlocal boundary condition, the system cannot be automatically solved by a computer algebra system such as Matlab of Mathematica. A numerical method needs to be built for system (13.23) and coded in Matlab, Fortran, or C. In the next subsection, we discuss how to discretize the system.

13.3.3 Numerical Method for the Time-Since-Recovery Model

In this section, we build a numerical method and code model (13.23). The numerical method is a finite difference method that discretizes both the age and time variables and computes the solution at a number of points that form a mesh.

As a first step, we need to discretize the domain of the system (13.23). Recall that the domain is given by

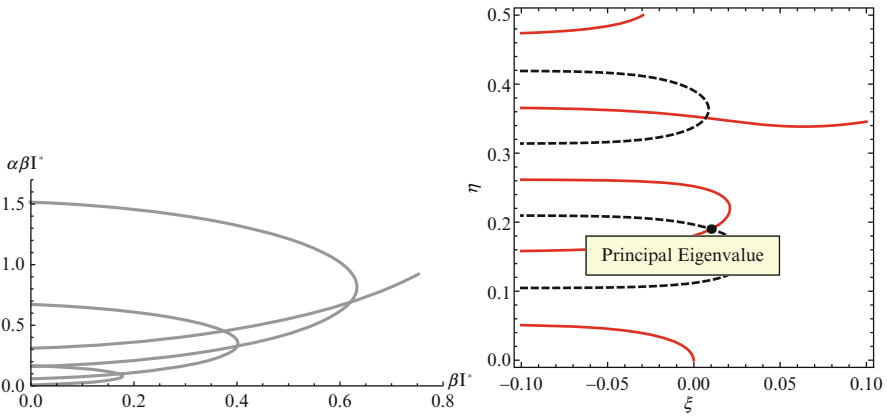

Fig. 13.3 The *left* figure gives the parametric plot in the $(\beta I^*, \alpha\beta I^*)$-plane. The *right* figure shows the level curves of system (13.47). The level curves of the first equation are given by a *continuous curve*, and the level curves of the second equation are given in *dashed curves*. The eigenvalues are given by the intersection of *continuous* and *dashed curves*. The principal eigenvalue is the one that is farthest to the *right*. The figure indicates it with a point. The principal eigenvalue has $\xi = 0.01$, as set in the computation (see text)

$$\mathscr{D} = \{(\tau, t) : \tau \geq 0, t \geq 0\}.$$

The domain $\mathscr{D}$ is an infinite domain. We cannot compute with infinite domains, so we have to truncate it in both the age and time directions. We will consider the finite domain

$$\bar{\mathscr{D}} = \{(\tau, t) : 0 \leq \tau \leq G, 0 \leq t \leq T\}.$$

What is a sensible way to choose G so that when we truncate the infinite integral in the boundary condition, we do not make too much of an error? One way is to choose G large enough that $e^{-\mu G}$ is almost zero. Since the solutions decay with $e^{-\mu\tau}$, computing in τ until this exponent becomes zero, at least in a computational sense, will guarantee that the error of replacing the infinite integral with a finite one will not modify the solution too much.

To discretize, we take the points along the age direction equally spaced with a step $\Delta\tau$: $\tau_k = k\Delta\tau$. Since both age and time progress simultaneously, we discretize the time with same step $\Delta t = \Delta\tau$. The points in the time direction are given by $t_n = n\Delta t$. These points discretize the domain $\bar{\mathscr{D}}$ with a discrete square mesh. We define the number of steps made in each direction as

$$K = \left[\frac{G}{\Delta t}\right], \qquad N = \left[\frac{T}{\Delta t}\right],$$

where $[\cdot]$ denotes the integer part of the expression. We may modify G and T a little so that without loss of generality, we may assume that

$$G = K\Delta t, \qquad T = N\Delta t.$$

To discretize the time-since-recovery model (13.23), we assume $S(t_n) \approx S^n$, $r(\tau_k, t_n) \approx r_k^n$, $I(t_n) \approx I^n$. We first discretize the equation for the susceptibles, which is a first-order ODE. We can use a backward difference to replace the time derivative. Thus, we evaluate the equation at time level t_{n+1} and apply a backward finite difference for the time derivative. We obtain

$$\frac{S^{n+1} - S^n}{\Delta t} = \Lambda - \beta S^{n+1} I^{n+1} - \mu S^{n+1}.$$

From here, we should be able to compute S^{n+1}, knowing the values at the nth time level. However, as the equation stands now, this is not possible, because we do not know I^{n+1}. To simplify the computations, we "linearize" the nonlinear term and evaluate I at time level n rather than time level $n+1$. This is legitimate in numerical methods, since I^n and I^{n+1} are close, and so their values should be close. The equation above becomes

$$\frac{S^{n+1} - S^n}{\Delta t} = \Lambda - \beta S^{n+1} I^n - \mu S^{n+1}.$$

Now we can use this equation to compute S^{n+1} from values at level n. Since the equation for I contains both S and r as well as I, we compute that last. Next we discretize the PDE. We evaluate it at t_{n+1} and τ_k. We have

$$r_\tau(\tau_k, t_{n+1}) + r_t(\tau_k, t_{n+1}) = -\gamma(\tau_k) I(t_{n+1}) r(\tau_k, t_{n+1}) - \mu r(\tau_k, t_{n+1}).$$

We replace the derivative in τ with a forward difference and the derivative in time with a backward difference. We obtain the following difference equation:

$$\frac{r_{k+1}^{n+1} - r_k^{n+1}}{\Delta t} + \frac{r_k^{n+1} - r_k^n}{\Delta t} = -\gamma_k I^{n+1} r_k^{n+1} - \mu r_k^{n+1}.$$

The left-hand side can be simplified by canceling the two r_k^{n+1} terms. The right-hand side contains r_k^{n+1}, while the left-hand side contains only r_{k+1}^{n+1} and r_k^n. It makes sense to replace r_k^{n+1} on the right-hand side with one of the two on the left. The better choice is to replace them with r_{k+1}^{n+1}. This makes the method "implicit," that is, the right-hand side depends on the time level that we are computing. We need to solve the equation for r_{k+1}^{n+1}, but that is not difficult, since the equation is linear in r. As with the S equation, we "linearize" the nonlinear term by computing I at time level n rather than time level $n+1$. The discretization of the PDE becomes

$$\frac{r_{k+1}^{n+1} - r_k^n}{\Delta t} = -\gamma_k I^n r_{k+1}^{n+1} - \mu r_{k+1}^{n+1}.$$

This equation can be solved easily for r_{k+1}^{n+1}. It gives a formula for the computation of the next value of r along the characteristic line:

$$r_{k+1}^{n+1} = \frac{r_k^n}{1 + \gamma_k I^n \Delta t + \mu \Delta t}.$$

From the boundary condition, we have

$$r_0^{n+1} = \alpha I^{n+1}.$$

Here we do not "linearize" at the previous level. This means that we cannot compute the boundary condition until we have computed I^{n+1}. The reason we do not linearize here is that the αI in the equation for I will be computed at level $n+1$, so that the method is implicit, but the two terms have to cancel each other if we are to obtain the equation for the total population size. We may use the right-endpoint rule to compute the integral in the equation for I. In this way, we may avoid using the boundary condition for r in the equation for I. We compute the equation for I at time level $n+1$, discretize the derivative with a backward difference, and the integral with a right-endpoint rule sum:

$$\frac{I^{n+1} - I^n}{\Delta t} = \beta S^{n+1} I^{n+1} + I^{n+1} \sum_{k=1}^{K} \gamma_k r_k^{n+1} \Delta t - (\mu + \alpha) I^{n+1}.$$

We replace I^{n+1} with I^n in the terms with S and r so that they agree with the corresponding terms in the equations for S and r. We obtain

$$\frac{I^{n+1}-I^n}{\Delta t} = \beta S^{n+1} I^n + I^n \sum_{k=1}^{K} \gamma_k r_k^{n+1} \Delta t - (\mu+\alpha) I^{n+1}.$$

In this way, we can compute I^{n+1} before we compute the boundary condition for r. In case we want to use a different rule for the integral, such as the trapezoidal rule, we have to solve a system of equations to find the solution at time level $n+1$. With this scheme, the computation is performed time level after time level. To begin the computation, we initialize all variables with the initial conditions that give the values at time level zero:

$$S^0 = S_0 \qquad I^0 = I_0, \qquad r_k^0 = \phi_k \quad , k = 0, \ldots, K.$$

We summarize the numerical method below:

$$\begin{cases} S^{n+1} = \dfrac{\Lambda \Delta t + S^n}{1 + \beta I^n \Delta t + \mu \Delta t} & n = 0, \ldots, N-1, \\ I^{n+1} = \dfrac{I^n + \beta \Delta t S^{n+1} I^n + I^n \Delta t \sum_{k=1}^{K} \gamma_k r_k^{n+1} \Delta t}{1 + \alpha \Delta t + \mu \Delta t} & n = 0, \ldots, N-1, \\ r_{k+1}^{n+1} = \dfrac{r_k^n}{1 + \gamma_k I^n \Delta t + \mu \Delta t}, & k = 0, \ldots, K-1, \\ & n = 0, \ldots, N-1, \\ S^0 = S_0 & \\ I^0 = I_0 & \\ r_k^0 = \phi_k & k = 0, \ldots, K. \end{cases} \tag{13.48}$$

The numerical method in (13.48) is given by a *difference scheme*. It can be shown (but we will not do so here) that the solutions of the difference scheme converge to the solution of the continuous problem (13.23) with the same speed as $C\Delta t$ converges to zero as Δt converges to zero. Here C is an appropriate constant. In this case, we say that the method has *convergence rate* $\mathcal{O}(\Delta t)$. The method (13.48) has other important strengths. In particular, its solutions are always nonnegative for every value of the step Δt. Finally, it is easy to code and has relatively low computational complexity (number of operations). An appropriate size of the step for running this method is $\Delta t = 0.01$. Smaller step sizes are also appropriate, but one has to keep in mind that as the step size decreases, the time needed to perform the computation increases. We ran the method with the parameters estimated in the previous subsections. The number of infected individuals, which exhibits sustained oscillations, is plotted in Fig. 13.4.

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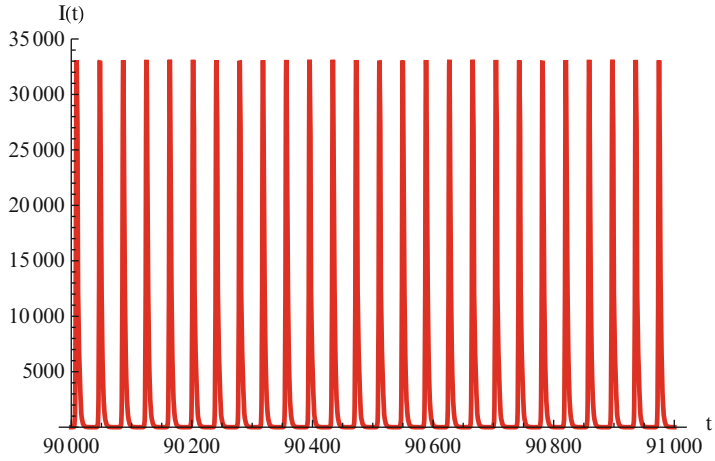

Fig. 13.4 Oscillations in the number of infected individuals $I(t)$

Appendix

In this appendix we include the Matlab code that executes the numerical method in the section.

```
function [S, I] = sir3(M,N,dt)



T = dt*N;
G = dt*M;

Lambda = 1000/365;
mu = 1/(70*365);
alpha = 0.520548;
beta = 0.0000482876;

S = zeros(N,1);
I = zeros(N,1);
rold = zeros(N,1);
rnew = zeros(N,1);

S(1) = 7000;
I(1) = 30000;

for i = 1:M
    rold(i) = 10;
end

t = 0:dt:T;
ttau = 0:dt:G;
```

```
27
28  for n = 1:N
29
30      S(n+1) = (Lambda*dt+S(n))/(1+beta*I(n)*dt + mu*dt);
31
32      Int = 0.0;
33
34      for i = 1:M
35
36          tau = i*dt;
37
38          if tau < 30
39
40              q = 0.0;
41
42          elseif   tau ≥ 30
43
44              q = 1;
45
46          end
47
48       rnew(i+1) = rold(i)/(1 + q*beta*I(n)*dt + mu*dt);
49
50       Int = Int + q*rnew(i+1)*dt;
51
52      end
53
54      I(n+1) = (I(n) + beta*S(n+1)*I(n)*dt + ...
            I(n)*dt*beta*Int)/(1 + (mu + alpha)*dt);
55
56      rnew(1) = alpha*I(n+1);
57
58
59      for i = 1:M
60
61          rold(i) = rnew(i);
62
63      end
64
65  end
66
67  plot(t, I, '-r')
68  xlim([90000,91000])
69
70
71  end
```

Problems

13.1. Consider the SIR model with age-of-infection (13.4). Assume that the transmission rate and the recovery rate are given by the following functions:

$$\gamma(\tau) = \begin{cases} 0 & \tau \le A \\ \gamma & \tau > A \end{cases} \tag{13.49}$$

and $\beta(\tau) = \beta\tau e^{k\tau}$.

(a) Compute the probability of survival in the infectious class: $\pi(\tau) = e^{-\mu\tau}e^{-\int_0^\tau \gamma(s)ds}$.
(b) Compute the reproduction number in terms of k and A.
(c) Compute the endemic equilibrium in terms of k and A.

13.2. Backward Bifurcation in the Time-Since-Recovery Model
Consider Eq. (13.27) with $\gamma(\tau) = \gamma$, a constant.

(a) Show that if $\gamma \le \beta$ and $\mathscr{R}_0 > 1$, the equation (13.27) has a unique nonzero solution. Furthermore, show that if $\gamma \le \beta$ and $\mathscr{R}_0 < 1$, the equation (13.27) has no solutions.
(b) Show that if $\gamma > \beta$ and $\mathscr{R}_0 < 1$, the equation (13.27) may have two solutions.
(c) For $\alpha = 0.05$, $\mu = 1/(365 * 70)$, $\beta = 0.021$, and $\gamma = 0.025$, use a computer algebra system to draw the backward bifurcation diagram of I^* with respect to $\mathscr{R}_0$.

13.3. Consider the model with time-since-recovery (13.23). Show that if $\mathscr{R}_0 < 1$, the disease-free equilibrium is locally asymptotically stable. Furthermore, show that if $\mathscr{R}_0 > 1$, the disease-free equilibrium is unstable.

13.4. HIV/AIDS Model
Consider the following model of HIV:

$$\begin{cases} S'(t) = \Lambda - \dfrac{S(t)}{N(t)}\displaystyle\int_0^\infty \beta(\tau)i(\tau,t)\,d\tau - \mu S(t), \\ i_\tau(\tau,t) + i_t(\tau,t) = -\gamma(\tau)i(\tau,t) - \mu i(\tau,t), \\ i(0,t) = \dfrac{S(t)}{N(t)}\displaystyle\int_0^\infty \beta(\tau)i(\tau,t)\,d\tau, \end{cases} \tag{13.50}$$

where $S(t)$ are the susceptible individuals, $i(\tau,t)$ is the density of the infected individuals, $N(t)$ is the total population size. We have to use standard incidence in HIV models. (Why?)

(a) Compute $\mathscr{R}_0$ and the disease-free equilibrium. Show that if $\mathscr{R}_0 < 1$, the disease-free equilibrium is locally stable and that otherwise, it is unstable.
(b) Compute the endemic equilibrium.
(c) Derive the characteristic equation of the endemic equilibrium.
(d) Take $\beta(\tau) = \tau e^{-c\tau}$. Is the endemic equilibrium stable or unstable in this case?

13.5. HIV/AIDS Model
Consider the following model of HIV:

$$\begin{cases} S'(t) = \Lambda - \dfrac{S(t)}{N(t)} \displaystyle\int_0^\infty \beta(\tau) i(\tau,t)\, d\tau - \mu S(t), \\ i_\tau(\tau,t) + i_t(\tau,t) = -\gamma(\tau) i(\tau,t) - \mu i(\tau,t), \\ i(0,t) = \dfrac{S(t)}{N(t)} \displaystyle\int_0^\infty \beta(\tau) i(\tau,t)\, d\tau, \end{cases} \tag{13.51}$$

where $S(t)$ are the susceptible individuals, $i(\tau,t)$ is the density of the infected individuals, $N(t)$ is the total population size. Assume

$$\beta(\tau) = \tau e^{-c\tau}.$$

(a) Compute $\mathscr{R}_0$ and the disease-free equilibrium.
(b) Compute the endemic equilibrium.
(c) Derive the characteristic equation of the endemic equilibrium.
(d) Is the endemic equilibrium stable or can it become unstable in this case?

13.6. HIV/AIDS Model
Consider the following model of HIV:

$$\begin{cases} S'(t) = \Lambda - \dfrac{S(t)}{N(t)} \displaystyle\int_0^\infty \beta(\tau) i(\tau,t)\, d\tau - \mu S(t), \\ i_\tau(\tau,t) + i_t(\tau,t) = -\gamma(\tau) i(\tau,t) - \mu i(\tau,t), \\ i(0,t) = \dfrac{S(t)}{N(t)} \displaystyle\int_0^\infty \beta(\tau) i(\tau,t)\, d\tau, \end{cases} \tag{13.52}$$

where $S(t)$ are the susceptible individuals, $i(\tau,t)$ is the density of the infected individuals, $N(t)$ is the total population size.

(a) Derive a numerical method for model (13.52).
(b) Write a Matlab code to simulate the method. How do you know whether your code computes correctly? Compare the equilibrium computed by the code with the one that you computed in Problem 13.5.

13.7. Time-Since-Vaccination Model
Many vaccines wane, and the waning depends on the time elapsed since the individual was vaccinated. Consider the following model with time-since-vaccination τ:

$$\begin{cases} S'(t) = \Lambda - \beta S(t) I(t) - (\mu + \psi) S(t) + \displaystyle\int_0^\infty \omega(\tau) v(\tau,t)\, d\tau, \\ I'(t) = \beta S(t) I(t) - (\mu + \alpha) I, \\ v_\tau + v_t = -\omega(\tau) v(\tau,t) - \mu v(\tau,t), \\ v(0,t) = \alpha I + \psi S, \end{cases} \tag{13.53}$$

where $v(\tau,t)$ is the density of vaccinated individuals structured by the time-since-vaccination τ, and ψ is the vaccination rate.

(a) Interpret all terms in the model. What is the assumed efficacy of the vaccine in this model?
(b) Compute the reproduction number $\mathscr{R}_0(\psi)$.
(c) Compute the disease-free equilibrium. Show that if $\mathscr{R}_0(\psi) < 1$, the disease-free equilibrium is locally asymptotically stable; otherwise, the disease-free equilibrium is unstable.
(d) Compute the endemic equilibrium.

13.8. Time-Since-Vaccination Model
Many vaccines wane, and the waning depends on the time elapsed since the individual was vaccinated. Consider the following model with time-since-vaccination τ:

$$\begin{cases} S'(t) = \Lambda - \beta S(t)I(t) - (\mu+\psi)S(t) + \int_0^\infty \omega(\tau)v(\tau,t)\,d\tau, \\ I'(t) = \beta S(t)I(t) - (\mu+\alpha)I, \\ v_\tau + v_t = -\omega(\tau)v(\tau,t) - \mu v(\tau,t), \\ v(0,t) = \alpha I + \psi S, \end{cases} \tag{13.54}$$

where $v(\tau,t)$ is the density of vaccinated individuals structured by the time-since-vaccination τ, and ψ is the vaccination rate.

(a) Write a numerical method for the model above. Show that your numerical method preserves the positivity of solutions.
(b) Write a Matlab code to simulate the model. How do you know whether your code computes correctly? Compare the equilibrium computed by the code with the one that you computed in Problem 13.7.

13.9. Time-Since-Infection Model of Vector-Borne Disease
Consider the following model of a vector-borne disease, structured by time-since-infection τ:

$$\begin{cases} S_v' = \Lambda_v - S_v \int_0^\infty \beta_H(\tau)i(\tau,t)d\tau - \mu_v S_v, \\ I_v' = S_v \int_0^\infty \beta_H(\tau)i(\tau,t)d\tau - \mu_v I_v, \\ S_H' = \Lambda_H - \beta_v S_H I_v - \mu_H S_H, \\ i_\tau + i_t = -(\alpha_H(\tau)+\mu_H)i(\tau,t), \\ i(0,t) = \beta_v S_H I_v, \\ R_H' = \int_0^\infty \alpha_H(\tau)i(\tau,t)d\tau - \mu_H R_H, \end{cases} \tag{13.55}$$

where S_v, I_v are the susceptible and infected vectors, S_H, $i(\tau,t)$, and R_H are the susceptible, infected, and recovered humans.

(a) Compute the reproduction number $\mathscr{R}_0$.
(b) Compute the disease-free equilibrium. Show that if $\mathscr{R}_0 < 1$, the disease-free equilibrium is locally asymptotically stable; otherwise, it is unstable.
(c) Compute the endemic equilibrium.
(d) Derive the characteristic equation of the endemic equilibrium. Can you show local stability of the endemic equilibrium?