Chapter 13

TIME DELAYS IN EPIDEMIC MODELS

Modeling and Numerical Considerations

J. Arino
Department of Mathematics,
University of Manitoba, Winnipeg, Manitoba, Canada
arionj@cc.umanitoba.ca

P. van den Driessche
Department of Mathematics and Statistics
University of Victoria BC, Canada
pvdd@math.uvic.ca

1. Introduction

Continuous time deterministic epidemic models are traditionally formulated as systems of ordinary differential equations for the numbers of individuals in various disease states, with the sojourn time in a state being exponentially distributed. Time delays are introduced to model constant sojourn times in a state, for example, the infective or immune state. Models then become delay-differential and/or integral equations. For a review of some epidemic models with delay see van den Driessche [228]. More generally, an arbitrarily distributed sojourn time in a state, for example, the infective or immune state, is used by some authors (see [69] and the references therein).

When introduced in an explicit way, time delays may change the qualitative behavior of a model; for example, an epidemic model with generalized logistic dynamics can have periodic solutions when the time in the infective stage is constant [112]. Qualitative differences that arise from including time delay in an explicit way in models that include vertical transmission are explored in [38, Chapter 4]. In population biology, a maturation time delay is used to explain observed oscillations [192]. This delay is included in an epidemic model by Cooke, van den Driessche and

O. Arino et al. (eds.), Delay Differential Equations and Applications, 539–578.

Zou [47]. A fixed time delay in the recruitment function for a disease model is considered by Brauer [33].

Many disease transmission models with delay are difficult to analyze, with even the linear stability problem reducing to a hard quasi-polynomial; see, *e.g.*, [27, 33] and references therein. Thus a combination of analytical and numerical techniques is often employed.

Here we proceed along the lines of van den Driessche [229], giving details about delay in models of disease transmission by concentrating on one particular model, namely work with two other coauthors, K. L. Cooke and J. Velasco-Hernández [13]. In Section 2, we first motivate the introduction of delay in epidemic models in which this delay results from assumptions on the sojourn time in a certain epidemiological state, *e.g.*, the infective state. We then (in Section 3) formulate a model including vaccination of susceptible individuals in which the vaccine waning time is arbitrarily distributed [13]. In Section 4, we specialize to two particular waning functions, concentrating on the step function case that leads to a system of delay integro-differential equations. Numerics on this system are reported in Section 5 (with program listings in Appendix 1). Some numerical warnings are given in Section 6, and we conclude with an annotated listing of available delay differential equations numerical packages (Appendix 2).

2. Origin of time delays in epidemic models

Various biological reasons lead to the introduction of time delays in models of disease transmission. Here we concentrate on one of the possible origins: the fact that sojourn times in certain states can have a general form, for example, can be approximately constant, as opposed to having an exponential distribution. A formal derivation of this uses probability theory and, in particular, survival analysis. A brief summary of these notions is given in Section 2.1. Then, survival analysis is tied to dynamical models of disease transmission in Section 2.2; see [225] for a more general and more detailed presentation.

2.1 Sojourn times and survival functions

Consider a system that can be in either one of two states A and B. Suppose that at time $t = 0$, the system is in state A. Suppose that when an event $\mathcal{E}$ takes place, the system switches to state B, and call X the (positive) random variable "time spent in state A before switching to state B". The cumulative distribution function (c.d.f.) $F(t)$ then characterizes the distribution of X, with $F(t) = \Pr\{X \leq t\}$, and so does the probability distribution function $f(t)$, where $F(t) = \int_0^t f(x)dx$.

Another characterization of the distribution of the random variable X is the *survival* (or *sojourn*) function. The survival function of state A is given by

$$\mathcal{S}(t) = 1 - F(t) = \Pr\{X > t\} \tag{2.1}$$

This function gives a description of the *sojourn time* of a system in a particular state. Note that $\mathcal{S}$ must be a nonincreasing function (since $\mathcal{S} = 1 - F$ with F a c.d.f., thus a nondecreasing function), and $\mathcal{S}(0) = 1$ (since X is a positive random variable).

The *average sojourn time* τ in state A is given by

$$\tau = \int_0^\infty t f(t) dt$$

Assuming that $\lim_{t\to\infty} t\mathcal{S}(t) = 0$ (which is verified for most probability distributions),

$$\tau = \int_0^\infty \mathcal{S}(t) dt$$

Suppose that the random variable X has exponential distribution $f(t) = \theta e^{-\theta t}$ for $t \geq 0$, with $\theta > 0$. Then the survival function for state A is of the form $\mathcal{S}(t) = e^{-\theta t}$, for $t \geq 0$, and the average sojourn time in state A is

$$\tau = \int_0^\infty e^{-\theta t} dt = \frac{1}{\theta}$$

If on the other hand, for some constant $\omega > 0$,

$$\mathcal{S}(t) = \begin{cases} 1, & 0 \leq t \leq \omega \\ 0, & \omega < t \end{cases}$$

which means that X has a Dirac delta distribution $\delta_\omega(t)$, then the average sojourn time is a constant, namely

$$\tau = \int_0^\omega dt = \omega$$

These two distributions can be regarded as extremes.

2.2 Sojourn times in an SIS disease transmission model

Consider a particular disease, and suppose that a population of individuals can be identified with respect to their epidemiological status: susceptible to the disease, infected by the disease, recovered from the disease, etc. To illustrate, consider a disease that confers no immunity. This is modeled by a very simple SIS model. Individuals are thus either *susceptible* to the disease, with the number of such individuals at time t denoted by $S(t)$, or *infected* by the disease (and are also *infective* in the sense that they propagate the disease), with the number of such individuals at time t denoted by $I(t)$. Suppose for simplicity that there is neither birth nor death. Hence $N \equiv N(t) = S(t) + I(t)$ is the (constant) total population. Infection is assumed to take place following a *standard incidence* pattern (see [181] for a discussion of transmission terms): the number of new infectives resulting from random contacts between susceptible and infective individuals per unit time is given by $\beta SI/N$. Here β is the *transmission coefficient*, it gives the probability of transmission of the disease in case of a contact, times the number of such contacts made by an infective per unit time.

Traditional epidemiological models assume that recovery from disease occurs with a rate constant γ. However, as in [112], the assumption is made here that, of the individuals who have become infective at time t_0, a fraction $P(t - t_0)$ remain infective at time $t \geq t_0$. Thus, considered for $t \geq 0$, the function $P(t)$ is a survival function. As such, it satisfies the properties given in Section 2.1, and in particular, $P(0) = 1$. The transfer diagram for the system then has the form shown in Figure 13.1.

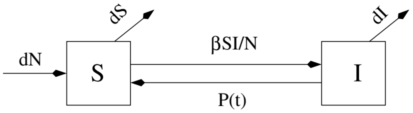

Figure 13.1. The transfer diagram for the SIS model.

Since N is constant, it follows that $S(t) = N - I(t)$ and the model reduces to the following integral equation for the number of infective individuals

$$I(t) = I_0(t) + \int_0^t \beta \frac{(N - I(u))I(u)}{N} P(t - u)du \tag{2.2}$$

Here $I_0(t)$ is the number of individuals who were infective at time $t = 0$ and who still are at time t. It suffices to assume that $I_0(t)$ is nonnegative, nonincreasing, and such that $\lim_{t\to\infty} I_0(t) = 0$. The term $P(t-u)$ in the integral is the proportion of individuals who became infective at time u and who still are at time t. Multiplying this with the contact term $\beta(N - I(u))I(u)/N$ and summing over $[0, t]$ gives the number of infective individuals at time t.

The two extreme cases for $P(t)$ considered in Section 2.1 illustrate various possibilities. First, suppose that $P(t)$ is such that the sojourn time in the infective state has an exponential distribution with mean $1/\gamma$, *i.e.*, $P(t) = e^{-\gamma t}$. Then (2.2) is

$$I(t) = I_0(t) + \int_0^t \beta \frac{(N - I(u))I(u)}{N} e^{-\gamma(t-u)} du$$

Taking the time derivative of $I(t)$ yields

$$\begin{aligned} I'(t) &= I_0'(t) - \gamma \int_0^t \beta \frac{(N - I(u))I(u)}{N} e^{-\gamma(t-u)} du + \beta \frac{(N - I(t))I(t)}{N} \\ &= I_0'(t) + \beta \frac{(N - I(t))I(t)}{N} + \gamma \left(I_0(t) - I(t) \right) \end{aligned}$$

In this case $I_0(t) = I_0(0)e^{-\gamma t}$, giving

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

which is the classical logistic type ordinary differential equation (ODE) for I in an SIS model without vital dynamics (see, *e.g.*, [34, p. 289]).

The *basic reproduction number*, denoted by $\mathcal{R}_0$, which is a key concept in mathematical epidemiology, is now introduced. It is defined (see, *e.g.*, [12, 58]) as the expected number of secondary cases produced, in a completely susceptible population, by the introduction of a typical infective individual. For this ODE model, $\mathcal{R}_0 = \beta/\gamma$. In terms of stability, the disease free equilibrium (DFE) with $I = 0$ is stable for $\mathcal{R}_0 < 1$ and unstable for $\mathcal{R}_0 > 1$. At the threshold $\mathcal{R}_0 = 1$, there is a forward bifurcation with a stable endemic equilibrium (with $I > 0$) for $\mathcal{R}_0 > 1$. Thus the value of $\mathcal{R}_0$ determines whether the disease dies out or tends to an endemic value.

The second case corresponds to $P(t)$ being a step function:

$$P(t) = \begin{cases} 1 \text{ if } t \in [0, \omega] \\ 0 \text{ otherwise} \end{cases}$$

i.e., the sojourn time in the infective state is a constant $\omega > 0$. In this case (2.2) becomes

$$I(t) = I_0(t) + \int_{t-\omega}^t \beta \frac{(N - I(u))I(u)}{N} du$$

which when differentiated, gives for $t \geq \omega$

$$I'(t) = I_0'(t) + \beta \frac{(N - I(t))I(t)}{N} - \beta \frac{(N - I(t-\omega))\, I(t-\omega)}{N}$$

Since $I_0(t)$ vanishes for $t > \omega$, this gives the delay differential equation (DDE)

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

cf. [34, Section 7.6] (where the disease transmission is modelled using mass action). Note that every constant value of I is an equilibrium, thus the integral form above gives a better description than the DDE. For this case, $\mathcal{R}_0 = \beta\omega$ again acts as a threshold. For $\mathcal{R}_0 < 1$, the DFE is stable; whereas for $\mathcal{R}_0 > 1$, the endemic equilibrium is locally asymptotically stable [34, Section 7.6].

More realistically, the survival function for the infective state is between an exponential and a step function (see, *e.g.*, [12, 225]), thus the two cases considered above can be regarded as extremes.

3. A model that includes a vaccinated state

We now use the ideas of the previous section in a different setting. Consider a disease for which there exists a vaccine. Suppose that, although there exists a vaccine, we can assume that developing the disease confers no immunity. For example, at a given time, there are several strains of influenza circulating in a given population. Vaccination usually focuses on particular strains, which are expected to be the dominant ones in a particular year. Vaccination gives partial protection from other strains as does contracting the disease. However, this protection is only partial, and some individuals can contract the disease several times. Thus if considered as one single disease, influenza can fit the above description. The assumptions also apply to models in which individuals can be in two groups depending on their transmission coefficients with respect to a given disease. They can move between these groups as education campaigns or policies influence their behavior.

Our model, which is similar to that in [13], has the transfer diagram shown in Figure 13.2. The number of individuals in the *susceptible*, *infective* and *vaccinated* states are given by $S(t)$, $I(t)$, $V(t)$, respectively. As noted above, $V(t)$ may alternatively correspond to an educated state, but we refer to it as vaccinated. Individuals move from one state to the other as their status with respect to the disease evolves. New individuals are born into the susceptible state with a birth rate constant $d > 0$, and all individuals, whatever their status, are subject to death with the same natural death rate constant d. It is assumed that the disease does not cause death, thus the total population $N = S(t)+I(t)+V(t)$ is constant, allowing for the simplification that the number of individuals in the S state is given by $S(t) = N - I(t) - V(t)$. Susceptible individuals are vaccinated with rate constant ϕ, and enter the V state. Note that the model in [13] further assumes that a fraction of newborns are vaccinated.

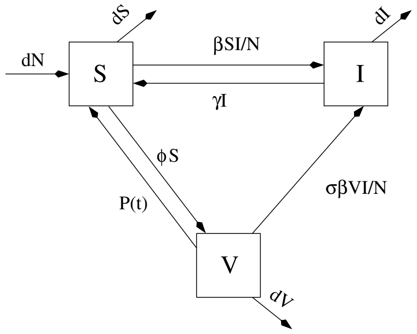

Figure 13.2. The transfer diagram for the SIV model.

As in Section 2.2, disease transmission is assumed to be of standard incidence type, thus susceptibles enter the infective state at a rate $\beta SI/N$, where $\beta > 0$ is the transmission coefficient. In addition, it is assumed that successfully vaccinated individuals may only be partially protected from infection (*i.e.*, the vaccine is leaky). Vaccinated individuals can contract the disease, but vaccination reduces transmission by a factor $\sigma \in [0, 1)$. Thus the number of new infectives produced by random contacts between I infectives and V vaccinated individuals per unit time is $\sigma\beta SI/N$, and vaccinated individuals enter the infective state at this rate.

Many vaccines wane with time, and so vaccinated individuals return to the susceptible state. In [130], this waning is assumed to be exponential but here we assume a more general waning function $P(t)$. We suppose that, at a given time t, there is a fraction $P(t)$ of the vaccinated individuals who are still under protection of the vaccine t units after being vaccinated. Since the waning function $P(t)$ is a survival function it is assumed to be nonnegative and nonincreasing with $P(0) = 1$, and moreover $\int_0^\infty P(u)du$ is positive and finite. Finally, it is assumed that the infective individuals can be cured, so that members of the I state return to the susceptible state, with rate constant $\gamma \geq 0$ (the *recovery* rate).

Since the total population remains constant, it is more convenient to use proportions (rather than number of individuals) in each state. Hereafter, we use $I(t)$ and $V(t)$ to denote the proportion of infective and vaccinated individuals, respectively, with $S(t) = 1 - I(t) - V(t)$, the proportion of susceptibles. Let the initial susceptible and infective proportions be $S(0) > 0, I(0) > 0$ and let $V_0(t)$ be the proportion of individuals who are initially in the vaccinated state and for whom the vaccine is still effective at time t. With the above assumptions, the following integro-differential system describes the model depicted in Figure 13.2.

$$\begin{aligned}\frac{dI(t)}{dt} &= \beta(1 - I(t) - (1-\sigma)V(t))I(t) - (d+\gamma)I(t) && (3.1\text{a})\\ V(t) &= V_0(t) + \int_0^t \phi S(u)P(t-u)e^{-d(t-u)}e^{-\sigma\beta\int_u^t I(x)dx}du && (3.1\text{b})\end{aligned}$$

The integral in (3.1b) sums the proportion of those who were vaccinated at time u and remain in the V state at time t. Specifically, $\phi S(u)$ is the proportion of vaccinated susceptibles, $P(t-u)$ is the fraction of the proportion vaccinated still protected by the vaccine $t-u$ time units after going in (*i.e.*, not returned to S), $e^{-d(t-u)}$ is the fraction of the proportion vaccinated not dead due to natural causes, and $e^{-\sigma\beta\int_u^t I(x)dx}$ is the fraction of the proportion vaccinated not infective (*i.e.*, not progressed to the I state). An expression for $V_0(t)$ can be obtained by formulating the model with vaccination state-age (see, *e.g.*, [13, 112]) as

$$V_0(t) = e^{-\int_0^t(\sigma\beta I(x)+d)dx}\int_0^\infty v(0,u)\frac{P(t+u)}{P(u)}du \qquad (3.2)$$

where $v(0,u) \geq 0$ is the density at $t = 0$ of the proportion of individuals in vaccination state-age u; thus $V_0(0) = \int_0^\infty v(0,u)du$. The above integral converges, and thus $V_0(t)$ is nonnegative, nonincreasing and $\lim_{t\to\infty} V_0(t) = 0$.

Define the subset $\mathcal{D}$ of the nonnegative orthant by

$$\mathcal{D} = \{(S,I,V); S \geq 0, I \geq 0, V \geq 0, S+I+V = 1\}$$

It is easy to show (see [13]) that the set $\mathcal{D}$ is positively invariant under the flow of (3.1) with $I(0) > 0, S(0) > 0$.

Differentiating (3.1b) gives

$$\frac{d}{dt}V(t) = \frac{d}{dt}V_0(t) + \phi S(t) - (d+\sigma\beta I(t))(V(t) - V_0(t)) + Q(t) \qquad (3.3)$$

where

$$Q(t) = \int_0^t \phi S(u)d_t(P(t-u))e^{-d(t-u)}e^{-\sigma\beta\int_u^t I(x)dx}du$$

With the assumed initial conditions in $\mathcal{D}$, the system defined by (3.1a) and (3.1b) is equivalent to the system defined by (3.1a) and (3.3). This latter system is of standard form, therefore results of Hale and Verd1uyn Lunel [105, p. 43] ensure the local existence, uniqueness and continuation of solutions of model (3.1).

Equation (3.1a) has $I = 0$ as an equilibrium and using $I = 0$ in equation (3.1b) as $t \to \infty$ gives the disease free equilibrium (DFE) as $I_{DFE} = 0$,

$$S_{DFE} = \frac{1}{1+\phi\tilde{P}}, \quad V_{DFE} = \frac{\phi\tilde{P}}{1+\phi\tilde{P}}$$

Here

$$\tilde{P} = \lim_{t\to\infty} \int_0^t P(v)e^{-dv}dv$$

which is the average length of time that an individual remains vaccinated (before losing vaccination protection or dying).

The basic reproduction number with vaccination is defined in terms of $\tilde{P}$ as

$$\mathcal{R}_{vac} = \mathcal{R}_0 \frac{\sigma\phi\tilde{P}+1}{\phi\tilde{P}+1} \tag{3.4}$$

in which $\mathcal{R}_0 = \frac{\beta}{d+\gamma}$ is the basic reproduction number with natural death but no vaccination. The number $\mathcal{R}_{vac}$ is the important quantity in this model that includes vaccination; $\mathcal{R}_{vac}$ is equal to the product of the mean infective period $1/(d+\gamma)$ and the sum of the contact rate constant in each of the susceptible and vaccinated states multiplied respectively by the proportion in that state at the DFE, namely $\beta S_{DFE} + \sigma\beta V_{DFE}$. Note that $\mathcal{R}_{vac} \le \mathcal{R}_0$, and in the case of no vaccination, that is $\phi = 0$, $\mathcal{R}_{vac} = \mathcal{R}_0$.

If $\mathcal{R}_0 < 1$, then the only equilibrium of (3.1a) is $I_{DFE} = 0$, thus the DFE is the only equilibrium of system (3.1) when $\mathcal{R}_0 < 1$. In this case, (3.1a) gives

$$\frac{dI}{dt} < (d+\gamma)\left((S+\sigma V)-1\right)I$$

which implies that $dI/dt < 0$, and so $I(t) \to 0 = I_{DFE}$ as $t \to \infty$, for all initial conditions $I(0) > 0$. Thus the disease dies out if $\mathcal{R}_0 < 1$.

The importance of $\mathcal{R}_{vac}$ can be seen from the following linear stability result.

Theorem 1 *For model (*3.1*) with a general waning function, if* $\mathcal{R}_{vac} < 1$*, then the DFE is locally asymptotically stable (l.a.s.); if* $\mathcal{R}_{vac} > 1$*, then it is unstable.*

Proof. Linearize (3.1a) and (3.1b) about the DFE, taking $t \to \infty$. Then the eigenvalues z of the linearized system at the DFE are given by

$$z = \beta(S_{DFE} + \sigma V_{DFE}) - (d+\gamma) = (d+\gamma)(\mathcal{R}_{vac} - 1) \tag{3.5a}$$

and the roots of

$$1 = -\phi \int_0^\infty P(v) e^{-(d+z)v} dv \tag{3.5b}$$

Let $z = x + iy$ be a root of equation (3.5b). Then by the proof of Lemma 2 in [230], if $x \geq 0$, then $y = 0$. But since $\phi \geq 0$, equation (3.5b) has no nonnegative real root, thus all of its roots have negative real parts. Hence, from (3.5a), the DFE is l.a.s if $\mathcal{R}_{vac} < 1$, and unstable if $\mathcal{R}_{vac} > 1$. ∎

4. Reduction of the system by using specific $P(t)$ functions

Here we show two examples of models resulting from the choice of specific vaccine waning functions $P(t)$ as the two extreme cases in Section 2.2. The first example (Section 4.1) is obtained when the distribution of waning times is exponential, and leads to the ODE system studied in [130]. As discussed in [130], for some parameter values, there is a *backward bifurcation*, a rather uncommon phenomenon in epidemiological models. This backward bifurcation is also present when the system consists of delay integro-differential equations, such as is the case in Section 4.2 when the waning function is assumed to be a step function corresponding to a constant sojourn time in the vaccinated state.

4.1 Case reducing to an ODE system

Assuming that the vaccine waning rate is a constant $\theta > 0$, *i.e.*, $P(t) = e^{-\theta t}$, then $V_0(t) = V_0(0)e^{-(d+\theta)t}e^{-\int_0^t \sigma\beta I(x)dx}$ from (3.2), equations (3.1a) and (3.3) give the ODE system

$$\frac{dI}{dt} = \beta(1 - I - (1-\sigma)V)I - (d+\gamma)I \tag{4.1a}$$

$$\frac{dV}{dt} = \phi(1 - I - V) - \sigma\beta IV - (d+\theta)V \tag{4.1b}$$

which is the model studied in [130]. The DFE with $I_{DFE} = 0$,

$$S_{DFE} = \frac{\theta + d}{d + \theta + \phi}, \quad V_{DFE} = \frac{\phi}{d + \theta + \phi}$$

always exists, and from (3.4) the basic reproduction number is

$$\mathcal{R}_{vac} = \mathcal{R}_0 \frac{d + \theta + \sigma\phi}{d + \theta + \phi}$$

Assume that $\mathcal{R}_0 > 1$, then endemic equilibria ($I > 0$) can be obtained analytically from a quadratic equation, and for $\sigma > 0$ (*i.e.*, a leaky vaccine) it is possible to have a backward bifurcation leading to two endemic equilibria for some parameter values. This occurs for a range of $\mathcal{R}_{vac}$, namely $\mathcal{R}_c < \mathcal{R}_{vac} < 1$ where $\mathcal{R}_c$ is the value of $\mathcal{R}_{vac}$ at the saddle node bifurcation point where the two endemic equilibria coincide; see [130] for details.

4.2 Case reducing to a delay integro-differential system

Assume that the vaccine waning period is constant and equal to $\omega > 0$, that is the function $P(t)$ takes the form of a step function on a finite interval:

$$P(t) = \begin{cases} 1 \text{ if } t \in [0, \omega] \\ 0 \text{ otherwise} \end{cases}$$

Since $S = 1 - I - V$, and $V_0(t) = 0$ for $t > \omega$, the integral equation (3.1b) becomes, for $t > \omega$

$$V(t) = \int_{t-\omega}^{t} \phi(1 - I(u) - V(u)) e^{-d(t-u)} e^{-\sigma\beta \int_u^t I(x)dx} du \tag{4.2}$$

Differentiating this last expression (see equation (3.3)), the model can be written as the two dimensional integro-differential equation system for $t > \omega$

$$\frac{dI(t)}{dt} = \beta(1 - I(t) - (1-\sigma)V(t))I(t) - (d + \gamma)I(t) \tag{4.3a}$$

$$\frac{dV(t)}{dt} = \phi(1-I(t)-V(t)) - \phi(1-I(t-\omega)-V(t-\omega))e^{-d\omega} e^{-\sigma\beta \int_{t-\omega}^{t} I(x)dx} - \sigma\beta IV - dV \tag{4.3b}$$

Hereafter, we shift time by ω so that these equations hold for $t > 0$. By introducing a third state variable

$$X(t) = \int_{t-\omega}^{t} I(x)dx \tag{4.4}$$

which gives $\frac{dX(t)}{dt} = I(t) - I(t - \omega)$, the system can be regarded as a three dimensional DDE system.

For a constant waning period, the basic reproduction number from (3.4) is

$$\mathcal{R}_{vac} = \mathcal{R}_0 \frac{d + \sigma\phi(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \tag{4.5}$$

The DFE is $I_{DFE} = 0$,

$$S_{DFE} = \frac{d}{d + \phi(1 - e^{-d\omega})},\ V_{DFE} = \frac{\phi(1 - e^{-d\omega})}{d + \phi(1 - e^{-d\omega})} \tag{4.6}$$

Note that the delay ω enters into these equilibrium values. If $\mathcal{R}_0 < 1$, then the system tends to the DFE and the disease dies out (see Section 3). For $\mathcal{R}_0 > 1$, from nullclines, there exists one (or more) (EEP) iff there exists $I^* \in (0, 1]$ such that

$$\frac{1 - 1/\mathcal{R}_0 - I^*}{1 - \sigma} = \frac{\phi(1 - I^*)(1 - e^{-d\omega - \sigma\beta\omega I^*})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I^*}) + d + \sigma\beta I^*} \tag{4.7}$$

5. Numerical considerations

We give some insights into numerical aspects by considering the delay integro-differential model (4.3). First, in Section 5.1 we set up the algorithm that is used to study the occurence of forward and backward bifurcations at $\mathcal{R}_{vac} = 1$. We use this algorithm in Section 5.2, and investigate the dynamical behavior of system (4.3) by running numerical integrations.

5.1 Visualising and locating the bifurcation

An EEP exists iff there exists an $I^* \in (0, 1]$ such that (4.7) holds. So we study the zeros of

$$H(I) = \frac{1 - 1/\mathcal{R}_0 - I}{1 - \sigma} - \frac{\phi(1 - I)(1 - e^{-d\omega - \sigma\beta\omega I})}{\phi(1 - e^{-d\omega - \sigma\beta\omega I}) + d + \sigma\beta I}$$

Note that $H(0) = \frac{\mathcal{R}_{vac} - 1}{(1-\sigma)\mathcal{R}_0}$ and $H(1) < 0$.

Let $\mathcal{A} = \{\beta, d, \gamma, \phi, \omega, \sigma\}$ be the set of parameters of the model. When needed, we denote $H(I, a)$ and $\mathcal{R}_{vac}(a)$, with $a \in \mathcal{A}$ a parameter, to indicate that the bifurcation is considered as a function of this parameter a; *e.g.*, $\mathcal{R}_{vac}(\beta)$ indicates that β is the bifurcation parameter that varies.

For a totally effective vaccine ($\sigma = 0$), a unique $I^* \in (0, 1]$ such that $H(I^*) = 0$ can be found explicitly for $\mathcal{R}_{vac} > 1$, and the bifurcation is forward with $\mathcal{R}_{vac}$ behaving as a (local) threshold [13]. For a leaky vaccine, $\sigma \in (0, 1)$, the zeros of $H(I)$ for $I \in (0, 1]$ cannot be found analytically. We proceed to obtain numerical estimates by using the following algorithm.

Choose a parameter $a \in \mathcal{A}$.

Fix the value of all other elements of $\mathcal{A}$.

Choose a_{min}, a_{max} and Δa for a.

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for $a_k = a_{min}$ to $a_{max}$ do
    Compute $I^*$ such that $H(I^*, a_k) = 0$, using MatLab's fzero function.
    Compute $\mathcal{R}_{vac}(a)$ for this value $a_k$.
    $a_k = a_k + \Delta a$.
end for
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Results of the use of this procedure give zero, one or two values of I^*. Thus two bifurcation scenarios are possible, as summarized in Figure 13.3. Example bifurcation diagrams are plotted in Figures 13.4(a) and 13.5.

In order to be able to characterize the nature of the bifurcation, we then need to define $\mathcal{R}_c$ as in Section 4.1. To obtain a numerical estimate of $\mathcal{R}_c$, we use the same procedure as for the visualization of the bifurcation: we find the value I^* such that $H(I^*, a) = 0$ and $dH(I^*, a)/dI = 0$, for a given parameter $a \in \mathcal{A}$ with all other elements of $\mathcal{A}$ fixed.

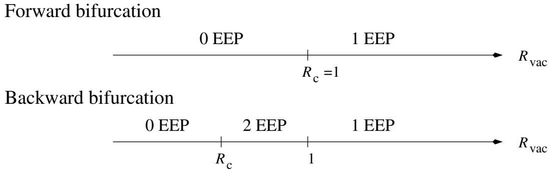


Figure 13.3. Possible bifurcation scenarios.

Suppose that $\mathcal{R}_0 > 1$ (otherwise there is no EEP, as was remarked in Section 3). When $\mathcal{R}_{vac} < \mathcal{R}_c$, there is no EEP as $H(0) < 0$ and numerical simulations indicate that $H < 0$ on $(0, 1)$; when $\mathcal{R}_{vac} > 1$, $H(0) > 0$ so there is an odd number of EEP (numerical simulations indicate this number is 1). When $\mathcal{R}_c = 1$, we are then in the case of a forward bifurcation, as illustrated in the first part of Figure 13.3 and in Figure 13.4(c). The backward bifurcation arises when $\mathcal{R}_c < 1$. In this case, when $\mathcal{R}_c < \mathcal{R}_{vac} < 1$, $H(0) < 0$ so there is an even number of zeros of H in $(0, 1]$. Numerical simulations indicate that the number of EEP is 2. The system then undergoes the transitions shown in the second part of Figure 13.3.

5.2 Numerical bifurcation analysis and integration

We use the following parameter values. We suppose a 3 weeks disease duration ($\gamma = 1/21$), taking the time unit as one day. The average lifetime is assumed to be 75 years ($d = 1/(75 \times 365)$), and the average number of adequate contacts per day is estimated as $\beta = 0.4$. The vaccine is assumed to be 10% leaky ($\sigma = 0.1$), and susceptibles are vaccinated at the rate $\phi = 0.1$. Finally, we assume that the vaccine stops being effective after 5 years, *i.e.*, $\omega = 1825$.

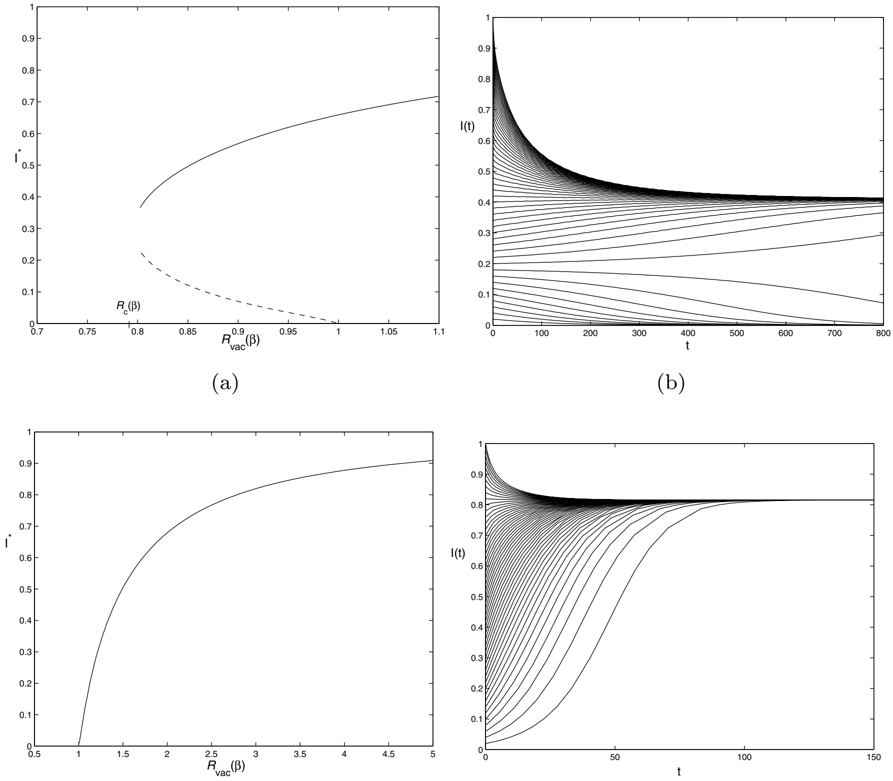
These parameters give $\mathcal{R}_0 = 8.3936$ and $\mathcal{R}_{vac}(\beta) = 0.8819$ from (4.5), which is in the range of the backward bifurcation since (using the above method) $\mathcal{R}_c(\beta)$ is estimated as 0.78. The bifurcation diagram is depicted in Figure 13.4(a). Note that in the vicinity of $\mathcal{R}_c$, it is very difficult for MatLab's `fzero` function to find solutions (since it detects sign changes and $\mathcal{R}_{vac} = \mathcal{R}_c$ corresponds to tangency); hence the non-closed curve. Numerical simulations of the DDE model indicate that there are no additional bifurcations; solutions either go to the DFE or to the (larger) EEP, as depicted in Figure 13.4(b), which shows some solutions for $I(t)$ with the above parameter values. These same parameter values, except that $\sigma = 0.3$, give $\mathcal{R}_{vac}(\beta) = 2.55$, and there is a forward bifurcation (see Figure 13.4(c)) with solutions going to the endemic equilibrium as depicted in Figure 13.4(d).

To obtain Figures 13.4(b), 13.4(d), system (4.3) is integrated numerically. These numerical simulations are run using `dde23` [205], an example code (as well as an example code with XPPAUT) being given in Appendix 1. Initial data is $I(t) = c$, for $t \in [-\omega, 0]$, with c varying from 0 to 1 by steps of 0.02.

Figure 13.5 shows the bifurcation for these parameter values as a function of ω. The situation is clearly different from that of Figure 13.4(a), since in Figure 13.5 every value of ω gives at least one endemic equilibrium. Let ω_m be the value of ω determined by solving $\mathcal{R}_{vac}(\omega) = 1$ with $\mathcal{R}_{vac}$ given by (4.5). If all other parameters are fixed as given at the beginning of this section, and for small waning time, $0 < \omega < \omega_m = 457.032$, giving $\mathcal{R}_{vac}(\omega) > 1$, the only stable equilibrium is a large endemic one. This is of course a highly undesirable state in terms of epidemic control. Then increasing ω (*i.e.*, increasing the waning time) past ω_m allows the DFE to become locally stable, and it is found numerically that solutions starting with $I(0)$ below the unstable endemic equilibrium tend to the DFE. Increasing ω beyond 1000 days seems ineffective in terms of disease control, since there is no increase in the initial value of infectives that tend to the DFE (see Figure 13.5).

6. A few words of warning

Even more so than with ordinary differential equations, great care has to be taken when running numerical integrations of delay differential equations. In [47], Cooke, van den Driessche and Zou study the dynamics



(a) (b)

(c) (d)

Figure 13.4. Bifurcation diagram and some solutions of (4.3). (a) and (b): Backward bifurcation case, parameters as in the text. (c) and (d): Forward bifurcation case, parameters as in the text except that $\sigma = 0.3$.

of the following equation for an adult population $N(t)$ with maturation delay:

$$N'(t) = be^{-aN(t-T)}N(t-T)e^{-d_1T} - dN(t) \tag{6.1}$$

Here $d > 0$ is the death rate constant, $b > d$ and $a > 0$ are parameters in the birth function, T is a developmental or maturation time and d_1 is the death rate constant for each life stage prior to the adult stage. In particular, they prove [47, Corollary 3.4] that Hopf bifurcation may occur for (6.1) even for $d_1 = 0$. For fixed values of the parameters, as T increases the equilibrium may switch from being stable to unstable, giving rise to periodic solutions. For $d_1 > 0$, it is possible for stability of the equilibrium to be regained as T increases further. They then proceed to illustrate the stability switches by numerical simulations of

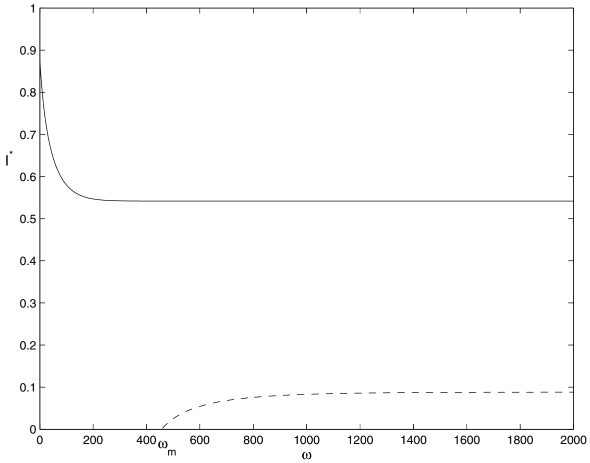


Figure 13.5. Value of I^* as a function of ω by solving $H(I,\omega)=0$, parameters as in text.

(6.1) using XPPAUT. For $d_1 > 0$, equation (6.1) has a delay dependent parameter. The introduction of delay dependent parameters can lead to dramatic differences in dynamics, see [27].

Using the demography of (6.1), the authors of [47] formulate the following SIS model with maturation delay [47, (4.2)]

$$\begin{aligned} I'(t) =& \quad \beta(N(t)-I(t))\tfrac{I(t)}{N(t)} - (d+\epsilon+\gamma)I(t) \\ N'(t) =& \quad be^{-a(t-T)}N(t-T)e^{-d_1T} - dN(t) - \epsilon I(t) \end{aligned} \tag{6.2}$$

where $S(t) = N(t) - I(t)$, $\epsilon \geq 0$ is the disease induced death rate constant, $\gamma \geq 0$ is the recovery rate constant, and standard incidence $\beta SI/N$ is assumed. They perform numerical simulations of (6.2), and, in particular, obtain periodic solutions for parameter values $a = d = d_1 = 1$, $b = 80$, $\gamma = 0.5$, $T = 0.2$, $\epsilon = 10$ and $\beta = 20$.

But... When documenting their delay differential equation numerical integrator `dde23` [205], Shampine and Thompson tested their algorithm on a large number of delay systems, among which were equation (6.1) and system (6.2). With parameters as in the paragraph above, they obtain a figure similar to Figure 13.6, which shows damped oscillations to an endemic steady state.

So, what is wrong? For delay differential equations, XPP (the numerical integrator part of XPPAUT) uses a fixed step-size numerical integrator, whereas `dde23` uses a variable step-size. With the particular values of the parameters chosen for $\beta = 20$, the fixed step-size is too

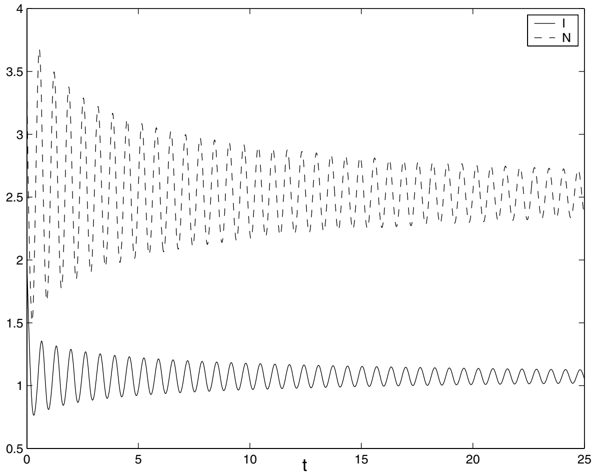


Figure 13.6. Plot of the solution of (6.2), with parameters as in the text, using `dde23`.

large (its default value is 0.05). In a case in which variables I and N undergo a very quick initial drop, this is overlooked by the first integration step of XPP, and the solver ends caught in the solution curve of a nearby periodic solution. Setting the step size in XPP to 0.005, as in the Erratum of [47], is sufficient to obtain a correct solution as shown in Figure 13.6.

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Appendix

1. Program listings

The following gives examples of code used with MatLab and XPPAUT to run numerical integrations of system (4.3). In both cases, constant initial data has been used, though both do allow for initial data of functional or of numerical type. In the case of constant initial data, both programs have the same behavior: they extend the given initial point to the interval $[-\omega, 0]$. Note that we make use of the third "fake" state variable $X(t)$ introduced in (4.4), and of its time derivative, in order to take care of the integral term in (4.3b).

1.1 MatLab code

The following is called `vaccddeRHS.m`. It defines the vector field of (4.3). This is done in a very similar manner to the definition of the vector field that would be used in a `MatLab` program with an ordinary differential equation solver. The one important difference is in the variable Z. `dde23` can handle many discrete delays. The variable Z, which is passed as an argument to the function, contains the state of the system at the different delays. Here, we have only one delay. But suppose we had two delays ω_1 and ω_2. Then each column of Z would contain the state variables corresponding to one of the delays:

$$Z = \begin{bmatrix} I_{\omega_1} & I_{\omega_2} \\ V_{\omega_1} & V_{\omega_2} \end{bmatrix}$$

```
function v = vaccddeRHS(t,y,Z,params)
beta=params(1);
d=params(2);
g=params(3); %MatLab hates gamma's other than gamma functions.
phi=params(4);
omega=params(5);
sigma=params(6);
ylag = Z(:,1);
v = zeros(3,1);
v(1) = beta*(1-y(1)-(1-sigma)*y(2))*y(1)-(d+g)*y(1);
v(2) = phi*(1-y(1)-y(2))...
       -phi*(1-ylag(1)-ylag(2))*exp(-d*omega)*exp(-sigma*beta*y(3))...
       -sigma*beta*y(1)*y(2)-d*y(2);
v(3) =  y(1) - ylag(1);
```

This function is then used by the main calling routine, which follows. This particular procedure will run a certain number of integrations of system (4.3). The initial condition for $V(0)$ (lines 16 and 17) is obtained from (4.2) by setting $t = 0$, that of $X(0)$ follows from (4.4).

```
path(path,'/home/jarino/programs/matlab/dde23/ddeall')
beta=0.4;
d=3.65297E-05;
g=0.047619048;
phi=0.1;
omega=1825;
sigma=0.1;

ylim([0,1]);
hold on;
for I0=0:0.02:1, %Loop on initial conditions
        % The delay must be added to the parameter vector since it
        % is used in the vector field.
        params=[beta, d, g, phi, omega, sigma];
        % Initial conditions: I0 is given, V0 and X0 are computed.
        V0=(phi*(1-I0)*(1-exp(-omega*(d+beta*sigma*I0))))...
            /(d+beta*sigma*I0+phi*(1-exp(-omega*(d+beta*sigma*I0))));
        X0=I0*omega; % Initial condition on X is easy to compute.
        IC=[I0,V0,X0]; % Extended to [-omega,0] if only given at 0.
        tspan=[0,800]; % Set integration time range.
        % Call the numerical routine.
        sol = dde23('vaccddeRHS',omega,IC,tspan,[],params);
        plot(sol.t,sol.y(1,:)); %Plot I(t) versus t
```

```
end;
xlabel('t'); ylabel('I','Rotation',0);
```

1.2 XPPAUT code

The following code allows the integration of system (4.3) with XPPAUT. Note that the initial conditions for V and X have to be computed explicitly from equations (4.2) and (4.4), since XPP does not allow inclusion of unevaluated formula in the code.

```
# Constants
p beta=0.4, d=3.65E-05, g=0.04762, phi=0.1, omega=1825, sigma=0.1;
# The system
dI/dt = beta*(1-I-V+sigma*V)*I - (d+g)*I
dV/dt = phi*(1-I-V)-phi*(1-delay(I,omega)-delay(V,omega))\
        *exp(-d*omega)*exp(-sigma*beta*X)-(sigma*beta*I*V)-d*V
dX/dt = I-delay(I,omega)
# Initial conditions
I(0)=0.1
V(0)=0.8650595334
X(0)=182.5
# set maxdelay
@ delay=2000
@ ylow=0
@ bell=0
@ bound=500
@ XP=I,YP=V
@ XHI=1,YHI=1
# done
d
```

2. Delay differential equations packages

Several packages and even software are available for the numerical integration and/or the study of bifurcations in delay differential equations. Here is a short list, elaborated from the list given by Koen Engelborghs[1].

2.1 Numerical integration

The following are numerical solvers for DDE's.

Archi (C.A.H. Paul) (Fortran 77) simulates a large class of functional differential equations. In particular, Archi can be used to estimate unknown scalar parameters in delay and neutral differential equations.

dde23 (L. Shampine, S. Thompson) (MatLab) is a MatLab package that integrates delay differential equations. It is integrated in the latest versions of MatLab (starting with Release 13).

DDVERK (H. Hiroshi, W. Enright) (Fortran 77) simulates retarded and neutral differential equations with several fixed discrete delays.

DifEqu (G. Makay) (DOS, Windows) simulates differential equations with discrete possibly varying delays.

---

[*] `http://www.cs.kuleuven.ac.be/ koen/delay`

DKLAG6 (S. Thompson) (Fortran 77, Fortran 90, C) simulates retarded differential equations with several fixed discrete delays.

Dynamics Solver (J. M. Aguirregabiria) simulates differential equations with discrete possibly varying delays.

RETARD (E. Hairer, G. Wanner) simulates retarded differential equations with several fixed discrete delays.

RADAR5 (N. Guglielmi, E. Hairer) (Fortran 90) simulates retarded differential-algebraic equations, including neutral problems with vanishing or small delays.

XPPAUT (G.B. Ermentrout) (Unix, Windows) simulates differential equations with several fixed discrete delays. XPPAUT is a standalone software.

2.2 Bifurcation analysis

The following software packages provide some means to carry out numerical bifurcation analysis of delay differential equations.

BIFDD (B.D. Hassard) (Fortran 77) normal form analysis of Hopf bifurcations of differential equations with several fixed discrete delays.

DDE-BIFTOOL (K. Engelborghs) (MatLab) allows computation and stability analysis of steady state solutions, their fold and Hopf bifurcations and periodic solutions of differential equations with several fixed discrete delays.

XPPAUT (G.B. Ermentrout) (Unix, Windows) allows limited stability analysis of steady state solutions of differential equations with several fixed discrete delays.

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