SOME EPIDEMIOLOGICAL MODELS WITH DELAYS

P. VAN DEN DRIESSCHE

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P. VAN DEN DRIESSCHE
Mathematics and Statistics, University of Victoria
Victoria, British Columbia V8W 3P4 Canada

Dedicated to the memory of Stavros Busenberg

ABSTRACT

Deterministic models for disease transmission often take the form of a system of nonlinear, ordinary, differential equations. However, these become more complicated when time delays are used to model mechanisms in the dynamics of epidemics. Some models including delays are surveyed, with latent period, temporary immunity and length of infection as examples of such mechanisms. Threshold parameters are identified, and in some cases periodic solutions are found to arise by Hopf bifurcation. Current investigations include a model for bovine tuberculosis in a constant population cattle herd, and a variable population SIS model.

1. Introduction

The goal here is to survey some deterministic epidemiological models with delays, giving a flavor of the modeling process, the mathematical tools used and the results obtained. The informal style reflects the lecture that is the basis for this writeup. It is a somewhat personal survey, influenced by models studied by the author and co-workers. Other important models and authors are unavoidably omitted. Some references are added as a result of conversations with conference participants after the lecture.

Infectious diseases considered are caused by viruses or bacteria, and are spread by direct individual-to-individual contact in a population. Diseases caused by viruses include childhood diseases (*e.g.*, measles, chickenpox, rubella) as well as influenza, hepatitis A, and HIV/AIDS. Bacteria are the infectious agents for other diseases, including gonorrhea, pneumonia and tuberculosis; see Hethcote[15], Table 1.

The models discussed are all deterministic and spatially homogeneous. Emphasis is on human diseases, except in Section 5 where a model for bovine tuberculosis is considered. Infection is assumed to be passed only by horizontal transmission (*i.e.*, susceptible individuals contract the disease by contact with infectious individuals), except in Section 7 where vertical transmission from infected parent to offspring is also included.

Time delays are used to model mechanisms in the disease dynamics. Examples of such mechanisms are temporary immunity (Sections 3, 4, 7), latent period (Sections 5, 7) and length of infection (Sections 6, 8). Inclusion of time delay means that the models can be formulated as functional differential and/or integral equations. One important aim is to investigate the consequences of time delays. In particular, parameters relevant for disease control are identified, and the possibility of periodic solutions is investigated. Periodic behavior has been observed in the incidence of many infectious diseases, including biennial oscillations in measles[1], yearly outbreaks of chickenpox[15], and

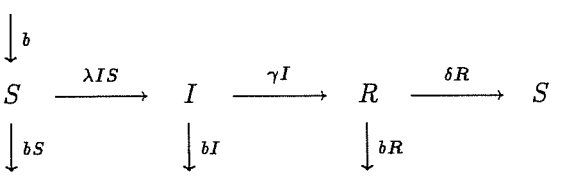
influenza[28]. Known ways in which periodic solutions can arise in epidemiological models were surveyed in 1981 by Hethcote *et al.*[20], and in 1989 by Hethcote and Levin[16]. Mechanisms that can lead to periodic solutions include periodic coefficients, temporary immunity, nonlinear incidence and variable population size.

In the following models, class $S(t)$ denotes the number of individuals in the population that is susceptible (not yet infected) at time t, $E(t)$ the number that is latent (*i.e.*, infected but not yet infectious), $I(t)$ the number that is infectious (transmitting the disease), and $R(t)$ the number that is removed (by immunity or death). In all models, except that for bovine tuberculosis in Section 5, and a model with vertical transmission in Section 7, the latent period is assumed to be negligible, thus infected individuals are also infectious, and $E(t)$ is ignored. Models are labelled according to the flow between classes, and are conveniently depicted by transfer diagrams. In Sections 2, 3 and 4, cyclic $SIRS$ models with constant total population number $N(t)$ are considered. Thus $N(t) = S(t) + I(t) + R(t)$ is constant, and is normalized to 1 so that $S(t)$, $I(t)$, $R(t)$ may be considered as fractions of the population that are susceptible, infectious, removed, respectively. In Sections 6, 7 and 8, the population size varies, thus there is an interplay between the demographic and disease dynamics.

To introduce further concepts and notation, a basic $SIRS$ model (without time delay) is first briefly presented in Section 2.

2. *SIRS* ode Model

A qualitative $SIRS$ model for spread of an infectious disease in which recovery gives temporary immunity was formulated and analyzed by Hethcote[14]. This may be appropriate for the spread of influenza. The model assumptions and the results are now briefly stated. The total population is assumed constant, thus births and natural deaths occur with equal rate constant b, and all newborns are susceptible. When $b > 0$, the mean lifetime is $\frac{1}{b}$; when $b = 0$, vital dynamics are ignored. The contact rate constant $\lambda > 0$ is the average number of adequate contacts per infective per day. Thus the average number of susceptibles infected per day is $\lambda I(t)S(t)$. For fractions, this is bilinear incidence (mass action), and gives the rate at which the susceptible fraction becomes infectious. (Note that this incidence corresponds to the standard incidence for numbers.) Infectious individuals recover with a recovery rate constant $\gamma > 0$. The waiting time in the infectious class is exponentially distributed with mean waiting time $\frac{1}{\gamma}$, thus the death adjusted mean period of infectivity is $\frac{1}{(\gamma+b)}$. Individuals are assumed to recover with temporary immunity, the probability of remaining recovered t units after becoming recovered is $\exp(-\delta t)$, with death adjusted mean period of immunity given by $\frac{1}{(\delta+b)}$. As temporary immunity fades, individuals re-enter the susceptible class. The transfer diagram for this cyclic $SIRS$ model (with S as the susceptible class) can be represented as:



The initial value problem for this $SIRS$ model is formuated as the 2-d ordinary differential equation (ode) system:

$$\begin{aligned} S' &= b - \lambda IS + \delta(1 - I - S) - bS, \\ I' &= \lambda IS - (\gamma + b)\, I, \end{aligned} \tag{2.1}$$

with $S(0)$, $I(0) > 0$, and $R = 1 - I - S$. Here $S = S(t)$ and $S' = \frac{dS}{dt}$. Define region

$$D = \{(S, I) : S \geq 0, \quad I \geq 0, \quad S + I \leq 1\},$$

and parameter

$$\sigma = \lambda/(\gamma + b). \tag{2.2}$$

Then σ is the *contact* (*basic reproduction*) *number*, which is the number of adequate contacts of an infectious individual during the death adjusted infective period. This parameter gives a sharp threshold for the model, as shown by the following result[14] which is proved by planar ode techniques (including Lyapunov functions and Poincaré-Bendixson).

Result 2.1. *Consider the model* (2.1). *If* $\sigma \leq 1$, *then* D *is the asymptotically stable region for the disease free equilibrium* $(S, I) = (1, 0)$. *If* $\sigma > 1$, *then* $D - \{(S, 0) : 0 \leq S \leq 1\}$ *is the asymptotically stable region for the endemic equilibrium* (S^*, I^*) *with* $S^* = \frac{1}{\sigma}$, $I^* = \frac{(\delta + b)(\sigma - 1)}{(\lambda + \delta\sigma)}$.

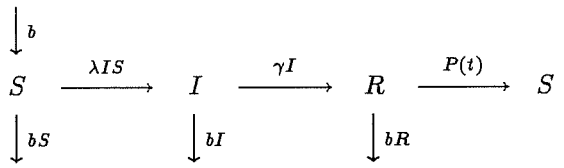
Solutions always approach an equilibrium, the disease dying out if $\sigma \leq 1$, but approaching an endemic value if $\sigma > 1$; no periodic solutions occur. The contact number σ (often written $\mathcal{R}_0$ when it is called the basic reproduction number) for each disease determines the fraction that must be vaccinated to eradicate the disease. Note that this basic model includes important, simpler models as special cases. For $\delta \to \infty$, it becomes an SIS model, appropriate for diseases that confer no immunity, *e.g.* gonorrhea. When $\delta = 0$, and R is interpreted as the permanently recovered class, then it becomes an SIR model, appropriate for some childhood diseases.

3. *SIRS* Model with Delay in *R*

A general probability of still being in the I (or R) class t units after entering it, corresponds to a distributed delay in the I (or R) class. For example, a step function probability corresponds to a constant period of infection (or immunity). Busenberg and Cooke[7] pointed out the importance of proper integral conditions in such delay differential equation models. Cooke and Yorke[11] and Greenberg and Hoppensteadt[12] considered SIS models with distributed delays in I, and found that all solutions approach constants. However, Hethcote *et al.*[18] found the possibility of periodic solutions in an $SIRS$ model with constant period of immunity with no vital dynamics. This $SIRS$ model is now formulated with $P(t)$ denoting the probability of remaining recovered t units after becoming recovered. It is assumed that $P(t) \geq 0$ is nonincreasing, piecewise continuous and satisfies

$$P(0^+) = 1, \qquad P(\infty) = 0, \qquad \int_0^\infty P(u)\, du = \omega.$$

Here ω is the average period of immunity. (Note that the ode model in Section 2 is the special case with $P(t) = \exp(-\delta t)$, $\delta = \frac{1}{\omega}$.) For this more general $SIRS$ model, the transfer diagram is:



The equations governing this constant population $SIRS$ model are

$$\begin{aligned} I'(t) &= \lambda\, I(t)\, S(t) - (\gamma + b)\, I(t), \\ R(t) &= R_0(t) + \gamma \int_0^t I(x)\ \exp\big(-b(t-x)\big)\ P(t-x)\, dx, \\ \text{with } S(t) &= 1 - I(t) - R(t), \quad S(0) > 0, \quad I(0) > 0. \end{aligned} \tag{3.1}$$

Here $R_0(t)$ is the fraction of the initial recovered population still recovered at time t, with $R_0(t)$ continuous, nonnegative and $\lim_{t\to\infty} R_0(t) = 0$.

Assume that $P(t)$ is a step function, namely

$$P(t) = \begin{cases} 1, & 0 \le t \le \omega, \\ 0, & t > \omega, \end{cases} \tag{3.2}$$

where ω is now the constant period of immunity. The model can be reduced to the following integro-differential equation for $I(t)$ when $t \ge \omega$

$$\begin{aligned} I'(t) = &-(\gamma + b)\, I(t) + \lambda\, I(t) \\ &\cdot \left[1 - I(t) - \gamma \int_{-\omega}^{0} I(t+u)\ \exp(bu)\, du\right]. \end{aligned}$$

Defining the contact number as in (2.2), namely $\sigma = \frac{\lambda}{(\gamma+b)}$, the following result is shown in van den Driessche[33], see also Hethcote *et al.*[18] when vital dynamics are ignored.

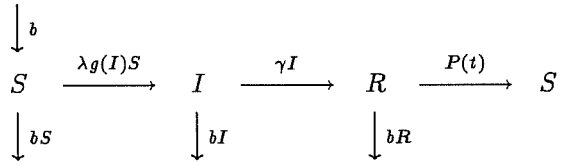
Result 3.1. *Consider the model* (3.1) *with step function* $P(t)$ *given by* (3.2). *If* $\sigma \le 1$, *then all solutions approach the disease free equilibrium* $(S, I) = (1, 0)$ *as* $t \to \infty$. *If* $\sigma > 1$, *then the endemic equilibrium* (S^*, I^*) *with* $S^* = \frac{1}{\sigma}$ *is locally asymptotically stable for some parameter values. For other parameter values (increasing* $w\gamma$*) Hopf bifurcation gives rise to periodic solutions around this equilibrium.*

The presence of periodic solutions thus depends on $P(t)$, there are none when $P(t)$ is a negative exponential (Section 2), but they are possible when $P(t)$ is a step function (3.2). Thus the inclusion of a time delay has changed the qualitative behavior of the $SIRS$ model. This model is a special case of a more general $SIRS$ model, which we now proceed to give in more detail.

4. *SIRS* Model with Delay and Nonlinear Incidence

In Section 2, it was assumed that the incidence rate is bilinear, *i.e.*, linear in each of the variables I and S. Deviations from this bilinear incidence rate (due, for example, to saturation or multiple

exposures) lead to nonlinear incidence rates. Liu *et al.*[25,26] considered ode $SEIRS$ models with nonlinear incidence $\lambda I^p S^q$, and found that the dynamical behavior is not qualitatively changed by taking $q \neq 1$, but is significantly changed by taking $p \neq 1$. Specifically, for $p > 1$, multiple equilibra and periodic solutions arising from Hopf bifurcation can occur for some parameter values. Hethcote *et al.*[17] also found these phenomena in an $SIRS$ model with nonlinear incidence $\lambda I^p S$ and a time delay in the removed class with vital dynamics ignored. This was extended[22] to more general nonlinear incidence $\lambda g(I)S$ with vital dynamics. This is the model now summarized (see details in Hethcote and van den Driessche[22]), and depicted in the following transfer diagram:



The force of infection is $\lambda g(I)$, where $g(I)$ satisfies

$$g(0^+) = 0, \quad g(I) > 0 \text{ for } I \in (0,1], \quad g \in C^3(0,1].$$

Note that the classical bilinear incidence has $g(I) = I$ (see Sections 2, 3), and λ is then the contact rate constant. The probability $P(t)$ is assumed to be the step function (3.2), thus ω is the constant period of temporary immunity. For $t > \omega$, the governing equations become

$$\begin{aligned} I'(t) &= \lambda\, g\big(I(t)\big)\, S(t) - (\gamma + b)\, I(t), \\ R(t) &= \gamma \int_{t-\omega}^{t} I(x)\, \exp\big(-b(t-x)\big)\, dx, \end{aligned} \tag{4.1}$$

with $S(t) + I(t) + R(t) = 1$. This model is well posed, always has the disease free equilibrium with $S = 1$, $I = R = 0$, and (possible) endemic equilibria (S^*, I^*, R^*) with $I = I^*$ satisfying

$$\begin{aligned} &\frac{\gamma + b}{\lambda} = \frac{1}{\sigma} = \frac{g(I)}{I}\left[1 - \frac{I}{H}\right] = f(I) \\ &\text{with} \\ &\frac{1}{H} = 1 + \frac{\gamma}{b}\left(1 - \exp(-b\omega)\right). \end{aligned} \tag{4.2}$$

The number of such equilibria depends on the incidence function $g(I)$, in particular on $f(I)$ defined above; see Liu *et al.*[26]. The following result is from[22] with the global stability proved by Lin and van den Driessche[24].

Result 4.1 *Consider the model* (4.1) *under the above assumptions. Then the disease free equilibrium is locally asymptotically stable iff* $\sigma < \frac{1}{f(0)}$. *If it is the only equilibrium, then the disease free equilibrium is the global attractor when* $\sigma < \frac{1}{f(0)}$. *Assume that* $f(0) = 0$, $f''(I) < 0$ *on* $(0, H]$, *and*

$f(I)$ has a unique interior maximum at $I = I_m$. If $\sigma > \sigma^* = \frac{1}{f(I_m)}$, then there are two nontrivial equilibria I_1, I_2 with $0 < I_1 < I_m < I_2 < H < 1$.

Local stability of a nontrivial equilibrium I^* is governed by the characteristic equation

$$z + \omega b + a + c\frac{(1 - \exp(-(z + \omega b)))}{z + \omega b} = 0, \tag{4.3}$$
$$\text{with} \quad a = \omega\gamma - \omega\lambda\, g'(I^*)\, S^* + \omega\lambda\, g(I^*), \quad \text{and} \quad c = \omega^2\, \lambda\gamma\, g(I^*) > 0.$$

The quasipolynomial (4.3) was investigated by Hao and Brauer[13] and by Hethcote and van den Driessche[22]. Typically the birth rate constant b is small, and in the limiting case with $b = 0$, then $\sigma = \lambda/\gamma$, $1/H = 1+\gamma\omega$ from (4.2), and equation (4.3) reduces to the characteristic equation analyzed by Hethcote *et al.*[17,19] where vital dynamics are ignored.

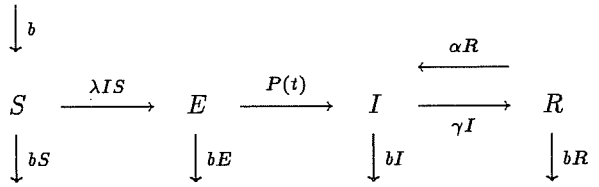
Result 4.2. *Consider the model as in Result* 4.1, *with $b = 0$. Then if $\sigma > \sigma^*$, the smaller endemic equilibrium I_1 is an unstable saddle, and at the larger endemic equilibrium I_2 Hopf bifurcation can occur giving rise to stable periodic solutions for some parameter values.*

The Hopf bifurcation theorem for functional differential equations[31] is used to prove the existence of a Hopf bifurcation; and numerical calculations are also given[17] to demonstrate limit cycle solutions. For $g(I) = \lambda I^p$ with $p > 1$, the disease free equilibrium is always stable, and so the threshold condition (see Section 2) is lost. The disease dies out for $\sigma < \sigma^*$ and also for some initial conditions when $\sigma > \sigma^*$.

5. Model for Bovine Tuberculosis

This section is based on some work in preparation (Rich and van den Driessche[29]) on a model of bovine tuberculosis (*Mycobacterium bovis*) in a cattle herd. In approximately the last 15 years, this disease has resurged, while at the same time the incidence of tuberculosis in humans has been rising. Thus current interest is in understanding the dynamics of this disease, with the aim of managing herds to control spread of the disease.

M. bovis is spread from one animal in the herd to another mainly through direct aerosol contact[32]. There is evidence that possums in New Zealand[3,30,34], and badgers in the U.K.[2,32], are a reservoir host for *M. bovis*, and play a significant role in the transmission of cattle infection; but the model considered here deals only with the cattle population. Since cattle rarely die from the disease, and births and purchases approximately balance sales and slaughter, the herd population is assumed to be constant. For an animal to be infectious, the disease must progress to the formation of tubercules that can rupture and release bacilli. This may occur between 4-14 months after exposure, a constant time (9 months) is assumed for this model. A latent class is thus introduced, with $E(t)$ equal to the fraction exposed to infection but not yet infectious. Once bacilli are released, lesions may temporarily heal and remove the animal from the infectious class. Depending on individual health, an animal can revert to the infectious state with rate constant α. For this model, $R(t)$ denotes the fraction previously infectious but temporarily reverted to the noninfectious state, thus R acts like a second exposed class. The disease transmission diagram is taken as:



Here the input b is from births and purchases, and the output $b(S+E+I+R) = b$ is from sales and slaughter. The function $P(t)$ is taken as a step function, as in Section 3, except that $\int_0^\infty P(u)\,du = \tau$, the latent period. For $t > \tau$, the model equations are

$$\begin{aligned} S'(t) &= b - \lambda\, I(t)\, S(t) - b\, S(t), \\ E'(t) &= \lambda\, I(t)\, S(t) - \lambda\, \exp(-b\tau)\, I(t-\tau)\, S(t-\tau) - bE(t), \\ I'(t) &= \lambda\, \exp(-b\tau)\, I(t-\tau)\, S(t-\tau) + \alpha R(t) - (\gamma + b)\, I(t), \\ \text{with} \quad R(t) &= 1 - S(t) - E(t) - I(t). \end{aligned} \tag{5.1}$$

For this model, define

$$\sigma = \lambda\, \exp(-b\tau)\, \frac{(\alpha + b)}{b(\gamma + \alpha + b)}. \tag{5.2}$$

Then σ is the contact number, which is the product of the contact rate λ, with the fraction surviving the latent class $(\exp(-b\tau))$ and the death adjusted mean time in I (namely, $(\alpha + b)/b(\gamma + \alpha + b)$). Here σ gives a sharp threshold, as shown by the following.

Result 5.1. *Consider the model given by* (5.1)*with* σ *as in* (5.2). *If* $\sigma \leq 1$, *then the disease free equilibrium* $(S = 1)$ *is the only equilibrium and it is locally asymptotically stable. If* $\sigma > 1$, *then there is a unique endemic equilibrium* (S^*, E^*, I^*, R^*) *with* $S^* = \frac{1}{\sigma}$, *and it is locally asymptotically stable.*

Local asymptotic stability of the endemic state is proved by linearization giving rise to a characteristic equation similar to but not identical with (4.3). No periodic solutions are found, but global stability is an open problem.

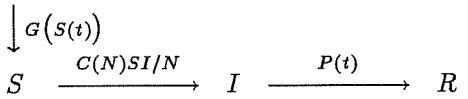
From preliminary data, $b << \alpha = \gamma$, thus the contact number is approximated by $\sigma = \frac{\lambda\, \exp(-b\tau)}{2b}$, with values ranging from approximately 5×10^{-1} to 2.5×10. Note that the threshold value $(\sigma = 1)$ lies in this interval. Thus more exact parameter values are needed to determine the course of the disease.

Hethcote and Tudor[21] considered a constant population $SEIR$ model for a disease with permanent immunity with distributed delays in E and I. Asymptotic behavior is the same as in the ode model, distributed delays again do not lead to periodic solutions. Also constant population size $SEIS$ models with delays have asymptotically stable endemic equilibria[7,19].

6. Fatal Disease Model

In previous sections the total population remains constant, now it is assumed that this population varies. Thus $S(t)$, $I(t)$ are *numbers* of susceptibles, infectives, respectively. In this section an SIR model of a fatal disease is presented, thus R is the dead class, and $N(t) = S(t) + I(t)$. A simple SIR model was presented by Brauer[4] and this is briefly summarized here. The author has recently extended this model in several ways[5,6].

The transfer diagram is



with $P(t)$ taken as a step function so that $\int_0^\infty P(u)\,du = \tau$, the constant infective period. For this model, $G(S(t))$ is the rate of change of population size in the absence of disease; for example, $G(S)$ is proportional to $S(1-S/K)$ with carrying capacity $K > 0$. The infectious class does not contribute to the birth (or recruitment) rate and has no natural deaths. The function $C(N)$ gives the number of contacts per infective per unit time, and is assumed to satisfy for $N > 0$

$$C(N) > 0, \quad C'(N) \geq 0, \quad \big(C(N)/N\big)' \leq 0.$$

These assumptions on $C(N)$ may be appropriate for sexually transmitted diseases (see Castillo-Chavez *et al.*[10]) as well as virally transmitted diseases. For example, $C(N) = \lambda N$ gives the mass action (bilinear) incidence, whereas $C(N) = \lambda$ gives the standard incidence for numbers. Equations can be set up for this model, there is a contact number $C(K)\tau$, and the following is contained in Brauer[4].

Result 6.1. *Consider the model described above. If $C(K)\tau < 1$, then the disease free equilibrium $(S, I) = (K, 0)$ is locally asymptotically stable. If $C(K)\tau > 1$, then the disease free equilibrium is unstable, and there is an endemic equilibrium $\big(S^*,\, \tau G(S^*)\big)$ with S^* given by*

$$\tau\, SC\big(S + \tau G(S)\big) = S + \tau\, G(S).$$

This equilibrium is locally asymptotically stable if $C(K)\tau$ is close to 1. However, with $C(N) = \lambda N$, if $C(K)\tau$ is sufficiently large, then there is a bifurcation to a periodic solution.

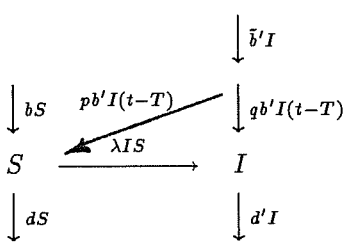
For this model, $C(K)\tau$ acts as a threshold parameter and periodic solutions are possible when this parameter is large; the analysis involves the characteristic equation as for Result 4.2. By contrast, for $P(t) = \exp(-t/\tau)$, the resulting ode model has the endemic equilibrium remaining locally stable for all values of $C(K)\tau$, see Brauer[4] and Pugliese[27]. In this model, the inclusion of time delay qualitatively changes the dynamics. Thus for fatal diseases, the possibility of instability depends on the distribution of infective period. Brauer[5] extended the model by allowing natural deaths in the infective class. The qualitative behavior is unaltered when the death rate is a constant.

When vertical transmission is included[6], the contact number is then the sum of the term due to direct contact (namely, $C(K)\tau$) and a term due to vertical transmission.

7. *SI* Model with Vertical Transmission

In the models of previous sections the passage of infection is by horizontal transmission only. In many diseases (*e.g.*, rubella, AIDS, Chagas' disease) vertical transmission of disease from an infective parent to offspring also occurs. The recent book by Busenberg and Cooke[8] provides an excellent survey of modeling on vertically transmitted diseases; Chapter 4 contains delay differential equation models. One of these models is now summarized. This is originally due to Busenberg *et al.*[9] see also Busenberg and Cooke[8], Section 4.3.

For this epidemiological model, $S(t)$, $I(t)$ denote the numbers of susceptibles, infectives with b, $\tilde{b}'$, and d, d' denoting the birth rate, and death rate constants for susceptibles, infectives, respectively. The population of offspring of infectives that are susceptible after a period of temporary immunity T_0 is denoted by p, with $q = 1 - p$ giving the proportion of offspring of infectives that are infective after a latent period T_1. Thus two delays are incorporated into the model, and for simplicity these are assumed equal, namely $T_0 = T_1 = T$. Also for ease of notation $b' = \tilde{b}' \exp(-d'T)$. This special case can be represented by the simple transfer diagram:



Note that the total population $S(t) + I(t)$ varies, and mass action incidence is assumed. The delay differential equations describing the disease progression are

$$\begin{aligned} S'(t) &= (b-d)\,S(t) + pb'\,I(t-T) - \lambda I(t)\,S(t), \\ I'(t) &= -d'\,I(t) + q\,b'I(t-T) + \lambda\,I(t)\,S(t), \end{aligned} \tag{7.1}$$

with initial conditions

$$S(0) \geq 0, \quad I(t) = I_0(t) \geq 0 \text{ for } -T \leq t \leq 0.$$

An endemic equilibrium (S^*, I^*) with $I^* = \frac{(b-d)}{(d'-b')}\,S^*$ exists provided $b > d$ and $d' > b'$. When these inequalities are satisfied, Busenberg *et al.*[9], Theorem 2.3, Busenberg and Cooke[8], Theorem 4.2, give the following.

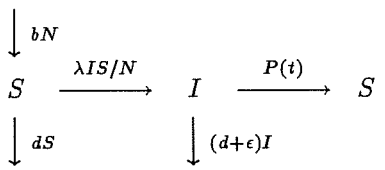
Result 7.1. *Consider model* (7.1) *with* $T > 0$, $p > 0$, $b > d$ *and* $d' > b'$. *If* $0 < q < q^*(d', b)$ *and* $0 < \frac{(b-d)}{(d'-b')} < \xi(d', b', q)$, *then there exists a* T^* *such that for* $T > T^*$ *but close to* T^*, *the endemic equilibrium* (S^*, I^*) *is unstable and the system has a periodic solution near* (S^*, I^*).

The functions q^* and ξ are given explicitly in the above references, and the proof involves analysis

of a characteristic equation (*cf.* (4.3)). The result shows that it is possible for vertical transmission to lead to periodic solutions in an SI model. Analysis of the general case in which the temporary immunity and latent period are not equal ($T_0 \neq T_1$) remains open.

8. *SIS* Model with Variable Population Size

This personal survey ends with a brief description of a model currently under investigation with H.W. Hethcote[23]; it was inspired by a conversation on using proportional variables that I had with Stavros Busenberg. This model is for a disease that confers no immunity but may cause death. Here $S(t)$, $I(t)$ denote the numbers of susceptibles, infectives, respectively, with birth rate constant b and natural death rate constant d the same in each class. There is excess death due to disease in the infective class, $\epsilon \geq 0$ is the disease related death rate constant. The probability that an individual remains in the infective class for at least t units is given by $P(t)$ with $\int_0^\infty P(u)\,du = \omega$ equal to the mean infective period. All newborns are assumed susceptible (thus vertical transmission is not included). Standard incidence is assumed, thus the number of new cases per unit time is $\lambda IS/N$, where $N(t) = S(t) + I(t)$. The following transfer diagram shows the disease progression.



The integral equation for the infective number after a time large enough so that initial perturbations have died out is

$$I(t) = \int_0^t \lambda \frac{I(u)\,S(u)}{N(u)}\,P(t-u)\,\exp\{-(d+\epsilon)(t-u)\}\,du.$$

The total population satisfies the differential equation

$$N'(t) = (b-d)\,N(t) - \epsilon I(t).$$

Defining proportions of susceptibles and infectives in the population by $s(t) = S(t)/N(t)$, $i(t) = I(t)/N(t)$, the equation for the infective fraction becomes

$$i(t) = \int_0^t \lambda i(u)s(u)\,P(t-u)\,\exp\left\{-(b+\epsilon)(t-u) + \epsilon\int_u^t i(p)\,dp\right\}\,du, \tag{8.1}$$

with $s(t) + i(t) = 1$. It can be shown that there exists a unique, continuous solution that exists for all larger time.

When $P(t) = \exp(-t/\omega)$, the waiting time in the infective class is exponential, then the equation for $i(t)$ corresponds to a logistic equation. However, when $P(t)$ is the step function in (3.2), with ω the constant period of infection, then the infective fraction satisfies the following delay-integro-differential equation for $t \geq \omega$

$$\begin{aligned} i'(t) = {} & \lambda[1-i(t)]\,i(t) - \lambda[1-i(t-\omega)]\,i(t-\omega) \\ & \cdot \exp\left\{-(b+\epsilon)\omega + \epsilon\int_{t-\omega}^t i(p)\,dp\right\} - (b+\epsilon)\,i(t) + \epsilon i^2(t). \end{aligned} \tag{8.2}$$

A modified contact number θ appropriate here is the product of λ and the expected time in the i class, namely

$$\theta = \lambda\left(1 - \exp\{-(b+\epsilon)\omega\}\right)/(b+\epsilon). \tag{8.3}$$

Note that the birth rate b occurs here, *cf.* σ in (2.2); parameter θ is important here as the following result shows.

Result 8.1. *Consider the model equation* (8.2). *The disease free equilibrium in proportional variables* $(s,i) = (1,0)$ *always exists. If* $\theta < 1$, *then it is the only equilibrium and it is locally asymptotically stable. If* $\theta > 1$, *then it is unstable and there is a unique endemic equilibrium* (s^*, i^*) *with* $0 < i^* < 1$.

Stability of this endemic equilibrium is under investigation. Linear stability is governed by a characteristic equation (more complicated than (4.3)) containing s^* which is known only implicitly. In the special case of no disease related deaths ($\epsilon = 0$), then $s^* = 1/\theta$, with $\theta = \lambda\big(1 - \exp(-b\omega)\big)/b$ from (8.3), and for $\theta > 1$, this unique endemic equilibrium is locally asymptotically stable. Thus, in this special case, the threshold is sharp. However, for $\epsilon >> b$, periodic solutions around the endemic equilibrium are possible. Although these occur for somewhat unrealistic parameter values, this gives another example of time delay leading to periodic solutions in a relatively simple epidemiological model. More complicated models using proportional variables are also under investigation, and pose challenging mathematical problems.

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