ON THE COMPUTATION OF R_0 AND ITS ROLE ON GLOBAL STABILITY

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ON THE COMPUTATION OF $\mathcal{R}_0$ and ITS ROLE ON GLOBAL STABILITY

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Abstract

In this paper we outline the second generation operator approach developed by Diekmann and collaborators for the computation of the basic reproductive number, $\mathcal{R}_0$. The use of this method is illustrated on epidemic models, mostly developed by the authors, that incorporate various degree of host and pathogen heterogeneity. Finally, conditions that clarify the connections between $\mathcal{R}_0$ and its relationship to the global asymptotic stability of the disease-free equilibrium are discussed.

0. Introduction

Threshold phenomena is prevalent in the study of scientific phenomena. The computation of nondimensional quantities that determine the nature of dynamic transitions, "tipping" or bifurcation points, have a long tradition in epidemiology. Sir Ronald Ross, who received the Nobel Prize for his work on malaria (1902), founded the field of mathematical epidemiology with his quest for establishing (within the epidemiology community) what must have appeared obvious to him, that is, that *it is not necessary to drive a vector (mosquito) population to extinction to eliminate malaria.* He made his point effectively only after he introduced a mathematical model for malaria in 1911. He used his model to show that bringing a mosquito population below a certain threshold was sufficient to eliminate malaria. This threshold naturally depended on biological factors such as the biting rate and vectorial capacity (ratio of the vector to host population). His mathematical work has been used extensively not only in the study malaria (MacDonald 1957) but also in the study of other diseases (see Anderson and May 1982; Busenberg and Cooke 1993).

The importance of contact processes (well recognized by Ross on his work on malaria) is at the center of the study of threshold phenomena (see Busenberg and Castillo-Chavez 1991; Castillo et al. 1994). In their recent book Diekmann and Heesterbeek (2000) present an extensive and systematic study of threshold phenomena. The following tutorial notes also used the next generation approach for the systematic computation of the basic reproductive number. The examples used come mostly from our own work. Connections between threshold phenomena and stability are also explored.

The basic reproductive number $\mathcal{R}_0$ is *typically* defined (see Diekmann and Heestterbeek, 2000) as: *the average number of secondary cases produced by a "typical" infected (assumed infectious) individual during his/her entire life as infectious (infectious period) when introduced in a population of susceptibles.* This nondimensional quantity cannot be computed explicitly in most cases because the mathematical description of what is a "typical" infectious individual is difficult to quantify in populations with high degree of heterogeneity.

Regardless of whether or not $\mathcal{R}_0$ can be computed explicitly, its role on the study of the stability of equilibria can still be determined. Most reasonable epidemic models support at least two type of equilibria: a disease-free equilibria and a positive (endemic) equilibria. "Typically" one can show that the disease-free equilibrium is locally asymptotically stable (l.a.s.) if $\mathcal{R}_0 < 1$ and unstable whenever $\mathcal{R}_0 > 1$. Furthermore, in many

examples, it has been shown that $\mathcal{R}_0 > 1$ implies the existence of a unique (l.a.s.) endemic equilibrium. Many models found in the literature have been used to show that when $\mathcal{R}_0$ crosses the threshold, $\mathcal{R}_0 = 1$, a transcritical bifurcation takes place. That is, asymptotic local stability is transferred from the infectious-free state to the new (emerging) endemic (positive) equilibria. In some situations, it can be shown that the transfer of asymptotic stability is indepenedent of initial conditions, that is, it is global (Feng et al., 2000; Zhou et al. 2001; Song et al. 2001).

In this article, we revisit several models of infectious diseases involving a discrete and continuous stratification of host and pathogen. We compute $\mathcal{R}_0$ for each model using the approach developed by Diekmann and his collaborators. Finally, we look at the role of $\mathcal{R}_0$ on the global stability of the disease-free equilibrium.

This paper is organized as follows: Section 1 outlines the next generation operator approach for the computation of $\mathcal{R}_0$. Section 2 gives a series of examples with various degrees of host and pathogen heterogeneity. The models used come from the study of communicable, vector and sexually-transmitted diseases. Examples are drawn from our published work, work in progress, or the work of others. These models have been used in the study of questions associated with the dynamics of Tuberculosis, HIV, Dengue, Gonorrhea and childhood diseases. Our examples include group, gender, host-structure, and pathogen heterogeneity. Section 3 states and proves a theorem on the relationship between local and global asymptotic stability for the infection free state. The tutorial ends with an example where the conditions of the last theorem are not met: a model that is capable of supporting multiple endemic equilibria when $\mathcal{R}_0 < 1$.

1. The next generation operator approach

$\mathcal{R}_0$ is often found through the study and computation of the eigenvalues of the Jacobian at the disease- or infectious-free equilibrium. Diekmann *et al. 1990* follow a different approach: *the next generation operator approach.* They define $\mathcal{R}_0$ as the spectral radius of the "next generation operator". The details of this approach are outlined in the rest of this section. First, we consider the case where heterogeneity is discrete, that is, the case where heterogeneity is defined using groups defined by fixed characteristics, that is, for

epidemiological models that can be written in the form:

$$\begin{aligned} \frac{d\mathbf{x}}{dt} &= f(\mathbf{x}, \mathbf{E}, \mathbf{I}), \\ \frac{d\mathbf{E}}{dt} &= g(\mathbf{x}, \mathbf{E}, \mathbf{I}), \\ \frac{d\mathbf{I}}{dt} &= h(\mathbf{x}, \mathbf{E}, \mathbf{I}), \end{aligned} \tag{1.1}$$

where $\mathbf{x} \in \mathbf{R}^r$, $\mathbf{E} \in \mathbf{R}^s$, $\mathbf{I} \in \mathbf{R}^n$, $r, s, n \geq 0$, and $h(\mathbf{x}, 0, 0) = 0$. The components of $\mathbf{x}$ denote the number of susceptibles, recovered, and other classes of non-infected individuals. The components of $\mathbf{E}$ represent the number of infected individuals who do not transmit the disease (various latent or non-infectious stages). The components of $\mathbf{I}$ represent the number of infected individuals capable of transmitting the disease (e.g., infectious and non-quarentined individuals).

Let $\mathbf{U}_0 = (\mathbf{x}^*, 0, 0) \in \mathbf{R}^{r+s+n}$ denote the disease-free equilibrium, that is, at $\mathbf{U}_0 = (\mathbf{x}^*, 0, 0)$, $f(\mathbf{x}^*, 0, 0) = g(\mathbf{x}^*, 0, 0) = h(\mathbf{x}^*, 0, 0) = 0$. Assume that the equation $g(\mathbf{x}^*, \mathbf{E}, \mathbf{I}) = 0$ implicitly determines a function $\mathbf{E} = \widetilde{g}(\mathbf{x}^*, \mathbf{I})$. Let $A = D_{\mathbf{I}} h(\mathbf{x}^*, \widetilde{g}(\mathbf{x}^*, 0), 0)$ and further assume that A can be written in the form $A = M - D$, with $M \geq 0$ (that is, $m_{ij} \geq 0$) and $D > 0$, a diagonal matrix.

The spectral bound of matrix B is denoted by $m(B) = \sup\{\Re\lambda : \lambda \in \sigma(B)\}$, where $\Re\lambda$ means the real part of λ, while $\rho(B) = \lim_{n\to\infty} \|B^n\|^{\frac{1}{n}}$ denotes the spectral radius of B. The proof of the following theorem involving matrix A is found in Diekmann et al., (1990):
Either

$$m(A) < 0 \Longleftrightarrow \rho(MD^{-1}) < 1$$

or

$$m(A) > 0 \Longleftrightarrow \rho(MD^{-1}) > 1.$$

The *basic reproductive number* is defined as the spectral radius (dominant eigenvalue) of the matrix MD^{-1}, that is,

$$\mathcal{R}_0 = \rho(MD^{-1}). \tag{1.2}$$

Examples using (1.1) to compute $\mathcal{R}_0$ are provided in Section 2.

An analogous formula for $\mathcal{R}_0$ when a heterogenous population is stratified by continuous characteristics (see Diekmann et al. 1990) can be similarly computed. In fact, let $S(\xi)$ denote the population density function that describes the (steady) demographic

state in the absence of disease where $\xi \in \Omega_h$ (h stands for heterogeneity). Furthermore, let $A(\tau, \xi, \eta)$ denote the current (expected) infectivity of an individual who was infected τ units of time ago while at stage η, that is, $A(\tau, \xi, \eta)$ denotes the average infectivity that can be exercised on an uninfected individual at stage ξ (provided the uninfected population finds itself at the steady demographic state $S(\xi)$). The function $A(\tau, \xi, \eta)$ combines information on the probability (per unit of time) that contacts between certain stages take place and the probability that, given a contact, the disease agent is actually transmitted.

Under the special assumption of proportionate-mixing (see Busenberg and Castillo-Chavez, 1991), $A(\tau, \xi, \eta)$ can be written in the form $A(\tau, \xi, \eta) = f(\xi)g(\tau, \eta)$. $\mathcal{R}_0$, the spectral radius of the "next generation operator", can be computed under proportionate mixing. In fact, it is given by the following formula:

$$R_0 = \int_\Omega \int_0^\infty g(\tau, \eta) S(\eta) f(\eta) d\tau d\eta. \tag{1.3}$$

The key element, in the computation of $\mathcal{R}_0$ in formula (1.3), is the infectivity function $A(\tau, \xi, \eta)$.

2. Examples

Several models taken from prior work by others or us are used to illustrate the computation of $\mathcal{R}_0$ via Formulas (1.2) and (1.3).

Example 1(a). McKendrick, like Sir Ronald Ross, was a physician commissioned by the English Army to India. McKendrick became involved in the study of epidemic diseases using mathematical models through the direct encouragement of Ross. His simple epidemic model was published in a joint paper with Kermack (Kermack and McKendrick, 1927). It involved the study of the transmission dynamics of a communicable disease that provide permanent immunity after recovery. Their model was used to study single epizootic outbreaks. Their mathematical work led to the first widely recognized threshold theorem in epidemiology (the threshold theorem of Ross came from the study of vector-transmitted diseases sisxteen years earlier). Kermack and Mckendrick's model is an SIR (Susceptible-Infected- Recovered) model without vital (births and deaths) dynamics. The model equations are:

$$\frac{dS}{dt} = -\beta S \frac{I}{N},$$
$$\frac{dI}{dt} = \beta S \frac{I}{N} - \gamma I,$$

$$\frac{dR}{dt} = \gamma I,$$
$$N = S + I + R.$$

S denotes the number of susceptibles, I is the number of infected (assumed infectious), and R is the number of recovered individuals (assumed to be permanently immune). β is the average number of susceptibles infected by one infectious individual per unit of time while γ is the per capita recovery rate (at which an infected individual leaves the I class). Note that $\mathbf{x} = (S, R)$, $\mathbf{I} = I$, $\mathbf{U}_0 = (S^*, R^*, I^*) = (N, 0, 0)$, $A = \beta - \gamma$ (there are no latent classes, that is, $s = 0$). Hence, $M = \beta$, $D = \gamma$ and

$$\mathcal{R}_0 = MD^{-1} = \frac{\beta}{\gamma}.$$

The threshold theorem of Kermack and McKendrick says that if $\mathcal{R}_0 > 1$ then an outbreak will take place while if $\mathcal{R}_0 < 1$ there will be no outbreaks.

Example 1(b). The addition of vital dynamics to the SIR model of Kermack and McKendrick, leads to the follwing system:

$$\frac{dS}{dt} = \Lambda - \beta S\frac{I}{N} - \mu S,$$
$$\frac{dI}{dt} = \beta S\frac{I}{N} - (\mu + \gamma)I,$$
$$\frac{dR}{dt} = \gamma I - \mu R,$$
$$N = S + I + R.$$

Λ is the birth rate and μ is the per capita natural death rate both assumed constant. Note that in this case $\mathbf{x} = (S, R)$, $\mathbf{I} = I$, $\mathbf{U}_0 = (\frac{\Lambda}{\mu}, 0, 0)$, and $A = \beta - (\mu + \gamma)$. Hence, $M = \beta$, $D = \mu + \gamma$ and

$$R_0 = MD^{-1} = \frac{\beta}{\mu + \gamma}.$$

The threshold theorem of Kermack and McKendrick in this setting says that if $\mathcal{R}_0 > 1$ then an outbreak will take place and the disease will persist while if $\mathcal{R}_0 < 1$ the disease will die out.

Remark: Note that β is the average number of susceptibles infected by one infectious individual per unit of time and $\frac{1}{\mu+\gamma}$ is the (death-adjusted) mean length of infectious period (see Thieme's paper in this volume for extensions and clarifications of this interpretation). Therefore $\mathcal{R}_0 = \frac{\beta}{\mu+\gamma}$ gives the number of secondary infectious cases produced by an infectious individual who has been introduced into a population of susceptibles during the

individual's period of infectiousness. The expressions for $\mathcal{R}_0$ computed here, agree with those found by Brauer in his tutorial epidemiological notes included in this volume.

Example 2. Many communicable diseases can be modeled using models that include compartments for the suceptible, exposed, infected and recovered epidemiological classes. An $SEIR$ model for a homogeneously mixing population is given by the following set of equations:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta S\frac{I}{N} - \mu S,\\
\frac{dE}{dt} &= \beta S\frac{I}{N} - (\mu + k)E,\\
\frac{dI}{dt} &= kE - (\gamma + \mu)I,\\
\frac{dR}{dt} &= \gamma I - \mu R,
\end{aligned}$$

where E is the number of latent individuals and k is the rate at which a latent individual becomes infectious. Letting $\mathbf{x} = (S, R)$, $\mathbf{E} = E$, $\mathbf{I} = I$, $\mathbf{U}_0 = (\frac{\Lambda}{\mu}, 0, 0, 0)$ and $\widetilde{g}(\mathbf{x}^*, \mathbf{I}) = \frac{\beta I}{\mu+k}$ gives $M = \frac{k\beta}{\mu+k}$ and $D = \gamma + \mu$. Hence

$$\mathcal{R}_0 = MD^{-1} = \frac{k\beta}{(\mu + k)(\mu + \gamma)}.$$

Example 3. The following model (see Castillo-Chavez and Feng, 1997) describes the disease transmission dynamics of both drug-sensitive and drug-resistant strains of TB. The host population is divided into the following epidemiological subgroups: Susceptibles (S); Latent with strain i ($i = 1$ represents the sensitive strain and $i = 2$ the resistant strain) of TB (E_i); Infectious with strain i (I_i); and (effectively) Treated (T) individuals. The two-strain model for the dynamics of TB is given by:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - \beta_1 S\frac{I_1}{N} - \beta_2 S\frac{I_2}{N} - \mu S,\\
\frac{dE_1}{dt} &= \beta_1 S\frac{I_1}{N} - (\mu + k_1 + r)E_1 + p\tilde{r}I_1 + \sigma\beta_1 T\frac{I_1}{N} - \beta_2 E_1\frac{I_2}{N},\\
\frac{dI_1}{dt} &= k_1 E_1 - (\mu + d_1 + \tilde{r})I_1,\\
\frac{dT}{dt} &= rE_1 + (1 - p - q)\tilde{r}I_1 - \sigma\beta_1 T\frac{I_1}{N} - \beta_2 T\frac{I_2}{N} - \mu T,\\
\frac{dE_2}{dt} &= q\tilde{r}I_1 - (\mu + k_2)E_2 + \beta_2(S + E_1 + T)\frac{I_2}{N},\\
\frac{dI_2}{dt} &= k_2 E_2 - (\mu + d_2)I_2,\\
N &= S + E_1 + I_1 + T + E_2 + I_2,
\end{aligned}$$

where d_i $(i = 1, 2)$ denotes the per capita disease induced death rate due to strain i; r, $\tilde{r}$ denote the per capita treatment rates; $p + q$ the proportion of treated individuals who did not complete the treatment; $\sigma \leq 1$ the reduction in infection rate due to the immunity obtained from treatment. The proportion p modifies the rate of departure from the latent class while $q\tilde{r}I_1$ denotes the rate at which individuals acquire resistant-TB as a result of not completing treatment for active TB.

Letting $\mathbf{x} = (S, T)$, $\mathbf{E} = (E_1, E_2)$, $\mathbf{I} = (I_1, I_2)$, $\mathbf{U}_0 = (\Lambda/\mu, 0, 0, 0)$ and $\widetilde{g}(\mathbf{x}^*, \mathbf{I}) = (\widetilde{g}_1(\mathbf{x}^*, \mathbf{I}), \widetilde{g}_2(\mathbf{x}^*, \mathbf{I}))$ with

$$\begin{aligned}
\widetilde{g}_1(\mathbf{x}^*, \mathbf{I}) &= \frac{(\beta_1 + p\tilde{r})I_1}{\mu\beta_2 I_2/\Lambda + \mu + k_1 + r}, \\
\widetilde{g}_2(\mathbf{x}^*, \mathbf{I}) &= \frac{q\tilde{r}I_1 + \beta_2 I_2}{\mu + k_2} + O(2),
\end{aligned}$$

where $O(2)$ denotes terms of order two and higher in I_i gives

$$M = \begin{pmatrix} \frac{k_1(\beta_1 + p\tilde{r})}{\mu + k_1 + r} & 0 \\ c_1 & \frac{k_2\beta_2}{\mu + k_2} \end{pmatrix} \quad \textit{and} \quad D = \begin{pmatrix} -(\mu + d_1 + \tilde{r}) & 0 \\ c_2 & -(\mu + d_2) \end{pmatrix}.$$

The two eigenvalues λ_1 and λ_2 of MD^{-1} are:

$$\lambda_1 = \frac{k_1(\beta_1 + p\tilde{r})}{(\mu + k_1 + r)(\mu + d_1 + \tilde{r})} \quad \textit{and} \quad \lambda_2 = \frac{k_2\beta_2}{(\mu + k_2)(\mu + d_2)}.$$

It follows that $\mathcal{R}_0 = \max\{\lambda_1, \lambda_2\}$.

Example 4. In this example, we introduce a minimal degree of host heterogeneity by dividing the host population in two groups. Such division could be the result of differences in socio economic status or other characteristics that are likely to remain fixed in the time scale of the epidemic process. To illustrate the computation of $\mathcal{R}_0$ in this case, we use the following SIR model with two groups:

$$\begin{aligned}
\frac{dS_i}{dt} &= \Lambda_i - S_i\left(\beta_{ii}\frac{I_i}{N} + \beta_{ij}\frac{I_j}{N}\right) - \mu S_i, \\
\frac{dI_i}{dt} &= S_i\left(\beta_{ii}\frac{I_i}{N} + \beta_{ij}\frac{I_j}{N}\right) - \mu I_i - k_i I_i, \\
\frac{dR_i}{dt} &= k_i I_i - \mu R_i, \qquad i = 1, 2.
\end{aligned}$$

where the subscript i identifies each group (i = 1 or i = 2). In this case, $\mathbf{I} = (I_1, I_2)$,

$$M = \begin{pmatrix} \beta_{11}\frac{\Lambda_1}{\Lambda_1 + \Lambda_2} & \beta_{12}\frac{\Lambda_1}{\Lambda_1 + \Lambda_2} \\ \beta_{21}\frac{\Lambda_2}{\Lambda_1 + \Lambda_2} & \beta_{22}\frac{\Lambda_2}{\Lambda_1 + \Lambda_2} \end{pmatrix}, \qquad D = \begin{pmatrix} \mu + k_1 & 0 \\ 0 & \mu + k_2 \end{pmatrix},$$

and

$$MD^{-1} = \begin{pmatrix} \frac{\beta_{11}}{\mu+k_1}\frac{\Lambda_1}{\Lambda_1+\Lambda_2} & \frac{\beta_{12}}{\mu+k_2}\frac{\Lambda_1}{\Lambda_1+\Lambda_2} \\ \frac{\beta_{21}}{\mu+k_1}\frac{\Lambda_2}{\Lambda_1+\Lambda_2} & \frac{\beta_{22}}{\mu+k_2}\frac{\Lambda_2}{\Lambda_1+\Lambda_2} \end{pmatrix} =: (\alpha_{ij}).$$

Since the dominant eigenvalue of MD^{-1} is

$$\lambda = \frac{1}{2}\left(\alpha_{11} + \alpha_{22} + \sqrt{(\alpha_{11}-\alpha_{22})^2 + 4\alpha_{12}\alpha_{21}}\right)$$

then $\mathcal{R}_0 = \lambda$.

Example 5. The following model was developed to study the dynamics of multiple strains of a sexually transmitted diseases (like gonorrhea) on a population that included a high degree of host heterogeneity (see Castillo-Chavez, Huang & Li 1997). The model included populations of males and females as well as a highly active female population (core group) since one of our main goals was to study the impact of female prostitution on disease persistence. The model equations are:

$$\begin{aligned}
\frac{dS^m}{dt} &= \Lambda^m - B^m - \mu S^m + \sum_{i=1}^{2} \gamma_i^m I_i^m, \\
\frac{dI_i^m}{dt} &= B_i^m - (\mu + \gamma_i^m) I_i^m, \\
\frac{dS^f}{dt} &= \Lambda^f - B^f - \mu S^f + \sum_{i=1}^{2} \gamma_i^f I_i^f, \\
\frac{dI_i^f}{dt} &= B_i^f - (\mu + \gamma_i^m) I_i^f, \\
\frac{dS^c}{dt} &= \Lambda^c - B^c - \mu^c S^c + \sum_{i=1}^{2} \gamma_i^c I_i^c, \\
\frac{dI_i^c}{dt} &= B_i^c - (\mu + \gamma_i^c) I_i^c, \qquad i = 1, 2,
\end{aligned} \tag{2.1}$$

where

$$\begin{aligned}
B_i^m &= r^m(T^m, T^f, T^c) S^m \left(\beta_i^f \frac{I_i^f}{T^f} + \beta_i^c \frac{I_i^c}{T^c}\right), \\
B_i^f &= r^f(T^m, T^f, T^c) S^f \beta_i^m \frac{I_i^m}{T^m}, \\
B_i^c &= r^c(T^m, T^f, T^c) S^c \beta_i^m \frac{I_i^m}{T^m}, \quad i = 1, 2, \\
B^m &= \sum_{i=1}^{2} B_i^m, \quad B^f = \sum_{i=1}^{2} B_i^f, \quad B^c = \sum_{i=1}^{2} B_i^c,
\end{aligned}$$

with the natural constraint

$$r^m(T^m,T^f,T^c)T^m = r^f(T^m,T^f,T^c)T^f + r^c(T^m,T^f,T^c)T^c.$$

Here Λ^k ($k = m$ (male), f (female), c (core group, females)) denote the input flow or (constant) recruitment into the corresponding sexually active sub-population; $1/\mu^c$ is the average sexual life span for group c while $1/\mu$ is the average sexual life span for individuals not in group c; γ_i^k are the per capita rates of recovery; $T^k = S^k + \sum_j I_j^k$ are the total number of males or females (group f and group c), respectively; r^k, as functions of T^m, T^f, T^c, denote the numbers of partners per individual per unit of time; and, β_i^k denote the rates of infection. The constraint simply states that the total number of partners per unit of time for each gender (this is a purely heterosexual model) must match.

The dynamics of the above system are equivalent to those of limiting system (see Castillo-Chavez and Huang and Li, 1997) below:

$$\begin{aligned}
\frac{dI_i^m}{dt} &= -(\mu+\gamma_i^m)I_i^m + b^m\Big(\frac{\Lambda^m}{\mu} - \sum_j I_j^m\Big)\Big(\beta_i^f\frac{\mu}{\Lambda^f}I_i^f + \beta_i^c\frac{\mu^c}{\Lambda^c}I_i^c\Big),\\
\frac{dI_i^f}{dt} &= -(\mu+\gamma_i^m)I_i^f + \frac{\mu b^f\beta_i^m}{\Lambda^m}\Big(\frac{\Lambda^f}{\mu} - \sum_j I_j^f\Big)I_i^m,\\
\frac{dI_i^c}{dt} &= -(\mu^c+\gamma_i^c)I_i^c + \frac{\mu b^c\beta_i^m}{\Lambda^m}\Big(\frac{\Lambda^c}{\mu^c} - \sum_j I_j^c\Big)I_i^m, \quad i=1,2.
\end{aligned} \tag{2.2}$$

where

$$\begin{aligned}
&\sigma_i^c = (\mu^c+\gamma_i^c),\ p^c = \frac{\Lambda^c}{\mu^c},\ \sigma_i^k = (\mu+\gamma_i^k),\ p^k = \frac{\Lambda^k}{\mu}, \quad k=m,f,\\
&a_i^m = \frac{b^m\beta_i^f}{p^f},\ a_i^f = \frac{b^f\beta_i^m}{p^m},\ a_i^c = \frac{b^c\beta_i^m}{p^m},\ a_i^{mc} = \frac{b^m\beta_i^c}{p^c}. \quad i=1,2.
\end{aligned}$$

System (2.2) can be rewritten as

$$\begin{aligned}
\frac{dI_i^m}{dt} &= -\sigma_i^m I_i^m + (p^m - \sum_j I_j^m)(a_i^m I_i^f + a_i^{mc} I_i^c),\\
\frac{dI_i^f}{dt} &= -\sigma_i^f I_i^f + a_i^f(p^f - \sum_j I_j^f)I_i^m,\\
\frac{dI_i^c}{dt} &= -\sigma_i^c I_i^c + a_i^c(p^c - \sum_j I_j^c)I_i^m, \quad i=1,2.
\end{aligned} \tag{2.3}$$

Linearizing about the infection-free equilibrium of (2.3) gives

$$\begin{pmatrix} \frac{dI_i^m}{dt} \\ \frac{dI_i^f}{dt} \\ \frac{dI_i^c}{dt} \end{pmatrix} = \begin{pmatrix} -\sigma_i^m & p^m a_i^m & p_i^m a_i^{mc} \\ p^f a_i^f & -\sigma_i^f & 0 \\ p^c a_i^c & 0 & -\sigma_i^c \end{pmatrix} \begin{pmatrix} I_i^m \\ I_i^f \\ I_i^c \end{pmatrix}, \quad i = 1, 2.$$

In this case

$$\mathbf{I} = (\mathbf{I}_1, \mathbf{I}_2), \quad M = \begin{pmatrix} M_1 & 0 \\ 0 & M_2 \end{pmatrix}, \qquad D = \begin{pmatrix} D_1 & 0 \\ 0 & D_2 \end{pmatrix},$$

where $\mathbf{I}_i = (I_i^m, I_i^f, I_i^c)$,

$$M_i = \begin{pmatrix} 0 & p^m a_i^m & p^m a_i^{mc} \\ p^f a_i^f & 0 & 0 \\ p^c a_i^c & 0 & 0 \end{pmatrix} \quad \textit{and} \quad D_i = \begin{pmatrix} \sigma_i^m & 0 & 0 \\ 0 & \sigma_i^f & 0 \\ 0 & 0 & \sigma_i^c \end{pmatrix}.$$

$\mathcal{R}_0 = \max\{\mathcal{R}_1, \mathcal{R}_2\}$ where $\mathcal{R}_i$ is the dominant eigenvalue of $M_i D_i^{-1}$. Since the characteristic equation of $M_i D_i^{-1}$ is

$$\lambda(\lambda^2 - \frac{a_i^{mc} p^m p^c a_i^c}{\sigma_i^c \sigma_i^m} - \frac{p^m a_i^m p^f a_i^f}{\sigma_i^f \sigma_i^m}) = 0$$

then

$$\mathcal{R}_i = \sqrt{\frac{a_i^{mc} a_i^c p^m p^c \sigma_i^f + a_i^m a_i^f p^f p^m \sigma_i^c}{\sigma_i^f \sigma_i^m \sigma_i^c}}.$$

Example 6. Dengue is vector-transmitted disease that exhibits strain heterogeneity. Furthermore, a host's prior immunological history with Dengue strains can have a critical impact on the probability of host survival to infections from other strains. The model below was used to study the dynamics of two strains of Dengue (see Feng and Velasco-Hernandez, 1997) on a human population. Secondary infections were only allowed to be experienced by human hosts, that is, It was assumed infected mosquitos never recovered and could not be infected by additionals strains. The situation for human hosts was assumed to be different. Two scenarios were possible: either an I_1 *previously* infected individual who became now infected with strain 2 (through contact with V_2, infected mosquitoes) became a Y_2 infected host or a *previously* I_2 infected individual who become now infected with strain 1 (through contact with V_1 mosquitoes) became a Y_1 infected-host. The rates at which these two forms of host infection occur are given by $\sigma_1 B_1 I_2$ and $\sigma_2 B_2 I_1$, respectively. Here

σ_i is a positive real number used to model either cross-immunity ($\sigma_i < 1$) or increased susceptibility ($\sigma_i > 1$). The model is given by the following set of equations:

$$\begin{aligned}
\frac{dS}{dt} &= \Lambda - (B_1 + B_2)S - \mu S, \\
\frac{dI_1}{dt} &= B_1 S - \sigma_2 B_2 I_1 - \mu I_1, \\
\frac{dI_2}{dt} &= B_2 S - \sigma_1 B_1 I_2 - \mu I_2, \\
\frac{dY_1}{dt} &= \sigma_1 B_1 I_2 - (e_1 + \mu + r)Y_1, \\
\frac{dY_2}{dt} &= \sigma_2 B_2 I_1 - (e_2 + \mu + r)Y_2, \\
\frac{dR}{dt} &= r(Y_1 + Y_2) - \mu R,
\end{aligned}$$

and

$$\begin{aligned}
\frac{dW}{dt} &= q - (A_1 + A_2)W - \delta W, \\
\frac{dV_1}{dt} &= A_1 W - \delta V_1, \\
\frac{dV_2}{dt} &= A_2 W - \delta V_2,
\end{aligned}$$

where

$$B_i = \frac{\beta_i V_i}{c + w_h N}, \; A_i = \frac{\alpha_i (I_i + Y_i)}{c + w_v N}. \; i = 1, 2.$$

$N = S + I_1 + I_2 + Y_1 + Y_2 + R$ and W is the number of susceptible mosquitoes. If we let $\mathbf{x} = (S, R, W)$, and $\mathbf{I} = (I_1, I_2, Y_1, Y_2, V_1, V_2)$ then $\mathbf{U}_0 = (\Lambda/\mu, 0, q/\delta, 0, 0, 0, 0, 0, 0)$,

$$M = \begin{pmatrix}
0 & 0 & 0 & 0 & \beta_1 C_h & 0 \\
0 & 0 & 0 & 0 & 0 & \beta_2 C_h \\
0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 \\
\alpha_1 C_\nu & 0 & 0 & 0 & 0 & 0 \\
0 & \alpha_2 C_\nu & 0 & 0 & 0 & 0
\end{pmatrix},$$

and

$$D = \begin{pmatrix}
\mu & 0 & 0 & 0 & 0 & 0 \\
0 & \mu & 0 & 0 & 0 & 0 \\
0 & 0 & e_1 + \mu + r & 0 & 0 & 0 \\
0 & 0 & 0 & e_2 + \mu + r & 0 & 0 \\
0 & 0 & 0 & 0 & \delta & 0 \\
0 & 0 & 0 & 0 & 0 & \delta
\end{pmatrix},$$

where $C_h = S^*/(c + w_h N^*)$, $C_\nu = S^*/(c + w_h N^*)$ and $S^* = N^* = \Lambda/\mu$. Hence

$$MD^{-1} = \begin{pmatrix} 0 & 0 & 0 & 0 & \frac{\beta_1}{\mu}C_h & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{\beta_2}{\mu}C_h \\ 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \frac{\alpha_1}{\delta}C_v & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{\alpha_2}{\delta}C_v & 0 & 0 & 0 & 0 \end{pmatrix},$$

with eigenvalues:

$$\lambda_{1,2} = 0, \quad \lambda_{3,4} = \pm\sqrt{\frac{\alpha_1\beta_1 C_h C_v}{\delta\mu}} \quad and \quad \lambda_{5,6} = \pm\sqrt{\frac{\alpha_2\beta_2 C_h C_v}{\delta\mu}}.$$

Consequently

$$\mathcal{R}_0 = \max\left\{\sqrt{\frac{\alpha_1\beta_1 C_h C_v}{\delta\mu}}, \sqrt{\frac{\alpha_2\beta_2 C_h C_v}{\delta\mu}}\right\}.$$

Example 7. Huang, Cooke, & Castillo-Chavez (1992) studied the sexual-transmission of HIV in a homosexually active population stratified by degree of sexual activity and (implicitly) sexual practices. Their model showed that asymmetric transmission rates between groups were capable of generating multiple endemic equilibria via a backward bifurcation. Their model is given by the following set of equations:

$$\begin{aligned} \frac{dS_i(t)}{dt} &= \Lambda_i - B_i(t) - \mu S_i(t), \\ \frac{dI_i(t)}{dt} &= B_i(t) - (\alpha_i + \mu)I_i(t), \\ \frac{dA_i(t)}{dt} &= \alpha_i I_i(t) - (d_i + \mu)A_i(t), \\ B_i(t) &= S_i(t)c_i \sum_{j=1}^{n} \lambda_{ij} p_{ij}(t) \frac{I_i(t)}{T_j(t)}, \quad i = 1, \cdots, n, \end{aligned} \tag{2.4}$$

where A denotes number of individuals with AIDS, $T_j = S_j + I_j$, and c_i, λ_{ij}, and $p_{ij}(t)$ denotes the mixing matrix. Proportionate mixing was assumed, that is they took $p_{ij} = p_j = c_j T_j/N$ where $N = \sum_{k=1}^{n} c_k T_k$. The constants α_i and d_i denote the per capita disease-induced death rates. The notation $\theta_i = \eta_i \lambda_{ii} c_i$, and $l_{ij} = c_i c_j \lambda_{ij}$ used in Huang et al. (1992) helps rewrite System (2.4) (without the A equation) in the form:

$$\begin{aligned} \frac{dS_i}{dt} &= \Lambda_i - S_i\left(\frac{\theta_i I_i}{T_i} + \frac{1}{N}\sum_{j=1}^{n} l_{ij} I_j\right) - \mu S_i, \\ \frac{dI_i}{dt} &= S_i\left(\frac{\theta_i I_i}{T_i} + \frac{1}{N}\sum_{j=1}^{n} l_{ij} I_j\right) - (\alpha_i + \mu)I_i. \quad i = 1, \cdots, n. \end{aligned} \tag{2.5}$$

Note that at the disease-free state of (2.5) $S_i^* = T_i^* = \frac{\Lambda_i}{\mu}$ and $N^* = \sum_{k=1}^n c_k T_k^*$. Hence, under proportionate mixing with $\mathbf{I} = (I_1, I_2, \cdots, I_n)$ one gets

$$M = \begin{pmatrix} \theta_1 + \frac{S_1^* l_{11}}{N^*} & \frac{S_1^* l_{12}}{N^*} & \cdots & \frac{S_1^* l_{1n}}{N^*} \\ \frac{S_2^* l_{21}}{N^*} & \theta_2 + \frac{S_2^* l_{22}}{N^*} & \cdots & \frac{S_2^* l_{2n}}{N^*} \\ \cdot & \cdot & & \cdot \\ \cdot & \cdot & & \cdot \\ \cdot & \cdot & & \cdot \\ \frac{S_n^* l_{n1}}{N^*} & \frac{S_n^* l_{n2}}{N^*} & \cdots & \theta_n + \frac{S_n^* l_{nn}}{N^*} \end{pmatrix}$$

and

$$D = \begin{pmatrix} \alpha_1 + \mu & 0 & & \cdots & 0 \\ 0 & \alpha_2 + \mu & 0 & \cdots & 0 \\ \cdot & \cdot & & & \cdot \\ \cdot & \cdot & & & \cdot \\ \cdot & \cdot & & & \cdot \\ 0 & \cdots & & 0 & \alpha_n + \mu \end{pmatrix}.$$

M and D can be rewritten as:

$$M = \text{diag}(\theta_i) + \frac{1}{K}\text{diag}(\Lambda_i)L, \quad D = \text{diag}(\mu(\sigma_i + 1)),$$

where $K = \sum_{k=1}^n c_k \Lambda_k$, $L = (l_{ij})_{n \times n}$, and $\sigma_i = \alpha_i / \mu$.

Clearly

$$MD^{-1} = \frac{1}{\mu}\text{diag}\left(\frac{\theta_i}{\sigma_i + 1}\right) + \frac{1}{\mu}\text{diag}\left(\frac{\Lambda_i}{K(\sigma_i + 1)}\right)L.$$

If μ_0 (notation used by Huang et al.) denotes the spectral radius of the matrix

$$\text{diag}\left(\frac{\theta_i}{\sigma_i + 1}\right) + \text{diag}\left(\frac{\Lambda_i}{K(\sigma_i + 1)}\right)L,$$

then

$$R_0 = \frac{\mu_0}{\mu}.$$

Example 8. There is a vaccine for TB that is widely used around the world. A model was developed and analyzed by Castillo-Chavez and Feng (1997) to help determine the optimal (according to some appropriate set of criteria) vaccination age. The role of $\mathcal{R}_0$ was also critical in establishing of a useful concept of optimality. Hence, its explicit computation was critical to the analysis. Let's introduce this model and compute its $\mathcal{R}_0$. We let $s(t, a)$ denote the density function of the susceptible class ($S(t) = \int_0^\infty s(t, a)da$ gives the number

of susceptibles at t) and let $v(t,a)$, $l(t,a)$, $i(t,a)$, and $j(t,a)$ denote the density functions of the vaccinated, latent, infectious, and treated classes, respectively. The model reads

$$
\begin{aligned}
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})s = -\beta(a)c(a)B(t)s - \mu(a)s - \psi(a)s,\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})v = \psi(a)s - \mu(a)v - \delta\beta(a)c(a)B(t)v,\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})l = \beta(a)c(a)B(t)\big(s+\sigma j+\delta v\big) - (k+\mu(a))l,\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})i = kl - (r+\mu(a))i,\\
&(\frac{\partial}{\partial t}+\frac{\partial}{\partial a})j = ri - \sigma\beta(a)c(a)B(t)j - \mu(a)j,\\
&\qquad B(t) = \int_0^\infty \frac{i(t,a')}{n(t,a')}p(t,a')da',\\
&\qquad p(t,a') = \frac{c(a')n(t,a')}{\int_0^\infty c(u)n(t,u)du},\\
&s(t,0)=\Lambda,\quad v(t,0)=l(t,0)=i(t,0)=j(t,0)=0,\\
&s(0,a)=s_0(a),\ v(0,a)=v_0(a),\ l(0,a)=l_0(a),\\
&i(0,a)=i_0(a),\ j(0,a)=j_0(a),
\end{aligned}
$$

where $n=s+v+l+i+j$; Λ is the birth rate; $\mu(a)$ is the age specific per capita natural death rate; $\beta(a)$ is the age specific (average) probability of becoming infected through contacts with infectious individuals; $c(a)$ is the age specific per capita contact/activity rate; σ and δ represent the reduction in risk of infection due to treatment and vaccination, respectively, $0\le\sigma,\ \delta\le 1$; k is the per capita rate of progression to active TB; r is the per capita treatment rate; $\psi(a)$ is the per capita vaccination rate. In addition, $p(t,a,a')$ gives the "probability" that an individual of age a has a contact with an individual of age a' given that the individual had a contact with a member of the population. Again, we assume proportionate mixing (otherwise the explicit computation of R_0 is impossible), that is, we take $p(t,a,a')=p(t,a')$ (as already defined above).

The steady demographic state (that is, the state where the infection is absent) of the system is given by the following nonuniform age-distribution:

$$
n(a)=\Lambda e^{-\mu a},\ s(a)=\Lambda e^{-\mu a}\mathcal{F}_\psi(a),\ v(a)=\Lambda e^{-\mu a}\big(1-\mathcal{F}_\psi(a)\big),\ l=i=j=0,
$$

where

$$
\mathcal{F}(a)=e^{-\int_0^a\mu(s)ds},\quad \mathcal{F}_\psi(a)=e^{-\int_0^a\psi(b)db}.
$$

The probability that an individual of age $\alpha + \tau$, who was infected τ units of time ago, is still in class i, is given by

$$\gamma(\tau, \alpha) = \int_0^\tau k e^{-(\mu+k)u} e^{-(r+\mu)(\tau-u)} du =: \mathcal{K}(\tau) e^{-\mu\tau}$$

where

$$\mathcal{K}(\tau) = \frac{k}{r-k}(e^{-k\tau} - e^{-r\tau}). \tag{2.6}$$

Thus the expected infectivity is given by

$$A(\tau, a, \alpha) = \beta(a)c(a)p(\alpha+\tau)\frac{\gamma(\tau,\alpha)}{n(\alpha+\tau)},$$

where $p(a) = c(a)n(a)/\int_0^\infty c(u)n(u)du$. Letting $A(\tau, a, \alpha) = f(a)g(\tau, \alpha)$ where $f(a) = \beta(a)c(a)$ and $g(\tau, \alpha) = p(\alpha+\tau)\gamma(\tau, \alpha)/n(\alpha+\tau)$ and Formula (1.3) leads to the computation of the reproductive number associated with the vaccination strategy ψ. Namely,

$$\mathcal{R}(\psi) = \int_0^\infty \int_0^\infty p(\alpha+\tau)\beta(\alpha)c(\alpha)\mathcal{K}(\tau)\mathcal{V}_\psi(\alpha)d\tau d\alpha,$$

where $\mathcal{V}_\psi(a) = \mathcal{F}_\psi(a) + \delta(1 - \mathcal{F}_\psi(a)) < 1$ ($\mathcal{K}(\tau)$ is given by (2.6)). Hence, in the absence of a vaccine, that is, whenever, $\psi(a) = 0$, the above formula reduces to the basic reproductive number

$$\mathcal{R}_0 = \int_0^\infty \int_0^\infty p(\alpha+\tau)\beta(\alpha)c(\alpha)\mathcal{K}(\tau)d\tau d\alpha.$$

An alternative method for computing $\mathcal{R}_0$ can be found in Castillo-Chavez and Feng (1997).

Example 9. The following model was introduced and partially analyzed in Busenberg and Castillo-Chavez (1991). The focus of their paper was not the study of the transmission dynamics of HIV/AIDS per se but rather the development of general methods for modeling the mixing structure of a population. This paper focussed on the modeling of social structures since they often play a critical role in the study of the spread of disease. A model for the transmission dynamics of HIV/AIDS in a homosexually-active population stratified by risk and age was used to illustrate their approach. In order to introduce this model, we let $S(r, a, t)$, $I(r, a, \tau, t)$ and $A(r, a, \tau, t)$ denote the density functions of susceptible, infectious, and AIDS classes, respectively. Here, a denotes chronological age;

τ is the age of infection for the I and A groups; and r denotes the sexual activity level. The model reads:

$$\begin{aligned}
&\frac{\partial S}{\partial t}+\frac{\partial S}{\partial a}=\Lambda(r,a,t,T(r,a,t))-B(r,a,t)-\mu(a)S,\\
&\frac{\partial I}{\partial t}+\frac{\partial I}{\partial a}+\frac{\partial I}{\partial \tau}=-\big(\mu(a)+\nu(a,\tau)+\gamma(a,\tau)\big)I,\\
&\frac{\partial A}{\partial t}+\frac{\partial A}{\partial a}+\frac{\partial A}{\partial \tau}=\gamma(a,\tau)I-\big(\mu(a)+\delta(a,\tau)\big)A,
\end{aligned}$$

where at $a=0$, $S=I=A=0$, and $I(r,a,0,t)=B(r,a,t)$,

$$\begin{aligned}
B(r,a,t)=&c(r,a)\int_0^\infty\int_0^\infty\int_0^\infty \beta(r,a,\tau,r',a')\rho(r,a,r',a')\frac{I(r',a',\tau,t)}{T(r',a',t)}dr'da'd\tau,\\
T(r,a,t)=&S(r,a,t)+\int_0^\infty I(r,a,\tau,t)d\tau.
\end{aligned}$$

At the steady demographic state

$$T(r,a)=\tilde{S}(r,a)=\int_0^a e^{-\int_x^a \mu(y)dy}\Lambda(r,x)dx. \tag{2.7}$$

Under the assumption of proportionate mixing, that is, with the use of

$$\begin{aligned}
&\rho(r,a,r',a')=\frac{c(r',a')T(r',a')}{\int_0^\infty\int_0^\infty c(r',a')T(r',a')dr'da'},\\
&\beta(r,a,r',a',\tau)=\beta(r',a',\tau),
\end{aligned}$$

one finds that the infectivity function is given by

$$A(r,a,r',a'-\tau,\tau)=\beta(r',a',\tau)c(r,a)\rho(r',a')\frac{\mathcal{F}(a',\tau)}{T(r',a')}=:f(r,a)g(r',a'-\tau,\tau),$$
$$0\le\tau\le a',$$

where

$$\mathcal{F}(a',\tau)=e^{-\int_0^\tau\left(\mu(a'-\tau+s)+\nu(a'-\tau+s,\tau)+\gamma(a'-\tau+s,\tau)\right)ds}, \tag{2.8}$$

and

$$f(r,a)=c(r,a),\quad g(r',a'-\tau,\tau)=\frac{\beta(r',a',\tau)c(r',a')\mathcal{F}(a',\tau)}{\int_0^\infty\int_0^\infty c(r',a')T(r',a')dr'da'}.$$

We again compute the basic reproductive number using (1.3)

$$
\begin{aligned}
R_0 &= \int_0^\infty \int_0^\infty \int_0^{a'} f(r', a'-\tau)\tilde{S}(r', a'-\tau)g(r', a'-\tau, \tau)d\tau dr' da' \\
&= \int_0^\infty \int_0^\infty \int_0^{a'} c(r', a'-\tau)\Big(\int_0^{a'-\tau} e^{-\int_x^{a'-\tau}\mu(y)dy}\Lambda(r', x)dx \Big) \\
&\quad \times \frac{\beta(r', a', \tau)c(r', a')\mathcal{F}(a', \tau)}{\int_0^\infty \int_0^\infty c(r', a')T(r', a')dr'da'} d\tau dr' da' \\
&= \frac{1}{\int_0^\infty \int_0^\infty c(r', a')T(r', a')dr'da'} \int_0^\infty \int_0^\infty c(r', a')\Big\{ \int_0^{a'} \beta(r', a', \tau)c(r', a'-\tau)\mathcal{F}(a', \tau) \\
&\quad \times \Big(\int_0^{a'-\tau} e^{-\int_x^{a'-\tau}\mu(y)dy}\Lambda(r', x)dx \Big) d\tau \Big\} dr' da',
\end{aligned}
$$

where $T(r, a)$ and $\mathcal{F}(a', \tau)$ are given in (2.7), (2.8).

Example 10. The model of this last example was develop to determine optimal vaccination policies for models for infectious diseases (see Hadeler and Müller, 1995). The "general" age structure model for communicable diseases is typically given by the following system of three partial differential equations:

$$
\begin{aligned}
u_t + u_a &= -\mu(a)u - \psi(a)u + \gamma(a)w - \beta(a)u\frac{V}{N}, \\
w_t + w_a &= -\mu(a)w + \psi(a)u + \alpha(a)v - \gamma(a)w - \tilde{\beta}(a)w\frac{V}{N} \\
v_t + v_a &= -\tilde{\mu}(a)v - \alpha(a)v + (\beta(a)u + \tilde{\beta}(a)w)\frac{V}{N},
\end{aligned}
$$

with boundary conditions

$$
u(t, 0) = \int_0^L [b(a)(u(t, a) + w(t, a)) + \tilde{b}(a)v(t, a)]da, \quad w(t, 0) = 0, \quad v(t, 0) = 0.
$$

Here, $N(t) = \int_0^L [(u(t, a) + w(t, a)) + v(t, a)]da$ denotes the total population size while $V(t) = \int_0^L k(a)v(t, a)da$ gives the average number of contacts per unit of time of infectious with susceptible individuals. Furthermore, L represents maximum age; $\psi(a)$ denotes the age dependent vaccination rate; $k(a)$ the age specific contact distribution; $\alpha(a)$ denotes the age dependent recovery rate; and $\gamma(a)$ is the age specific loss of immunity.

The steady demographic state, in the presence of an age specific vaccination policy $\psi(a)$, is $(\bar{u}(a), \bar{w}(a), \bar{v}(a))$ where

$$
\bar{u}(a) = P(a)D(a), \quad \bar{w}(a) = P(a) - \bar{u}(a), \quad \bar{v}(a) = 0,
$$

and

$$P(a) = e^{-\int_0^a \mu(s)ds},$$
$$D(a) = e^{-\int_0^a (\gamma(s)+\psi(s))ds} + \int_0^a e^{-\int_s^a (\gamma(\tau)+\psi(\tau))d\tau}\gamma(s)ds.$$

If $A_u(\tau,\xi,\eta)$ and $A_v(\tau,\xi,\eta)$ denote the infectivity functions corresponding to susceptibles $\bar{u}(\xi)$ and vaccinated individuals $\bar{v}(\xi)$, respectively, then

$$A_u(\tau,\xi,\eta) = f_u(\xi)g(\tau,\eta), \quad A_v(\tau,\xi,\eta) = f_v(\xi)g(\tau,\eta),$$

where

$$f_u(\xi) = \beta(\xi), \quad f_v(\xi) = \tilde{\beta}(\xi), \quad g(\tau,\eta) = k(\eta+\tau)\frac{e^{-\int_0^\tau [\tilde{\mu}(\eta+s)+\alpha(\eta+s)]ds}}{N}.$$

Using Formula (1.3) again, we compute the basic reproductive number:

$$\begin{aligned} R(\psi) &= \int_0^L \int_0^L f_u(\eta)\bar{u}(\eta)g(\tau,\eta)d\tau d\eta + \int_0^L \int_0^L f_v(\eta)\bar{w}(\eta)g(\tau,\eta)d\tau d\eta \\ &= \frac{1}{N}\int_0^L \int_0^L k(\eta+\tau)e^{-\int_0^\tau [\tilde{\mu}(\eta+s)+\alpha(\eta+s)]ds}(\beta(\eta)\bar{u}(\eta) + \tilde{\beta}(\eta)\bar{w}(\eta))d\tau d\eta. \end{aligned}$$

Some changes of variables and exchanges in the order of integrations leads to

$$R(\psi) = \frac{\int_0^L \int_0^\theta k(\theta)P(\eta)e^{-\int_\eta^\theta (\tilde{\mu}(r)+\alpha(r))dr}\left(\beta(\eta)D(\eta) + \tilde{\beta}(\eta)(1-D(\eta))\right)d\eta d\theta}{\int_0^L P(a)da}. \tag{2.9}$$

Note that $P(\eta)P(\tau) = P(\eta+\tau)$ and $\delta(a) = \tilde{\mu}(a) - \mu(a)$. It can be checked that (2.9) gives the same formula for $\mathcal{R}(\psi)$ as that found in the paper by Hadeler and Müller (Formula (3.20)).

3. Global stability conditions for the disease-free equilibrium when $\mathcal{R}_0 < 1$

For all the differential equation examples of Section 2, it can be established that the disease-free equilibrium is locally asymptotic stable (l.a.s.) whenever $\mathcal{R}_0 < 1$ and unstable when $\mathcal{R}_0 > 1$. In this section, we list two conditions that if met, also guarantee the global asymptotic stability of the disease-free state. First, System (1.1) must be written in the form:

$$\begin{aligned} \frac{d\mathbf{x}}{dt} &= F(\mathbf{x},\mathbf{I}), \\ \frac{d\mathbf{I}}{dt} &= G(\mathbf{x},\mathbf{I}), \quad G(\mathbf{x},0) = 0, \end{aligned} \tag{3.1}$$

where $\mathbf{x} \in \mathbf{R}^m$ denotes (its components) the number of uninfected individuals and $\mathbf{I} \in \mathbf{R}^n$ denotes (its components) the number of infected individuals including latent, infectious, etc. $\mathbf{U}_0 = (x^*, 0)$ denotes the disease-free equilibrium of this system.

The conditions (H1) and (H2) below must be met to guarantee local asymptotic stability.

(H1) For $\frac{d\mathbf{x}}{dt} = F(\mathbf{x}, 0)$, $\mathbf{x}^*$ is globally asymptotically stable (g.a.s.),

(H2) $G(\mathbf{x}, \mathbf{I}) = A\mathbf{I} - \widehat{G}(\mathbf{x}, \mathbf{I})$, $\widehat{G}(\mathbf{x}, \mathbf{I}) \geq 0$ for $(\mathbf{x}, \mathbf{I}) \in \Omega$,

where $A = D_{\mathbf{I}} G(\mathbf{x}^*, 0)$ is an M-matrix (the off diagonal elements of A are nonnegative) and Ω is the region where the model makes biological sense.

If System (3.1) satisfies the above two conditions then the following theorem holds:

Theorem The fixed point $\mathbf{U}_0 = (x^*, 0)$ *is a globally asymptotic stable (g.a.s.) equilibrium of (3.1) provided that* $\mathcal{R}_0 < 1$ *(l.a.s.) and that assumptions (H1) and (H2) are satisfied*

Proof: Let $I_0 = I(0)$, observe that $I(t) \geq 0$ if $I_0 > 0$ and that e^{At} is a positive semigroup (since A is an M-matrix). Hence, using the variation-of-constant formula, we have

$$\begin{aligned} 0 \leq I(t) &= e^{At} I_0 - \int_0^t e^{A(t-s)} \widehat{G}(\mathbf{x}(\mathbf{s}), \mathbf{I}(\mathbf{s})) ds \\ &\leq e^{At} I_0. \end{aligned}$$

Since A is an M-matrix, A has a dominant eigenvalue $m(A)$ with $m(A) < 0$ for $\mathcal{R}_0 < 1$. Thus

$$\lim_{t \to \infty} \|e^{At}\| = 0, \implies \lim_{t \to \infty} I(t) = 0.$$

Note that $\mathbf{x}^*$ is a g.a.s. equilibrium of $\frac{d\mathbf{x}}{dt} = F(\mathbf{x}, 0)$, a limiting system of $\frac{d\mathbf{x}}{dt} = F(\mathbf{x}(\mathbf{t}), \mathbf{I}(\mathbf{t}))$. Thus,

$$\lim_{t \to \infty} \mathbf{x}(t) = \mathbf{x}^*.$$

Remark: If A is irreducible and some additional conditions on $\widehat{G}(\mathbf{x}, \mathbf{I})$, then the theorem remains true for $\mathcal{R}_0 \leq 1$.

Rewrite Example 2 in the form of (3.1, then $\mathbf{x} = (S, R)$, $\mathbf{I} = (E, I)$, $F(\mathbf{x}, 0) = \begin{pmatrix} \Lambda - \mu S \\ 0 \end{pmatrix}$, and

$$A = \begin{pmatrix} -(\mu + k) & \beta \\ k & -(\mu + \gamma) \end{pmatrix}, \quad \widehat{G}(\mathbf{x}, \mathbf{I}) = \begin{pmatrix} \beta I (1 - \frac{S}{N}) \\ 0 \end{pmatrix}.$$

Since $0 \leq S \leq N$, it is clear that $\widehat{G}(\mathbf{x}, \mathbf{I}) \geq 0$. It is also clear that $\mathbf{x}^* = (\Lambda/\mu, 0)$ is a g.a.s equilibrium of $\frac{d\mathbf{x}}{dt} = F(\mathbf{x}, 0)$. Hence, by the above theorem $\mathbf{U}_0$ is g.a.s.

If the model in Example 3 is re-written in the form of (3.1) then $\mathbf{x} = (S, T)$, $\mathbf{I} = (E_1, I_1, E_2, I_2)$, $F(\mathbf{x}, 0) = \begin{pmatrix} \Lambda - \mu S \\ 0 \end{pmatrix}$,

$$A = \begin{pmatrix} -(\mu + k_1 + r) & \beta_1 + p\tilde{r} & 0 & 0 \\ k & -(\mu + d_1 + \tilde{r}) & 0 & 0 \\ 0 & q\tilde{r} & -(\mu + k_2) & \beta_2 \\ 0 & 0 & k_2 & -(\mu + d_2) \end{pmatrix},$$

and

$$\widehat{G}(\mathbf{x}, \mathbf{I}) = \begin{pmatrix} \beta_1 I_1 (1 - \frac{S + \sigma T}{N}) + \beta_2 E_1 \frac{I_2}{N} \\ 0 \\ \beta_2 I_2 (1 - \frac{S + E_1 + T}{N}) \\ 0 \end{pmatrix}.$$

Since $\sigma \leq 1$ and $0 \leq S + \sigma T \leq S + E_1 + T \leq N$ then $\widehat{G}(\mathbf{x}, \mathbf{I}) \geq 0$. The global stability of $\mathbf{x}^* = (\Lambda/\mu, 0)$ of the system $\frac{d\mathbf{x}}{dt} = F(\mathbf{x}, 0)$ is easy to check. Hence, $\mathbf{U}_0$ is g.a.s.

The next example illustrates a case in which one of the assumptions of the theorem is violated. For this model, it was shown that a backward bifurcation occurs at $\mathcal{R}_0 = 1$, that is , it was shown that multiple endemic equilibria can exist even though $\mathcal{R}_0 < 1$. Consider the TB model with reinfection studied in Feng, Castillo-Chavez, and Capurro (2000):

$$\begin{aligned} \frac{dS}{dt} &= \Lambda - \beta S \frac{I}{N} - \mu S, \\ \frac{dE}{dt} &= \beta S \frac{I}{N} - p\beta E \frac{I}{N} - (\mu + k)E + \sigma\beta T \frac{I}{N}, \\ \frac{dI}{dt} &= p\beta E \frac{I}{N} + kE - (\mu + r + d)I, \\ \frac{dT}{dt} &= rI - \sigma\beta T \frac{I}{N} - \mu T, \\ N &= S + E + I + T. \end{aligned}$$

Here, $p\beta E \frac{I}{N}$ denotes the reinfection rate, $0 \leq p < 1$. Whenever $p = 0$ the model becomes equivalent to the model in Example 2.

If $0 < p < 1$ then $\mathbf{x} = (S, T)$, $\mathbf{I} = (E, I)$, $\mathbf{U}_0 = (S^*, T^*, E^*, I^*) = (\Lambda/\mu, 0, 0, 0,)$ and

$$\widehat{G}(\mathbf{x}, \mathbf{I}) = \begin{pmatrix} \widehat{G}_1(\mathbf{x}, \mathbf{I}) \\ \widehat{G}_2(\mathbf{x}, \mathbf{I}) \end{pmatrix} = \begin{pmatrix} \beta I (1 - \frac{S + \sigma T}{N}) + p\beta E \frac{I}{N} \\ -p\beta E \frac{I}{N} \end{pmatrix}.$$

Hence $\widehat{G}_2(\mathbf{x}, \mathbf{I}) < 0$, that is, (H2) is not satisfied. Consequently, $\mathbf{U}_0$ may not be globally asymptotic stable. It was proved in Feng, Castillo-Chavez, and Capurro (2000) that a backward bifurcation occurs at $\mathcal{R}_0 = 1$ and that two endemic equilibria can be supported as long as $\mathcal{R}_c < \mathcal{R}_0 < 1$ (where $\mathcal{R}_c$ is an appropriate positive constant).

4. Conclusions

For a long period of time $\mathcal{R}_0 < 1$ was considered the key to understanding the dynamics of epidemiological models. This view arose from the work of Lajmanovich and Yorke (1976) on gonorrhea transmission (these authors studied what appeared to be quite a general epidemiological model) and from relationship of many epidemic models to monotone systems. Recent work (beginning with Castillo-Chavez et al. (1989) and Huang et al. (1992)) showed that this was not the case. Their work arose in the context of the study of HIV/AIDS dynamics, that is from models that had to incorporate selection (differential mortality). The incorporation of differential mortality has had a dramatic impact in the field of theoretical and mathematical epidemiology (see Hadeler and Castillo-Chavez (1995) and Feng et al. (2000), for applications to HIV and TB, respectively). The theorem in the last section not only connects $\mathcal{R}_0$ to the concept of global asymptotic stability but also identifies some mathematical conditions that must be met for a transcritical bifurcation (with transfer of stability and "boring" (predictable) dynamics) to occur.

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