Further Notes on the Basic Reproduction Number

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Summary. The basic reproduction number, $\mathcal{R}_0$ is a measure of the potential for disease spread in a population. Mathematically, $\mathcal{R}_0$ is a threshold for stability of a disease-free equilibrium and is related to the peak and final size of an epidemic. The purpose of these notes is to give a precise definition and algorithm for obtaining $\mathcal{R}_0$ for a general compartmental ordinary differential equation model of disease transmission. Several examples of calculating $\mathcal{R}_0$ are included, and the epidemiological interpretation of this threshold parameter is connected to the local and global stability of a disease-free equilibrium.

1 Introduction

The *basic reproduction number*, $\mathcal{R}_0$ is defined as the expected number of secondary infections produced by an index case in a completely susceptible population [1, 8]. This number is a measure of the potential for disease spread within a population. If $\mathcal{R}_0 < 1$, then a few infected individuals introduced into a completely susceptible population will, on average, fail to replace themselves, and the disease will not spread. If, on the other hand, $\mathcal{R}_0 > 1$, then the number of infected individuals will increase with each generation and the disease will spread. Note that the basic reproduction number is a threshold parameter for invasion of a disease organism into a completely susceptible population; once the disease has begun to spread, conditions favouring spread will change and $\mathcal{R}_0$ may no longer be a good measure of disease transmission. However, in many disease transmission models, the peak prevalence of infected hosts and the final size of the epidemic are increasing functions of $\mathcal{R}_0$, making it a useful measure of spread.

Many researchers use *reproductive* in place of *reproduction* and *rate* or *ratio* in place of *number*. Convincing arguments can be made for each combination: $\mathcal{R}_0$ can be specified as either a *ratio* of *rates*, or a *number* of secondary cases per index

case. In the context of differential equation models (or, more generally, evolution equation models), $\mathcal{R}_0$ arises through dimensional analysis as a dimensionless *rate* of transmission. At the time this manuscript was being prepared, a search of the Biological Abstracts indicated that each combination was equally popular!

The purpose of this chapter is threefold:

- to give a mathematical definition of $\mathcal{R}_0$ for compartmental ordinary differential equation (ODE) models,
- to show the connection between $\mathcal{R}_0$ and the local and global asymptotic stability of an ODE model, and
- to illustrate the possible bifurcations of the solution sets of the ODE models as $\mathcal{R}_0$ passes through the threshold.

This chapter is based on the papers of Castillo-Chavez et al. [6] and van den Driessche and Watmough [18] and the book of Diekmann and Heesterbeek [8]. Results on the theory of nonnegative matrices are taken from Berman and Plemmons [3]. An excellent review of basic compartmental disease transmission models is given by Hethcote [12]. A recent review of $\mathcal{R}_0$ in a broader context is given by Heffernan et al. [11].

2 Compartmental disease transmission models

This chapter focuses on compartmental models for disease transmission. Individuals are characterized by a single, discrete state variable and are sorted into compartments based on this state. A compartment is called a *disease compartment* if the individuals therein are infected. Note that this use of the term *disease* is broader than the clinical definition and includes asymptomatic stages of infection as well as symptomatic. Suppose there are n disease compartments and m nondisease compartments, and let $x \in \mathbb{R}^n$ and $y \in \mathbb{R}^m$ be the subpopulations in each of these compartments. Further, denote by $\mathcal{F}_i$ the rate secondary infections increase the i^{th} disease compartment and by $\mathcal{V}_i$ the rate disease progression, death and recovery decrease the i^{th} compartment. The compartmental model can then be written in the following form:

$$x_i' = \mathcal{F}_i(x,y) - \mathcal{V}_i(x,y)\,, \quad i = 1,\dots,n, \tag{1a}$$

$$y_j' = g_j(x,y)\,, \quad j = 1,\dots,m, \tag{1b}$$

where $'$ denotes differentiation with respect to time. Note that the decomposition of the dynamics into $\mathcal{F}$ and $\mathcal{V}$ and the designation of compartments as infected or uninfected may not be unique; different decompositions correspond to different epidemiological interpretations of the model. The definitions of $\mathcal{F}$ and $\mathcal{V}$ used here differ slightly from those in [18].

The derivation of the basic reproduction number is based on the linearization of the ODE model about a disease-free equilibrium. The following assumptions are made to ensure the existence of this equilibrium and to ensure the model is well posed.

(A1) Assume $\mathcal{F}_i(0,y) = 0$ and $\mathcal{V}_i(0,y) = 0$ for all $y \geq 0$ and $i = 1,\ldots,n$. All new infections are secondary infections arising from infected hosts; there is no immigration of individuals into the disease compartments.

(A2) Assume $\mathcal{F}_i(x,y) \geq 0$ for all nonnegative x and y and $i = 1,\ldots,n$. The function $\mathcal{F}$ represents new infections and cannot be negative.

(A3) Assume $\mathcal{V}_i(x,y) \leq 0$ whenever $x_i = 0$, $i = 1,\ldots,n$. Each component, $\mathcal{V}_i$, represents a net outflow from compartment i and must be negative (inflow only) whenever the compartment is empty.

(A4) Assume $\sum_{i=1}^{n} \mathcal{V}_i(x,y) \geq 0$ for all nonnegative x and y. This sum represents the total outflow from all infected compartments. Terms in the model leading to increases in $\sum_{i=1}^{n} x_i$ are assumed to represent secondary infections and therefore belong in $\mathcal{F}$.

(A5) Assume the disease-free system $y' = g(0,y)$ has a unique equilibrium that is asymptotically stable. That is, all solutions with initial conditions of the form $(0,y)$ approach a point $(0,y_o)$ as $t \to \infty$. We refer to this point as the disease-free equilibrium.

Assumption (A1) ensures that the disease-free set, which consists of all points of the form $(0,y)$, is invariant. That is, any solution with no infected individuals at some point in time will be free of infection for all time. This in turn ensures that the disease-free equilibrium is also an equilibrium of the full system.

Suppose a single infected person is introduced into a population originally free of disease. The initial ability of the disease to spread through the population is determined by an examination of the linearization of (1a) about the disease-free equilibrium $(0,y_o)$. Using Assumption (A1), it can be shown that

$$\frac{\partial \mathcal{F}_i}{\partial y_j}(0,y_o) = \frac{\partial \mathcal{V}_i}{\partial y_j}(0,y_o) = 0$$

for every pair (i,j). This implies that the linearized equations for the disease compartments, x, are decoupled from the remaining equations and can be written as

$$x' = (F - V)x, \tag{2}$$

where F and V are the $n \times n$ matrices with entries

$$F = \frac{\partial \mathcal{F}_i}{\partial x_j}(0,y_o) \qquad \text{and} \qquad V = \frac{\partial \mathcal{V}_i}{\partial x_j}(0,y_o).$$

Using Assumption (A5), linear stability of the system (1) is completely determined by the linear stability of $(F - V)$ in (2); see Section 5.

3 The basic reproduction number

The number of secondary infections produced by a single infected individual can be expressed as the product of the expected duration of the infectious period and the rate secondary infections occur. For the general model with n disease compartments, these are computed for each compartment for a hypothetical index case. The expected time the index case spends in each compartment is given by the integral

$\int_0^\infty \phi(t, x_o)\, dt$, where $\phi(t, x_o)$ is the solution to (2) with $F = 0$ (no secondary infections) and nonnegative initial conditions, x_o, representing an infected index case:

$$x' = -Vx, \qquad x(0) = x_o. \tag{3}$$

In effect, this solution shows the path of the index case through the disease compartments from the initial exposure through to death or recovery with the i^{th} component of $\phi(t, x_o)$ interpreted as the probability that the index case (introduced at time $t = 0$) is in disease state i at time t. The solution to (3) is $\phi(t, x_o) = e^{-Vt}x_o$, where the exponential of a matrix is defined by the Taylor series

$$e^A = I + A + \frac{A^2}{2} + \frac{A^3}{3!} + \cdots + \frac{A^k}{k!} + \cdots$$

This series converges for all t (see, for example, [13]). Thus $\int_0^\infty \phi(t, x_o)\, dt = V^{-1}x_o$, and the (i, j) entry of the matrix V^{-1} can be interpreted as the expected time an individual initially introduced into disease compartment j spends in disease compartment i.

The (i, j) entry of the matrix F is the rate secondary infections are produced in compartment i by an index case in compartment j. Hence, the expected number of secondary infections produced by the index case is given by

$$\int_0^\infty Fe^{-Vt}x_o\, dt = FV^{-1}x_o.$$

Following Diekmann and Heesterbeek [8], the matrix $K = FV^{-1}$ is referred to as the *next generation matrix* for the system at the disease-free equilibrium. The (i, j) entry of K is the expected number of secondary infections in compartment i produced by individuals initially in compartment j, assuming, of course, that the environment seen by the individual remains homogeneous for the duration of its infection.

As we shall see in Section 5, the next generation matrix, $K = FV^{-1}$, is nonnegative and therefore has a nonnegative eigenvalue, $\mathcal{R}_0 = \rho(FV^{-1})$, such that there are no other eigenvalues of K with modulus greater than $\mathcal{R}_0$ and there is a nonnegative eigenvector ω associated with $\mathcal{R}_0$ [3, Theorem 1.3.2]. This eigenvector is in some sense the distribution of infected individuals that produces the greatest number, $\mathcal{R}_0$, of secondary infections per generation. Thus, $\mathcal{R}_0$ and the associated eigenvector ω suitably define a "typical" infective and the basic reproduction number can be rigorously defined as the spectral radius of the next generation matrix, K. The *spectral radius* of a matrix K, denoted $\rho(K)$, is the maximum of the moduli of the eigenvalues of K. If K is irreducible, then $\mathcal{R}_0$ is a simple eigenvalue of K and is strictly larger in modulus than all other eigenvalues of K. However, if K is reducible, which is often the case for diseases with multiple strains, then K may have several positive real eigenvectors corresponding to reproduction numbers for each competing strain of the disease.

4 Examples

For a given model, neither the next generation matrix, K, nor the basic reproduction number, $\mathcal{R}_0$, are uniquely defined; there may be several possible decompositions of

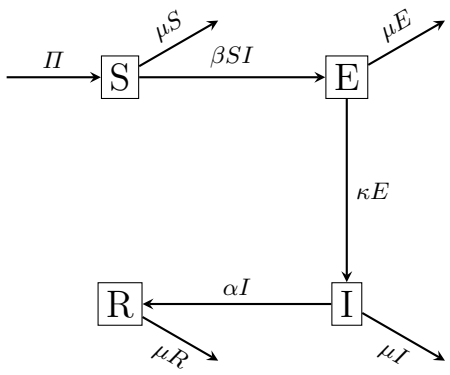

Fig. 1. Progression of infection from susceptible (S) individuals through the exposed (E), infected (I), and treated (R) compartments for the simple SEIR model.

the dynamics into the components $\mathcal{F}$ and $\mathcal{V}$ and thus many possibilities for K. Usually only a single decomposition has a realistic epidemiological interpretation. These ideas are illustrated by the following examples.

4.1 The SEIR model

In the SEIR model for a childhood disease such as measles, the population is divided into four compartments: susceptible (S), exposed and latently infected (E), infectious (I) and recovered with immunity (R). Let S, E, I and R denote the subpopulations in each compartment. The usual SEIR model is written as follows:

$$S' = \Pi - \mu S - \beta SI, \tag{4a}$$
$$E' = \beta SI - (\mu + \kappa)E, \tag{4b}$$
$$I' = \kappa E - (\mu + \alpha)I, \tag{4c}$$
$$R' = \alpha I - \mu R, \tag{4d}$$

together with nonnegative initial conditions.

The progression through the compartments is illustrated in Figure 1. New infections in compartment E arise by contacts between susceptible and infected individuals in compartments S and I at a rate βSI. Individuals progress from compartment E to I at a rate κ and develop immunity at a rate α. In addition, natural mortality claims individuals at a rate μ. For simplicity, the model assumes a constant recruitment, Π, of susceptible individuals. With incidence βSI and β constant this is commonly referred to as the mass action model. More generally, β may be taken as a function of the total population $N = S + E + I + R$.

The system has a unique disease-free equilibrium, with $S_o = \Pi/\mu$. Taking the infected compartments to be E and I gives

$$\mathcal{F} = \begin{pmatrix} \beta SI \\ 0 \end{pmatrix} \qquad \text{and} \qquad \mathcal{V} = \begin{pmatrix} (\mu+\kappa)E \\ -\kappa E + (\mu+\alpha)I \end{pmatrix}.$$

Hence,

$$F = \begin{pmatrix} 0 & \beta S_o \\ 0 & 0 \end{pmatrix},$$

$$V = \begin{pmatrix} (\mu+\kappa) & 0 \\ -\kappa & (\mu+\alpha) \end{pmatrix},$$

and the next generation matrix is

$$K = FV^{-1} = \begin{pmatrix} \dfrac{\kappa\beta S_o}{(\mu+\kappa)(\mu+\alpha)} & \dfrac{\beta S_o}{\mu+\alpha} \\ 0 & 0 \end{pmatrix}. \tag{5}$$

The (1,2) entry of K is the expected number of secondary infections produced in compartment E by an individual initially in compartment I over the course of its infection. To interpret this term, recall that βS_o is the rate of infection for our single infected individual in a population of S_o susceptible individuals, and $1/(\mu+\alpha)$ is the expected duration of the infectious period. The ratio $\kappa/(\mu+\kappa)$ is the fraction of individuals that progress from E to I. Hence, the (1,1) entry of K is the expected number of secondary infections produced in compartment E by an infected individual originally in compartment E. The eigenvalues of K are 0 and

$$\mathcal{R}_0 = \frac{\kappa\beta S_o}{(\mu+\kappa)(\mu+\alpha)}. \tag{6}$$

4.2 A variation on the basic SEIR model

In the basic SEIR model of Section 4.1, suppose that individuals in compartment E are mildly infectious and produce secondary infections at the reduced rate $\epsilon\beta SE$ with $0 < \epsilon < 1$. This gives rise to an additional nonzero entry in F, and K becomes

$$K = FV^{-1} = \begin{pmatrix} \dfrac{\epsilon\beta S_o}{\mu+\kappa} + \dfrac{\kappa\beta S_o}{(\mu+\kappa)(\mu+\alpha)} & \dfrac{\beta S_o}{\mu+\alpha} \\ 0 & 0 \end{pmatrix}. \tag{7}$$

The reproduction number is now

$$\mathcal{R}_0 = \frac{\epsilon\beta S_o}{\mu+\kappa} + \frac{\kappa\beta S_o}{(\mu+\kappa)(\mu+\alpha)}. \tag{8}$$

The two terms of $\mathcal{R}_0$ are the number of secondary infections produced by an index case initially in compartment E, just as with the model of Section 4.1. The first term is the number of secondary infections during the earlier, mildly infectious stage and the second term is the number of secondary infections during the fully infectious stage.

4.3 A simple treatment model

To illustrate the mathematical ambiguity in the choice of $\mathcal{R}_0$, consider the basic SEI model with treatment of infective individuals. Suppose infectious individuals are treated at a rate r_2, but that treatment is only partially effective: a fraction q of treated infectious individuals recover with partial immunity, and a fraction $p = 1-q$ return to a latent stage of infection. The ambiguity in $\mathcal{R}_o$ arises from the two possible interpretations of treatment failure. Treatment of latently infected individuals, at a rate r_1, is also included in the model and always results in recovery.

The dynamics of the model are illustrated in Figure 2. The model maintains the basic structure of the SEIR model of Section 4.1, but the R compartment is replaced by a compartment of treated individuals (T) and standard (rather than mass action) incidence is assumed. Since treatment confers only partial immunity, treated individuals are reinfected at a rate $\beta_2 T/N$, where $N = S + E + I + T$. The constant recruitment rate used in the previous example is generalized to a density dependent rate, but all other parameters retain their earlier interpretations. The disease transmission model consists of the following differential equations together with nonnegative initial conditions:

$$S' = b(N) - \mu S - \beta_1 SI/N, \tag{9a}$$
$$E' = \beta_1 SI/N + \beta_2 TI/N - (\mu + \kappa + r_1)E + pr_2 I, \tag{9b}$$
$$I' = \kappa E - (\mu + r_2)I, \tag{9c}$$
$$T' = -\mu T + r_1 E + qr_2 I - \beta_2 TI/N. \tag{9d}$$

This model is a caricature of the more complex models for tuberculosis proposed by Blower et al. [4] and Castillo-Chavez and Feng [5]. Further analysis and discussion can be found in those papers.

The disease compartments are E and I, as before, and treatment failure, modelled by the term $pr_2 I$ in the second equation, is interpreted as part of progression of an

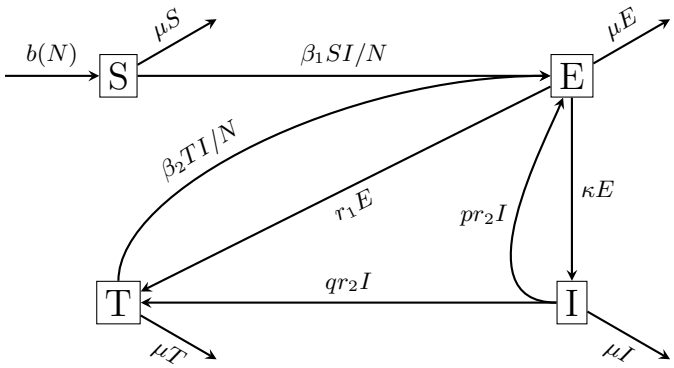

Fig. 2. Progression of infection from susceptible (S) individuals through the exposed (E), infected (I), and treated (T) compartments for the treatment model (9).

infected individual through the disease compartments, rather than a new infection. With this interpretation, $\mathcal{F}$ and $\mathcal{V}$ are as follows:

$$\mathcal{F} = \begin{pmatrix} \beta_1 SI/N + \beta_2 TI/N \\ 0 \end{pmatrix}, \qquad \mathcal{V} = \begin{pmatrix} (\mu+\kappa+r_1)E - pr_2 I \\ -\kappa E + (\mu + r_2)I \end{pmatrix}.$$

An equilibrium solution with $E = I = 0$ must have $T = 0$ and $S = S_o$, where S_o is any positive solution of $b(S_o) = \mu S_o$. This will be locally stable, and therefore a DFE, if $b'(S_o) < \mu$. Assuming this to be the case, evaluating the derivatives of $\mathcal{F}$ and $\mathcal{V}$ at $S = S_o$, $E = I = T = 0$ leads to the following expressions for F and V.

$$F = \begin{pmatrix} 0 & \beta_1 \\ 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \mu+\kappa+r_1 & -pr_2 \\ -\kappa & \mu + r_2 \end{pmatrix}.$$

As with the SEIR model, FV^{-1} has rank one, and a straightforward calculation shows the spectral radius to be

$$\mathcal{R}_C = \frac{\beta_1 \kappa}{(\mu+\kappa+r_1)(\mu+r_2) - \kappa p r_2}. \tag{10}$$

The notation $\mathcal{R}_C$ is used to denote the reproduction number with control measures in place. A heuristic derivation of $\mathcal{R}_C$ is given in [18]. Briefly, $\mathcal{R}_C$ can be written as the geometric series $(h_1 + h_1^2 h_2 + h_1^3 h_2^2 + \ldots)\beta_1/(\mu + r_2)$, where $h_1 = \kappa/(\mu+\kappa+r_1)$ is the fraction of individuals leaving compartment E who progress to compartment I, and $h_2 = pr_2/(\mu + r_2)$ is the fraction of individuals leaving compartment I who re-enter compartment E. The product $h_1^k h_2^{k-1}$ is the fraction of exposed individuals who pass through compartment I at least k times, and the sum of these products is the expected number of times an exposed individual passes through compartment I. Multiplying by $\beta_1/(\mu + r_2)$ gives $\mathcal{R}_C$, since each time an individual enters the infectious compartment I, they spend, on average, $1/(\mu + r_2)$ time units there producing, on average, $\beta_1/(\mu + r_2)$ secondary infections.

In contrast, if treatment failure is considered to be a new infection, then $\mathcal{F}$ and $\mathcal{V}$ are as follows:

$$\mathcal{F} = \begin{pmatrix} \beta_1 SI/N + \beta_2 TI/N + pr_2 I \\ \\ 0 \end{pmatrix}, \qquad \mathcal{V} = \begin{pmatrix} (\mu+\kappa+r_1)E \\ \\ -\kappa E + (\mu + r_2)I \end{pmatrix}.$$

Differentiation at the disease-free equilibrium then leads to the following expressions for F, V and the spectral radius:

$$F = \begin{pmatrix} 0 & \beta_1 + pr_2 \\ 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \mu+\kappa+r_1 & 0 \\ -\kappa & \mu + r_2 \end{pmatrix},$$

$$\rho(FV^{-1}) = \frac{\beta_1 \kappa + pr_2 \kappa}{(\mu+\kappa+r_1)(\mu+r_2)}. \tag{11}$$

Note that since $T = 0$ at the disease-free equilibrium, the reinfection term does not appear in either linearization and the choice of whether to place the $\beta_2 TI/N$ term in $\mathcal{F}$ or $\mathcal{V}$ is of little practical consequence.

Mathematically the two resulting thresholds are equivalent since the conditions $\mathcal{R}_C < 1$ from (10) and $\rho(FV^{-1}) < 1$ from (11) yield the same portion of parameter

space. The difference between the two expressions (10) and (11) lies in their epidemiological interpretation. For example, in the second interpretation, the infection rate is $\beta_1 + pr_2$ and an exposed individual is expected to spend $\kappa/((\mu+\kappa+r_1)(\mu+r_2))$ time units in compartment I. The flaw in this reasoning is that treatment failure does not give rise to a *newly infected* individual, but only changes the infection status of an already infected individual. If the conditions are used simply as threshold parameters, then the difference between the two choices does not matter. However, any analysis of the sensitivity of $\mathcal{R}_C$ to control parameters should be done on an epidemiological meaningful threshold.

4.4 A vaccination model

Consider the following SI vaccination model proposed by Gandon et al. [10].

$$\begin{aligned} S' &= (1-p)\Pi - \mu S - (\beta I + \beta_v I_v)\, S, \\ S'_v &= p\Pi - \mu S_v - (1-r)\,(\beta I + \beta_v I_v)\, S_v, \\ I' &= (\beta I + \beta_v I_v)\, S - (\mu+\nu) I, \\ I'_v &= (1-r)\,(\beta I + \beta_v I_v)\, S_v - (\mu+\nu_v) I_v. \end{aligned}$$

S, I, S_v and I_v denote the subpopulations in the unvaccinated susceptible, unvaccinated infectious, vaccinated susceptible and vaccinated infectious compartments, respectively. Susceptible individuals are recruited at a rate Π and a fraction, p, of these recruits are vaccinated immediately. Individuals leave the population at a rate μ, with additional disease-induced host mortality at the rates ν and ν_v. Vaccination of infectious individuals reduces the transmission rate from β to β_v and vaccination of susceptible individuals reduces the probability of transmission by a fraction r.

The system has a unique disease-free equilibrium, given by $S_o = (1-p)N_o$ and $S_{vo} = pN_o$, where $N_o = \Pi/\mu$. The disease compartments are I and I_v, V is the diagonal matrix

$$V = \begin{pmatrix} \mu+\nu & 0 \\ 0 & \mu+\nu_v \end{pmatrix},$$

and F is a rank one matrix that can be expressed as the product of the two vectors $\omega = \begin{pmatrix} S_o, & (1-r)S_{vo} \end{pmatrix}^T$ and $\beta = \begin{pmatrix} \beta, & \beta_v \end{pmatrix}^T$ as follows:

$$F = \omega\beta^T = \begin{pmatrix} \beta S_o & \beta_v S_o \\ (1-r)\beta S_{vo} & (1-r)\beta_v S_{vo} \end{pmatrix}. \tag{12}$$

Since F has rank one, the next generation matrix also has rank one. The spectral radius of a rank one matrix is its trace. Hence,

$$\mathcal{R}_C = \rho\left(FV^{-1}\right) = \beta^T V^{-1}\omega = \frac{\beta S_o}{\mu+\nu} + \frac{(1-r)\beta_v S_{vo}}{\mu+\nu_v}.$$

The simplest interpretation to place on this number is that it is the sum of the number of secondary infections of unvaccinated susceptible individuals produced by an index case in I and the number of secondary infections of vaccinated susceptible individuals produced by an index case in I_v. This simple interpretation is misleading.

The correct, although not immediately obvious, interpretation is that $\mathcal{R}_C$ is the number of secondary infections, both vaccinated and unvaccinated, produced by an "index case", ω, distributed in both infectious compartments, with one part in I and $(1-r)S_{vo}/S_o$ parts in I_v. Quite simply, $\mathcal{R}_C$ is the eigenvalue of K with largest modulus and ω is an associated eigenvector.

This simple vaccination model assumes the effects of the vaccine on susceptible and infectious individuals are separable, which leads to a rank one next generation matrix and a simple expression for $\mathcal{R}_C$. Replacing the four incidence parameter combinations β, β_v, $(1-r)\beta$ and $(1-r)\beta_v$, with the four parameters β_{uu}, β_{uv}, β_{vu} and β_{vv} respectively, leads to the next generation matrix

$$K = \begin{pmatrix} \dfrac{\beta_{uu}S_o}{\mu+\nu} & \dfrac{\beta_{uv}S_o}{\mu+\nu_v} \\ \dfrac{\beta_{vu}S_{ov}}{\mu+\nu} & \dfrac{\beta_{vv}S_{ov}}{\mu+\nu_v} \end{pmatrix}. \tag{13}$$

Denoting the four entries of K as $\mathcal{R}_{uu}$, $\mathcal{R}_{uv}$, $\mathcal{R}_{vu}$ and $\mathcal{R}_{vv}$, the spectral radius of K is

$$\mathcal{R}_C = \frac{\mathcal{R}_{uu}+\mathcal{R}_{vv}}{2} + \frac{1}{2}\sqrt{(\mathcal{R}_{uu}+\mathcal{R}_{vv})^2 - 4\mathcal{R}_{uu}\mathcal{R}_{vv} + 4\mathcal{R}_{uv}\mathcal{R}_{vu}}. \tag{14}$$

Although this expression defies interpretation as anything other than the spectral radius of K, the threshold condition

$$\mathcal{R}_C < 1$$

is equivalent to the pair of conditions

$$\frac{1}{2}\left(\mathcal{R}_{uu}+\mathcal{R}_{vv}\right) < 1,$$
$$\mathcal{R}_{uu}+\mathcal{R}_{vv}+\mathcal{R}_{uv}\mathcal{R}_{vu}-\mathcal{R}_{uu}\mathcal{R}_{vv} < 1.$$

Note that these conditions only hold for nonnegative matrices and differ slightly from the more general Jury conditions. Several authors [7, 14] have interpreted the left hand side of the second inequality as the reproduction number for the model. The danger in this interpretation is that the magnitude of this expression does not give any insight into the solutions of the model. As Roberts and Heesterbeek [17] point out, this distinction is important if $\mathcal{R}_C$ is used as a measure of the effectiveness of disease control measures.

4.5 A vector-host model

Some diseases, notably Dengue fever, malaria and West Nile virus, are not transmitted directly from host to host, but through a vector. The simplest vector-host model couples a simple SIS model for the hosts with an SI model for the vectors. Susceptible hosts (S_h) become infectious hosts (I_h) at a rate $\beta_h S_h I_v$ through contact with infected vectors (I_v). Similarily, susceptible vectors (S_v) become infectious vectors (I_h) at a rate $\beta_v S_v I_h$ by contacts with infected hosts. The model is given by the following equations together with nonnegative initial conditions:

$$I_h' = \beta_h S_h I_v - (\mu_h + \gamma) I_h, \tag{15a}$$
$$I_v' = \beta_v S_v I_h - \mu_v I_v, \tag{15b}$$
$$S_h' = \Pi_h - \mu_h S_h - \beta_h S_h I_v + \gamma I_h, \tag{15c}$$
$$S_v' = \Pi_v - \mu_v S_v - \beta_v S_v I_h. \tag{15d}$$

As before, μ_h and μ_v represent removal rates and Π_h and Π_v recruitment rates. The parameter γ is the recovery rate for infected hosts. Vectors are assumed to remain infected for life. This simple model forms the core of many vector-host models. More detailed analyses and discussions of vector-host models can be found in such papers as Feng and Velasco-Hernández [9] on Dengue fever, and Wonham et al. [20] on West Nile virus.

The two disease compartments are I_h and I_v. The disease-free equilibrium has host and vector populations of $S_{ho} = \Pi_h/\mu_h$ and $S_{vo} = \Pi_v/\mu_v$ respectively. Hence

$$F = \begin{pmatrix} 0 & \beta_h S_{ho} \\ \beta_v S_{vo} & 0 \end{pmatrix}, \quad V = \begin{pmatrix} (\mu_h + \gamma) & 0 \\ 0 & \mu_v \end{pmatrix}, \quad K = \begin{pmatrix} 0 & \dfrac{\beta_h S_{ho}}{\mu_v} \\ \dfrac{\beta_v S_{vo}}{\mu_h + \gamma} & 0 \end{pmatrix}.$$

The entries of K are interpreted as the number of secondary infections produced by infected vectors and hosts during the course of their infection. Note that infected hosts produce infected vectors and *vise versa*. The positive eigenvalue of K is

$$\mathcal{R}_0 = \sqrt{\frac{\beta_h \beta_v S_{ho} S_{vo}}{(\mu_h + \gamma)\mu_v}}.$$

The square root arises since it takes two generations for infected hosts to produce new infected hosts. That is

$$K^2 = \begin{pmatrix} \dfrac{\beta_h \beta_v S_{ho} S_{vo}}{(\mu_h + \gamma)\mu_v} & 0 \\ 0 & \dfrac{\beta_h \beta_v S_{ho} S_{vo}}{(\mu_h + \gamma)\mu_v} \end{pmatrix}$$

In practise, what we have given as K^2 is often taken as K and the square root is left off the reproduction number. Indeed, this was the original interpretation of MacDonald (see [1]).

4.6 A model with two strains

The reproduction number for models with multiple strains is usually the larger of the reproduction numbers for the two strains in isolation. However, many such models also posess multiple endemic equilibria, and there is a threshold similar to the basic reproduction number connected with the ability of one strain to invade and outcompete another. As a simple example, consider the special case of the n-strain SIR model of Andreasen et al. [2] given by the following system of equations together with nonnegative initial conditions:

$$S' = \Pi - \mu S - \beta_1 S(I_2 + I_{12}) - \beta_1 S(I_1 + I_{21}), \tag{16a}$$
$$I_1' = \beta_1 S(I_1 + I_{21}) - (\mu + \gamma_1) I_1, \tag{16b}$$
$$I_2' = \beta_1 S(I_2 + I_{12}) - (\mu + \gamma_2) I_2, \tag{16c}$$
$$S_1' = \gamma_1 I_1 - \sigma_1 \beta_2 S_1 (I_2 + I_{12}) - \mu S_1, \tag{16d}$$
$$S_2' = \gamma_2 I_2 - \sigma_2 \beta_1 S_2 (I_1 + I_{21}) - \mu S_2, \tag{16e}$$
$$I_{21}' = \sigma_2 \beta_1 S_2 (I_1 + I_{21}) - (\mu + \gamma_1) I_{21}, \tag{16f}$$
$$I_{12}' = \sigma_1 \beta_2 S_1 (I_2 + I_{12}) - (\mu + \gamma_2) I_{12}. \tag{16g}$$

Naive individuals (S) are infected with strain one at a rate $\beta_1(I_1 + I_{21})S$ or strain two at a rate $\beta_2(I_2 + I_{12})S$. Individuals in compartment S_1 have recovered, at rate γ_1, from an infection with strain one, with full immunity to reinfection with strain one and partial immunity, modelled by the factor σ_1, to infection with strain two. Upon infection with strain two, which occurs at a rate $\sigma_1\beta_2(I_2 + I_{12})S_1$, they enter compartment I_{12}. Thus I_{12} is the number of individuals who are currently infected with strain two and had a previous infection with strain one.

The model has four equilibria. We will only concern ourselves with two of the equilibria in this discussion. Further analysis of a more detailed model including treatment can be found in Nuno et al. [16]. Linearizing the model equations about the disease-free equilibrium, $S = S_o = \Pi/\mu$, $I_1 = S_1 = I_2 = S_2 = I_{21} = I_{12} = 0$, leads to the following expressions for F and V.

$$F = \begin{pmatrix} \beta_1 S_o & 0 & \beta_1 S_o & 0 \\ 0 & \beta_2 S_o & 0 & \beta_2 S_o \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \qquad V = \begin{pmatrix} \mu + \gamma_1 & 0 & 0 & 0 \\ 0 & \mu + \gamma_2 & 0 & 0 \\ 0 & 0 & \mu + \gamma_1 & 0 \\ 0 & 0 & 0 & \mu + \gamma_2 \end{pmatrix}.$$

The next generation matrix, $K = FV^{-1}$, and the Jacobian matrix, $(F - V)$, are reducible. The equations for the infected subpopulations decouple near the disease-free equilibrium, and K has two positive eigenvalues corresponding to the reproduction numbers for each strain:

$$\mathcal{R}_i = \frac{\beta_i S_o}{\mu + \gamma_i}, \qquad i = 1, 2. \tag{17}$$

The basic reproduction number for the system is the maximum of the two. That is,

$$\mathcal{R}_0 = \max_{i \in \{1,2\}} \mathcal{R}_i. \tag{18}$$

There is also a reproduction number associated with the strain one equilibrium, $S = \bar{S}$, $I_1 = \bar{I}_1$, $S_1 = \bar{S}_1$, $I_2 = S_2 = I_{21} = I_{12} = 0$, where

$$\bar{S} = \frac{\mu + \gamma_1}{\beta_1},$$
$$\bar{I}_1 = \frac{\Pi}{\mu + \gamma_1}\left(1 - \frac{1}{\mathcal{R}_1}\right),$$
$$\bar{S}_1 = \frac{\Pi \gamma_1}{\mu(\mu + \gamma_1)}\left(1 - \frac{1}{\mathcal{R}_1}\right).$$

Linearizing about the strain one equilibrium then gives

$$F = \begin{pmatrix} \beta_2\bar{S} & 0 & \beta_2\bar{S} \\ 0 & 0 & 0 \\ \sigma_1\beta_2\bar{S}_1 & 0 & \sigma_1\beta_2\bar{S}_1 \end{pmatrix}, \qquad V = \begin{pmatrix} \mu+\gamma_2 & 0 & 0 \\ 0 & \mu+\gamma_1 & 0 \\ 0 & 0 & \mu+\gamma_2 \end{pmatrix}.$$

These are found by considering I_2, I_{21} and I_{12} to be disease variables and S, I_1, S_1 and S_2 to be nondisease variables. Thus, the spectral radius of FV^{-1}, given by

$$\mathcal{R}_{12} = \frac{\mathcal{R}_2}{\mathcal{R}_1} + \frac{\sigma_1\gamma_1\mathcal{R}_2}{\mu+\gamma_1}\left(1 - \frac{1}{\mathcal{R}_1}\right), \tag{19}$$

is the reproduction number for strain two near the strain one equilibrium. This, of course, is only valid if $\mathcal{R}_1 > 1$. It is reasonable to assume that all parameters are positive and $0 < \sigma_1 < 1$, so that $\mathcal{R}_{12} < \mathcal{R}_2$. This implies that there is a range of values for β_2 for which strain two can invade a disease-free population, but can not invade a population in which strain one is endemic. Strain one may protect the host population from strain two.

5 $\mathcal{R}_0$ and the local stability of the disease-free equilibrium

The reproduction number for a disease is the number of secondary infections produced by an infected individual in a population of susceptible individuals. If the reproduction numbers, $\mathcal{R}_0 = \rho(FV^{-1})$, computed in the previous examples are consistent with the differential equation model, then it should follow that the disease-free equilibrium is stable if $\mathcal{R}_0 < 1$ and unstable if $\mathcal{R}_0 > 1$. This is shown through a series of lemmas.

If each entry of a matrix T is nonnegative we write $T \geq 0$ and refer to T as a *nonnegative matrix*. A matrix of the form $A = sI - B$, with $B \geq 0$, is said to have the Z sign pattern. These are matrices whose offdiagonal entries are negative or zero. If in addition, $s \geq \rho(B)$, then A is called an M-matrix. Note that in this section, I denotes an identity matrix, not a population of infectious individuals. The following lemma is a standard result from [3].

Lemma 1. *If A has the Z sign pattern, then $A^{-1} \geq 0$ if and only if A is a nonsingular M-matrix.*

From Assumptions (A1) and (A2) it follows that each entry of F is nonnegative. From Assumptions (A1) and (A3) it follows that the offdiagonal entries of V are negative or zero. Thus V has the Z sign pattern. Assumption (A4) with Assumption (A1) ensures that the column sums of V are positive or zero, which, together with the Z sign pattern, implies that V is a (possibly singular) M-matrix [3, condition M_{35} of Theorem 6.2.3]. In what follows, it is assumed that V is nonsingular. In this case, $V^{-1} \geq 0$, by Lemma 1. Hence, $K = FV^{-1}$ is also nonnegative.

Lemma 2. *If F is nonnegative and V is a nonsingular M-matrix, then $\mathcal{R}_0 = \rho(FV^{-1}) < 1$ if and only if all eigenvalues of $(F - V)$ have negative real parts.*

Proof. Suppose $F \geq 0$ and V is a nonsingular M-matrix. By the proof of Lemma 1, $V^{-1} \geq 0$. Thus, $(I - FV^{-1})$ has the Z sign pattern, and by Lemma 1, $(I - FV^{-1})^{-1} \geq 0$ if and only if $\rho(FV^{-1}) < 1$. From the equalities $(V - F)^{-1} = V^{-1}(I - FV^{-1})^{-1}$ and $V(V - F)^{-1} = I + F(V - F)^{-1}$, it follows that $(V - F)^{-1} \geq 0$ if and only if $(I - FV^{-1})^{-1} \geq 0$. Finally, $(V - F)$ has the Z sign pattern, so by Lemma 1, $(V - F)^{-1} \geq 0$ if and only if $(V - F)$ is a nonsingular M-matrix. Since the eigenvalues of a nonsingular M-matrix all have positive real parts, this completes the proof. □

Theorem 1. *Consider the disease transmission model given by (1). The disease-free equilibrium of (1) is locally asymptotically stable if $\mathcal{R}_0 < 1$, but unstable if $\mathcal{R}_0 > 1$, where $\mathcal{R}_0$ is defined as in Section 3.*

Proof. Let F and V be as defined in Section 2, and let J_{21} and J_{22} be the matrices of partial derivatives of g with respect to x and y evaluated at the disease-free equilibrium. The Jacobian matrix for the linearization of the system about the disease-free equilibrium has the block structure

$$J = \begin{pmatrix} F - V & 0 \\ J_{21} & J_{22} \end{pmatrix}.$$

The disease-free equilibrium is locally asymptotically stable if the eigenvalues of the Jacobian matrix all have negative real parts. Since the eigenvalues of J are those of $(F - V)$ and J_{22}, and the latter all have negative real parts by Assumption (A5), the disease-free equilibrium is locally asymptotically stable if all eigenvalues of $(F - V)$ have negative real parts. By the assumptions on $\mathcal{F}$ and $\mathcal{V}$, F is nonnegative and V is a nonsingular M-matrix. Hence, by Lemma 2 all eigenvalues of $(F - V)$ have negative real parts if and only if $\rho(FV^{-1}) < 1$. It follows that the disease-free equilibrium is locally asymptotically if $\mathcal{R}_0 = \rho(FV^{-1}) < 1$.

Instability for $\mathcal{R}_0 > 1$ can be established by a continuity argument. If $\mathcal{R}_0 \leq 1$, then for any $\epsilon > 0$, $((1 + \epsilon)I - FV^{-1})$ is a nonsingular M matrix and, by Lemma 1, $((1 + \epsilon)I - FV^{-1})^{-1} \geq 0$. By the proof of Lemma 2, all eigenvalues of $((1 + \epsilon)V - F)$ have positive real parts. Since $\epsilon > 0$ is arbitrary, and eigenvalues are continuous functions of the entries of the matrix, it follows that all eigenvalues of $(V - F)$ have nonnegative real parts. To reverse the argument, suppose all the eigenvalues of $(V - F)$ have nonnegative real parts. For any positive ϵ, $(V + \epsilon I - F)$ is a nonsingular M-matrix, and by the proof of Lemma 2, $\rho(F(V + \epsilon I)^{-1}) < 1$. Again, since $\epsilon > 0$ is arbitrary, it follows that $\rho(FV^{-1}) \leq 1$. Thus, $(F - V)$ has at least one eigenvalue with positive real part if and only if $\rho(FV^{-1}) > 1$, and the disease-free equilibrium is unstable whenever $\mathcal{R}_0 > 1$. □

6 $\mathcal{R}_0$ and global stability of the disease-free equilibrium

The change of local stability at the threshold $\mathcal{R}_0 = 1$, corresponds to a transcritical bifurcation in the solutions to (1). It can be shown that there is a branch of endemic equilibria emanating from the bifurcation point at $\mathcal{R}_0 = 1$, $(x, y) = (x_o, y_o)$. For an introduction to the general theory of these bifurcations in the context of differential equations, see Wiggins [19].

For the simple example of Section 4.1, there is an equilibrium with

$$
\begin{aligned}
S_e &= \frac{S_o}{\mathcal{R}_0}, \\
I_e &= \frac{\Pi\kappa}{(\mu+\alpha)(\mu+\kappa)}\left(1-\frac{1}{\mathcal{R}_0}\right), \\
E_e &= \frac{(\mu+\alpha)I_e}{\kappa}, \\
R_e &= \frac{\alpha I_e}{\mu},
\end{aligned}
$$

defined for $\mathcal{R}_0 > 1$. Since the endemic equilibria only exist for $\mathcal{R}_0 > 1$, the bifurcation is said to be in the forward direction, and the disease-free equilibrium is the only equilibrium of the system when $\mathcal{R}_0 < 1$. In models for which endemic equilibria exist near the disease-free equilibrium for $\mathcal{R}_0 < 1$ the bifurcation is called a backward bifurcation.

Castillo-Chavez et al.[6] use a comparison theorem to derive sufficient conditions for the global asymptotic stability of the disease-free equilibrium of a general disease transmission model when $\mathcal{R}_0 < 1$. Clearly, in the case of a backward bifurcation this equilibrium can not be globally asymptotically stable whenever $\mathcal{R}_0 < 1$. In most models, however, one expects a second threshold for global stability. A slight change to the argument of [6] gives a sufficient condition for global stability in this case as well.

Consider the disease transmission model (1) written in the form

$$x' = -Ax - \hat{f}(x,y), \tag{20a}$$
$$y' = g(x,y). \tag{20b}$$

Theorem 2. *If A is a nonsingular M-matrix and $\hat{f} \geq 0$, then the disease-free equilibrium of (20) is globally asymptotically stable.*

Proof. Integrating (20a) leads to

$$x(t) = e^{-tA}x(0) - \int_0^t e^{-(t-s)A}\hat{f}(x(s),y(s))\,ds. \tag{21}$$

It can be shown that $e^{-tA} \geq 0$ whenever A is an M-matrix. Since solutions of (20) remain nonnegative, it follows that

$$0 \leq x(t) \leq e^{-tA}x(0). \tag{22}$$

Finally, since $e^{-tA} \to 0$ as $t \to \infty$, it follows that $x(t) \to 0$ as $t \to \infty$. □

For the SEIR model of Section 4.1, take $A = V - F$ and write (4) as follows

$$x' = -(V-F)x - \begin{pmatrix} \beta(S_o - S)I \\ 0 \end{pmatrix}, \tag{23a}$$
$$S' = \Pi - \mu S - \beta SI, \tag{23b}$$
$$R' = \alpha I - \mu R. \tag{23c}$$

From the previous section, we know that $(V-F)$ is a nonsingular M-matrix whenever $\mathcal{R}_0 < 1$. Hence, to show that the disease-free equilibrium is globally asymptotically stable for $\mathcal{R}_0 < 1$, it is sufficient to show that $S \leq S_o$. The total population $N =$

$S + E + I + R$ satisfies $N' = \Pi - \mu N$, so that $N(t) = S_o - (S_o - N(0))\, e^{-\mu t}$, with $S_o = \Pi/\mu$. If $N(0) \leq S_o$, then $S(t) \leq N(t) \leq S_o$ for all time. If, on the other hand, $N(0) > S_o$, then $N(t)$ decays exponentially to S_o, and either $S(t) \to S_o$, or there is some time T after which $S(t) < S_o$. Thus, from time T onward, $x(t)$ is bounded above, in each component, by $e^{-(t-T)(V-F)}x(T)$, which decays exponentially to zero. Note that for the argument of global stability we are not concerned with the size of $x(T)$. In fact, if $N(0) > S_o$, $x(T)$ may be much larger than $x(0)$. In this case the exponential bound on $x(t)$ concerns a decay following an epidemic, not an immediate elimination of the disease. In contrast, if $N(0) < S_o$, then the bound on $x(t)$ is $e^{-(t-T)(V-F)}x(0)$, and no epidemic occurs.

A simple model with a backward bifurcation is the vaccination model proposed by Kribs-Zaleta and Velasco-Hernández [15].

$$S' = \Pi - (\mu + \xi)S + \theta S_v - \beta SI + \gamma I, \tag{24a}$$

$$S_v^{'} = \xi S - (\mu + \theta)S_v - \beta(1 - r)S_v I, \tag{24b}$$

$$I' = \beta(S + (1 - r)S_v)I - (\gamma + \mu)I. \tag{24c}$$

As with the model of Section 4.4, vaccination reduces the force of infection by a factor r. However, in this model, susceptible individuals are vaccinated continuously at a rate ξ, and the protection aquired from vaccination wanes at a rate θ. Additionally, individuals recover from infection with no immunity, regardless of their vaccination history. The model has a unique disease-free equilibrium, where $S_o = (1-p)N_o$ and $S_{vo} = pN_o$ with $N_o = \Pi/\mu$ and $p = \xi/(\mu+\theta+\xi)$. In keeping with the conventions of the literature, we denote by $\mathcal{R}_0$, the basic reproduction number in the absence of vaccination, and by $\mathcal{R}_C$, the control reproduction number, or the basic reproduction number in the presence of vaccination. For the model above we have

$$\mathcal{R}_0 = \frac{\beta N_o}{\gamma + \mu},$$

$$\mathcal{R}_C = \frac{\beta\,(S_o + (1 - r)S_{vo})}{\gamma + \mu} < \mathcal{R}_0.$$

The disease-free equilibrium is locally asymptotically stable if $\mathcal{R}_C < 1$ and unstable if $\mathcal{R}_C > 1$.

Equation (24c) can be written as

$$I' = (\gamma + \mu)(\mathcal{R}_0 - 1)I - \beta\big(No - S - (1 - r)S_v\big)I. \tag{25}$$

The matrix A in this example is simply $(\gamma+\mu)(1-\mathcal{R}_0)$. As with our previous example, we can assume that $S+S_v \leq N_o$, since N approaches N_o asymptotically. Hence, the second term in the above equation eventually becomes and remains negative and the disease-free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1$.

The disease-free equilibrium may be locally asymptotically stable, but not globally asymptotically stable if $\mathcal{R}_C < 1 < \mathcal{R}_0$. It is known that there may be multiple endemic equilibria for parameter values in this range; further details can be found in Kribs-Zaleta and Velasco-Hernández [15].

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