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The Dynamics of Vector-Borne Relapsing Diseases

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THE DYNAMICS OF VECTOR-BORNE RELAPSING DISEASES

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The Dynamics of Vector-Borne Relapsing Diseases

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We begin this dissertation with a review of the relevant history and theory behind disease modeling, investigating important motivating examples. The concept of the fundamental reproductive ratio of a disease, R_0, is introduced through these examples. The compartmental theory of disease spread and its results are introduced, particularly the next-generation method of computing R_0. We review center manifold theory, as it is critical to the reduction of the dimension of our problems. We review diseases that have a relapsing character and focus in on relapsing diseases that are spread by vectors in a host population. The primary example of such a disease is Tick-Borne Relapsing Fever (TBRF). Motivated by TBRF we establish a general model for the spread of a vector-borne relapsing disease. We then compare our model to current literature.

With a model in hand we confirm that it meets the required hypotheses for the use of compartmental theory. A technical computation then leads to an explicit form of R_0 that is given in terms of the number of relapses. Further technical computations then allow us to describe the bifurcation at $R_0 = 1$, finding that it is always transcritical regardless of the number of relapses. We also show the existence of a unique endemic equilibrium for all values of R_0 greater than 1.

Variations of the simple model are explored. Adding in removal to the recovered compartment, in which individuals leave an earlier relapse state and recover, we find how this changes R_0 and show that the bifurcation at R_0 is still transcritical. We investigate the addition of latent infective compartments and describe how they affect R_0. We also find the reproductive ratio when there are two host species that undergo the same number of relapses.

We establish a continuity result between the reproductive ratios of systems with differing numbers of compartments. This allows us to state the reproductive ratio of a smaller system as a limit of the reproductive ratio of a larger system. This result is then used to compute the reproductive ratio for a coupled host-vector system where the hosts undergo a different number of relapses. We close with some conclusions and directions for future work.

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Introduction

1.1 A Brief History of Disease Modeling

The first use of calculus to describe the spread of disease was by Daniel Bernoulli in 1760. Using calculus techniques he argued that inoculation against smallpox is something the State should promote to the people. D'Alembert would criticize Bernoulli's assumptions, and suggest that insufficient data was available to determine whether inoculation increased life expectancy [3].

As scientists learned more about the mechanics of disease spread they began to ask what contributions a mathematical model could make to their understanding and treatment of diseases. In 1911 Ronald Ross, a British doctor, wrote *The Prevention of Malaria* which looked at the steady states of a set of ODEs that only considered the number of infected mosquitoes and the number of infected individuals. Ross' goal was to mathematically establish his claim that malaria could be "... eradicated simply by reducing the number of mosquitoes" [3, p.66]. Ross discovered that in a steady state the number of infected humans I and infected mosquitoes i would only be positive in the case that the total number of mosquitoes n satisfied

the inequality

$$n > \frac{amN}{b^2pp'}.$$

Where a is the rate at which humans recover from malaria, m is mosquito mortality, N is the total human population, b is the biting rate, p is the probability of transmission from human to mosquito, and p' is the probability of transmission from mosquito to human. The existence of such a threshold gave credence to Ross' theory; by making n sufficiently small this inequality cannot hold. Finding such thresholds is now a standard problem in mathematical epidemiology.

SIR Models and R_0

The first person to investigate disease models which included the susceptible, recovered, and infected individuals was A.G. McKendrick. In 1926 he published an article entitled "Applications of mathematics to medical problems" in which he introduced a continuous time model for epidemics. A population of size N was considered, and the members of that population fell into one of three categories *susceptible* S, *infected* I, and *recovered* R, and members flowed from one compartment to another:

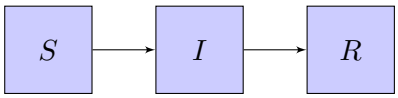

Figure 1.1.1: McKendrick's compartments.

McKendrick then focused on computing the probability that epidemic would end after infecting n people. Starting in 1927 McKendrick began collaborating with W.O. Kermack, who three years earlier had been blinded in a laboratory explosion. They published a series of papers called *Contributions to the mathematical theory of epidemics* where they did not seek to answer probabilistic questions, but instead studied deterministic models. The simplified

form of their model is

$$\begin{aligned} \frac{dS}{dt} &= -aSI, \\ \frac{dI}{dt} &= aSI - bI, \\ \frac{dR}{dt} &= bI. \end{aligned} \tag{1.1}$$

A natural assumption is that $S(0) > 0$, $I \geq 0$, and $R(0) = 0$. The following is informal; complete discussion see is found in [3]. The total population $N(t) = S(t) + I(t) + R(t)$ is constant since

$$\frac{dN}{dt} = \frac{d}{dt}(S + I + R) = S' + I' + R' = -aSI + aSI - bI + bI = 0.$$

Since $a, b \geq 0$, S is decreasing, and R is increasing. The constant population then implies that there must be a lower bound for S (S_∞) and an upper bound for R (R_∞) as $t \to \infty$. These limits imply that I also has a limit, I_∞. Rewrite the first equation of (1.1) as

$$\frac{S'}{S} = -aI \Rightarrow \frac{d}{dt}(\ln(S)) = -aI,$$

and integrate from 0 to ∞:

$$\ln(S_\infty) - \ln(S_0) = -a\int_0^\infty I\,dt \Rightarrow -\ln\left(\frac{S_\infty}{S_0}\right) = a\int_0^\infty I\,dt,$$

where $S_0 = S(0)$. Rewriting the second equation of (1.1), we have

$$\frac{dI}{dt} = -\frac{dS}{dt} - bI.$$

Again integrating we obtain:

$$I_\infty - I_0 = S_0 - S_\infty - b\int_0^\infty I\,dt \Rightarrow \frac{(S_0 + I + 0) - (I_\infty + S_\infty)}{b} = \int_0^\infty I\,dt.$$

Since $S_0 + I + 0 = N - R_0 = N$ and $S_\infty + I_\infty = N - R_\infty$, we have

$$\int_0^\infty I\,dt = \frac{N - (N - R_\infty)}{b} = \frac{R_\infty}{b},$$

and so,

$$-\ln\left(\frac{S_\infty}{S_0}\right) = \frac{a}{b}\,R_\infty. \tag{1.2}$$

Suppose $I_\infty \neq 0$, then $\displaystyle\int_0^\infty Idt \propto R_\infty$ implies $R_\infty = \infty$, which is impossible. Hence, $I_\infty = 0$ and so, $R_\infty = N - S_\infty$. Substitution of this into the above equation gives an implicit solution for S_∞. Since the initial number of infections tends to be small, we say $S_0 \approx N$ and then

$$-\ln\left(\frac{S_\infty}{S_0}\right) \approx -\ln\left(\frac{S_\infty}{N}\right) = -\ln\left(\frac{N - R_\infty}{N}\right). \tag{1.3}$$

Using (1.2):

$$-\ln\left(\frac{N - R_\infty}{N}\right) \approx \frac{a}{b}R_\infty = \frac{aN}{b}\frac{R_\infty}{N}.$$

Replacing $\approx$ with $=$, we find when solutions of this equation exist. Letting $x = \dfrac{R_\infty}{N}$ the equation becomes

$$-\ln(1 - x) = \left(\frac{aN}{b}\right)x.$$

The graphs of these functions intersect at $x = 0$. Taking the derivative of the left hand side gives $\dfrac{1}{1-x}$, and we see that $-\ln(1-x)$ has a slope larger than 1 for positive x and is increasing as $x \to 1$. Hence the only way the curves represented by the right hand side and the left hand side of the above equation can intersect is if $\dfrac{aN}{b}$ is strictly larger than 1, else the graph of the right hand side lies below $-\ln(1-x)$ for $0 < x < 1$. If $\dfrac{aN}{b}$ is less than 1, then no R_∞ can exist that satisfies (1.3).

Computations like these led McKendrick and Kermack to the conclusion that no epidemic could occur unless $\frac{aN}{b}$ took values larger then 1. aN is the number of people that a single infected individual will infect in a single unit of time and $\frac{1}{b}$ is the average length of time an individual stays infected. Thus $\frac{aN}{b}$ will be the total number of individuals infected by a single infected individual while they carry the disease. This value is generally called R_0 in disease modeling. McKendrick and Kermack would develop several variations of this model for disease spread that took other factors into account, e.g., they discussed how the amount of time an individual is infected affects the infectiousness of that individual.

This concept of R_0 was not new. It was researched by several others including Ross in his work on malaria [13]. It is generally known as the *basic reproductive ratio* or *the basic reproduction number*. In disease modeling it represents the threshold at which invasion of the susceptible population is possible, and in many models there are important values that are functions of R_0 (see p. 160 in [1]), e.g. the final size of the epidemic. What follows is the theory needed to give R_0 a precise mathematical definition.

1.2 Compartmental Models

Compartmental models are an extension of McKendrick and Kermack's SIR model. Given here is a brief description of these models, following their development in [21]. Suppose a population can be separated into n homogeneous compartments and the number of members in each compartment will be represented by the vector $\boldsymbol{x} \in \mathbb{R}^n$ where the first m compartments represent infected states while the remaining $n - m$ compartments are uninfected states. It is natural to insist that $\boldsymbol{x} \geq \mathbf{0}$ (inequality is taken componentwise) since we are dealing with populations. Let $\boldsymbol{X}_s = \{\boldsymbol{x} \geq \mathbf{0} : x_i = 0, i = 1, \dots m\}$ be the set of disease free states. Let $\mathcal{F}_i(\boldsymbol{x})$ be the number of new infections in compartment i (autonomy is assumed). $\mathcal{V}_i^+(\boldsymbol{x})$ is the rate of transfer of individuals into compartment i and $\mathcal{V}_i^-(\boldsymbol{x})$ is the rate of transfer out

of compartment i. Assume that these functions are at least twice continuously differentiable. The disease transmission model can be written as

$$\dot{x}_i = f_i(\boldsymbol{x}) = \mathcal{F}_i(\boldsymbol{x}) + \mathcal{V}_i^+(\boldsymbol{x}) - \mathcal{V}_i^-(\boldsymbol{x}) \qquad i = 1, \dots n. \tag{1.4}$$

There are five conditions associated with compartmental models.

Condition 1.

$$\boldsymbol{x} \geq 0 \Rightarrow \mathcal{F}_i, \mathcal{V}_i^+, \mathcal{V}_i^- \geq 0. \tag{1.5}$$

This is natural to assume since these functions represent a transfer of individuals between compartments.

Condition 2.

$$x_i = 0 \Rightarrow \mathcal{V}_i(\boldsymbol{x}) = 0. \tag{1.6}$$

This condition requires that no individuals can transfer out of an empty compartment. In particular, if we are in $\boldsymbol{X}_s$ then we have $\mathcal{V}_i = 0$ for $i = 1, 2, \dots m$. These two conditions are sufficient to prove that solutions of the ODE will remain nonnegative when the initial conditions are nonnegative [21, p.31].

Condition 3.

$$\mathcal{F}_i = 0 \textit{ for } i > m. \tag{1.7}$$

Hence, there are no new infections in the non-infected compartments.

Condition 4.

$$\boldsymbol{x} \in \boldsymbol{X}_s \Rightarrow \mathcal{F}_i(\boldsymbol{x}) = 0 \textit{ and } \mathcal{V}_i^+(\boldsymbol{x}) = 0 \textit{ for } i = 1, \dots, m. \tag{1.8}$$

In disease free states there are no new infections and no individuals are transferred into infected compartments. Let $\boldsymbol{x_0} \in \boldsymbol{X}_s$ be a fixed point of (1.4). Such points are called Disease

Free Equilibria (DFE). Compartmental models require DFE to be stable in the absence of infection.

Condition 5. *If* $\mathcal{F}(\boldsymbol{x}) = (\mathcal{F}_1(\boldsymbol{x}), \ldots, \mathcal{F}_n(\boldsymbol{x}))^T$, *then*

$$\mathcal{F}(\boldsymbol{x}) \equiv \mathbf{0} \Rightarrow \quad \textit{The DFE is stable.} \tag{1.9}$$

Let $\mathcal{V}_i = \mathcal{V}_i^- - \mathcal{V}_i^+$ and $\mathcal{V} = (\mathcal{V}_1, \ldots, \mathcal{V}_n)^T$ then $f = \mathcal{F} - \mathcal{V}$. From the above conditions we can show

$$Df(\boldsymbol{x}_0) = D\mathcal{F}(\boldsymbol{x}_0) - D\mathcal{V}(\boldsymbol{x}_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix} - \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}.$$

Also, the $n \times n$ matrix F is nonnegative, the $n \times n$ matrix V is nonsingular and J_4 has eigenvalues with positive real parts. The matrix FV^{-1} is known as *the next generation matrix.*

To motivate our interest in this matrix consider the linearization of (1.4) about $\boldsymbol{x}_0$ with no new infections,

$$\dot{\boldsymbol{x}} = -D\mathcal{V}(\boldsymbol{x}_0)(\boldsymbol{x} - \boldsymbol{x}_0),$$

and add in a small number of infected individuals $\phi(0) = (\phi_1(0), \ldots, \phi_m(0))^T$. Reducing to only the infected compartments we have:

$$\phi' = -V\phi,$$

which has solution $\phi(t) = e^{-Vt}\phi(0)$. The new infections created by these individuals at a given time is given by $F\phi(t)$. The total number of new infections produced by these individuals is

$$\int_0^\infty F\phi(t)\, dt = \int_0^\infty Fe^{-Vt}\phi(0)\, dt = -FV^{-1}e^{-Vt}\phi(0)\, dt\Big|_0^\infty = FV^{-1}\phi(0).$$

We can now interpret the entries of $FV^{-1} = (a_{ik})$. We can compute the total number of new infections from a single individual in the kth compartment by setting $\phi(0) = (0, \ldots, 0, 1, 0, \ldots 0)$,

where the 1 is in the kth position, and evaluating

$$FV^{-1}\phi(0) = \begin{pmatrix} a_{1k} \\ \vdots \\ a_{mk} \end{pmatrix}.$$

Thus a_{ik} is the number of new infections in the ith compartment by an infected individual in the kth compartment. $\phi(0)$ infected individuals lead to $FV^{-1}\phi(0)$ total infected individuals. These newly infected will produce another generation of infected individuals resulting in $(FV^{-1})^2\phi(0)$ total individuals. This is why FV^{-1} is known as the *next generation matrix*. At the kth generation there are $(FV^{-1})^k\phi(0)$ total infected individuals. If we want the disease to be removed from the population for arbitrary initial conditions we need

$$\lim_{k\to\infty}(FV^{-1})^k = 0.$$

By Fact 9.8.4 of [5] this happens when the maximum absolute value of the eigenvalues of FV^{-1} (the spectral radius) is strictly less than one. This motivates the definition $R_0 = \rho(FV^{-1})$, where ρ is the spectral radius. It should be noted that R_0 is defined with respect to a particular DFE.

We have motivated the definition, but we have not established anything about the stability of the DFE for various values of R_0. The following is Theorem 2 of [21].

Theorem 1.2.1. *If a system* (1.4) *with a DFE* $\boldsymbol{x}_0$ *satisfies Conditions 1-5, then* $\boldsymbol{x}_0$ *is asymptotically stable if* $\rho(FV^{-1}) < 1$ *and unstable if* $\rho(FV^{-1}) > 1$.

1.3 Center Manifold Theory

A large amount of material has been written on 1 dimensional and 2 dimensional systems of ODEs. Compartmental models can be very large and so it is desirable to attempt to reduce the dimension of the system to 1 or 2 dimensions in order to take advantage of well known results. One method in achieving this is center manifold theory which is introduced here, following [6].

Consider a linear system of ODEs $\dot{\boldsymbol{x}} = A\boldsymbol{x}$, when $A \in \mathbb{R}^{n\times n}$. It is clear that the origin is a fixed point of this system. The stability of this fixed point is determined by the eigenvalues of A. In particular, if all the eigenvalues have negative real parts, it is stable, and if there is an eigenvalue that has a positive real part it is unstable. The generalized eigenspaces corresponding to these eigenvalues are invariant subspaces of the system, and solutions on these manifolds have simple stable-unstable exponential behavior. The generalized eigenspaces corresponding to the negative real part eigenvalues are called the stable subspace E^s, and the generalized eigenspaces corresponding to the positive real part eigenvalues are called the unstable subspace E^u. However, when there is an eigenvalue with zero real part, we get an invariant manifold E^c, which is the generalized eigenspaces corresponding to the zero real part eigenvalues. The general behavior of solutions on E^c is not prescribed as in E^u and E^s. But since the linear system is completely integrable the behavior on E^c is easily found by examining the solution.

Now consider a system of nonlinear ODEs

$$\begin{aligned} \dot{\boldsymbol{x}} &= A\boldsymbol{x} + f(\boldsymbol{x}, \boldsymbol{y}), \\ \dot{\boldsymbol{y}} &= B\boldsymbol{y} + g(\boldsymbol{x}, \boldsymbol{y}), \end{aligned} \tag{1.10}$$

where $\boldsymbol{x} \in \mathbb{R}^c$, $\boldsymbol{y} \in \mathbb{R}^s$ and f and g are r times differentiable. With a suitable change of basis and translation (1.1C of [24]) we can assume, without loss of generality, that in a neighborhood

of the origin

$$f(\mathbf{0},\mathbf{0}) = g(\mathbf{0},\mathbf{0}) = 0 \text{ and } Df(\mathbf{0},\mathbf{0}) = \mathbf{0}_{c\times c}, Dg(\mathbf{0},\mathbf{0}) = \mathbf{0}_{s\times s},$$

and that the eigenvalues of A all have zero real part, and the eigenvalues of B have all negative real part (one can add in a matrix with eigenvalues with positive real part and get the same results, they seem to be left out of the literature for convenience's sake).

If $c = 0$ then the origin becomes a *hyperbolic fixed point*, and we can take advantage of the Hartman-Grobman Theorem [17], which states that in the behavior of the solutions in a neighborhood of the origin matches the behavior of the linearization, making the qualitative analysis relatively easy.

When $c > 0$, we will need other methods to determine the behavior of the solutions near the fixed point. To this end, we define a *center manifold*:

Definition 1.3.1. *Let $h : \mathbb{R}^c \to \mathbb{R}^s$ be C^1 with $h(\mathbf{0}) = 0$, and $Dh(\mathbf{0}) = \mathbf{0}_{s\times c}$. Suppose there is a $\delta > 0$ such that*

$$W^c = \{(\boldsymbol{x},\boldsymbol{y}) : |\boldsymbol{x}| < \delta, \boldsymbol{y} = h(\boldsymbol{x})\},$$

is an invariant manifold of (1.10)*. Then we say that W^c is a local center manifold.*

The first result, as you might expect, is related to the existence of such a manifold.

Theorem 1.3.2. (1.10) *has a center manifold, with $h \in C^r$.*

This is proved in [6], Theorem 1. The proof is an application of the Fixed Point Theorem for contraction maps and Gronwall's inequality. The existence of the center manifold then characterizes the dynamics restricted to W^c as satisfying the reduced system

$$\dot{\boldsymbol{u}} = A\boldsymbol{u} + f(\boldsymbol{u}, h(\boldsymbol{u})), \quad \boldsymbol{u} \in \mathbb{R}^c. \tag{1.11}$$

If we know how $\boldsymbol{u}$ behaves, we can use $\boldsymbol{y} = h(\boldsymbol{u})$ to find how $\boldsymbol{y}$ behaves on the center manifold. When c is small, say 1 or 2, the dynamics on the center manifold are quite tractable. Theorem 2 of [6] tells us to what extent the dynamics of (1.11) govern the dynamics of (1.10) near the fixed point:

Theorem 1.3.3. *(a) If* $\mathbf{0}$ *is a stable (asymptotically stable) (unstable) fixed point of* (1.11)*, then* $(\mathbf{0}, \mathbf{0})$ *is a stable (asymptotically stable) (unstable) fixed point of* (1.10)*.*

The unstable case is trivially true since instability on the manifold implies instability in the whole system. When the origin is stable, we can estimate the solutions of (1.10) using the solution of (1.11)

Theorem 1.3.3. *(b) Let* $(\boldsymbol{x}(t), \boldsymbol{y}(t))$ *be a solution of* (1.10)*, with* $(\boldsymbol{x}(0), \boldsymbol{y}(0))$ *sufficiently close to the origin. Then there is a solution* $\boldsymbol{u}(t)$ *of* (1.11) *such that*

$$\boldsymbol{x}(t) = \boldsymbol{u}(t) + \mathcal{O}(e^{-\gamma t}),$$

$$\boldsymbol{y}(t) = h(\boldsymbol{u}(t)) + \mathcal{O}(e^{-\gamma t})$$

as $t \to \infty$*, where* $\gamma > 0$ *depends only on the matrix* B*.*

The practical content of these theorems is straightforward: We can determine the stability of a nonhyperbolic fixed point by merely finding the stability of the fixed point on the center manifold. This leads to a significant dimension reduction of the problem. However, this comes at quite a cost: finding the function h. We cannot solve the system (1.11) unless we know something about h, but h is the fixed point of a contraction map, and thus is not constructed explicitly in the proof of the existence theorem for center manifolds. [24] suggests an approach for finding h analytically: since $\boldsymbol{y} = h(\boldsymbol{x})$ on W^c, differentiate with respect to time to get $\dot{\boldsymbol{y}} = Dh(\boldsymbol{x})\dot{\boldsymbol{x}}$. Using (1.10) we then get that $B\boldsymbol{y} + g(\boldsymbol{x}, \boldsymbol{y}) = Dh(\boldsymbol{x})(A\boldsymbol{x} + f(\boldsymbol{x}, \boldsymbol{y}))$. Using the

fact that we are on W^c gives

$$Bh(\boldsymbol{x}) + g(\boldsymbol{x}, h(\boldsymbol{x})) = Dh(\boldsymbol{x})(A\boldsymbol{x} + f(\boldsymbol{x}, h(\boldsymbol{x})).$$

This is a PDE that could be solved in h. However, we have now made the problem of finding h more difficult than finding solutions to (1.10).

The solution to this dilemma comes in the form of approximation. Define an operator on C^1 functions $\phi : \mathbb{R}^c \to \mathbb{R}^s$ by

$$M\phi = D\phi(\boldsymbol{x})(A\boldsymbol{x} + f(\boldsymbol{x}, \phi(\boldsymbol{x})) - B\phi(\boldsymbol{x}) - g(\boldsymbol{x}, \phi(\boldsymbol{x})).$$

Then Theorem 3 of [6] says

Theorem 1.3.4. *If $\phi(\mathbf{0}) = 0$, $D\phi(\mathbf{0}) = \mathbf{0}_{s\times c}$, and there is a $q > 1$ such that $M\phi = \mathcal{O}(|\boldsymbol{x}|^q)$ as $\boldsymbol{x} \to \mathbf{0}$, then*

$$|h(\boldsymbol{x}) - \phi(\boldsymbol{x})| = \mathcal{O}(|\boldsymbol{x}|^q)$$

as $\boldsymbol{x} \to \mathbf{0}$.

So then, finding approximate polynomial solutions to $M\phi = 0$ (which is not too difficult with undetermined coefficients; see [24]) gives approximations of h to the same order.

Center manifolds need not be unique. In fact some systems have uncountably many center manifolds through a fixed point. However, there are some important properties that are necessarily captured by every center manifold. Of particular importance to us will be fixed points. First note that any fixed point $\boldsymbol{x}_0$ of (1.11) produces a fixed point of (1.10) $(\boldsymbol{x}_0, h(\boldsymbol{x}_0))$, meaning that if we can prove that a fixed point exists in the reduced system, there must also be a fixed point in the original system. If there is another fixed point of (1.10) sufficiently close to the origin, it must be contained in every center manifold about the origin, which means we do not have to worry about choosing the correct manifold about the origin to study

the stability of a fixed point near the origin [6]. The final thing to note here is that we have described the center manifold when the system is transformed into (1.10), but since invariant manifolds persist under linear transformations and translations we can change the system back into its original coordinates and W^c will still exist and be tangent to E^c.

We shall see in the next section that the systems we will be dealing with have the potential to be quite large. We will be taking advantage of the results of center manifold theory to tease out results that would otherwise be intractable by direct analysis.

1.4 Host-Vector and Relapsing Disease Modeling

1.4.1 Host-Vector Systems

Returning to Ross' work in malaria modeling we note that there are two distinct parts to the population: The hosts, I, and the vectors, i, i.e., people and mosquitoes. As was the case for many of the models created at the time it was stochastic in nature. Ross' equations for the spread of malaria were given as

$$\begin{aligned} \frac{dI}{dt} &= fp'i\frac{N-I}{N} - aI, \\ \frac{di}{dt} &= fp(n-i)\frac{I}{N} - mi, \end{aligned}$$

where a is the rate at which humans recover from malaria, m is mosquito mortality, N is the total human population, m is the total mosquito population, f is the biting rate, p is the transmission probability from human to mosquito, and p' is the transmission probability from mosquito to human. There are some features worth noting in this model that are common to vector-host models. The first term of the first equation is a product of four things: the

biting rate, the probability of the disease being passed, the number of mosquitoes and the ratio of the susceptible hosts $(N - I)$ and the total population. Terms like this are common in vector-host models since they have the following important properties:

- If the mosquitoes do not bite $(f = 0)$ there are no new infections.
- If the probability of the mosquitoes passing on the disease is 0 $(p' = 0)$, there are no new infections.
- If there are no infected mosquitoes $(i = 0)$ there are no new infections.
- If the whole human population is infected $(N = I)$ there are no new infections.

The second equation of this model involves the spread of the disease among the vectors themselves, as a result of biting the host. Note the similarity between the first term of the second equation and the first term of the first, and note that the analogous properties hold.

Transitioning to deterministic models we will not have to deal with probability terms in our equations. Instead we will encode this information in coefficients that reflect *vector competency*, which are usually determined by experimentation. In the context of deterministic compartmental models, the equations for a vector-host model from 6.4.5 of [1] are

$$\begin{aligned} I_h' &= \beta_h S_h I_v - (\mu_h + \gamma) I_h, \\ I_v' &= \beta_v S_v I_h - \mu_v I_v, \\ S_h' &= \Pi_h - \mu_h S_h - \beta_h S_h I_v + \gamma I_h, \\ S_v' &= \Pi_v - \mu_v S_v - \beta_v S_v I_h, \end{aligned} \tag{1.12}$$

where μ_h and μ_v are removal (death) rates, and Π_h and Π_v are recruitment (birth) rates. I_h and I_v are infected hosts and vectors respectively, and S_h and S_v are susceptible hosts and vectors. β_h and β_v are constants that reflect the likelihood that an infected host or vector transfers the disease to a susceptible vector or host when the two interact. γ represents the

rate of recovery from the disease. Note that we have to include equations for the susceptible portions of both the vector and host populations, else the compartmental strategy cannot be used. A particular feature of this model is that there is no lateral transmission, i.e., the disease cannot be spread from host to host, but only through a vector. Examples of such diseases include Dengue fever and West Nile virus. Using the analysis of the previous section, determining R_0 from these equations is not difficult. The compartments for this system are I_h, I_v, S_h, S_v. For each compartment the new infections are given by

$$\mathcal{F}(I_h, I_v, S_h, S_v) = \begin{pmatrix} \beta_h S_h I_v \\ \beta_v S_v I_h \\ 0 \\ 0 \end{pmatrix}.$$

The transfers are given by

$$\mathcal{V}(I_h, I_v, S_h, S_v) = \begin{pmatrix} (\mu_h + \gamma) I_h \\ \mu_v I_v \\ -\Pi_h + \mu_h S_h + \beta_h S_h I_v - \gamma I_h \\ -\Pi_v + \mu_v S_v + \beta_v S_v I_h \end{pmatrix}.$$

Finding the disease free equilibrium (DFE) is trivial. In order for the system to be disease free we need $I_h = I_v = 0$. Then we solve

$$\begin{aligned} 0 &= \Pi_h - \mu_h S_h, \\ 0 &= \Pi_v - \mu_v S_v, \end{aligned}$$

which has the solutions $S_{h0} = \frac{\Pi_h}{\mu_h}$ and $S_{v0} = \frac{\Pi_v}{\mu_v}$. Computing the Jacobians at this DFE gives

$$D\mathcal{F}(0,0,S_{h0},S_{v0}) = \begin{pmatrix} 0 & \beta_h S_{h0} & 0 & 0 \\ \beta_v S_{v0} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$D\mathcal{V}(0,0,S_{h0},S_{v0}) = \begin{pmatrix} \mu_h+\gamma & 0 & 0 & 0 \\ 0 & \mu_v & 0 & 0 \\ -\gamma & \beta_h S_{h0} & \mu_h & 0 \\ \beta_v S_{v0} & 0 & 0 & \mu_v \end{pmatrix}.$$

From this we can see that

$$F = \begin{pmatrix} 0 & \beta_h S_{h0} \\ \beta_v S_{v0} & 0 \end{pmatrix} \quad V = \begin{pmatrix} \mu_h+\gamma & 0 \\ 0 & \mu_v \end{pmatrix};$$

V^{-1} is easy to compute, and thus

$$FV^{-1} = \begin{pmatrix} 0 & \frac{\beta_h S_{h0}}{\mu_v} \\ \frac{\beta_v S_{v0}}{\mu_h+\gamma} & 0 \end{pmatrix}.$$

Computing the eigenvalues,

$$\lambda = \pm\sqrt{\frac{\beta_h S_{h0}\beta_v S_{v0}}{\mu_v(\mu_h+\gamma)}}.$$

Both eigenvalues have the same absolute value. Thus

$$R_0 = \sqrt{\frac{\beta_h S_{h0}\beta_v S_{v0}}{\mu_v(\mu_h+\gamma)}}.$$

This form allows us to easily determine how changes in certain parameters affect the spread of the disease. For example, R_0 can be made smaller by increasing either the removal rates

or the recovery rate. Increasing the steady state values of either susceptible population will raise R_0 as will increasing the β_h or β_v. From this form we can easily verify Ross' assertion that if we only reduce the number of mosquitoes (increase μ_v) we can reduce R_0 below 1 and stop an epidemic. Notice that the recruitment rates for either population do not factor into the value of R_0.

1.4.2 Relapsing Dynamics

An antigen is a structural element (for our purposes on a pathogen) to which the antibodies of an immune system can bind, which is critical to the immune response. However, certain bacteria can vary the antigens on their surface. The mechanisms which drive the variation of these antigens are complex and diverse, and can include both random and programmed variation. The control of the antigenic genes can be activated by DNA recombination, alterations in DNA repeat length, or no DNA alterations at all [8, p.4]. Once the antigen has changed, different antibodies are required to identify the pathogen to the immune system, and this can lead to a relapse of the disease.

We want to quantify the effect relapses of a disease have on the dynamics. The compartmental model is apt for this situation. Suppose a disease relapses only one time, then we could consider a simple compartmental setup, see Figure 1.4.1. So far we have not been concerned

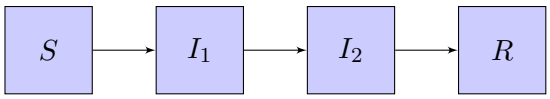

Figure 1.4.1: A single relapsing disease model.

with recruitment and removal in the compartmental models. For the sake of generality, from now on we will add recruitment and removal to the models. See Figure 1.4.2. What is not contained in the conceptual diagrams for the models is how disease is spread from one individual to the other. That will need to be specified in the model equations in the transmission

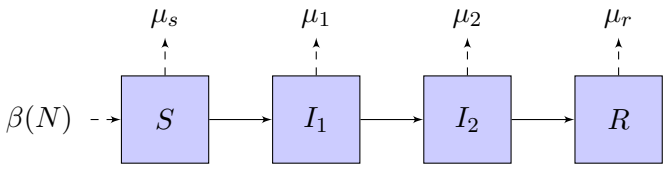

Figure 1.4.2: One relapse with recruitment and removal. N is the total population.

term. Additional relapses can be added into the model in the obvious way.

Of particular interest is the combination of the host-vector and the relapsing systems. To start off, we can consider a host population N and a vector population $\widetilde{N}$. $\widetilde{S}$ and $\widetilde{I}$ will represent susceptible and infected vectors. When a susceptible host S is brought into contact with an infected vector $\widetilde{I}$, the disease will be transferred at some rate. The infected host will now begin to traverse the relapse stages of the disease, of which there could be arbitrarily many. While in this infected state, the infected host at relapse i, I_i may come into contact with a susceptible vector $\widetilde{S}$, who then acquires the disease and spreads it among other susceptible hosts, while the infected host eventually recovers (R). For the sake of simplicity we will suppose that the vectors are not subject to relapses themselves and once infected remain infected. Figure 1.4.3 gives the conceptual model for a one relapse vector host system. The

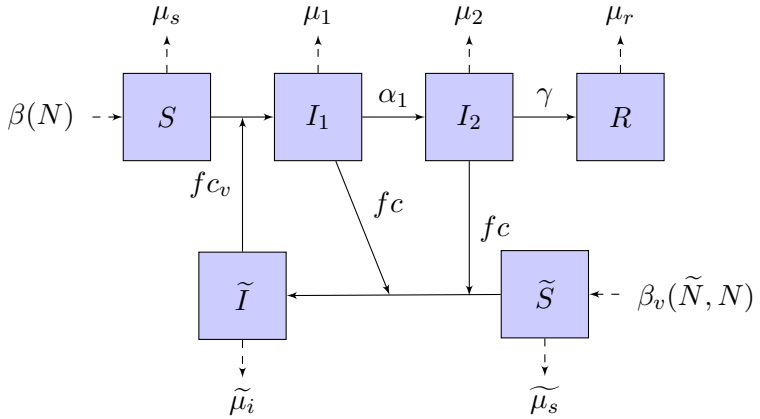

Figure 1.4.3: One relapse vector-host system.

various parameters are as follows:

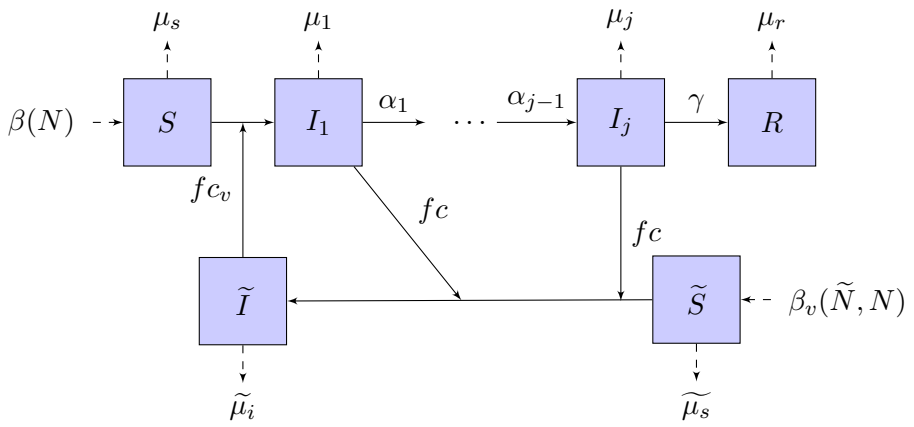

Figure 1.4.4: The case of $j-1$ relapses.

- f is the biting rate.
- α_i is the rate of transfer between relapses.
- c_v is the vector competency, a number reflecting how likely the vector is to give the disease to the host. In particular, if k_v is the number of bites of the vector that successfully transfer the disease per unit time, then $c_v \propto \dfrac{1}{k_v}$.
- c is the "host competency", a number reflecting how likely an infected host is to give the disease to a susceptible vector. Similar to above, if k is the number of bites that result in the vector getting infected per unit time, then $c \propto \dfrac{1}{k}$.
- γ is the recovery rate.

We require that the recruitment for the vectors depends on the total host population N and the total vector population $\widetilde{N}$. The equations for this model are given below. First the host

equations

$$\begin{aligned} S' &= \beta(N) - fc_v\widetilde{I}\frac{S}{N} - \mu_s S, \\ I_1' &= fc_v\widetilde{I}\frac{S}{N} - \alpha_1 I_1 - \mu_1 I_1, \\ I_2' &= \alpha_1 I_1 - \alpha_2 I_2 - \mu_2 I_2, \\ &\vdots \\ I_{j-1}' &= \alpha_{j-2} I_{j-2} - \alpha_{j-1} I_{j-1} - \mu_{j-1} I_{j-1}, \\ I_j' &= \alpha_{j-1} I_{j-1} - \gamma I_j - \mu_j I_j, \\ R' &= \gamma I_j - \mu_r R, \end{aligned} \tag{1.13}$$

and now the vector equations:

$$\begin{aligned} \widetilde{S}' &= \beta_v(\widetilde{N}, N) - \frac{fc\widetilde{S}}{N}\sum_{k=1}^{j} I_k - \widetilde{\mu}_s\widetilde{S}, \\ \widetilde{I}' &= \frac{fc\widetilde{S}}{N}\sum_{k=1}^{j} I_k - \widetilde{\mu}\widetilde{I}. \end{aligned} \tag{1.14}$$

1.5 Examples of Relapsing and Host-Vector Systems

1.5.1 Tick-borne Relapsing Fever (TBRF)

The model given at the end of the previous section is motivated by TBRF. The description given here comes from the text and references of Ch. 15 of [8]. Relapsing fever (RF) is characterized by three or more episodes of high fever, with a week of good health between them. Clinical descriptions of RF date back to ancient Greece, and they were the first recognized example of antigenic variation. TBRF is transferred to a host from a bite of a soft bodied tick of the genus *Ornithidoros*. The relative immobility of these ticks generally means that they live their lives in animal (generally rodent) habitations, they will usually feed on one type of animal in their lifetime, and the feedings often occur at night. Humans come into contact with these ticks while sleeping in rodent infested cabins in mountainous areas. Bitten humans often will not notice the tick bite itself, but after a few days they will have a fever of 39°C

or more. The fever itself is a result of the *Borrelias* spirochetes, filamentous bacteria with more than three spirals, reproducing throughout the body. Experiments have shown that a single spirochete can initiate a RF infection, and they multiply at a rate of one cell division every 6-12 hours. At the peak of the first fever episode there can be between 10^5 and 10^7 extracellular spirochetes per millilitre of blood, but between episodes the spirochetes are not visually detectable. Muscle and joint aches are also common symptoms during the relapses.

Louse borne relapsing fever, caused by *Borrelia recurrentis*, behaves much in the same way as TBRF, but differs in the transfer mechanics. While TBRF can be caused by some different Borrelias, louse born relapsing fever is caused exclusively by *Borrelia recurrentis*. It is carried in the feces of the louse, and is introduced into the body when the host scratches the bite site. This is the only Borrelia infection that occurs in epidemics, and it generally infects only humans.

1.5.2 Tuberculosis

Tuberculosis in humans is generally transmitted from one person to another by the coughing and sneezing, etc. What makes TB interesting from a modeling perspective is the existence of a latency period, where an individual is asymptomatic and will not infect others. Among those infected approximately 5% develop into active disease in the first few years, but most stay in the latent state. Of those who develop active symptoms, 5%-10% will relapse and develop TB later in life. So, modeling the spread involves splitting the population into susceptible S, exposed E, infected I, and recovered R. Analysis of the most basic $SEIR$ model is not difficult. However, the addition of other factors can complicate the analysis. For example, individuals with HIV are at higher risk for TB infection and relapse. In [20] the population is split into 11 compartments based on the current state of their TB and HIV/AIDS infections.

Bovine TB involves TB infections of cows. As with normal TB, there is a latent period, and

it is spread by contact from cow to cow. However it can sometimes be spread with opossums and badgers acting as vectors [16]. There is no current research on this interaction from a compartmental perspective.

1.5.3 Gambian Sleeping Sickness

Sleeping sickness is spread by the tsetse fly among humans and other animals. Like TB, it has a latency period in which the infected host is asymptomatic. The paper [2] uses a compartmental model that also takes into account re-invasion of flies from outside sources. Sleeping sickness is also peculiar in that the tsetse flies can only obtain an infection from the host when they are less than three days old. In addition, by adding in weights for certain portions of the population the authors have taken into account the feeding preferences of the fly. It is shown that fairly low prevalence of sleeping sickness in the invading flies can cause large changes in the prevalence rate among humans.

1.5.4 Diffusion with Latency and Relapse

In [23] a diffusive model with latency and relapse is considered. It is an SEIR model with the assumption that the quantities are functions of time and position. Each equation looks very much like a normal SEIR model with diffusion terms $d_i \frac{\partial^2 .}{\partial x^2}$ added in. Neumann boundary conditions are used, which are interpreted as the population not crossing the boundary. R_0 is defined in the same general way, as the number of secondary infections from single infected individual. Travelling wave solutions are solutions of the form $S(x,t) = \phi(x+ct)$, $I(x,t) = \varphi(x+ct)$. The authors prove that when the diffusion coefficients d_i are equal and $R_0 > 1$, then there is a travelling wave solution connecting the disease free state and an endemic steady state.

1.5.5 Rift Valley Fever

Rift Valley fever is an Old World mosquito-borne illness. It is spread among livestock, and it has two vector species. In [11] a compartmental model that involves two vectors is given. One the vectors, *Aedes* mosquitoes, spread the disease to their offspring, while the other vector, *Culex* mosquitoes, do not. This means that there is a lateral transmission of the disease among one species of vectors and not the other. The model also assumes a latency period for both vectors and hosts, and relapses are not considered. The authors of [11] give an expression for R_0 following the method of [21].

1.6 Comparison with the Relapsing Model

With the previous section in mind, some time can be spent discussing what the model (1.4.3) offers over those mentioned above. Relapsing fever is not a condition of moving from an infected state into a latent state and then infected again. It truly is moving between distinct infected compartments, each defined by the antigenic variation of the Borrelia. In fact, in Africa many cases of TBRF are misdiagnosed as failure of malarial treatment [9]. [9] discusses the reemergence of relapsing fevers, citing a relatively recent outbreak in France of louse-borne relapsing fever among the homeless. But louse-borne relapsing fever is limited to humans and TBRF can infect many more hosts, which presents a challenge in controlling the spread of the disease, and understanding its potential for spread to a region. Perhaps analysis of the model for the spread of the disease can shed some light on these issues.

Mathematically, the model offers more generality than the ones above, which is more of a mathematical advantage than a biological one. Analysis of (1.4.3) can tell us how the addition of a relapse state will affect the dynamics of the disease, in particular the stability of the DFE. Dealing with an arbitrary number of compartments, particularly when employing the methods

of [21], can lead to some difficult calculations, and so, most of the models tend to have a set number of compartments so that computations can be concrete. Hence, the methods used in the analysis of this model could also be used in the analysis of other models with an arbitrary number of compartments.

Chapter 2

Vector-Borne Relapsing Diseases: A Simple Model

Recall the equations for the vector-borne relapsing disease. First the host equations:

$$\begin{aligned} S' &= \beta(N) - fc_v\widetilde{I}\frac{S}{N} - \mu_s S, \\ I_1' &= fc_v\widetilde{I}\frac{S}{N} - \alpha_1 I_1 - \mu_1 I_1, \\ I_2' &= \alpha_1 I_1 - \alpha_2 I_2 - \mu_2 I_2, \\ &\vdots \\ I_{j-1}' &= \alpha_{j-2} I_{j-2} - \alpha_{j-1} I_{j-1} - \mu_{j-1} I_{j-1}, \\ I_j' &= \alpha_{j-1} I_{j-1} - \gamma I_j - \mu_j I_j, \\ R' &= \gamma I_j - \mu_r R, \end{aligned} \tag{2.1}$$

and the vector equations:

$$\begin{aligned} \widetilde{S}' &= \beta_v(\widetilde{N}, N) - \frac{fc\widetilde{S}}{N}\sum_{k=1}^{j} I_k - \widetilde{\mu}_s\widetilde{S}, \\ \widetilde{I}' &= \frac{fc\widetilde{S}}{N}\sum_{k=1}^{j} I_k - \widetilde{\mu}\widetilde{I}. \end{aligned} \tag{2.2}$$

c_v represents the vector competency, a number which reflects how often a biting vector will transfer the disease to the host. c plays a similar role but in the other direction: how often an infected host will pass the infection to a susceptible vector. The growth rates β and β_v are logistic, given as follows:

$$\beta(N) = \beta_1 N - \left(\frac{\beta_1 - \mu_s}{\overline{S}}\right) N^2,$$

$$\beta_v(\widetilde{N}, N) = \beta_{v1}\widetilde{N}N - \left(\frac{\beta_{v1}N - \widetilde{\mu}_s}{\overline{S}_v}\right)\widetilde{N}^2.$$

Here $\overline{S}$ and $\overline{S}_v$ are constants. It is then easy to see that

$$(S, I_1, \ldots, I_j, R, \widetilde{S}, \widetilde{I}) = (\overline{S}, 0, \ldots, \overline{S}_v, 0)$$

is a fixed point of the system, a so-called Disease Free Equilibrium (DFE). We will make the natural assumptions in this model that $\mu_i \geq \mu_s$, $\mu_r \geq \mu_s$, and that $\widetilde{\mu} \geq \widetilde{\mu}_s$. We are assuming that having the disease will only serve to increase the death rate compared to the susceptible population. This leads to the following result:

Proposition 2.0.1. *The manifolds $N = \overline{S}$ and $\widetilde{N} = \overline{S}_v$ are invariant if and only if $\mu_s = \mu_i$, $\mu_s = \mu_r$, and $\widetilde{\mu} = \widetilde{\mu}_s$.*

Proof. First suppose that $\mu_s = \mu_i$ and $\mu_s = \mu_r$. Substituting this into the system (3.9), and summing the equations, we have that

$$N' = \beta(N) - \mu_s N = \beta_1 N - \frac{(\beta_1 - \mu_s)N^2}{\overline{S}} - \mu_s N = (\beta_1 - \mu_s)N\left(1 - \frac{N}{\overline{S}}\right).$$

So we can see that if $N(0) = \overline{S}$, then $N(t) = \overline{S}$, and $N = \overline{S}$ is invariant.

Now assume that $N = \overline{S}$ is invariant. Then if $N(0) = \overline{S}$, N is constant. The first equation then reduces to

$$S' = \mu_s(\overline{S} - S) - \frac{f c_v \widetilde{I} S}{\overline{S}}.$$

Then, summing the equations gives that

$$N' = \mu_s S + \sum_{k=1}^{j} \mu_k I_k + \mu_r R - \mu_s \overline{S}.$$

But since N is constant we get that $N' = 0$, and we use the fact that $s + \sum_k I_k + R = \overline{S}$ so the above equation becomes

$$0 = \sum_k \left(\frac{\mu_k}{\mu_s} - 1 \right) I_k + \left(\frac{\mu_r}{\mu_s} - 1 \right) R.$$

Now, $I_k, r \geq 0$, and since $\mu_i \geq \mu_s$ and $\mu_r \geq \mu_s$ we have

$$\frac{\mu_i}{\mu_s} \geq 1 \text{ and } \frac{\mu_r}{\mu_s} \geq 1.$$

Since each term is nonnegative, the only way the sum can add to zero is if each term is zero. Since I_k and R can, at some time, be nonzero we must have $\frac{\mu_i}{\mu_s} - 1 = 0$ and $\frac{\mu_r}{\mu_s} - 1 = 0$. Thus $\mu_s = \mu_i = \mu_r$.

The proof for the manifold $\widetilde{N} = \overline{S}_v$ follows in the exact same way. □

When the death rates are equal the host population has simple logistic dynamics:

$$N' = (\beta_1 - \mu_s) N \left(1 - \frac{N}{\overline{S}} \right).$$

In particular, if $\beta_1 > \mu_s$ and $\widetilde{N}(0) = \overline{S}_v$, we have $(N, \widetilde{N}) = (\overline{S}, \overline{S}_v)$ is an attracting fixed point of the system. We can then apply the results from Chapter 2 of [15]: a fixed point that is asymptotically stable when restricted to the manifold $N = \overline{S}$ is asymptotically stable. This will be relevant to our discussion of endemic equilibria later.

Before we can use the theory of compartmental models from the first chapter we must first confirm that our model meets the needed conditions.

Proposition 2.0.2. *The system* (3.9), (2.2) *satisfies Conditions 1-5.*

Proof. First we rearrange the system into the form described in [21]:

$$\frac{d}{dt}\begin{pmatrix} I_1 \\ I_2 \\ \vdots \\ I_{j-1} \\ I_j \\ \widetilde{I} \\ S \\ R \\ \widetilde{S} \end{pmatrix} = \begin{pmatrix} fc_v\widetilde{I}\dfrac{S}{N} \\ 0 \\ \vdots \\ 0 \\ 0 \\ \dfrac{fc\widetilde{S}}{N}\displaystyle\sum_{k=1}^{j} I_k \\ 0 \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} 0 \\ \alpha_1 I_1 \\ \vdots \\ \alpha_{j-2}I_{j-2} \\ \alpha_{j-1}I_{j-1} \\ 0 \\ \beta(N) \\ \beta(N,\widetilde{N}) \\ \gamma I_j \end{pmatrix} - \begin{pmatrix} (\alpha_1+\mu_1)I_1 \\ (\alpha_2+\mu_2)I_2 \\ \vdots \\ (\alpha_{j-1}+\mu_{j-2})I_{j-2} \\ (\alpha_{j-1}+\mu_{j-1})I_{j-1} \\ (\gamma+\mu_j)I_j \\ \widetilde{\mu}\widetilde{I} \\ fc_v\widetilde{I}\dfrac{S}{N}+\mu_s S \\ \dfrac{fc\widetilde{S}}{N}\displaystyle\sum_{k=1}^{j} I_k + \widetilde{\mu}_s\widetilde{S} \\ \mu_r R \end{pmatrix}. \tag{2.3}$$

Having written the system in this way (1.4), we see that conditions 1,2 and 3 follow directly. Setting $I_1 = \ldots = I_j = \widetilde{I} = 0$ gives condition 4. For the final condition, assume that the first vector on the right hand side of the above equation is $\mathbf{0}$. Then, taking the Jacobian will yield a lower triangular matrix. Furthermore, the elements of the diagonal of this matrix, when evaluated at a DFE $(0,\ldots,0,\overline{S},\overline{R},\overline{S}_v)$, are

$$-(\alpha_1+\mu_1),\ldots,-(\alpha_{j-1}+\mu_{j-1}),-(\gamma+\mu_j),-\widetilde{\mu},-\mu_s,-\mu_r,-\widetilde{\mu}_s,$$

and since all the parameters are held to be positive, the diagonal elements, which are also the eigenvalues, are all negative. □

2.1 R_0 for the single host-vector system with $j-1$ relapses.

2.1.1 Dimensionless Form

To ease some calculation we will put equations (3.9) and (2.2) in dimensionless form. Letting $\tau = \gamma t$, and scaling all the population variables by the corresponding initial total populations $N(0)$ and $\widetilde{N}(0)$ gives the dimensionless form:

$$\frac{ds}{d\tau} = a_1 n - a_2 n^2 - k i_v \frac{s}{n} - b_s s,$$

$$\frac{di_i}{d\tau} = k i_v \frac{s}{n} - q_1 i_1 - b_1 i_1,$$

$$\frac{di_2}{d\tau} = q_1 i_1 - q_2 i_2 - b_2 i_2,$$

$$\vdots$$

$$\frac{di_{j-1}}{d\tau} = q_{j-2} i_{j-2} - q_{j-1} i_{j-1} - b_{(j-1)} i_{j-1},$$

$$\frac{di_j}{d\tau} = q_{j-1} i_{j-1} - i_j - b_j i_j,$$

$$\frac{dr}{d\tau} = i_j - b_r r,$$

$$\frac{d\widetilde{s}}{d\tau} = a_{v1} \widetilde{n} n - a_2 \widetilde{n}^2 - \frac{l\widetilde{s}}{n} \sum_{m=1}^{j} i_m - \widetilde{b}_s s_v,$$

$$\frac{d\widetilde{i}}{d\tau} = \frac{l\widetilde{s}}{n} \sum_{m=1}^{j} i_m - \widetilde{b}_i \widetilde{i},$$

with $n = \dfrac{N}{\overline{S}}$, $\widetilde{n} = \dfrac{\widetilde{N}}{\overline{S}_v}$, $s = \dfrac{S}{\overline{S}}$, $\widetilde{s} = \dfrac{\widetilde{S}}{\overline{S}_v}$, $i_k = \dfrac{I_k}{\overline{S}}$, $\widetilde{i} = \dfrac{\widetilde{I}}{\overline{S}_v}$, $r = \dfrac{R}{\overline{S}}$, $b_s = \dfrac{\mu_s}{\gamma}$, $b_k = \dfrac{\mu_k}{\gamma}$, $q_k = \dfrac{\alpha_k}{\gamma}$, $\widetilde{b}_s = \dfrac{\widetilde{\mu}_s}{\gamma}$, $k = fc_v/\gamma$ and $l = fc/\gamma$.

2.1.2 General form for R_0

Following [21], we consider the reduced equations

$$\frac{d}{d\tau}\begin{bmatrix} i_1 \\ i_2 \\ \vdots \\ i_{j-1} \\ i_j \\ \widetilde{i} \end{bmatrix} = \begin{bmatrix} k\widetilde{i}\dfrac{s}{n} \\ 0 \\ \vdots \\ 0 \\ 0 \\ \dfrac{l\widetilde{s}}{n}\displaystyle\sum_{k=1}^{j} i_k \end{bmatrix} - \begin{bmatrix} q_1 i_1 + b_1 i_1 \\ -q_1 i_1 + q_2 i_2 + b_2 i_2 \\ \vdots \\ -q_{j-2} i_{j-2} + q_{j-1} i_{j-1} + b_{j-1} i_{j-1} \\ -q_{j-1} i_{j-1} + i_j + b_j i_j \\ \widetilde{b}_i \widetilde{i} \end{bmatrix} = \boldsymbol{w} - \boldsymbol{v}.$$

Next, we take the Jacobians of $\boldsymbol{w}$ and $\boldsymbol{v}$ and evaluate them at the disease free equilibrium in order to find the matrices W and V, i.e.

$$W = \begin{bmatrix} 0 & \dots & 0 & k\dfrac{s}{n} \\ 0 & \dots & 0 & 0 \\ \vdots & & \vdots & \vdots \\ \dfrac{l\widetilde{s}}{n} & \dots & \dfrac{l\widetilde{s}}{n} & 0 \end{bmatrix}\Bigg|_{DFE}.$$

At the DFE we note that the entire host and vector populations are susceptible and there are no hosts in any of the relapse states. This means that $n = s = \overline{s}$ and $\widetilde{n} = \widetilde{s} = \overline{s_v}$ (the carrying capacities of each population). Hence

$$W = \begin{bmatrix} 0 & \dots & 0 & k \\ 0 & \dots & 0 & 0 \\ \vdots & & \vdots & \vdots \\ \dfrac{l\overline{s_v}}{\overline{s}} & \dots & \dfrac{l\overline{s_v}}{\overline{s}} & 0 \end{bmatrix}.$$

For V, we note that the Jacobian is made up of constant values, namely

$$V = \begin{bmatrix} q_1+b_1 & 0 & 0 & \dots & 0 & 0 & 0 & 0 \\ -q_1 & q_2+b_2 & 0 & \dots & 0 & 0 & 0 & 0 \\ 0 & -q_2 & q_3+b_3 & \dots & 0 & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & & \vdots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -q_{j-2} & q_{j-1}+b_{j-1} & 0 & 0 \\ 0 & 0 & 0 & \dots & 0 & -q_{j-1} & 1+b_j & 0 \\ 0 & 0 & 0 & \dots & 0 & 0 & 0 & \widetilde{b}_i \end{bmatrix}.$$

Clearly the matrix V is invertible (lower triangular, nonzero diagonal elements), although computing such an inverse is nontrivial. However, all we require is the dominant eigenvalue of WV^{-1}. Because W is fairly sparse we will not need to know all the entries of V^{-1} to extract it. Also, note that W and V are both $(j+1)\times(j+1)$ matrices.

The action of W on V^{-1} is to multiply the last row by k, make middle rows 0, and sum the first j elements of each columns and multiply it by the constant $\rho = \frac{l\overline{s_v}}{\overline{s}}$. Let us denote the elements of the last row of V^{-1} by ϵ_k and the sums of the first j elements of the kth column by δ_k. WV^{-1} then has a relatively simple form

$$WV^{-1} = \begin{bmatrix} k\epsilon_1 & \dots & k\epsilon_{j+1} \\ 0 & \dots & 0 \\ \vdots & & \vdots \\ 0 & \dots & 0 \\ \rho\delta_1 & \dots & \rho\delta_{j+1}. \end{bmatrix}$$

From here we can move ahead with the eigenvalue calculation. This involves computing the

determinant of

$$WV^{-1}-\lambda I=\begin{bmatrix} k\epsilon_1-\lambda & k\epsilon_2 & \dots & k\epsilon_{j+1} \\ 0 & -\lambda & \dots & 0 \\ \vdots & \vdots & & \vdots \\ 0 & 0 & \dots & 0 \\ \rho\delta_1 & \rho\delta_2 & \dots & \rho\delta_{j+1}-\lambda \\ . & & & \end{bmatrix}$$

Expanding along the first column we have

$$\det(WV^{-1}-\lambda I)=(k\epsilon_1-\lambda)\cdot\det\begin{bmatrix} -\lambda & 0 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ \rho\delta_2 & \rho\delta_3 & \dots & \rho\delta_{j+1}-\lambda \end{bmatrix}$$
$$+(-1)^{j+2}\rho\delta_1\cdot\det\begin{bmatrix} k\epsilon_2 & \dots & k\epsilon_j & k\epsilon_{j+1} \\ -\lambda & \dots & 0 & 0 \\ \vdots & & \vdots & \vdots \\ 0 & \dots & -\lambda & 0 \end{bmatrix}.$$

Computing the determinants in this expression is straightforward, noting that both are $j\times j$ matrices and that the first is a lower triangular matrix, and thus the determinant is the product of the diagonal elements $(-\lambda)^{j-1}(\rho\delta_{j+1}-\lambda)$. For the second we expand along the last column to see that the determinant is

$$(-1)^{j+1}k\epsilon_{j+1}\cdot\det(-\lambda I)=(-1)^{j+1}k\epsilon_{j+1}(-\lambda)^{j-1}$$

Hence

$$\det(WV^{-1}-\lambda I)=(k\epsilon_1-\lambda)(-\lambda)^{j-1}(\rho\delta_{j+1}-\lambda)+(-1)^{j+2}\rho\delta_1(-1)^{j+1}k\epsilon_{j+1}(-\lambda)^{j-1},$$

and the characteristic polynomial only involves ϵ_1, ϵ_{j+1}, δ_1 and δ_{j+1}, and we need only to

know the first and the last column of V^{-1}. These can be computed by looking at the first and last rows of the cofactor matrix. For ϵ_1 we look at the minor of $v_{j+1,1}$, and note that the top row is all 0's, so that the minor, and thus the cofactor are 0, and thus, $\epsilon_1 = 0$. To find δ_{j+1} we must find the cofactors of the first j elements on the bottom row of V, but when the bottom row is eliminated to compute the cofactor, the last column is all 0's, and hence, each of the cofactors is 0. Thus $\delta_{j+1} = 0$. The characteristic polynomial then reduces to

$$(-\lambda)^{j-1}\lambda^2 - (-\lambda)^{j-1}\rho k\delta_1\epsilon_{j+1}.$$

Setting this expression equal to 0 and factoring we get

$$\lambda = \pm\sqrt{\rho k\delta_1\epsilon_{j+1}}.$$

We have reduced finding the largest magnitude eigenvalue to computing the last element of the last column of V^{-1} (ϵ_{j+1}) and the sum of the first j elements in the first column of V^{-1} (δ_1).

To find ϵ_{j+1}, we note that the last row of V times the last column of V^{-1} should be equal to 1. Multiplying the last column by the last row gives

$$\widetilde{b}_i\epsilon_{j+1} = 1 \Rightarrow \epsilon_{j+1} = \frac{1}{\widetilde{b}_i}.$$

Finding δ_1 will involve a similar approach. Let u_{ij} be the elements of V^{-1}. Taking the first row of V and multiplying it by the first column of V^{-1} yields

$$u_{11} = \frac{1}{q_1 + b_1}.$$

Taking the next row multiplied by the 2nd column of V^{-1} will produce

$$\frac{-q_1}{q_1 + b_1} + u_{21}(q_2 + b_2) = 0,$$

and thus

$$u_{21} = \frac{q_1}{(q_1+b_1)(q_2+b_2)}.$$

Continuing the process, the $(k+1)$st row of V has $v_{k+1,k} = -q_k$, $v_{k+1,k+1} = q_{k+1}+b_{k+1}$, and the rest of the entries are 0, so

$$u_{k,1} = \frac{\prod_{\ell=1}^{k-1} q_\ell}{\prod_{\ell=1}^{k}(q_\ell+b_\ell)}.$$

Then

$$-q_k u_{1,k} + (q_{k+1}+b_{k+1})u_{k+1,1} = 0,$$

and thus,

$$u_{k+1,1} = \frac{q_k u_{1,k}}{(q_{k+1}+b_{k+1})} = \frac{q_k}{(q_{k+1}+b_{k+1})}\frac{\prod_{\ell=1}^{k-1} q_\ell}{\prod_{\ell=1}^{k}(q_\ell+b_{i\ell})} = \frac{\prod_{\ell=1}^{k} q_\ell}{\prod_{\ell=1}^{k+1}(q_\ell+b_\ell)}.$$

We have established the form of $u_{1,k}$ for $2 \le k \le j-1$. For $u_{j,1}$ we compute

$$-q_{j-1}u_{j-1,1} + (1+b_j)u_{j,1} = 0,$$

and thus,

$$u_{j,1} = \frac{q_{j-1}u_{j-1,1}}{1+b_j} = \frac{q_{j-1}}{1+b_j}\frac{\prod_{\ell=1}^{j-2} q_\ell}{\prod_{\ell=1}^{j-1}(q_\ell+b_\ell)},$$

If we define $q_0 = 1$ and $q_j = 1$, then

$$\delta_1 = \sum_{k=1}^{j} u_{k,1} = \sum_{k=1}^{j} \frac{\prod_{\ell=0}^{k-1} q_\ell}{\prod_{\ell=1}^{k}(q_\ell+b_\ell)} = \sum_{k=1}^{j}\prod_{\ell=1}^{k}\frac{q_{\ell+1}}{q_\ell+b_\ell}.$$

We can rewrite this sum as

$$\delta_1 = \frac{1}{q_1+b_1}\left(1+\frac{q_1}{q_2+b_2}\left(1+\frac{q_2}{q_3+b_3}\left(1+\ldots\frac{q_{j-2}}{q_{j-1}+b_{j-1}}\left(1+\frac{q_{j-1}}{1+b_j}\right)\ldots\right)\right)\right).$$

This gives that

$$R_0 = \sqrt{\frac{\rho k}{\widetilde{b}_i}\frac{1}{q_1+b_1}\left(1+\frac{q_1}{q_2+b_2}\left(1+\frac{q_2}{q_3+b_3}\left(1+\ldots\frac{q_{j-2}}{q_{j-1}+b_{j-1}}\left(1+\frac{q_{j-1}}{1+b_j}\right)\ldots\right)\right)\right)}.$$

Recall that $\rho = \dfrac{l\,\overline{s_v}}{\overline{s}}$. Moving out of dimensionless form, we find

$$R_0 = f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\frac{1}{\alpha_1+\mu_1}\left(1+\frac{\alpha_1}{\alpha_2+\mu_2}\left(1+\frac{\alpha_2}{\alpha_3+\mu_3}\left(1+\ldots\frac{\alpha_{j-2}}{\alpha_{j-1}+\mu_{j-1}}\left(1+\frac{\alpha_{j-1}}{\gamma+\mu_j}\right)\ldots\right)\right)\right)}.$$

This is the form that was conjectured in [14]. Alternatively,

$$R_0 = f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\sum_{k=1}^{j}\prod_{l=1}^{k}\frac{\alpha_{l-1}}{\alpha_l+\mu_l}},$$

where $\alpha_0 = 1$ and $\alpha_j = \gamma$. We can now apply Theorem 1.2.1 and see that a bifurcation occurs at $R_0 = 1$.

Notice that R_0 is directly proportional to the biting rate f, the roots of the competencies c and c_v, and the root of the carrying capacity of the vector population. R_0 is inversely proportional to the death rate of the vectors $\widetilde{\mu}$ and the carrying capacity of the host population $\overline{S}$. Thus, R_0 can be completely controlled by these parameters. It is also worth noting that R_0 only depends on the ratio of the vector and host populations and not just on the size of each. If the ratio of the populations is the same, R_0 is the same.

To investigate how R_0 depends on the transfer rates α_i, consider a model with $\mu_i = 0$. Then, letting $\beta = f\sqrt{\dfrac{cc_v\overline{S}_v}{\mu\overline{S}}}$, we have

$$R_0^2 = \beta^2\left(\frac{1}{\alpha_1}\left(1+\frac{\alpha_1}{\alpha_2}\left(1+\frac{\alpha_2}{\alpha_3}\left(1+\ldots\frac{\alpha_{j-2}}{\alpha_{j-1}}\left(1+\frac{\alpha_{j-1}}{\alpha_j}\right)\ldots\right)\right)\right)\right)$$

$$= \beta^2\left(\frac{1}{\alpha_1}+\frac{1}{\alpha_2}\left(1+\frac{\alpha_2}{\alpha_3}\left(1+\ldots\frac{\alpha_{j-2}}{\alpha_{j-1}}\left(1+\frac{\alpha_{j-1}}{\alpha_j}\right)\ldots\right)\right)\right)$$

$$= \beta^2 \left(\frac{1}{\alpha_1} + \frac{1}{\alpha_2} + \frac{1}{\alpha_3} \left(1 + \ldots \frac{\alpha_{j-2}}{\alpha_{j-1}} \left(1 + \frac{\alpha_{j-1}}{\alpha_j} \right) \ldots \right) \right)$$

and so on, until

$$R_0^2 = \beta^2 \left(\frac{1}{\alpha_1} + \frac{1}{\alpha_2} + \frac{1}{\alpha_3} + \ldots + \frac{1}{\alpha_{j-1}} + \frac{1}{\alpha_j} \right).$$

Let T_i be the average amount of time spent in the ith compartment, then $T_i \propto \frac{1}{\alpha_i}$, so that

$$R_0^2 \propto \beta^2 \sum T_i.$$

As the rates increase, the T_i will decrease, and thus, R_0 will decrease as well. Also, we can add relapses to the model, but keep R_0 the same by fixing the total amount of time spent in the relapsing states. Thus, the addition of relapses to the model increases R_0 because we are increasing the amount of time that an infected host spends being infectious.

2.2 The Bifurcation at $R_0 = 1$.

Using Theorem 1.2.1 we have established that the DFE undergoes a bifurcation at $R_0 = 1$. We wish to learn more about the bifurcation. To do this we shall take advantage of center manifold theory introduced in the previous chapter. Namely, if the zero eigenvalue of the linearization is simple, then the dynamics on the center manifold are one dimensional, and we can discover with relative ease the existence and stability of an additional equilibrium.

Consider the system (3.9), (2.2). It is an easy exercise to show that the Jacobian of this

system takes the form

$$\begin{pmatrix}
-\alpha_1-\mu_1 & 0 & 0 & \dots & 0 & 0 & \frac{fc_vS}{N} & 0 & 0 & 0 \\
\alpha_1 & -\alpha_2-\mu_2 & 0 & \dots & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & \alpha_2 & -\alpha_3-\mu_3 & \dots & 0 & 0 & 0 & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \dots & \alpha_{j-1} & -\gamma-\mu_j & 0 & 0 & 0 & 0 \\
\frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & \dots & \frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & -\widetilde{\mu} & 0 & 0 & 0 \\
0 & 0 & 0 & \dots & 0 & 0 & -\frac{fc_vS}{N} & -\mu_s & 0 & 0 \\
-\frac{fc\widetilde{S}}{N} & -\frac{fc\widetilde{S}}{N} & -\frac{fc\widetilde{S}}{N} & \dots & -\frac{fc\widetilde{S}}{N} & -\frac{fc\widetilde{S}}{N} & 0 & 0 & -\widetilde{\mu}_s & 0 \\
0 & 0 & 0 & \dots & 0 & \gamma & 0 & 0 & 0 & -\mu_r
\end{pmatrix}.$$

We evaluate this at the DFE and then determine the algebraic multiplicity of the zero eigenvalue when $R_0 = 1$. The eigenvalue matrix is

$$\begin{pmatrix}
\lambda+\alpha_1+\mu_1 & 0 & 0 & \dots & 0 & 0 & -fc_v & 0 & 0 & 0 \\
-\alpha_1 & \lambda+\alpha_2+\mu_2 & 0 & \dots & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\alpha_2 & \lambda+\alpha_3+\mu_3 & \dots & 0 & 0 & 0 & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \dots & -\alpha_{j-1} & \lambda+\gamma+\mu_j & 0 & 0 & 0 & 0 \\
-\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \dots & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \lambda+\widetilde{\mu} & 0 & 0 & 0 \\
0 & 0 & 0 & \dots & 0 & 0 & fc_v & \lambda+\mu_s & 0 & 0 \\
\frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & \dots & \frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & 0 & 0 & \lambda+\widetilde{\mu}_s & 0 \\
0 & 0 & 0 & \dots & 0 & -\gamma & 0 & 0 & 0 & \lambda+\mu_r
\end{pmatrix}.$$

The Jacobian matrix has block form

$$Df(\boldsymbol{x}_0) = \begin{pmatrix} T & 0 \\ L & D \end{pmatrix},$$

and the multiplicity of the zero eigenvalue will be the sum of the multiplicities of the diagonal

blocks [5]. However, the multiplicity of 0 in D is 0, since it is diagonal. Hence, we need only to compute the multiplicity of zero in T. The relevant calculation is

$$p(\lambda) = \det \begin{pmatrix} \lambda+\alpha_1+\mu_1 & 0 & 0 & \dots & 0 & 0 & -fc_v \\ -\alpha_1 & \lambda+\alpha_2+\mu_2 & 0 & \dots & 0 & 0 & 0 \\ 0 & -\alpha_2 & \lambda+\alpha_3+\mu_3 & \dots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -\alpha_{j-1} & \lambda+\gamma+\mu_j & 0 \\ -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \dots & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \lambda+\widetilde{\mu} \end{pmatrix}.$$

First, we expand along the top row

$$p(\lambda) = (\lambda+\alpha_1+\mu_1)\det \begin{pmatrix} \lambda+\alpha_2+\mu_2 & 0 & \dots & 0 & 0 & 0 \\ -\alpha_2 & \lambda+\alpha_3+\mu_3 & \dots & 0 & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & \dots & -\alpha_{j-1} & \lambda+\gamma+\mu_j & 0 \\ -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \dots & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \lambda+\widetilde{\mu} \end{pmatrix}$$

$$+(-1)^j(-fc_v)\det \begin{pmatrix} -\alpha_1 & \lambda+\alpha_2+\mu_2 & 0 & \dots & 0 & 0 \\ 0 & -\alpha_2 & \lambda+\alpha_3+\mu_3 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -\alpha_{j-1} & \lambda+\gamma+\mu_j \\ -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \dots & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} \end{pmatrix}.$$

The determinant of the first matrix is the product of the diagonals, being that it is lower triangular. To compute the determinant of the second matrix we divide the bottom row by $-\frac{fc\bar{S}_v}{\bar{S}}$. For the value of the determinant to stay the same, we also multiply it by the same

amount. Hence, we compute

$$(-1)^j \frac{f^2 c c_v \bar{S}_v}{\bar{S}} \det \begin{pmatrix} -\alpha_1 & \lambda+\alpha_2+\mu_2 & 0 & \dots & 0 & 0 \\ 0 & -\alpha_2 & \lambda+\alpha_3+\mu_3 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -\alpha_{j-1} & \lambda+\gamma+\mu_j \\ 1 & 1 & 1 & \dots & 1 & 1 \end{pmatrix},$$

by expanding along the bottom row. Then at each step of the expansion we will take the determinant of a block diagonal matrix, and each matrix along the diagonal will be a triangular matrix. In particular, once the kth column and the bottom row are removed, the diagonal to the left of the column has the elements $-\alpha_1, \dots, -\alpha_{k-1}$ with the only other nonzero elements above this diagonal. To the right of the column the diagonal elements are $\lambda + \alpha_{k+1} + \mu_{k+1}, \dots, \lambda + \gamma + \mu_j$, and on this side the only other nonzero elements are above the diagonal. Thus the minors can be written in this form:

$$\begin{pmatrix} A & 0 \\ 0 & B \end{pmatrix}.$$

According to [5] the determinant of this minor will be the product of the determinants of the diagonal matrices, and as we have already mentioned A is upper triangular and B is lower triangular. Thus, the determinant of the minor is the product of the diagonal elements. The signs for the minors along the bottom are $(-1)^{j+k}$. Furthermore we will multiply the $k-1$ negative elements in the upper matrix. Hence, the sign of each term is $(-1)^{j+k+k-1} = (-1)^{j+2k-1} = (-1)^{j-1}$. None of these depend on k; we can factor it out and combine it with the $(-1)^j$ on the outside, and have $(-1)^{j+j-1} = -1$. Thus, the characteristic polynomial

takes the form

$$\begin{aligned} p(\lambda) =&(\lambda+\alpha_1+\mu_1)\dots(\lambda+\gamma+\mu_j)(\lambda+\widetilde{\mu}) \\ &-\frac{f^2cc_v\bar{S}_v}{\bar{S}}\left[(\lambda+\alpha_2+\mu_2)\dots(\lambda+\gamma+\mu_j)\right. \\ &+\alpha_1(\lambda+\alpha_3+\mu_3)\dots(\lambda+\gamma+\mu_j) \\ &\left.+\dots\alpha_1\dots\alpha_k(\lambda+\alpha_{k+2}+\mu_{k+2})\dots(\lambda+\gamma+\mu_j)+\dots+\alpha_1\dots\alpha_{j-1}\right] \end{aligned}$$

To show that 0 is a simple eigenvalue, we must show that when $R_0 = 1$, the constant term of this polynomial is 0 and the linear term is nonzero. In order to ease some of the calculation we next build up some notation. For indexing purposes define $\alpha_0 = 1$. Now let $\xi_i = \alpha_i + \mu_i$ for $1 \le i \le j-1$, and $\xi_j = \gamma + \mu_j$, and $\xi_{j+1} = \widetilde{\mu}$. This sets up a consistent notation for the parameters. Also, we need to take products of all but one of these parameters, so we define the following

$$\xi_1\dots\hat{\xi}_i\dots\xi_j = \xi_1\dots\xi_{i-1}\xi_{i+1}\dots\xi_j.$$

The hat tells us which of the parameters is deleted from the product. We can now rewrite R_0 using this notation

$$R_0 = f\sqrt{\frac{cc_v\bar{S}_v}{\bar{S}\xi_{j+1}}\sum_{k=1}^{j}\frac{\alpha_0\dots\alpha_{k-1}}{\xi_1\dots\xi_k}},$$

and $p(\lambda)$ becomes

$$p(\lambda) = \prod_{i=1}^{j}(\lambda+\xi_i) - \frac{f^2cc_v\bar{S}_v}{\bar{S}}\sum_{i=0}^{j-1}\alpha_0\dots\alpha_i(\lambda+\xi_{i+2})\dots(\lambda+\xi_j). \tag{2.4}$$

The constant term is found by evaluating $p(0)$:

$$p(0) = \prod_{i=1}^{j}\xi_i - \frac{f^2cc_v\bar{S}_v}{\bar{S}}\sum_{i=0}^{j-1}\alpha_0\dots\alpha_i\xi_{i+2}\dots\xi_j.$$

Next, we solve $p(0) = 0$.

$$1 = \frac{f^2 c c_v \bar{S}_v}{\bar{S}} \frac{1}{\xi_1 \dots \xi_j \xi_{j+1}} \sum_{i=0}^{j-1} \alpha_0 \dots \alpha_i \xi_{i+2} \dots \xi_j$$

$$= \frac{f^2 c c_v \bar{S}_v}{\bar{S}\xi_{j+1}} \sum_{i=0}^{j-1} \frac{\alpha_0 \dots \alpha_i \xi_{i+2} \dots \xi_j}{\xi_1 \dots \xi_j}$$

$$= \frac{f^2 c c_v \bar{S}_v}{\bar{S}\xi_{j+1}} \sum_{i=0}^{j-1} \frac{\alpha_0 \dots \alpha_i}{\xi_1 \dots \xi_{i+1}}.$$

Letting $k = i + 1$, this becomes

$$= \frac{f^2 c c_v \bar{S}_v}{\bar{S}\xi_{j+1}} \sum_{k=1}^{j} \frac{\alpha_0 \dots \alpha_{k-1}}{\xi_1 \dots \xi_k} = R_0^2.$$

This implies that the linear term is 0 if and only if $R_0 = 1$. This only establishes that the 0 has nontrivial algebraic multiplicity (which we knew already because there is a bifurcation). To establish simplicity we check that the coefficient of the linear term is nonzero when $R_0 = 1$. Given a product of factors

$$(\lambda + a_1) \dots (\lambda + a_n),$$

the coefficient of the linear term, in the "hat" notation, is

$$\sum_{i=1}^{n} a_1 \dots \hat{a}_i \dots a_n.$$

Applying this to (2.4) we find the coefficient of the linear term of the characteristic polynomial to be

$$\sum_{i=1}^{j+1} \xi_1 \dots \hat{\xi}_i \dots \xi_{j+1} - \frac{f^2 c c_v \bar{S}_v}{\bar{S}} \sum_{k=0}^{j-2} \alpha_0 \dots \alpha_k \sum_{i=k+2}^{j} \xi_{k+2} \dots \hat{\xi}_i \dots \xi_j.$$

Assume that this is equal to zero when $R_0 = 1$, and we will arrive at a contradiction. Multi-

plying the second term by $\frac{\xi_{j+1}}{\xi_{j+1}}$,

$$0 = \sum_{i=1}^{j+1} \xi_1 \dots \hat{\xi}_i \dots \xi_{j+1} - \frac{f^2 c c_v \bar{S}_v}{\bar{S}\xi_{j+1}} \sum_{k=0}^{j-2} \sum_{i=k+2}^{j} \alpha_0 \dots \alpha_k \xi_{k+2} \dots \hat{\xi}_i \dots \xi_j \xi_{j+1},$$

where, upon some manipulation, the expression yields

$$1 = \frac{\frac{f^2 c c_v \bar{S}_v}{\bar{S}\xi_{j+1}} \sum_{k=0}^{j-2} \sum_{i=k+2}^{j} \alpha_0 \dots \alpha_k \xi_{k+2} \dots \hat{\xi}_i \dots \xi_j \xi_{j+1}}{\sum_{i=1}^{j+1} \xi_1 \dots \hat{\xi}_i \dots \xi_{j+1}}.$$

But $R_0^2 = 1$, so

$$\frac{f^2 c c_v \bar{S}_v}{\bar{S}\xi_{j+1}} \sum_{k=1}^{j} \frac{\alpha_0 \dots \alpha_{k-1}}{\xi_1 \dots \xi_k} = \frac{\frac{f^2 c c_v \bar{S}_v}{\bar{S}\xi_{j+1}} \sum_{k=0}^{j-2} \sum_{i=k+2}^{j} \alpha_0 \dots \alpha_k \xi_{k+2} \dots \hat{\xi}_i \dots \xi_j \xi_{j+1}}{\sum_{i=1}^{j+1} \xi_1 \dots \hat{\xi}_i \dots \xi_{j+1}}.$$

Canceling the constant in front, and multiplying by the denominator, we get

$$\sum_{i=1}^{j} \sum_{k=1}^{j+1} \frac{\alpha_0 \dots \alpha_{i-1} \xi_1 \dots \hat{\xi}_k \dots \xi_{j+1}}{\xi_1 \dots \xi_i} = \sum_{k=0}^{j-2} \sum_{i=k+2}^{j} \alpha_0 \dots \alpha_k \xi_{k+2} \dots \hat{\xi}_i \dots \xi_j \xi_{j+1}.$$

We can split the first sum into two parts depending on the largest value of k. In particular, when $k \leq i$, ξ_k will not cancel out of the denominator, but when $k \geq i+1$ the whole denominator will cancel. So we write

$$\sum_{i=1}^{j} \sum_{k=1}^{i} \frac{\alpha_0 \dots \alpha_{i-1} \xi_{i+1} \dots \xi_{j+1}}{\xi_k} + \sum_{i=1}^{j} \sum_{k=i+1}^{j} \alpha_0 \dots \alpha_{i-1} \xi_{i+1} \dots \hat{\xi}_k \dots \xi_{j+1}$$

$$= \sum_{k=0}^{j-2} \sum_{i=k+2}^{j} \alpha_0 \dots \alpha_k \xi_{k+2} \dots \hat{\xi}_i \dots \xi_j \xi_{j+1}.$$

Exchanging i and k on the right hand side, we obtain

$$\sum_{i=1}^{j}\sum_{k=1}^{i}\frac{\alpha_0\dots\alpha_{i-1}\xi_{i+1}\dots\xi_{j+1}}{\xi_k}+\sum_{i=1}^{j}\sum_{k=i+1}^{j}\alpha_0\dots\alpha_{i-1}\xi_{i+1}\dots\hat{\xi}_k\dots\xi_{j+1}$$

$$=\sum_{i=0}^{j-2}\sum_{k=i+2}^{j}\alpha_0\dots\alpha_i\xi_{i+2}\dots\hat{\xi}_k\dots\xi_j\xi_{j+1}.$$

Shifting the i index up by 1 on the RHS yields

$$\sum_{i=1}^{j}\sum_{k=1}^{i}\frac{\alpha_0\dots\alpha_{i-1}\xi_{i+1}\dots\xi_{j+1}}{\xi_k}+\sum_{i=1}^{j}\sum_{k=i+1}^{j}\alpha_0\dots\alpha_{i-1}\xi_{i+1}\dots\hat{\xi}_k\dots\xi_{j+1}$$

$$=\sum_{i=1}^{j-1}\sum_{k=i+1}^{j}\alpha_0\dots\alpha_{i-1}\xi_{i+1}\dots\hat{\xi}_k\dots\xi_j\xi_{j+1}.$$

Thus we have that

$$\sum_{i=1}^{j}\sum_{k=1}^{i}\frac{\alpha_0\dots\alpha_{i-1}\xi_{i+1}\dots\xi_{j+1}}{\xi_k}+\alpha_0\dots\alpha_{j-1}=0.$$

However, this cannot be so because all of the rates are positive. Hence a contradiction and the conclusion that the linear term cannot be 0 when $R_0 = 1$, and 0 is a simple eigenvalue of $Df(x_0)$. As mentioned at the beginning of the section, this implies that the dynamics near the DFE are 1-dimensional. We use this fact to investigate the stability of the EE near $R_0 = 1$. To do this, we insert a parameter μ into the equations, where

$$\mu = 0 \iff R_0 = 1.$$

We will do this by defining $\mu = R_0 - 1$, and so

$$f=\frac{\mu+1}{\sqrt{\frac{cc_v\overline{S}_v}{\tilde{\mu}\tilde{S}}\frac{1}{\alpha_1+\mu_1}\left(1+\frac{\alpha_1}{\alpha_2+\mu_2}\left(1+\frac{\alpha_2}{\alpha_3+\mu_3}\left(1+\dots\frac{\alpha_{j-2}}{\alpha_{j-1}+\mu_{j-1}}\left(1+\frac{\alpha_{j-1}}{\gamma+\mu_j}\right)\dots\right)\right)\right)}}.$$

All other parameters being constant, we abbreviate this as $f = \dfrac{\mu+1}{\zeta}$. The Jacobian of the system at the DFE can be written in block form

$$\begin{pmatrix} F-V & 0 \\ -J_3 & -J_4 \end{pmatrix}.$$

Let v and w be the left and right eigenvectors corresponding to the eigenvalue 0. Without loss of generality we can choose these such that $vw = 1$. In the proof of Lemma 3 in [21] we see that we can also say that $v_1, w_i \geq 0$ for $1 \leq i \leq m$. Define

$$a = \sum_{i,j,k=1}^{m} v_i w_j w_k \left(\frac{1}{2} \frac{\partial^2 f_i}{\partial x_j \partial x_k}(x_0, 0) + \sum_{l=m+1}^{n} \varepsilon_{lk} \frac{\partial^2 f_i}{\partial x_j \partial x_l}(x_0, 0) \right),$$

$$b = \sum_{i,j=1}^{n} v_i w_j \frac{\partial^2 f_i}{\partial x_j \partial \mu}(x_0, 0),$$

where ε_{lk}, $l = m+1, \ldots, n$, $k = 1, \ldots, m$ are the $(l-m, k)$ entries of $-J_4^{-1} J_3$, when $R_0 = 1$. The following theorem is found in [21].

Theorem 2.2.1. *In a disease transmission model satisfying conditions 1-5, with the parameter μ as described above, with zero as a simple eigenvalue, and $b \neq 0$ there is a $\delta > 0$ such that*

- *if $a < 0$, then there are locally asymptotically stable endemic equilibria near x_0 for $0 < \mu < \delta$;*
- *if $a > 0$, then there are unstable endemic equilibria near x_0 for $-\delta < \mu < 0$.*

The proof of this theorem relies on restricting to the center manifold described by the equation

$$\boldsymbol{x}(u) = \boldsymbol{x}_0 + uw + \mathcal{O}(u^2).$$

The dynamics restricted to this manifold are given by

$$\dot{u} = au^2 + \mu bu + \mathcal{O}(u^3).$$

For $\delta > 0$ sufficiently small, the dynamics of this ODE match $\dot{u} = au^2 + \mu bu$. It is apparent that this system has a fixed point $u = \dfrac{-b\mu}{a}$, and by Theorem 1.3.3(a) the stability of this new fixed point in the original system is determined by the reduced dynamics, and thus, the conclusion of the theorem. We will prove for (2.3) that $a < 0$ and $b \neq 0$.

Lemma 2.2.2. $b \neq 0$

Proof. First note that the last three components of v are 0. This follows from the fact that

$$J_4 = \begin{pmatrix} \mu_s & 0 & 0 \\ 0 & \widetilde{\mu}_s & 0 \\ 0 & 0 & \mu_r \end{pmatrix}$$

is invertible. Because

$$f = \frac{\mu + 1}{\zeta},$$

the only nonzero derivatives in the expression for b are in the I and $\widetilde{I}$ compartments, since these are the only ones that involve μ. As the last three components of v are 0, we have

$$b = v_1 \left(\sum_{k=1}^{j} w_k \frac{\partial f_1}{\partial I_k \partial \mu} + w_{j+1} \frac{\partial f_1}{\partial \widetilde{I} \partial \mu} + w_{j+1} \frac{\partial f_1}{\partial S \partial \mu} + w_{j+3} \frac{\partial f_1}{\partial \widetilde{S} \partial \mu} + w_{j+4} \frac{\partial f_1}{\partial R \partial \mu} \right)$$

$$+ v_{j+1} \left(\sum_{k=1}^{j} w_k \frac{\partial f_{j+1}}{\partial I_k \partial \mu} + w_{j+1} \frac{\partial f_{j+1}}{\partial \widetilde{I} \partial \mu} + w_{j+2} \frac{\partial f_{j+1}}{\partial S \partial \mu} + w_{j+3} \frac{\partial f_{j+1}}{\partial \widetilde{S} \partial \mu} + w_{j+4} \frac{\partial f_{j+1}}{\partial R \partial \mu} \right).$$

Taking derivatives and evaluating at the DFE gives that

$$b = v_1(0 + w_{j+1} \frac{c_v}{\zeta} + 0 + 0 + 0) + v_{j+1} \left(\sum_{k=1}^{j} w_k \frac{c\overline{S}_v}{\overline{S}\zeta} + 0 + 0 + 0 + 0 \right)$$

$$= v_1 w_{j+1} \frac{c_v}{\zeta} + \frac{v_{j+1} c \overline{S}_v}{\overline{S}\zeta} \sum_{k=1}^{j} w_k.$$

We need to show that this is nonzero. First we claim that at least one of the w_i are nonzero. Suppose not, and that we have $w_1 = \ldots = w_{j+1} = 0$. Then since $v_{j+2} = v_{j+3} = v_{j+4} = 0$,

$$vw = \sum_{i=1}^{j+4} v_i w_i = 0,$$

which is a contradiction. Next, we claim that $v_1 \neq 0$ or $v_{j+1} \neq 0$. Suppose to the contrary that $v_1 = v_{j+1} = 0$. Then, because

$$(v_1, \ldots, v_{j+1}, 0, 0, 0) Df(x_0) = 0,$$

it follows that

$$(0, v_2, \ldots, v_j, 0, 0, 0, 0) Df(x_0) = 0,$$

which implies

$$(v_2, \ldots, v_j) \begin{pmatrix} \alpha_1 & -\alpha_2 - \mu_2 & \ldots & 0 & 0 \\ \vdots & \ddots & \ddots & \vdots & \vdots \\ 0 & 0 & \vdots & -\alpha_{j-1} - \mu_{j-1} & 0 \\ 0 & 0 & \vdots & \alpha_{j-1} & -\gamma - \mu_j \end{pmatrix} = 0.$$

The last column shows that $v_j = 0$, so the expression further reduces to

$$(v_2, \ldots, v_{j-1}) \begin{pmatrix} \alpha_1 & -\alpha_2 - \mu_2 & \ldots & 0 \\ \vdots & \ddots & \ddots & \vdots \\ 0 & 0 & \vdots & -\alpha_{j-1} - \mu_{j-1} \end{pmatrix} = 0.$$

Again, the last column implies that $v_{j-1} = 0$, and so on. This means $v = 0$, but $vw = 1$, which is a contradiction. Then, because all the terms in b are nonnegative, with some of them being nonzero, we arrive at $b \neq 0$. □

Lemma 2.2.3. $a < 0$.

Proof. First, note that

$$J_3 = \begin{pmatrix} 0 & \dots & 0 & fc_v \\ \dfrac{fc\overline{S}_v}{\overline{S}} & \dots & \dfrac{fc\overline{S}_v}{\overline{S}} & 0 \\ 0 & \dots & \gamma & 0 \end{pmatrix},$$

and

$$J_4^{-1} = \begin{pmatrix} \dfrac{1}{\mu_s} & 0 & 0 \\ 0 & \dfrac{1}{\widetilde{\mu}_s} & 0 \\ 0 & 0 & \dfrac{1}{\mu_r} \end{pmatrix}.$$

Thus,

$$-J_4^{-1}J_3 = \begin{pmatrix} 0 & \dots & 0 & \dfrac{fc_v}{\mu_s} \\ \dfrac{fc\overline{S}_v}{\widetilde{\mu}_s\overline{S}} & \dots & \dfrac{fc\overline{S}_v}{\widetilde{\mu}_s\overline{S}} & 0 \\ 0 & \dots & \dfrac{\gamma}{\mu_r} & 0 \end{pmatrix}.$$

We can list the nonzero elements of this matrix : $\varepsilon_{1(j+1)}, \varepsilon_{21}, \dots, \varepsilon_{2j}, \varepsilon_{3j}$. The second derivatives of the infected components with respect to an infected variable are all zero, since the equations are first order in all inected variables. When differentiating with respect to an infected variable and an uninfected variable, the derivatives of the I_2 through I_j components will be zero as they contain no uninfected variables. The nonzero derivatives are

$$\frac{\partial^2 f_1}{\partial\widetilde{I}\partial S} = \frac{fc_v}{\overline{S}},$$

$$\frac{\partial^2 f_{j+1}}{\partial I_k\partial\widetilde{S}} = \frac{fc}{\overline{S}}.$$

So, then

$$a = \sum_{i,j,k=1}^{j+1} v_i w_j w_k \left(0 - \frac{f^2c_v^2}{\overline{S}\mu_s} - \sum_{l=1}^{j} \frac{f^2c^2\overline{S}_v}{\overline{S}^2\widetilde{\mu}_s}\right)$$

$$= - \sum_{i,j,k=1}^{j+1} v_i w_j w_k \left(\frac{f^2 c_v^2}{\overline{S}\mu_s} + \frac{f^2 c^2 \overline{S}_v}{\overline{S}^2 \widetilde{\mu}_s}] \right).$$

As we have already shown, the $v_i, w_i \geq 0$, and since the parameters are positive, $a < 0$. □

We can then apply Theorem 2.2.1 to our system, which states that there are asymptotically stable equilibria near the DFE when R_0 is sufficiently close to, but greater than 1.

2.3 Existence of the Endemic Equilibria

Having established the existence of a branch of stable endemic equilibria (EE) near the bifurcation, there is a natural question regarding the behavior of these EE outside of the neighborhood of the bifurcation. We want to discover how the local branch found in the previous section extends for larger (or smaller) values of R_0. The complex form of R_0 and the arbitrary number of equations appear to make this problem quite difficult. But the majority of the equations have a simple linear form, and from these we can derive a simple recurrence relation for nontrivial equilibrium values of the I_2 through I_{j+1} in terms of I_1. What remains is a fixed number of equations to solve. We make the following proposition.

Proposition 2.3.1. *Given any $I_1 \geq 0$, there exist unique values $S, \widetilde{S}, R, I_2, \ldots, I_j$, and $\widetilde{I}$ such that*

$$S' = \widetilde{S}' = R' = I_2' = \ldots = I_j' = \widetilde{I}' = 0.$$

Proof. Let I_1 be fixed. Consulting the equations for I_2 through I_{j-1} we see that

$$I_k' = 0 \iff I_k = \frac{\alpha_{k-1} I_{k-1}}{\alpha_k + \mu_k} = c_{k-1} I_{k-1} \text{ for } 2 \leq k \leq j-1.$$

For I_j,

$$I_j' = 0 \iff I_j = \frac{\alpha_{j-1} I_{j-1}}{\gamma + \mu_j} = c_{j-1} I_{j-1},$$

and

$$R' = 0 \iff R = \frac{\gamma I_j}{\mu_r} = c_j I_j.$$

Then for $I_2, \ldots, I_j, R$ there is a simple multiplicative recurrence relation which is solved easily for I_k and R, namely

$$I_k = c_{k-1} \ldots c_1 I_1; \quad R = c_k \ldots c_1 I_1.$$

Thus the unique steady states for $I_2, \ldots I_j$ and R are determined uniquely by I_1. Now observe that at a steady state, inserting $c_0 = 1$,

$$\sum_{k=1}^{j} I_k = \sum_{k=1}^{j} c_{k-1} \ldots c_0 I_1.$$

Let $\xi = \sum_{k=1}^{j} c_{k-1} \ldots c_0$ and $\sum_{k=1}^{j} I_k = \xi I_1$. Then we have that

$$\widetilde{S}' = 0 \iff \widetilde{\mu}_s(\overline{S}_v - \widetilde{S}) - \frac{fc\widetilde{S}}{\overline{S}}\xi I_1 = 0,$$

and thus,

$$\widetilde{S} = \frac{\widetilde{\mu}_s \overline{S}_v}{\widetilde{\mu}_s + \frac{fcI_1}{\overline{S}}\xi}.$$

So, then $\widetilde{S}$ is uniquely determined by I_1. Now, since $\widetilde{I} = \overline{S}_v - \widetilde{S}$, we should confirm that this value gives $\widetilde{I}' = 0$ as follows.

$$\widetilde{I}' = \frac{fc\widetilde{S}I_1\xi}{\overline{S}} - \widetilde{\mu}(\overline{S}_v - \widetilde{S}) = \widetilde{S}\left(\frac{fcI_1\xi}{\overline{S}} + \widetilde{\mu}\right) - \widetilde{\mu}_s\overline{S}_v,$$

but since $\widetilde{\mu} = \widetilde{\mu}_s$, and given the equilibrium value for $\widetilde{S}$, we have

$$\widetilde{S}\left(\frac{fcI_1\xi}{\overline{S}} + \widetilde{\mu}_s\right) - \widetilde{\mu}_s\overline{S}_v = \widetilde{\mu}_s\overline{S}_v - \widetilde{\mu}_s\overline{S}_v = 0,$$

and I_1 uniquely determines the equilibrium value for $\widetilde{I}$. Lastly, we have that

$$S' = 0 \iff S = \frac{\mu_s \overline{S}}{\mu_s + \frac{fc_v\widetilde{I}}{\overline{S}}},$$

and as $\widetilde{I}$ is uniquely determined by I_1, then so is S. □

The consequence of this proposition is that the number of equilibrium points is determined by the number of values of I_1 such that $I_1' = 0$. Furthermore notice that $I_1 = 0$ implies that $S = \widetilde{S} = R = I_2 = \ldots = I_j = \widetilde{I} = 0$, and we have generated the DFE. So, we will only be looking for values such that $I_1 > 0$. We will also want to see how these values depend on R_0, so it will be useful to note the following form:

$$R_0 = f\sqrt{\frac{cc_v\overline{S}_v}{\overline{S}\widetilde{\mu}}\frac{1}{\alpha_1+\mu_1}\xi}.$$

Now, $I_1' = 0$ if and only if

$$I_1(\alpha_1+\mu_1) = \frac{fc_v\widetilde{I}S}{\overline{S}}.$$

But since we also have $S' = 0$, we get that

$$\frac{fc_v\widetilde{I}S}{\overline{S}} = \mu_s(\overline{S} - S).$$

Thus,

$$I_1 = \frac{\mu_s(\overline{S}-S)}{\alpha_1+\mu_1} = \frac{\mu_s\overline{S}}{\alpha_1+\mu_1}\left(1 - \frac{\mu_s}{\mu_s + \frac{fc_v\widetilde{I}}{\overline{S}}}\right) = \frac{\mu_s\overline{S}}{\alpha_1+\mu_1}\left(\frac{fc_v\widetilde{I}}{\mu_s\overline{S} + fc_v\widetilde{I}}\right).$$

Now, at an equilibria, we can write $\widetilde{I}$ uniquely in terms of I_1:

$$\widetilde{I} = \overline{S}_v - \widetilde{S} = \overline{S}_v - \frac{\widetilde{\mu}_s\overline{S}_v}{\widetilde{\mu}_s + \frac{fcI_1}{\overline{S}}\xi} = \overline{S}_v\left(1 - \frac{\widetilde{\mu}_s}{\widetilde{\mu}_s + \frac{fcI_1}{\overline{S}}\xi}\right) = \frac{\overline{S}_v fcI_1\xi}{\overline{S}\widetilde{\mu}_s + fcI_1\xi}.$$

Substituting this back into the above expression for I_1 we obtain

$$I_1 = \frac{\mu_s \overline{S}}{\alpha_1 + \mu_1} \left(\frac{\overline{S}_v f^2 c c_v I_1 \xi}{\overline{S}\mu_s(\overline{S}\widetilde{\mu}_s + fcI_1\xi) + \overline{S}_v f^2 c c_v I_1 \xi} \right).$$

Because we are interested in solutions where $I_1 \neq 0$, we can divide both sides of the equation by I_1 and multiply the denominator over:

$$\overline{S}^2 \mu_s \widetilde{\mu}_s + fc\overline{S}\mu_s \xi I_1 + \overline{S}_v f^2 c c_v \xi I_1 = \frac{\mu_s \overline{S}\,\overline{S}_v f^2 c c_v \xi}{\alpha_1 + \mu_1}.$$

Thus,

$$\begin{aligned} I_1 &= \frac{1}{fc\overline{S}\mu_s\xi + \overline{S}_v f^2 c c_v \xi} \left(\frac{\mu_s \overline{S}\,\overline{S}_v f^2 c c_v \xi}{\alpha_1 + \mu_1} - \overline{S}^2 \mu_s \widetilde{\mu}_s \right) \\ &= \frac{\overline{S}^2 \mu_s \widetilde{\mu_s}}{fc\overline{S}\mu_s\xi + \overline{S}_v f^2 c c_v \xi} \left(\frac{\overline{S}_v f^2 c c_v \xi}{\widetilde{\mu}_s \overline{S}(\alpha_1 + \mu_1)} - 1 \right), \end{aligned}$$

since $\widetilde{\mu}_s = \widetilde{\mu}$ this can be rewritten as

$$I_1 = \frac{\overline{S}^2 \mu_s \widetilde{\mu_s}(R_0^2 - 1)}{fc\overline{S}\mu_s\xi + \overline{S}_v f^2 c c_v \xi}.$$

Thus, we only have a nonzero equilibrium when $R_0 \neq 1$, and when $R_0 < 1$ the nonzero equilibrium is negative, and when $R_0 > 1$ there is one endemic equilibrium. The content of the above discussion is contained in the following theorem:

Theorem 2.3.2. *Given a simple relapsing disease model, for every value of $R_0 > 1$ there is one nonzero EE that is locally asymptotically stable near $R_0 = 1$.*

2.4 Discussion

Using the next generation method and standard matrix computation methods we have found a form for R_0 of vector-borne relapsing diseases with an arbitrary number of relapses. From this we conclude that R_0 increases as the number of relapses of the disease increases. We have also

taken advantage of results in [21] to show the existence of a branch of endemic equilibria that are locally asymptotically stable for R_0 sufficiently close to 1. A straightforward calculation also demonstrated that only one such branch of endemic equilibria can exist. Both of these results are independent of the number of relapses.

The computation of R_0 relied on the assumption of a constant population of the hosts. This assumption was shown to be equivalent to equal death rates in the infected host compartments. Allowing for variable death rates among the compartments changes the form of the Jacobians that make up the next generation matrix, though future work may show that the computations for R_0 are similar. However, in the case of equal death rates the constant population is found to be attracting and thus we need only study the dynamics restricted to this constant population.

2.5 Simulation

Simulations were constructed in MATLAB using estimated parameter values for the spread of TBRF among pine squirrels found in [14] with two relapses of the disease. With the given data $R_0 \approx .8396$. This number can be increased above one by running simulations with more than two relapses. Graphical results of the simulation can be found in Figure 2.5.1. It is observed that the dynamics are straightforward in this case. In this particular simulation we began with no infected hosts and after a peak infection the number of infected hosts decreases monotonically to 0. When the initial conditions are changed, the dynamics seem to remain the same. We can begin "far" (50 susceptibles, 400 infected, 200 in the relapses) from the DFE and still get the monotonic decline of the infections to 0 (Figure 2.5.2), suggesting that the DFE is globally stable when $R_0 < 1$. There are Lyapunov functions for vector-borne diseases; see [18], but the fact that the infected compartments in the relapsing model cannot be collapsed into a single infected variable keeps these forms from working in this case. We can make $R_0 > 1$ by increasing the biting rate from $f = .33$ to $f = .5$ to get $R_0 \approx 1.2712$. As

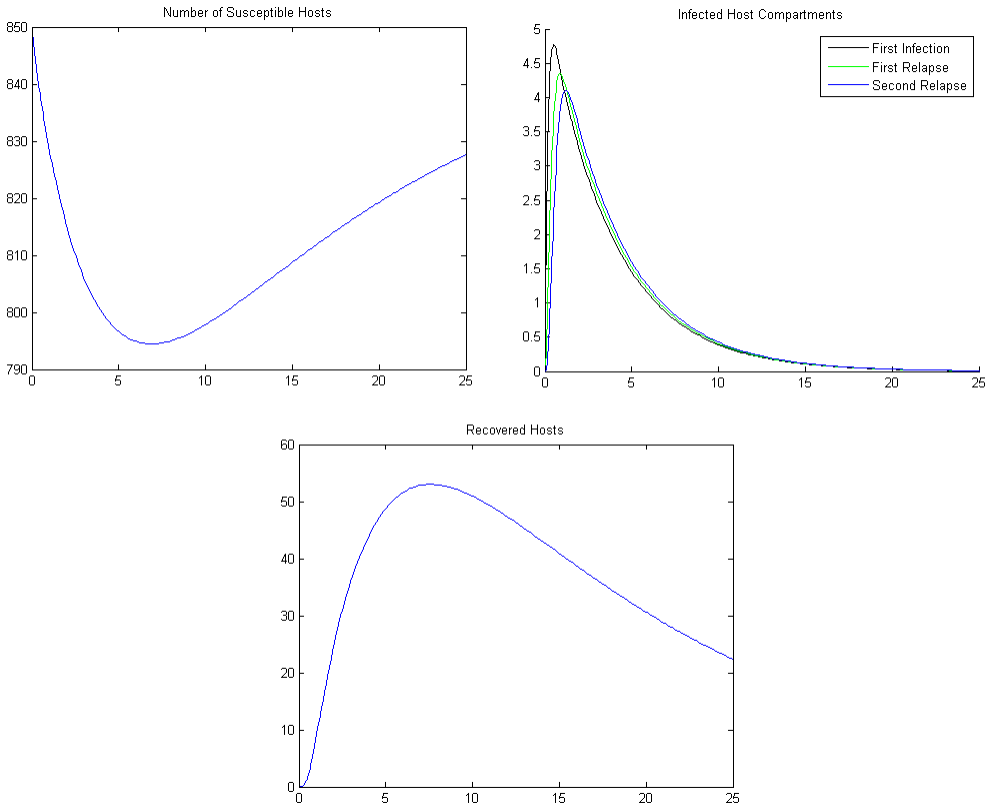

Figure 2.5.1: A simulation of the spread of TBRF with two relapses among pine squirrels on Wild Horse Island (WHI), Flathead Lake, MT, with $R_0 < 1$

we proved above, there is now an endemic equilibrium that is locally asymptotically stable. See Figure 2.5.3 for the simulations. Note the presence of oscillations after the fast peak of the disease. These observations are in line with the results of [18] suggesting future research along those lines. We showed above that there is only one branch of equilibria and we can plot the total number of infected hosts at the EE against R_0 and see that, with this data, it seems to level out around 50 and, as f increases, we could find no evidence that there was a change in the stability of the EE. As before, initial conditions "far" from the DFE are drawn into the EE, suggesting global stability e.g. Figure 2.5.4. For this figure, recall that the number of infected in each compartment at the EE is around 5, so even though the graph may appear to go to 0, that is just a result of the vertical scale of the figure.

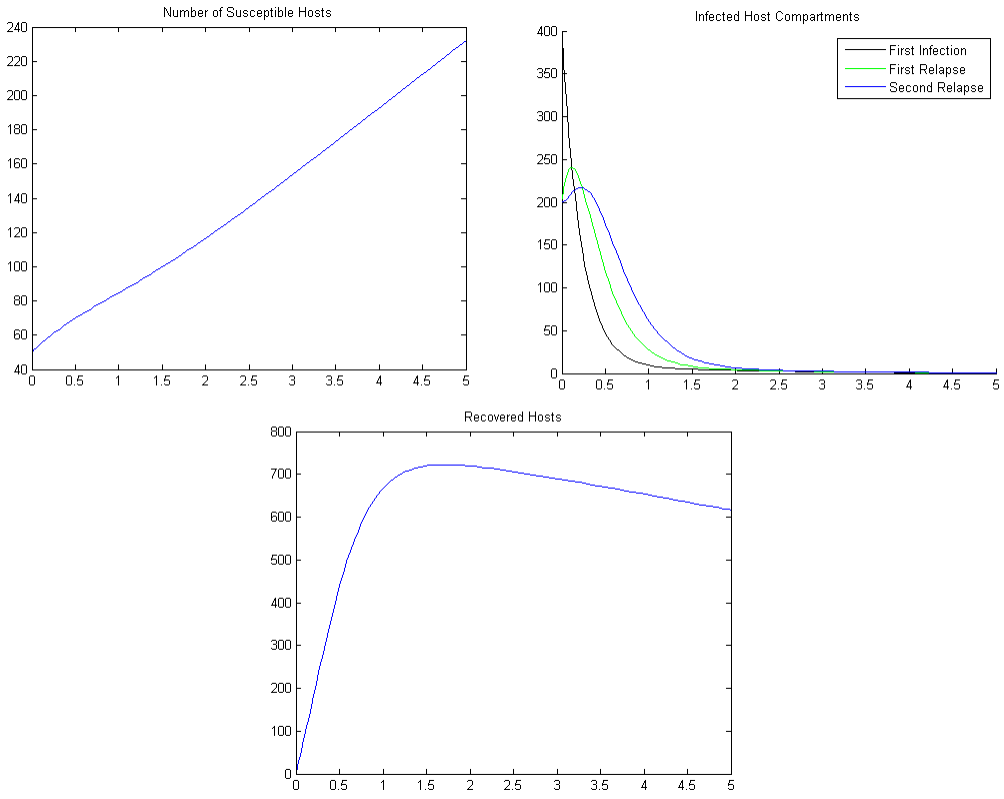

Figure 2.5.2: A simulation of the spread of TBRF with two relapses among pine squirrels on WHI with initial conditions "far" from the DFE.

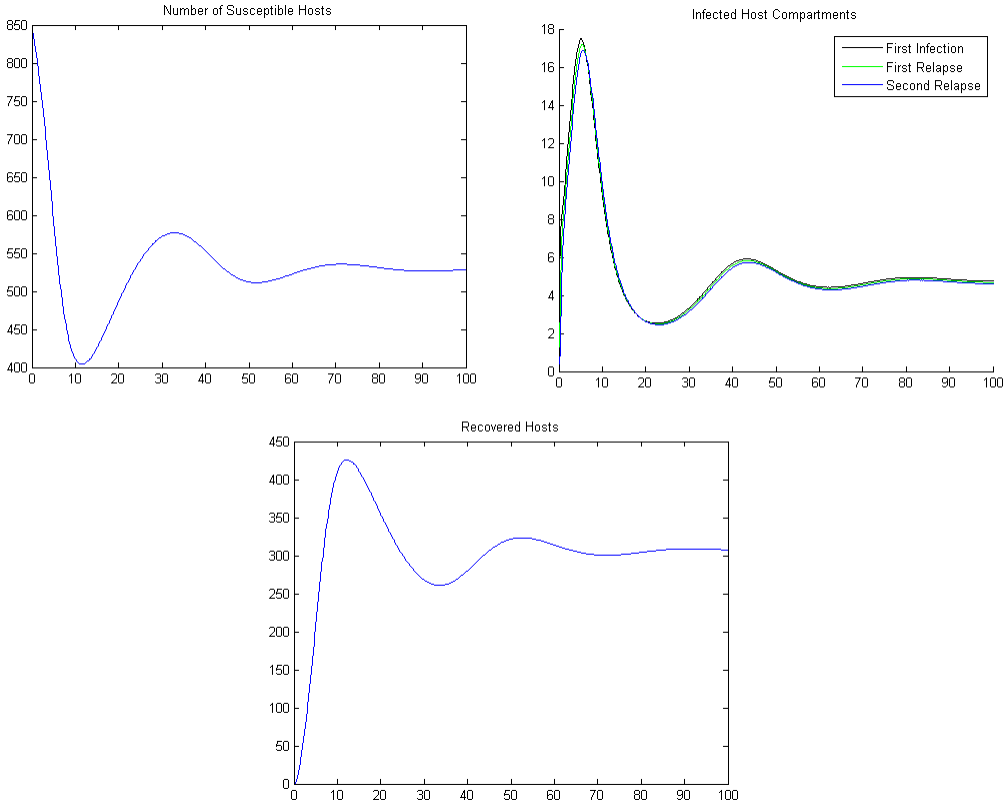

Figure 2.5.3: A simulation of the spread of TBRF with two relapses among pine squirrels on WHI with $R_0 > 1$.

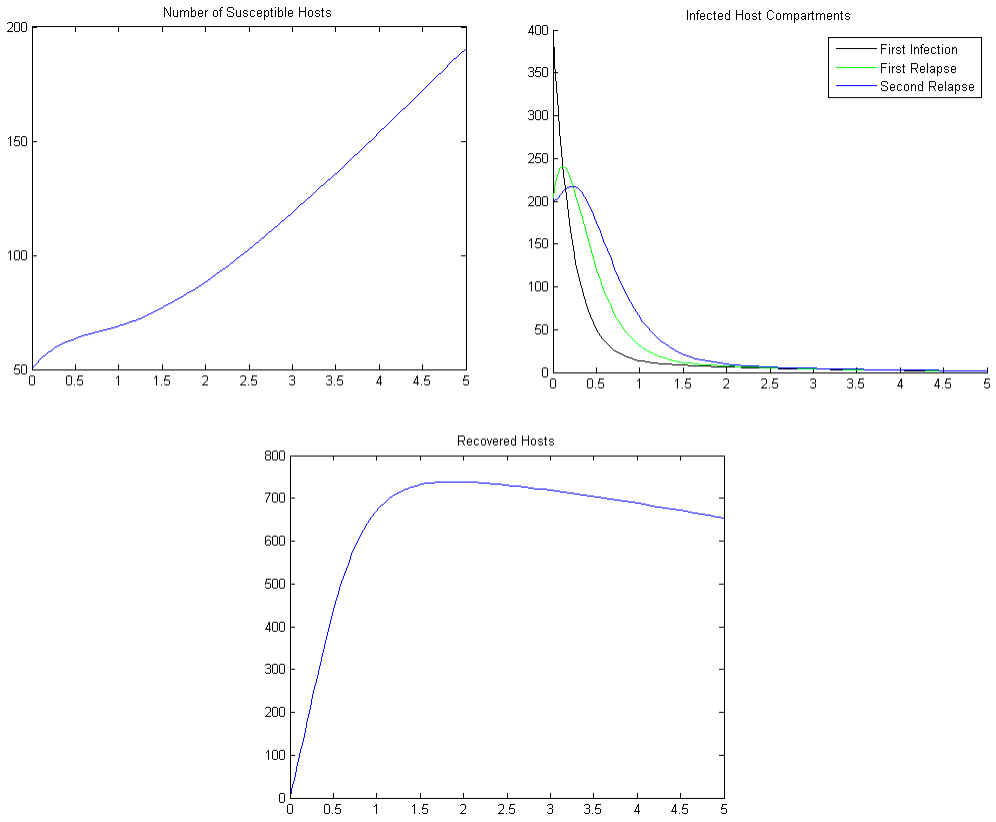

Figure 2.5.4: A simulation of the spread of TBRF with two relapses among pine squirrels on WHI with $R_0 > 1$ and initial conditions "far" from the DFE.

Chapter 3

Variations on the Simple Model

3.1 Removal to the Recovered Compartment

In TBRF there is some variation in the number of relapses in infected hosts. We will introduce this variation into our model by allowing individuals to leave an infected compartment and go directly to the recovered state. Let $\theta_i \geq 0$ be the transfer rate to the recovered compartment out of the ith infected compartment. The equations change only slightly: the μ_i get replaced with $\mu_i + \theta_i$ and the recovered equation changes.

$$\begin{aligned}
S' &= \beta(N) - fc_v\widetilde{I}\frac{S}{N} - \mu_s S, \\
I_1' &= fc_v\widetilde{I}\frac{S}{N} - \alpha_1 I_1 - (\mu_1 + \theta_1)I_1, \\
I_2' &= \alpha_1 I_1 - \alpha_2 I_2 - (\mu_2 + \theta_2)I_2, \\
&\vdots \\
I_{j-1}' &= \alpha_{j-2} I_{j-2} - \alpha_{j-1} I_{j-1} - (\mu_{j-1} + \theta_{j-1})I_{j-1}, \\
I_j' &= \alpha_{j-1} I_{j-1} - \gamma I_j - \mu_j I_j, \\
R' &= \sum_{i=1}^{j-1} \theta_i I_i + \gamma I_j - \mu_r R.
\end{aligned} \tag{3.1}$$

The vector equations remain unchanged:

$$\begin{aligned} \widetilde{S}' &= \beta_v(\widetilde{N}, N) - \frac{fc\widetilde{S}}{N}\sum_{k=1}^{j} I_k - \widetilde{\mu}_s\widetilde{S}, \\ \widetilde{I}' &= \frac{fc\widetilde{S}}{N}\sum_{k=1}^{j} I_k - \widetilde{\mu}\widetilde{I}. \end{aligned} \tag{3.2}$$

Under the assumption that the population is constant ($N = \overline{S}$) we sum these equations to get

$$0 = N' = \beta(\overline{S}) - \sum_{i=1}^{j-1} \mu_i I_i - \gamma I_j - \mu_r R,$$

and following the proof of Proposition 2.0.1 on page 26 we get that all the $\mu_i = \mu_r = \mu_s$. We can also see from that proof that if we assume $\mu_i = \mu_r = \mu_s$, then we have that $N = \overline{S}$ is invariant.

Now we want to show that this system satisfies the necessary conditions for the use of the next generation method.

Proposition 3.1.1. *The system* (3.1), (3.2) *satisfies Conditions 1-5.*

Proof. After rearranging the system as in the previous section the first four conditions are easily checked. Condition 5 follows from the fact that even with the addition of the infected terms in the recovered equation it contains no other susceptible variables, and thus, the Jacobian will still be lower triangular with negative values along the diagonal. Hence the fifth condition is met. □

Now we move ahead to compute R_0. However, note that this process involves only the infected equations and not the recovered equation. So the process is exactly the same as in the last section, but with μ_i replaced by $\mu_i + \theta_i$. Thus when we have removal to the recovered

compartment:

$$R_0 = f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\frac{1}{\alpha_1+\mu_1+\theta_1}\left(1+\frac{\alpha_1}{\alpha_2+\mu_2+\theta_2}\left(1+\frac{\alpha_2}{\alpha_3+\mu_3+\theta_3}\left(1+\ldots\frac{\alpha_{j-2}}{\alpha_{j-1}+\mu_{j-1}+\theta_{j-1}}\left(1+\frac{\alpha_{j-1}}{\gamma+\mu_j}\right)\ldots\right)\right)\right)}.$$

As one might expect, removal to the recovered compartment drives down R_0 since the $\theta_i \geq 0$ only appear in the denominators. The magnitude of this contribution is determined by the size of θ_i compared to α_{i-1}. If the recovery rate from the ith compartment is small compared to the rate at which individuals are being transferred into that compartment, then it has little effect on the spread of the disease. Conversely, if the direct recovery from the ith infected compartment is large compared to the rate at which individuals are transferred in, it will result in a more significant mitigation of the disease spread.

3.1.1 The Bifurcation at $R_0 = 1$

There are still questions about which results from the previous section are easily extended to the case with removal to the recovered compartment, e.g., the transcritical bifurcation at $R_0 = 1$ and the number of EE. As an opening step we consider the Jacobian matrix for this system:

$$\begin{pmatrix}
\alpha_1+\mu_1+\theta_1 & 0 & 0 & \ldots & 0 & 0 & -fc_v & 0 & 0 & 0 \\
-\alpha_1 & \alpha_2+\mu_2+\theta_2 & 0 & \ldots & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & -\alpha_2 & \alpha_3+\mu_3+\theta_3 & \ldots & 0 & 0 & 0 & 0 & 0 & 0 \\
\vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\
0 & 0 & 0 & \ldots & -\alpha_{j-1} & \gamma+\mu_j & 0 & 0 & 0 & 0 \\
-\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \ldots & -\frac{fc\bar{S}_v}{\bar{S}} & -\frac{fc\bar{S}_v}{\bar{S}} & \widetilde{\mu} & 0 & 0 & 0 \\
0 & 0 & 0 & \ldots & 0 & 0 & fc_v & \mu_s & 0 & 0 \\
\frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & \ldots & \frac{fc\widetilde{S}}{N} & \frac{fc\widetilde{S}}{N} & 0 & 0 & \widetilde{\mu}_s & 0 \\
-\theta_1 & -\theta_2 & -\theta_3 & \ldots & -\theta_{j-1} & -\gamma & 0 & 0 & 0 & \mu_r
\end{pmatrix}$$

To apply Theorem 2.2.1 we need to know the multiplicity for the 0 eigenvalue for this matrix. However, this matrix has the diagonal form that we have seen before:

$$Df(\boldsymbol{x}_0) = \begin{pmatrix} T & 0 \\ L & D \end{pmatrix},$$

and as we have mentioned before the multiplicity of the 0 eigenvalue is the sum of the multiplicities of the 0 eigenvalue of the diagonal blocks. D is a lower triangular matrix with nonzero diagonal entries, and thus does not have 0 as an eigenvalue. So then the multiplicity of the 0 eigenvalue of the Jacobian is determined by the multiplicity of the 0 eigenvalue of T, which is precisely the matrix that we dealt with in the previous section. Hence, based on previous calculations we can conclude that when we add in removal to the recovered compartment, the Jacobian still has a simple 0 eigenvalue.

Note that the proof that $b \neq 0$ (as defined in the previous sections) is precisely the same here as in the previous case. While we now have more nonzero elements in $-J_4^{-1}J_3$, the $\epsilon_{3,k}$, are cancelled out since the associated second derivatives in the equation for a are the derivative of an infected variable with respect to the recovered variable, and thus are 0. Thus, the computation for a is exactly the same and gives $a < 0$. Hence, we have the following Corollary of our previous computations.

Corollary 3.1.2. *The nontrivial DFE of the system* (3.1), (3.2) *undergoes a transcritical bifurcation as* R_0 *goes above 1, and has a branch of locally asymptotically stable EE for* R_0 *sufficiently close to 1.*

3.2 Relapsing Diseases with Latency

The most common example of a relapsing disease, TBRF, is driven by antigenic variation of *Borellia* spirochetes within the host. Preceding this change is the host's immune response

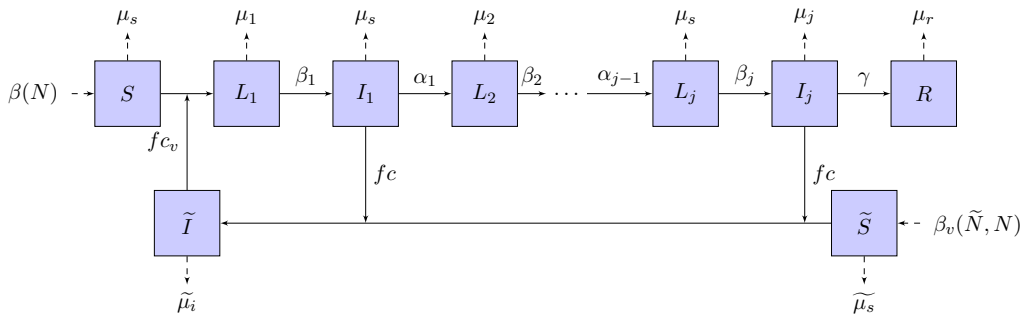

Figure 3.2.1: A compartmental model for a vector-borne relapsing disease with latency.

which nearly eradicates the bacteria from the host. However, *Borellia* can initiate a full infection with a single spirochete [8]. These factors combine and result in a week of apparent health between relapses of TBRF. In this stage the lack of spirochetes in the blood of the host means that any susceptible tick that bites the host will not become infected. Hosts in this latently infected stage will not drive the infection of susceptible vectors. We now wish to quantify the effect that this latent stage has on the spread of a relapsing disease.

3.2.1 Equations and Assumptions

The equations which model a vector-borne relapsing disease with latency are very similar to those which we have seen in the previous chapter. A conceptual model can be seen in Figure 3.2.1. The equations from this model are given as follows. For the hosts:

$$\begin{aligned}
S' &= \beta(N) - fc_v\widetilde{I}\frac{S}{N} - \mu_s S,\\
L_1' &= fc_v\widetilde{I}\frac{S}{N} - \beta_1 L_1 - \mu_s L_1,\\
I_1' &= \beta_1 L_1 - \alpha_1 I_1 - \mu_1 I_1,\\
L_2' &= \alpha_1 I_1 - \beta_2 L_2 - \mu_s L_2,\\
I_2' &= \beta_2 L_2 - \alpha_2 I_2 - \mu_2 I_2,\\
&\vdots\\
I_{j-1}' &= \beta_{j-2} I_{j-2} - \alpha_{j-1} I_{j-1} - \mu_{j-1} I_{j-1},\\
L_j' &= \alpha_{j-1} I_{j-1} - \beta_j L_j - \mu_s L_j,\\
I_j' &= \beta_j L_j - \gamma I_j - \mu_j I_j,\\
R' &= \gamma I_j - \mu_r R
\end{aligned} \tag{3.3}$$

And the vector equations are

$$\begin{aligned}
\widetilde{S}' &= \beta_v(\widetilde{N}, N) - \frac{fc\widetilde{S}}{N}\sum_{k=1}^{j} I_k - \widetilde{\mu}_s\widetilde{S},\\
\widetilde{I}' &= \frac{fc\widetilde{S}}{N}\sum_{k=1}^{j} I_k - \widetilde{\mu}\widetilde{I}.
\end{aligned} \tag{3.4}$$

One unique assumption that we are making in this case is that the death rates in the latent compartments are necessarily equal to the death rate for the susceptible population, i.e., you are truly healthy in between relapses. Otherwise the rest of the previous assumptions are the same. $\beta(N)$ and $\widetilde{\beta}(\widetilde{N}, N)$ are the same logistic growth rates as before which means that

$$(S, L_1, I_1, \ldots, L_j, I_j, R, \widetilde{S}, \widetilde{I}) = (\overline{S}, 0, 0, \ldots, 0, \overline{S}_v, 0)$$

is the DFE. As before, we will make the natural assumptions in this model that $\mu_i \geq \mu_s$, $\mu_r \geq \mu_s$, and that $\widetilde{\mu} \geq \widetilde{\mu}_s$. This leads to the same result in the case with no latency:

Proposition 3.2.1. *For the system* (3.3), (3.4) *the manifold* $N = \overline{S}$ *is invariant if and only if* $\mu_s = \mu_i$ *and* $\mu_s = \mu_r$.

The proof is exactly the same as Proposition 2.0.1.

We will seek to compute the reproductive ratio for the latent system (call it R_0^L) using the next generation method from the previous chapter. First, we must show that the method is applicable to this system.

Proposition 3.2.2. *The system* (3.3), (3.4) *satisfies conditions 1-5.*

Proof. The first four conditions are easily checked. Condition 5 follows from the fact that the Jacobian evaluated at the DFE has the same form as in the case with no latency with the exception that the row corresponding to $\widetilde{I}$ and $\widetilde{S}$ have alternating zero-nonzero terms. Hence it is still lower triangular and has negative eigenvalues, which means that condition 5 is satisfied. □

Having confirmed these conditions we have justified the use of the next generation method to compute R_0^L.

3.2.2 Computing R_0^L

As in the previous chapter we consider only the infected compartments and split their equations into new infections and transferred infections, writing the system as $\dot{\boldsymbol{x}} = \boldsymbol{w}(\boldsymbol{x}) - \boldsymbol{v}(\boldsymbol{x})$

where

$$\boldsymbol{x} = \begin{pmatrix} L_1 \\ I_1 \\ L_2 \\ I_2 \\ \vdots \\ I_j \\ \widetilde{I} \end{pmatrix}, \quad \boldsymbol{w} = \begin{pmatrix} \frac{fc_v\widetilde{I}S}{\overline{S}} \\ 0 \\ 0 \\ 0 \\ \vdots \\ 0 \\ \frac{fc\widetilde{S}}{,}\overline{S}\sum_{i=1}^{j} I_i \end{pmatrix} \quad \boldsymbol{v} = \begin{pmatrix} (\beta_1+\mu_s)L_1 \\ (\alpha_1+\mu_1)I_1 - \beta_1 L_1 \\ (\beta_2+\mu_s)L_2 - \alpha_1 I_1 \\ (\alpha_2+\mu_2)I_2 - \beta_2 L_2 \\ \vdots \\ (\gamma+\mu_j)I_j - \beta_j L_j \\ \widetilde{\mu}\widetilde{I} \end{pmatrix}.$$

Computing the Jacobians and evaluating them at the DFE we get a very familiar form

$$W = \begin{pmatrix} 0 & 0 & 0 & 0 & \dots & 0 & fc_v \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ 0 & \frac{fc\overline{S}_v}{\overline{S}} & 0 & \frac{fc\overline{S}_v}{\overline{S}} & \dots & 0 & \frac{fc\overline{S}_v}{\overline{S}} \end{pmatrix},$$

$$V = \begin{pmatrix} \beta_1+\mu_s & 0 & 0 & 0 & \dots & 0 & 0 & 0 \\ -\beta_1 & \alpha_1+\mu_1 & 0 & 0 & \dots & 0 & 0 & 0 \\ 0 & -\alpha_1 & \beta_2+\mu_s & 0 & \dots & 0 & 0 & 0 \\ 0 & 0 & -\beta_2 & \alpha_2+\mu_2 & \dots & 0 & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \dots & -\beta_j & \gamma+\mu_j & 0 \\ 0 & 0 & 0 & 0 & \dots & 0 & 0 & \widetilde{\mu} \end{pmatrix}.$$

As we saw from the previous chapters, we need to compute the spectral radius of WV^{-1}. Notice that V has the same form as for a relapsing disease with $2j$ relapses and no latency. We can use the results of the previous chapter to find the general form for the elements of V^{-1}. Furthermore, we note that the action of W on V will now be to add alternating rows

together. We can extend the calculations from the previous chapter by letting δ_k be the sum of the alternating elements in the kth column of V^{-1}. The construction of the characteristic polynomial is identical, which means that finding the largest eigenvalue amounts to finding the last element of the last column of V^{-1} and the sum of every other element in the first $2j$ rows of first column of V^{-1}. But since V has the same form as in Chapter 2, we can use the general form we computed there. As a result we have that

$$R_0^L = f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\sum_{k=1}^{j}\prod_{l=1}^{k}\left(\frac{\beta_l}{\beta_l+\mu_s}\right)\left(\frac{\alpha_{l-1}}{\alpha_l+\mu_l}\right)}$$

Note that R_0^L is similar to R_0 in form, and so the observations that we made previously regarding R_0 also hold for R_0^L. The inclusion of the $\dfrac{\beta_l}{\beta_l+\mu_s}$ factors into the sum gives that $R_0^L < R_0$. The addition of latent states has the net effect of decreasing the infectiveness of the disease. However, in the case of humans this effect is negligible since the rate of transfer out of the latent compartments is on the order of weeks, while the death rate is on the order of years. Since μ_s is small compared to β_l we get that

$$\frac{\beta_l}{\beta_l+\mu_s} \approx 1,$$

and thus, in the human case $R_0^L \approx R_0$.

3.3 The Coupled Host-Vector System

On WHI there are two species of animal that contribute to the spread of TBRF on the island: the pine squirrel and the deer mouse [14]. The presence of ticks in their nests, and potential interaction through visiting other nests leads to complicated infected interactions among the members of both species. We want to adjust our previous model to account for these interactions. We do this by coupling two systems together as in [14].

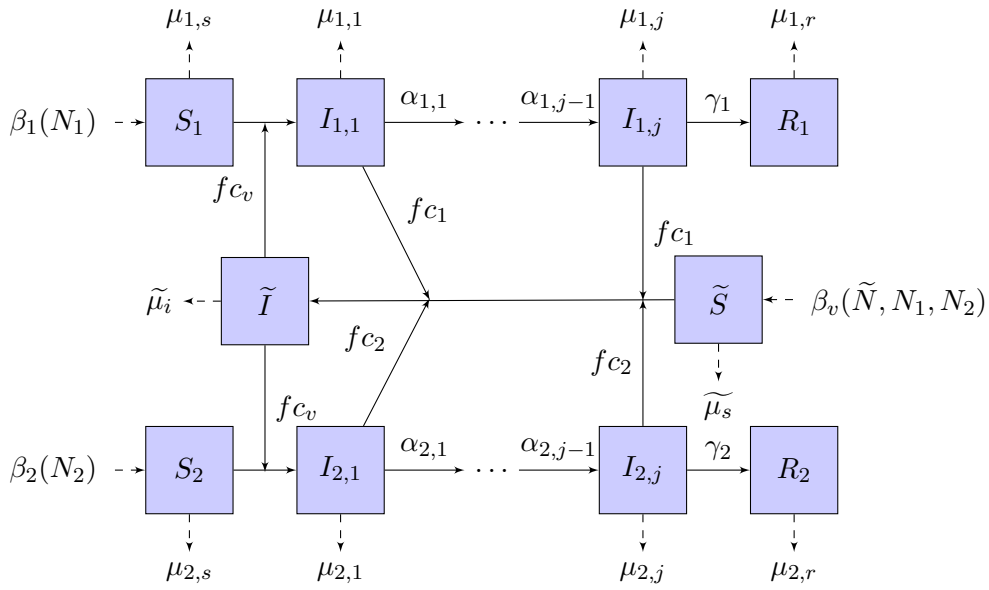

Figure 3.3.1: Conceptual diagram for a coupled host-vector system with $j-1$ relapses.

We consider two host species N_1 and N_2. These species can be infected by the vector species $\widetilde{N}$, but will not spread the disease between their respective populations, nor will the disease jump host species without first going through the vector species i.e. there is no lateral transmission of the disease among the hosts. Once a susceptible host (S_i, $i = 1, 2$) is infected it will go through $j-1$, relapses through j infected states $I_{i,k}$ for $1 \leq k \leq j$, and then recover (R_i). We will assume that both the host species go through the same number of relapses. The transmission of the disease from the vector to the host is controlled by the biting rate f and the vector competency c_v. We will assume that the vector competency is the same for both species. That is, both species have an equal chance of contracting the disease when bitten by an infected vector. However, we will not assume in general that the converse is true, that when a susceptible vector bites an infected host there is an equal chance of contracting the disease from both host species. We represent the corresponding host competencies by c_i. Figure 3.3.1 gives a conceptual diagram for this model. The equations [14] for the first host

species are

$$\begin{aligned}
S_1' &= \beta_1(N_1) - fc_v\widetilde{I}\frac{S_1}{N_1} - \mu_{1,s}S_1,\\
I_{1,1}' &= fc_v\widetilde{I}\frac{S_1}{N_1} - \alpha_{1,1}I_{1,1} - \mu_{1,1}I_{1,1},\\
I_{1,2}' &= \alpha_{1,1}I_{1,1} - \alpha_{1,2}I_{1,2} - \mu_{1,2}I_{1,2},\\
&\vdots\\
I_{1,j-1}' &= \alpha_{1,j-2}I_{1,j-2} - \alpha_{1,j-1}I_{1,j-1} - \mu_{1,j-1}I_{1,j-1},\\
I_{1,j}' &= \alpha_{1,j-1}I_{1,j-1} - \gamma_1 I_{1,j} - \mu_{1,j}I_{1,j},\\
R_1' &= \gamma_1 I_{1,j} - \mu_{1,r}R_1.
\end{aligned} \tag{3.5}$$

It is a very similar set of equations for the second host species:

$$\begin{aligned}
S_2' &= \beta_2(N_2) - fc_v\widetilde{I}\frac{S_2}{N_2} - \mu_{2,s}S_2,\\
I_{2,1}' &= fc_v\widetilde{I}\frac{S_2}{N_2} - \alpha_{2,1}I_{2,1} - \mu_{2,1}I_{2,1},\\
I_{2,2}' &= \alpha_{2,1}I_{2,1} - \alpha_{2,2}I_{2,2} - \mu_{2,2}I_{2,2},\\
&\vdots\\
I_{2,j-1}' &= \alpha_{2,j-2}I_{2,j-2} - \alpha_{2,j-1}I_{2,j-1} - \mu_{2,j-1}I_{2,j-1},\\
I_{2,j}' &= \alpha_{2,j-1}I_{2,j-1} - \gamma_2 I_{2,j} - \mu_{2,j}I_{2,j},\\
R_2' &= \gamma_2 I_{2,j} - \mu_{2,r}R_2.
\end{aligned} \tag{3.6}$$

Finally, the vector equations:

$$\begin{aligned}
\widetilde{S}' &= \beta_v(\widetilde{N}, N_1, N_2) - \frac{fc_1\widetilde{S}}{N_1}\sum_{k=1}^{j} I_{1,k} - \frac{fc_2\widetilde{S}}{N_2}\sum_{k=1}^{j} I_{2,k} - \widetilde{\mu}_s\widetilde{S},\\
\widetilde{I}' &= \frac{fc_1\widetilde{S}}{N_1}\sum_{k=1}^{j} I_{1,k} + \frac{fc_2\widetilde{S}}{N_2}\sum_{k=1}^{j} I_{2,k} - \widetilde{\mu}\widetilde{I}
\end{aligned} \tag{3.7}$$

The goal of this section is to explore how the dynamics of this coupled system differ from the dynamics of the single host vector system presented in the first chapter.

3.4 R_0 for the Coupled System

Recall from the Chapter 2 the computational difficulties we experienced when computing R_0. We shall seek to use our previous calculations as much as possible in order to ease the computational strain in this current situation. To this end, we alter the system by dividing the infected vectors into two classes: those whose infection came from an infected member of the first species $\widetilde{I}_1$, and those who were infected by the second species $\widetilde{I}_2$. This changes the system into

$$\begin{aligned}
S_1' &= \beta(N_1) - fc_v(\widetilde{I}_1 + \widetilde{I}_2)\frac{S_1}{N_1} - \mu_{1,s}S_1,\\
I_{1,1}' &= fc_v(\widetilde{I}_1 + \widetilde{I}_2)\frac{S_1}{N_1} - \alpha_{1,1}I_{1,1} - \mu_{1,1}I_{1,1},\\
I_{1,2}' &= \alpha_{1,1}I_{1,1} - \alpha_{1,2}I_{1,2} - \mu_{1,2}I_{1,2},\\
&\vdots\\
I_{1,j-1}' &= \alpha_{1,j-2}I_{1,j-2} - \alpha_{1,j-1}I_{1,j-1} - \mu_{1,j-1}I_{1,j-1},\\
I_{1,j}' &= \alpha_{1,j-1}I_{1,j-1} - \gamma_1 I_{1,j} - \mu_{1,j}I_{1,j},\\
R_1' &= \gamma_1 I_{1,j} - \mu_{1,r}R_1.
\end{aligned} \tag{3.8}$$

$$\begin{aligned}
S_2' &= \beta(N_2) - fc_v(\widetilde{I}_1 + \widetilde{I}_2)\frac{S_2}{N_2} - \mu_{2,s}S_2,\\
I_{2,1}' &= fc_v(\widetilde{I}_1 + \widetilde{I}_2)\frac{S_2}{N_2} - \alpha_{2,1}I_{2,1} - \mu_{2,1}I_{2,1},\\
I_{2,2}' &= \alpha_{2,1}I_{2,1} - \alpha_{2,2}I_{2,2} - \mu_{2,2}I_{2,2},\\
&\vdots\\
I_{2,j-1}' &= \alpha_{2,j-2}I_{2,j-2} - \alpha_{2,j-1}I_{2,j-1} - \mu_{2,j-1}I_{2,j-1},\\
I_{2,j}' &= \alpha_{2,j-1}I_{2,j-1} - \gamma_2 I_{2,j} - \mu_{2,j}I_{2,j},\\
R_2' &= \gamma_2 I_{2,j} - \mu_{2,r}R_2
\end{aligned} \tag{3.9}$$

$$\begin{aligned}
\widetilde{S}' &= \beta_v(\widetilde{N}, N_1, N_2) - \frac{fc_1\widetilde{S}}{N_1}\sum_{k=1}^{j} I_{1,k} - \frac{fc_2\widetilde{S}}{N_2}\sum_{k=1}^{j} I_{2,k} - \widetilde{\mu}_s\widetilde{S},\\
\widetilde{I}_1' &= \frac{fc_1\widetilde{S}}{N_1}\sum_{k=1}^{j} I_{1,k} - \widetilde{\mu}\widetilde{I}_1,\\
\widetilde{I}_2' &= \frac{fc_2\widetilde{S}}{N_2}\sum_{k=1}^{j} I_{2,k} - \widetilde{\mu}\widetilde{I}_2.
\end{aligned} \tag{3.10}$$

The equivalence of the systems is apparent in the equation $\widetilde{I} = \widetilde{I}_1 + \widetilde{I}_2$. This splitting will make it much more straightforward to apply our previous results in the computation of R_0 since the system associated with one of the two species only differs from the single host case by a single term.

Before proceeding as in Chapter 2 we note analogous preliminary results for the coupled system. The following results are trivial to show, given our previous work.

Proposition 3.4.1. *The manifolds $N_1 = \overline{S}_1$, $N_2 = \overline{S}_2$ are invariant if and only if $\mu_{1,s} = \mu_{1,k}$, $\mu_{2,s} = \mu_{2,k}$.*

Proposition 3.4.2. *The system* (3.8), (3.9), (3.10) *satisfies conditions 1-5 of Chapter 2.*

We will use the now familiar next generation method to compute R_0 for the coupled system. Reduction to the infected equations is done precisely as before, and the Jacobians are computed to construct the next generation matrix. Note that if F_i is the Jacobian of new infections for species i, when considered as a single system, we get that

$$F = \begin{pmatrix} F_1 & M \\ M & F_2 \end{pmatrix},$$

where M is the $(j+1) \times (j+1)$ matrix

$$\begin{pmatrix} 0 & \dots & 0 & fc_v \\ 0 & \dots & 0 & 0 \\ \vdots & \ddots & \vdots & \vdots \\ 0 & \dots & 0 & 0 \end{pmatrix}.$$

The transfer functions are the same as in the single host case, and thus, if we say they have Jacobians V_i, then

$$V = \begin{pmatrix} V_1 & 0 \\ 0 & V_2 \end{pmatrix}.$$

These imply that

$$FV^{-1} = \begin{pmatrix} F_1V_1^{-1} & MV_2^{-1} \\ MV_1^{-1} & F_2V_2^{-1} \end{pmatrix}.$$

It is apparent that the bottom row of V_i^{-1} is $\left(0, \ldots, 0, \frac{1}{\widetilde{\mu}}\right)$, and so,

$$MV_i^{-1} = \begin{pmatrix} 0 & \ldots 0 & & \frac{fc_v}{\widetilde{\mu}} \\ 0 & \ldots & 0 & 0 \\ \vdots & \ddots & \vdots & \vdots \\ 0 & \ldots & 0 & 0 \end{pmatrix}.$$

As we have seen previously, F_i has a sparse form

$$F_i = \begin{pmatrix} 0 & 0 & \ldots & 0 & fc_v \\ 0 & 0 & \ldots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \ldots & 0 & 0 \\ \frac{f_1c_1\overline{S}_v}{N_1} & \frac{f_1c_1\overline{S}_v}{N_1} & \ldots & \frac{f_1c_1\overline{S}_v}{N_1} & 0 \end{pmatrix}.$$

Using the same notation as before, letting $\delta_k^{(i)}$ be the sum of the first j elements in the kth column of V_i^{-1}, and by previous arguments (Chapter 2, Section 2.1) we have seen that $\delta_{j+1}^{(i)} = 0$, so that

$$F_iV_i^{-1} = \begin{pmatrix} 0 & 0 & \ldots & 0 & \frac{fc_1}{\widetilde{\mu}} \\ 0 & 0 & \ldots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \ldots & 0 & 0 \\ \frac{fc_i\overline{S}_v}{\overline{S}_i}\delta_1^{(i)} & \frac{fc_i\overline{S}_v}{\overline{S}_i}\delta_2^{(i)} & \ldots & \frac{fc_i\overline{S}_v}{\overline{S}_i}\delta_j^{(i)} & 0 \end{pmatrix}.$$

Given our previous calculations, we can refine this further:

$$F_i V_i^{-1} = \begin{pmatrix} 0 & 0 & \dots & 0 & \frac{f c_1}{\widetilde{\mu}} \\ 0 & 0 & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & 0 & 0 \\ \frac{\widetilde{\mu}}{f c_v} R_{0,i}^2 & K_{i,2} & \dots & K_{i,j} & 0 \end{pmatrix},$$

where $R_{0,i}$ is the reproductive ratio of the corresponding single species system. The $K_{i,k}$ are introduced to reduce notational complexity. We have already computed the characteristic polynomial of this matrix:

$$\det(F_i V_i^{-1} - \lambda I) = (-\lambda)^{j-1}(\lambda^2 - R_{0,i}^2).$$

We can now proceed with the calculation:

$$D = \det \begin{pmatrix} -\lambda & 0 & \dots & 0 & \frac{f c_v}{\widetilde{\mu}} & 0 & 0 \dots & 0 & \frac{f c_v}{\widetilde{\mu}} & \\ 0 & -\lambda & \dots & 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & -\lambda & 0 & 0 & 0 & \dots & 0 & 0 \\ \frac{\widetilde{\mu}}{f c_v} R_{0,1}^2 & K_{1,2} & \dots & K_{1,j} & -\lambda & 0 & 0 & \dots & 0 & 0 \\ 0 & 0 & \dots & 0 & \frac{f c_v}{\widetilde{\mu}} & -\lambda & 0 & \dots & 0 & \frac{f c_v}{\widetilde{\mu}} \\ 0 & 0 & \dots & 0 & 0 & 0 & -\lambda & \dots & 0 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & \dots & 0 & 0 & 0 & 0 & \dots & -\lambda & 0 \\ 0 & 0 & \dots & 0 & 0 & \frac{\widetilde{\mu}}{f c_v} R_{0,2}^2 & K_{2,2} & \dots & K_{2,j} & -\lambda \end{pmatrix}.$$

We expand the determinant along the first column

$$D = (-\lambda)^{j+1}\det(F_2V_2^{-1} - \lambda I) +$$

$$(-1)^{j+2}\frac{\widetilde{\mu}}{fc_v}R_{0,1}^2\det\begin{pmatrix} 0 & \dots & 0 & \frac{fc_v}{\widetilde{\mu}} & 0 & 0\dots & 0 & \frac{fc_v}{\widetilde{\mu}} \\ -\lambda & \dots & 0 & 0 & 0 & 0 & \dots & 0 & 0 \\ \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & \dots & -\lambda & 0 & 0 & 0 & \dots & 0 & 0 \\ 0 & \dots & 0 & \frac{fc_v}{\widetilde{\mu}} & -\lambda & 0 & \dots & 0 & \frac{fc_v}{\widetilde{\mu}} \\ 0 & \dots & 0 & 0 & 0 & -\lambda & \dots & 0 & 0 \\ \vdots & \ddots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & \dots & 0 & 0 & 0 & 0 & \dots & -\lambda & 0 \\ 0 & \dots & 0 & 0 & \frac{\widetilde{\mu}}{fc_v}R_{0,2}^2 & K_{2,2} & \dots & K_{2,j} & -\lambda \end{pmatrix}.$$

Expand along the first $j-1$ columns:

$$D = (-\lambda)^{j+1}\det(F_2V_2^{-1} - \lambda I) +$$

$$(-1)^{j+2}\frac{\widetilde{\mu}}{fc_v}R_{0,1}^2\lambda^{j-1}\det\begin{pmatrix} \frac{fc_v}{\widetilde{\mu}} & 0 & 0 & \dots & 0 & \frac{fc_v}{\widetilde{\mu}} \\ \frac{fc_v}{\widetilde{\mu}} & -\lambda & 0 & \dots & 0 & \frac{fc_v}{\widetilde{\mu}} \\ 0 & 0 & -\lambda & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & -\lambda & 0 \\ 0 & \frac{\widetilde{\mu}}{fc_v}R_{0,2}^2 & K_{2,2} & \dots & K_{2,j} & -\lambda \end{pmatrix}.$$

Expand along the first column

$$D = (-\lambda)^{j+1}\det(F_2V_2^{-1} - \lambda I) +$$

$$(-1)^{j+2}\frac{\widetilde{\mu}}{fc_v}R_{0,1}^2\lambda^{j-1}\left(\frac{fc_v}{\widetilde{\mu}}\det(F_2V_2^{-1}-\lambda I)-\frac{fc_v}{\widetilde{\mu}}\det\begin{pmatrix}0&0&\dots&0&\frac{fc_v}{\widetilde{\mu}}\\0&-\lambda&\dots&0&0\\\vdots&\vdots&\ddots&\vdots&\vdots\\0&0&\dots&-\lambda&0\\\frac{\widetilde{\mu}}{fc_v}R_{0,2}^2&K_{2,2}&\dots&K_{2,j}&-\lambda\end{pmatrix}\right)$$

$$=(-\lambda)^{j+1}\det(F_2V_2^{-1}-\lambda I)+$$
$$(-1)^{j+2}\frac{\widetilde{\mu}}{fc_v}R_{0,1}^2\lambda^{j-1}\left(\frac{fc_v}{\widetilde{\mu}}\det(F_2V_2^{-1}-\lambda I)-(-1)^{j+2}R_{0,2}^2\det\begin{pmatrix}0&\dots&0&\frac{fc_v}{\widetilde{\mu}}\\-\lambda&\dots&0&0\\\vdots&\ddots&\vdots&\vdots\\0&\dots&-\lambda&0\end{pmatrix}\right)$$

$$=(-\lambda)^{j+1}\det(F_2V_2^{-1}-\lambda I)+$$
$$(-1)^{j+2}\frac{\widetilde{\mu}}{fc_v}R_{0,1}^2\lambda^{j-1}\left(\frac{fc_v}{\widetilde{\mu}}\det(F_2V_2^{-1}-\lambda I)-(-1)^{j+2}R_{0,2}^2(-1)^{j+1}\frac{fc_v}{\widetilde{\mu}}(-\lambda)^{j-1}\right)$$

$$=(-\lambda)^{j+1}\det(F_2V_2^{-1}-\lambda I)+(-1)^jR_{0,1}^2\lambda^{j-1}(\det(F_2V_2^{-1}-\lambda I)+(-\lambda)^{j-1}R_{0,2}^2)$$

$$=(-\lambda)^{j+1}(-\lambda)^{j-1}(\lambda^2-R_{0,2}^2)+(-1)^jR_{0,1}^2\lambda^{j-1}((-\lambda)^{j-1}(\lambda^2-R_{0,2}^2)+(-\lambda)^{j-1}R_{0,2}^2)$$

$$=(\lambda)^{2j}(\lambda^2-R_{0,2}^2)+(-1)^jR_{0,1}^2\lambda^{j+1}((-\lambda)^{j-1}$$

$$=(\lambda)^{2j}(\lambda^2-R_{0,2}^2)=\lambda^{2j}R_{0,1}^2=\lambda^{2j}(\lambda^2-R_{0,2}^2-R_{0,1}^2).$$

The largest root, in absolute value, of this polynomial is easily found. This gives the reproductive ratio for the coupled host system:

$$R_0^c=\sqrt{R_{0,1}^2+R_{0,2}^2}.$$

3.5 Discussion

In this chapter we have addressed some immediate variations of the simple model given in the previous chapter. First, the case where we allow some individuals to abandon the relapsing process earlier than others, which was motivated by the variation in the number of relapses in TBRF. We found that this decreases the value of R_0, but the bifurcation at $R_0 = 1$ will remain transcritical.

We also considered how the addition of latent stages have a decreasing effect on R_0, but if the rate at which the infected hosts transfer out of the latent stages is much faster than their death rate, the inhibiting effect on R_0 is negligible. Lastly, we considered the case of coupled hosts, and we found that the R_0^c for the coupled system is the root of the sum of squares of the reproductive ratios for the uncoupled systems. In the latent and coupled cases it is possible that one could repeat the calculations to determine whether the bifurcation at $R_0 = 1$ remains transcritical, which we leave for future work.

Chapter 4

Continuity of R_0 in Vector-Borne Relapsing Disease Models.

Having computed R_0 for several types of systems, it is natural to investigate the relationship between the reproductive ratios for these systems. Similar work is done in [22], where the reproductive ratio of an ODE model for cholera is related to the reproductive ratio of the reaction-diffusion PDE model in the limit as the diffusion coefficient tends to 0. The goal of this chapter is to establish a similar result for reproductive ratios between models with differing numbers and types of compartments.

4.1 Motivation

Recall the simple model for vector-borne relapsing diseases. In the final compartment, the average amount of time spent by an individual in that compartment before moving into the recovered class or dying is $\frac{1}{\mu_j + \gamma}$. As γ becomes very large, this quantity becomes small. Since γ is the parameter that we are increasing, as the hosts enter the final infected compartment

they are instantly transferred directly to the recovered class. More simply, we are removing the final infected compartment and γ_{j-1} becomes the new rate of transfer from the I_{j-1} infected compartment to the recovered class. We can then use the form that we found for R_0 in Chapter 2 to get the reproductive ratio for the model with the removed compartment:

$$R_0^r = f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\sum_{k=1}^{j-1}\prod_{l=1}^{k}\frac{\alpha_{l-1}}{\alpha_l+\mu_l}},$$

where $\alpha_0 = 1$. Compare this to the form with last compartment included:

$$R_0 = f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\sum_{k=1}^{j}\prod_{l=1}^{k}\frac{\alpha_{l-1}}{\alpha_l+\mu_l}},$$

where $\alpha_0 = 1$ and $\alpha_j = \gamma$. Recall, though, that we formed the removed compartment model by sending $\alpha_j = \gamma \to \infty$. Notice then that

$$\lim_{\gamma\to\infty} R_0 = R_0^r$$

since the last term of the sum in R_0 has a γ in the denominator, and thus goes to 0. This example suggests a form of continuity in the reproductive ratio when compartments are removed. The goal of this chapter will be to enumerate the cases in which this continuity occurs and examine cases where it does not exist.

4.2 Some Linear Algebra

We begin by investigating the determinant of a matrix A as a diagonal element in the matrix tends to ∞. Note that $A_{[i,j]}$ represents the matrix formed by removing the ith row and jth column.

Lemma 4.2.1. *Let A be an $n \times n$ matrix and suppose that $A_{[i:i]}$ is nonsingular. Then*

$\lim_{a_{ii}\to\infty} \det A = \pm\infty$.

Proof. By Proposition 2.7.5 of [5]:

$$\det A = \sum_{k=1}^{n}(-1)^{i+k}a_{ik}\det(A_{[i,k]}) = a_{ii}\det A_{[i,i]} + \sum_{k\neq i}(-1)^{i+k}a_{ik}\det(A_{[i,k]})$$

The last sum does not involve a_{ii} and thus has a fixed value as $a_{ii} \to \infty$. Since $A_{[i,i]}$ is nonsingular it has a nonzero determinant, and thus, the leading term of the previous sum goes to $\pm\infty$ depending on the sign of $\det A_{[i,i]}$. □

As a result of this lemma we can see that there is a sufficiently large value of a_{ii} that makes A invertible, and the matrix remains invertible for all greater values. This is why we do not need the hypothesis of A being invertible in the next result, which tells us how to construct the inverse of $A_{[i,i]}$ from A^{-1}.

Lemma 4.2.2. *If $A_{[i,i]}$ is nonsingular then*

$$(A_{[i,i]})^{-1} = \lim_{a_{ii}\to\infty}(A^{-1})_{[i,i]}.$$

Furthermore,

$$\lim_{a_{ii}\to\infty}(A^{-1})_{ik} = \lim_{a_{ii}\to\infty}(A^{-1})_{ki} = 0.$$

Proof. We will need to consider this proof in four cases. The proof technique in each case is the same, though the indexing in each is different. Throughout let $B^{jk} = (b_{pq}) = A_{[j,k]}$ for $1 \leq p, q \leq n-1$. We will repeatedly use Corollary 2.7.6 of [5] which is a formula for the ij element of the inverse of a matrix. Also, the "..." denotes terms of a sum that do not involve a_{ii}.

Case 1. Assume that $1 \leq j, k < i$. Then, on the one hand,

$$\lim_{a_{ii}\to\infty}(A^{-1})_{kj} = \lim_{a_{ii}\to\infty}\frac{(-1)^{k+j}\det B^{jk}}{\det A}$$

$$= \lim_{a_{ii}\to\infty}\frac{(-1)^{k+j}\sum_{l=1}^{n-1}(-1)^{i-1+l}b_{i-1,l}\det B^{jk}_{[i-1,l]}}{a_{ii}\det A_{[i,i]}+\ldots}$$

after expanding $\det B^{jk}$ along its $i-1$ row. Now we want to identify the term that has a_{ii} in it. Note that, since $j, k < i$, we have that $a_{ii} = b_{i-1,i-1}$. So we let $l = i-1$ and we have

$$\lim_{a_{ii}\to\infty}(A^{-1})_{kj} = \lim_{a_{ii}\to\infty}\frac{(-1)^{k+j}(-1)^{2i-2}a_{ii}\det B^{jk}_{[i-1,i-1]}+\ldots}{a_{ii}\det A_{[i,i]}+\ldots}.$$

Since $b_{i-1,i-1} = a_{ii}$, we get

$$= \frac{(-1)^{k+j}\det B^{jk}_{[i-1,i-1]}}{\det A_{[i,i]}}.$$

On the other hand,

$$((A_{[i,i]})^{-1})_{kj} = \frac{(-1)^{k+j}\det(A_{[i,i]})_{[j,k]}}{\det A_{[i,i]}}.$$

Since $j, k < i$ we have that $(A_{[i,i]})_{[j,k]} = (A_{[j,k]})_{[i-1,i-1]} = B^{jk}_{[i-1,i-1]}$, so that

$$((A_{[i,i]})^{-1})_{kj} = \frac{(-1)^{k+j}\det B^{jk}_{[i-1,i-1]}}{\det A_{[i,i]}}.$$

Thus, when $j, k < i$, we have

$$((A_{[i,i]})^{-1})_{kj} = \lim_{a_{ii}\to\infty}(A^{-1})_{kj}.$$

Case 2. $n-1 \geq k, j \geq i$. On the one hand,

$$\lim_{a_{ii}\to\infty}(A^{-1})_{k+1,j+1} = \lim_{a_{ii}\to\infty}\frac{(-1)^{k+j+2}\det B^{j+1,k+1}}{\det A}$$

$$= \lim_{a_{ii}\to\infty} \frac{(-1)^{k+j}\sum_{l=1}^{n-1}(-1)^{i+l}b_{i,l}\det B^{j+1,k+1}_{[i,l]}}{a_{ii}\det A_{[i,i]}+\dots}$$

after expanding $\det B^{j+1,k+1}$ along its ith row. We have that $a_{ii} = b_{ii}$. So, then, we let $l = i$, and we have

$$\lim_{a_{ii}\to\infty}(A^{-1})_{kj} = \lim_{a_{ii}\to\infty} \frac{(-1)^{k+j}(-1)^{2i}a_{ii}\det B^{j+1,k+1}_{[i,i]}+\dots}{a_{ii}\det A_{[i,i]}+\dots}$$

$$= \frac{(-1)^{k+j}\det B^{j+1,k+1}_{[i,i]}}{\det A_{[i,i]}}.$$

On the other hand,

$$((A_{[i,i]})^{-1})_{kj} = \frac{(-1)^{k+j}\det(A_{[i,i]})_{[j,k]}}{\det A_{[i,i]}}.$$

Since $j, k \geq i$, we have that $(A_{[i,i]})_{[j,k]} = (A_{[j+1,k+1]})_{[i,i]} = B^{j+1,k+1}_{[i,i]}$, so that

$$((A_{[i,i]})^{-1})_{kj} = \frac{(-1)^{k+j}\det B^{j+1,k+1}_{[i,i]}}{\det A_{[i,i]}}.$$

Thus, when $j, k \geq i$, we have

$$((A_{[i,i]})^{-1})_{kj} = \lim_{a_{ii}\to\infty}(A^{-1})_{k+1,j+1}.$$

Case 3. $k = i, j < i$. On the one hand,

$$\lim_{a_{ii}\to\infty}(A^{-1})_{i+1,j} = \lim_{a_{ii}\to\infty} \frac{(-1)^{i+j+1}\det B^{j,i+1}}{\det A}$$

$$= \lim_{a_{ii}\to\infty} \frac{(-1)^{i+j+1}\sum_{l=1}^{n-1}(-1)^{i-1+l}b_{i-1,l}\det B^{j,i+1}_{[i-1,l]}}{a_{ii}\det A_{[i,i]}+\dots}$$

after expanding $\det B^{j,i+1}$ along its $i-1$th row. Since $j < i$, we have that $a_{ii} = b_{i-1,i}$. So we let $l = i$, and we have

$$\lim_{a_{ii}\to\infty}(A^{-1})_{i+1,j} = \lim_{a_{ii}\to\infty} \frac{(-1)^{i+j+1}(-1)^{2i-1}a_{ii}\det B^{j,i+1}_{[i-1,i]}+\dots}{a_{ii}\det A_{[i,i]}+\dots}$$

$$= \frac{(-1)^{i+j} \det B^{j,i+1}_{[i-1,i]}}{\det A_{[i,i]}}.$$

On the other hand,

$$((A_{[i,i]})^{-1})_{ij} = \frac{(-1)^{i+j} \det(A_{[i,i]})_{[j,i]}}{\det A_{[i,i]}}.$$

Since $j < i$, we have that $(A_{[i,i]})_{[j,i]} = (A_{[j,i+1]})_{[i-1,i]} = B^{j,i+1}_{[i-1,i]}$, so that

$$((A_{[i,i]})^{-1})_{ij} = \frac{(-1)^{i+j} \det B^{j,i+1}_{[i-1,i]}}{\det A_{[i,i]}}.$$

Thus, when $j < i$, we have

$$((A_{[i,i]})^{-1})_{ij} = \lim_{a_{ii} \to \infty} (A^{-1})_{i+1,j}.$$

Case 4. $k < i, j = i$. On the one hand,

$$\lim_{a_{ii} \to \infty} (A^{-1})_{k,i+1} = \lim_{a_{ii} \to \infty} \frac{(-1)^{i+k+1} \det B^{i+1,k}}{\det A}$$

$$= \lim_{a_{ii} \to \infty} \frac{(-1)^{i+j+1} \sum_{l=1}^{n-1} (-1)^{i+l} b_{i,l} \det B^{i+1,k}_{[i,l]}}{a_{ii} \det A_{[i,i]} + \dots}$$

after expanding $\det B^{i+1,k}$ along its ith row. Since $k < i$, we have that $a_{ii} = b_{i,i-1}$. So we let $l = i - 1$ and we have

$$\lim_{a_{ii} \to \infty} (A^{-1})_{k,i+1} = \lim_{a_{ii} \to \infty} \frac{(-1)^{i+k+1} (-1)^{2i-1} a_{ii} \det B^{i+1,k}_{[i,i-1]} + \dots}{a_{ii} \det A_{[i,i]} + \dots}$$

$$= \frac{(-1)^{i+k} \det B^{i+1,k}_{[i,i-1]}}{\det A_{[i,i]}}.$$

On the other hand,

$$((A_{[i,i]})^{-1})_{ki} = \frac{(-1)^{i+k} \det(A_{[i,i]})_{[i,k]}}{\det A_{[i,i]}}.$$

Since $k < i$, we have that $(A_{[i,i]})_{[i,k]} = (A_{[i+1,k]})_{[i,i-1]} = B^{i+1,k}_{[i,i-1]}$, so that

$$((A_{[i,i]})^{-1})_{ki} = \frac{(-1)^{i+k} \det B^{i+1,k}_{[i,i-1]}}{\det A_{[i,i]}}.$$

Thus, when $k < i$, we have

$$((A_{[i,i]})^{-1})_{ki} = \lim_{a_{ii} \to \infty} (A^{-1})_{k,i+1}.$$

The combination of these four cases gives the first result.

For the second result, we again use Corollary 2.7.6 of [5] to get that

$$\lim_{a_{ii} \to \infty} (A^{-1})_{ik} = \lim_{a_{ii} \to \infty} \frac{(-1)^{k+i} \det B^{ki}}{\det A}.$$

B^{ki} does not contain a_{ii}, and thus $\det B^{ik}$ remains constant for all values of a_{ii}, and by 4.2.1 we have that $\det A \to \pm\infty$. As a result

$$\lim_{a_{ii} \to \infty} \frac{(-1)^{k+i} \det B^{ki}}{\det A} = 0$$

The result for $(A^{-1})_{ki}$ is obtained in exactly the same way. □

Before discussing how this result relates to our previous work, it should be noted that the process of computing the inverse of a matrix after altering it is known in the literature as updating the inverse of a matrix [12]. The most famous example of this process are the Sherman-Morrison-Woodbury formulas which give a closed form expression for the inverse of a perturbation of a matrix in terms of its original inverse. While such methods have numerical applications [12], our method, since it contains a limit, is going to have a more analytical usage.

Lemmas 4.2.1 and 4.2.2 will allow us to prove a result about the spectral radius of the next

generation matrix:

Theorem 4.2.3. *Suppose that $V_{[i,i]}$ is nonsingular. Then*

$$\lim_{a_{ii}\to\infty} \rho(FV^{-1}) = \rho(F_{[i,i]}(V_{[i,i]})^{-1}).$$

Proof. Since eigenvalues are continuous with respect to the entries of a matrix, and the absolute value and maximum of a set of continuous functions is continuous, we have that

$$\lim_{a_{ii}\to\infty} \rho(FV^{-1}) = \rho(F \lim_{a_{ii}\to\infty} V^{-1}).$$

Let

$$(V_{[i,i]})^{-1} = \begin{pmatrix} V_1 & V_2 \\ V_3 & V_4 \end{pmatrix},$$

where $V_1 \in \mathbb{R}^{(i-1)\times(i-1)}$, $V_2 \in \mathbb{R}^{(i-1)\times(n-i)}$, $V_3 \in \mathbb{R}^{(n-i)\times(i-1)}$ and $V_4 \in \mathbb{R}^{(n-i)\times(n-i)}$. Then Lemma 4.2.2 says that

$$\lim_{a_{ii}\to\infty} V^{-1} = \begin{pmatrix} V_1 & \mathbf{0}_{(i-1)\times 1} & V_2 \\ \mathbf{0}_{1\times(i-1)} & 0 & \mathbf{0}_{1\times(n-i)} \\ V_3 & \mathbf{0}_{(n-i)\times 1} & V_4 \end{pmatrix}.$$

Let

$$F = \begin{pmatrix} F_1 & \boldsymbol{f}^{(1)}_{(i-1)\times 1} & F_2 \\ \boldsymbol{f}^{(2)}_{1\times(i-1)} & f_{ii} & \boldsymbol{f}^{(3)}_{1\times(n-i)} \\ F_3 & \boldsymbol{f}^{(4)}_{(n-i)\times 1} & F_4 \end{pmatrix},$$

where $F_1 \in \mathbb{R}^{(i-1)\times(i-1)}$, $F_2 \in \mathbb{R}^{(i-1)\times(n-i)}$, $F_3 \in \mathbb{R}^{(n-i)\times(i-1)}$, and $F_4 \in \mathbb{R}^{(n-i)\times(n-i)}$. This

gives that

$$F \lim_{a_{ii}\to\infty} V^{-1} = \begin{pmatrix} F_1V_1 + F_2V_3 & \mathbf{0}_{(i-1)\times 1} & F_1V_2 + F_2V_4 \\ \boldsymbol{f}^{(2)}_{1\times(i-1)}V_1 + \boldsymbol{f}^{(3)}_{1\times(n-1)}V_3 & 0 & \boldsymbol{f}^{(2)}_{1\times(i-1)}V_2 + \boldsymbol{f}^{(3)}_{1\times(n-1)}V_4 \\ F_3V_1 + F_4V_3 & \mathbf{0}_{(n-i)\times 1} & F_3V_2 + F_4V_4 \end{pmatrix}.$$

We wish to compute the spectral radius of this matrix, so we set up the eigenvalue problem

$$\det(F \lim_{a_{ii}\to\infty} V^{-1} - \lambda I_n) = \det \begin{pmatrix} F_1V_1 + F_2V_3 - \lambda I_{i-1} & \mathbf{0}_{(i-1)\times 1} & F_1V_2 + F_2V_4 \\ \boldsymbol{f}^{(2)}_{1\times(i-1)}V_1 + \boldsymbol{f}^{(3)}_{1\times(n-1)}V_3 & -\lambda & \boldsymbol{f}^{(2)}_{1\times(i-1)}V_2 + \boldsymbol{f}^{(3)}_{1\times(n-1)}V_4 \\ F_3V_1 + F_4V_3 & \mathbf{0}_{(n-i)\times 1} & F_3V_2 + F_4V_4 - \lambda I_{n-i} \end{pmatrix}$$

$$= -\lambda \det \begin{pmatrix} F_1V_1 + F_2V_3 - \lambda I_{i-1} & F_1V_2 + F_2V_4 \\ F_3V_1 + F_4V_3 & F_3V_2 + F_4V_4 - \lambda I_{n-i} \end{pmatrix} = -\lambda \det(F_{[i,i]}(V_{[i,i]})^{-1} - \lambda I_{n-1}).$$

So, the matrix $F \lim_{a_{ii}\to\infty} V^{-1}$ has the same eigenvalues as $F_{[i,i]}(V_{[i,i]})^{-1}$ with an additional 0 eigenvalue. Since the spectral radius is the maximum of the absolute value of the eigenvalues, the spectral radius of $F \lim_{a_{ii}\to\infty} V^{-1}$ is the maximum of the eigenvalues of $F_{[i,i]}(V_{[i,i]})^{-1}$. That is ,

$$\rho(F \lim_{a_{ii}\to\infty} V^{-1}) = \rho(F_{[i,i]}(V_{[i,i]})^{-1}),$$

which gives the result. □

4.3 Continuity of R_0 in Vector-Borne Relapsing Disease models.

The result of the previous section allows us to compute R_0 for reduced compartmental models. In particular, we consider a model in which we wish to remove the i^{th} compartment and have that the original Jacobians of the new infections F, and the transferred infections V, are

related to the corresponding Jacobians in the reduced model by $F^r = F_{[i,i]}$ and $V^r = V_{[i,i]}$. Making a parameter choice α such that $V_{ii} \to \infty$ as $\alpha \to \infty$ we have, using Theorem 4.2.3:

$$R_0^r = \rho(F_{[i,i]}(V_{[i,i]})^{-1}) = \rho(F \lim_{\alpha\to\infty} V^{-1}) = \lim_{\alpha\to\infty} \rho(FV^{-1}) = \lim_{\alpha\to\infty} R_0.$$

Note the similarity to the continuity results of [22] where the reproductive ratio of the ODE model is the limit of the reproductive ratio of the PDE as the diffusion coefficient tends to 0. We shall see now that this process is applicable to the multistage models we have been working on.

Consider the simple vector borne relapsing disease model from Chapter 2. Suppose we want to remove the ith relapsing state. Then the equation for I_{i+1} becomes

$$I'_{i+1} = \alpha_{i-1}I_{i-1} - (\alpha_{i+1} + \mu_{i+1})I_{i-1}.$$

It is then easy to see that the components of the next generation matrix are the original matrices F and V with the ith row and column removed. We can then make the obvious parameter choice in the original model and have $\alpha_i \to \infty$. Thus,

$$R_0^r = \lim_{\alpha_i\to\infty} R_0 = f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\frac{1}{\alpha_1+\mu_1}\left(1+\frac{\alpha_1}{\alpha_2+\mu_2}\left(1+\frac{\alpha_2}{\alpha_3+\mu_3}\left(1+\ldots\frac{\alpha_{j-2}}{\alpha_{j-1}+\mu_{j-1}}\left(1+\frac{\alpha_{j-1}}{\gamma+\mu_j}\right)\ldots\right)\right)\right)}$$

$$= \lim_{\alpha_i\to\infty} f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\frac{1}{\alpha_1+\mu_1}\left(1+\frac{\alpha_1}{\alpha_2+\mu_2}\left(1+\frac{\alpha_2}{\alpha_3+\mu_3}\left(1+\ldots\frac{\alpha_{i-1}}{\alpha_i+\mu_i}\left(1+\frac{\alpha_i}{\alpha_{i+1}+\mu_{i+1}}\left(1+\ldots\frac{\alpha_{j-2}}{\alpha_{j-1}+\mu_{j-1}}\left(1+\frac{\alpha_{j-1}}{\gamma+\mu_j}\right)\ldots\right)\right)\right)\right)\right)\right)}$$

$$= \lim_{\alpha_i\to\infty} f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\frac{1}{\alpha_1+\mu_1}\left(1+\frac{\alpha_1}{\alpha_2+\mu_2}\left(1+\frac{\alpha_2}{\alpha_3+\mu_3}\left(1+\ldots\left(\frac{\alpha_{i-1}}{\alpha_i+\mu_i}+\frac{\alpha_{i-1}}{\alpha_i+\mu_i}\frac{\alpha_i}{\alpha_{i+1}+\mu_{i+1}}\left(1+\ldots\frac{\alpha_{j-2}}{\alpha_{j-1}+\mu_{j-1}}\left(1+\frac{\alpha_{j-1}}{\gamma+\mu_j}\right)\ldots\right)\right)\right)\right)\right)\right)}$$

$$= f\sqrt{\frac{cc_v\overline{S}_v}{\widetilde{\mu}\overline{S}}\frac{1}{\alpha_1+\mu_1}\left(1+\frac{\alpha_1}{\alpha_2+\mu_2}\left(1+\frac{\alpha_2}{\alpha_3+\mu_3}\left(1+\ldots\left(0+\frac{\alpha_{i-1}}{\alpha_{i+1}+\mu_{i+1}}\left(1+\ldots\frac{\alpha_{j-2}}{\alpha_{j-1}+\mu_{j-1}}\left(1+\frac{\alpha_{j-1}}{\gamma+\mu_j}\right)\ldots\right)\right)\right)\right)\right)\right)}.$$

We note here then that this is, with a relabeling of the parameters, precisely R_0 for the model with $j-2$ relapses, as computed in Chapter 2.

We can also consider how the removal of a latent stage in (3.3), (3.4) changes R_0^L. Again,

noting that when the ith latent stage is removed the reduced system's new infection Jacobian is $F_{[i,1]}$, and the Jacobian for its transfers is $V_{[i,i]}$, we can then make the parameter choice $\beta_i \to \infty$. Then the reproductive ratio for this reduced system is $\lim_{\beta_i \to \infty} R_0^L$, i.e., it's R_0^L with $\dfrac{\beta_i}{\beta_i + \mu_s}$ replaced by 1. Repeating this process we can compute the reproductive ratio for any arrangement of latent and infectious compartments. Doing this with all the latent compartments confirms the easily observable result,

$$R_0 = \lim_{\beta_k \to \infty, 1 \le k \le j} R_0^L.$$

Another application of this continuity is with the coupled host system described at the end of Chapter 3. We computed R_0^c under the assumption that the two host species would go through the same number of relapses. For notation, let $R_{0,i,j}$, $i = 1, 2$, be the reproductive ratio for the species i with j relapses, and let $F_{j,k}$ and $V_{j,k}$ be the Jacobians for the system when the first host species undergoes j relapses and the second undergoes k relapses. Lastly, let $R_0^{l,k}$ be the reproductive ratio for the coupled system where the first species undergoes l relapses and the second species undergoes k relapses. It can easily be observed that $F_{j-1,j} = (F_{j,j})_{[j-1,j-1]}$ and $V_{j-1,j} = (V_{j,j})_{[j-1,j-1]}$. Combining the results from the previous chapters and sections, we have

$$R_0^{j-1,j} = \lim_{\alpha_{1,j} \to \infty} R_0^{j,j} = \sqrt{\lim_{\alpha_{1,j} \to \infty} (R_{0,1,j})^2 + (R_{0,2,j})^2} = \sqrt{R_{0,1,j-1}^2 + R_{0,2,j}^2}.$$

Repeating this procedure we can then say

$$R_0^{l,k} = \sqrt{R_{0,1,l}^2 + R_{0,2,k}^2}.$$

Hence, our continuity result has given us a simple way of computing the reproductive ratio for a coupled host-vector system where the host species undergo a different number of relapses.

4.4 Discussion

In this chapter we developed an analytical method for updating the inverse of a matrix when we remove a row and a column. This method is immediately applied to compute the spectral radius of the next generation matrix when rows and columns are removed. This result is then applied to the computation of R_0 when compartments are removed. We showed that, under certain conditions, the reproductive ratio of the reduced system is the limit of the original reproductive ratio as some parameters tend to infinity. This continuity result was used to compute R_0 for systems with different arrangements of latent and infectious states, and was also used to compute the reproductive ratio of the coupled host system when the hosts undergo a different number of relapses.

Chapter 5

Conclusions and Future Directions

5.1 Conclusions

Computing the reproductive ratio of an infectious disease is an important first step in describing the spread of the disease. We have computed R_0 for a vector-borne relapsing disease model and several simple variations of this model. Of note was the dependence of these ratios on the number of relapses. This was accomplished through careful calculation on arbitrarily sized matrices, and computing R_0 for the variations relied heavily on our computations for the simple model.

In the case of the simple model, we were also able to use results that take advantage of center manifold theory to describe the bifurcation at $R_0 = 1$. In particular, we discovered that it is always a transcritical bifurcation, where the stable DFE exchanges stability with an EE. While we cannot, due to the existence of the recovered compartment, combine the infected compartments into a single infected variable, our results show that the bifurcation does not change from transcritical even with the addition of the relapse states. We only established the stability of these equilibria in a neighborhood of $R_0 = 1$ and the size of the system limited us

from being able to do further analysis of the branch of EE. Furthermore we established that there is only one branch of EE with respect to R_0. Future work may repeat the calculations done on the simple model to extend these bifurcation results to the variations we explored in Chapter 3.

We also established a continuity result between the reproductive ratios and the number of compartments in a relapsing model. In particular, through a limit we were able to relate the reproductive ratios when compartments were removed. This also allowed us to easily compute R_0 for a coupled host-vector system when the host species undergo a different number of relapses.

5.2 Future Work

There are many directions that future work can take. Variations on this model could include lateral transmission among the hosts, infected hosts giving birth to infected individuals, and temporary infection of vectors. Such variations are motivated by Equine Infectious Anemia Virus (EIAV), a virus which is spread among horses by horse-flies [7]. The horse's immune system is able to control the spread of the virus, though there are periods of increased viral load in the horse's system which leads to a "relapse" of the disease [19]. However, a particular feature of EIAV is that infected hosts never recover from the disease. This allows us to collapse the infected host equations into a single infected variable. Thus, we remove the issue of the system's size at the cost of additional complexity.

Spatial considerations can be implemented analogous to [23] and a relationship between R_0 and the number of relapses may exist, similar to the results of Chapter 2. Also, as in [23], the existence of traveling wave solutions can also be studied. How the reproductive ratio changes as the diffusion coefficient goes to 0 can be examined to possibly yield convergence to the non-spatial R_0 computed in Chapter 2, as in [22].

As we have mentioned, the relapses in TBRF are driven by the antigenic variation of *Borellia* spirochetes in the body [8]. The relapses could be a potential sign of some rich dynamics in an in-host model. In-host models for the spread of viruses and their interaction with the immune system have been studied [19], and could potentially be modified for TBRF. Such a model for the growth of *Borellia* in the body could give some explanation for the variation in the number of relapses from case to case. A side effect to the treatment of TBRF is the Jarisch-Herxheimer Reaction (JHR), which is a reaction to antibacterial treatment of various diseases. Though its mechanisms are poorly understood the reaction is characterized by fever, chills, and worsening of cutaneous lesions about 24 hours after treatment [4]. Though it is usually associated with syphilis, JHR has occurred in significant association with the treatment of TBRF [10]. A target for future research would be to study JHR as an emergent behavior of an in-host model.

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