Reproductive Numbers for Periodic Epidemic Systems

by

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To my beautiful wife, who worked hard so that I could have the opportunity to finish school and to the math department at UTA which has been an amazing experience to get to study under and work with such amazing people.

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ABSTRACT

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When using mathematics to study epidemics, often times the goal is to determine when an infection can invade and persist within a population. This can be done in a variety of ways but the most common is to use threshold quantities called reproductive numbers. For models with only one infection, the basic reproductive number (BRN) is used to determine the stability of the disease-free equilibrium. For many years this was done solely for autonomous systems; however, many diseases exhibit seasonal behavior. If this seasonality is incorporated into models, it gives nonautonomous systems, which while more accurate in their description, are much more difficult to analyze.

The first chapter lays out methods to find the basic reproductive number for seasonal epidemic models. In the literature, two principal methods have been proposed to derive BRNs for periodic models. The first, using time-averages, does not always result in the correct threshold behavior. The more general one is also more complicated, and no detailed explanations of the necessary computations have yet been laid out. This chapter lays out such an explicit procedure and then identifies conditions (and some important classes of models) under which the two methods

agree. This allows the use of the more limited method, which is much simpler, when appropriate, and illustrates in detail the simplest possible case where they disagree.

There are many cases within epidemiology where infections will compete to persist within a population. In studying these types of models, one of the goals is to determine when certain infections can invade a population and persist when other infections are already resident within the population. To study this, invasion reproductive numbers (IRN) are used, which can help determine the stability of certain endemic equilibria. Methods for both autonomous and nonautonomous systems are given for finding the IRNs, as well as examples which illustrate the often complex computations required.

These methods are used for a single-host model of Chagas disease to determine if seasonality can explain why competitive exclusion does not seem to hold in certain sylvatic cycles of the disease. In this model there are two strains of the parasite, and studies show cross-immunity between strains. The single-host autonomous model predicts competitive exclusion, but there has been observed co-persistence in some host populations, in particular woodrats. To account for this, seasonality is added to the original model in the transmission parameters. For a set of biologically realistic parameters, seasonality even in just a single parameter is sufficient to make co-persistence possible.

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INTRODUCTION

1.1 Mathematical Epidemiology

Transmissible diseases are commonplace in today's world. Influenza, malaria, and cholera are just a few of the outbreaks that populate the news stories of the day. Infections are transmitted in many different ways: airborne (influenza, smallpox), vector-borne (malaria, rocky mountain fever), and food-borne (*E-coli*) to name a few. Diseases transmitted by viruses such as influenza and chicken pox do not allow for reinfection, as they give some immunity, while diseases transmitted from bacteria generally do not. Many human diseases are transmitted not by humans but from vectors, such as mosquitoes. Modeling can provide insight into the underlying dynamics of an infection as it spreads through populations. Mathematical modeling has become an important tool for analyzing and studying diseases. Many early results in mathematical epidemiology are due to public health officials. Daniel Bernouilli, a famous mathematician, was trained as a physician. He published a defense of inoculation against smallpox in 1760. Modern epidemiology developed from the work of such people as noted above, Sir Ronald Ross, W.O. Kermack and A.G. McKendrick, and W.H. Hamer who were mostly physicians [21].

One of the first major contributors to the area of mathematical epidemiology was Sir Ronald Ross, who earned the Nobel Prize in medicine for his work on malaria. A British medical doctor, Ross created a relatively simple model for the transmission of malaria. He was the first to discover the transmission cycle of malaria in mosquitoes, specifically the parasite which causes malaria is transmitted from a

mosquito to a human while the mosquito is taking a blood meal. He was able to show that to stop the transmission, one need only reduce the mosquito population by a certain amount. This threshold proved extremely important. Certainly his work on malaria alone would have earned him recognition, but Ross was also helpful in establishing the foundations for the study of disease dynamics [46]. He understood the need for new theory to study these disease transmission cycles using mathematical models.

Another example of mathematical epidemiologists is the work of Kermack and McKendrick, two coworkers studying how infectious diseases spread through populations. They were trying to understand diseases like plague and cholera, and seeing why certain epidemics would rise and fall. They devised several models of various types in the early 1900s. They were some of the first to establish theory for what is known as Susceptible-Infected-Recovered or Removed, or SIR models. These models split the population into compartments based on their infectiousness, where each compartment represents either a susceptible, infected, or recovered/removed class and simple assumptions are made about the transfer between them. These allowed a simple way to track groups of individuals in the context of disease outbreaks. Their analysis led to the notion of a threshold quantity which determines a pathogen's ability to spread, whether it will persist or go extinct.

1.2 Reproduction Numbers

For epidemic models a principal goal is to understand how the disease can be eradicated. One of the main ideas in mathematical epidemiology is that almost all models have this threshold behavior that Ross and Kermack and McKendrick discussed. This threshold is used to estimate whether an infection can invade and persist in a population [28]. Lotka was actually the first mathematician to denote this

threshold as R_0 [27]. It was not until 1952 that a general epidemiological definition came about from George MacDonald [27]. In his paper he stated that the basic reproductive rate is defined as the number of infections distributed in a community as the direct result of the presence in it of a single primary non-immune case [40]. Another definition came by Klaus Dietz in 1975 [17] similar to this one but it was Diekmann et al. in 1990 that [16] later gave a basic biological definition for this threshold that is widely used today. The basic reproductive number was defined as the expected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a completely susceptible population [16]. This threshold has been called different names: the basic reproductive ratio [16], the basic reproductive rate [5], and the basic reproductive number [50]. This paper recognizes there is no difference between the values and thus from here on it will use the term basic reproductive number, or BRN, and denote it R_0. Mathematically the BRN gives a threshold value that is used to determine stability of a disease-free equilibrium. It was proven that if $R_0 < 1$ the disease-free equilibrium is locally asymptotically stable, but unstable if $R_0 > 1$. It should be noted that R_0 is a dimensionless quantity and not a rate.

Initially there was disagreement over the calculation of the BRN. The question was how R_0 is characterized mathematically in heterogeneous populations [27]. There was a need for some canonical R_0 created by the complex transmission cycles of the models being created. Take for example vector-borne diseases which have different types of transmission paths between hosts and vectors, so the number of infections should be averaged somehow: one must look at new infections in regard to a generation basis [26]. Diekmann et al. and later van den Driessche and Watmough resolved this matter by developing next-generation methods [50, 16]. Diekmann et al. mathematically defined it as the dominant eigenvalue of a positive linear operator while van

den Driessche and Watmough [50] detailed a method for a general compartmental disease transmission model, extending on the work of Diekmann et al., for heterogeneous populations using ordinary differential equations. They derived an expression for the next generation matrix, where the (i, k) entry is the expected number of new infections in a compartment i produced by the infected individual originally introduced into compartment k. This matrix is used to get an expression for R_0, stating that R_0 is the spectral radius of the next generation matrix. This definition from Diekmann et al. of R_0 is used in a variety of models to evaluate the conditions in which the disease can invade a population. The next-generation methods provide the needed average overall compartments.

Besides having this threshold behavior, R_0 provides other useful tools. There is a concept called herd immunity, in which certain sections of the population who are not immune to an infection are protected by a large percentage of the population that becomes immune, say through vaccinations. In this respect not everyone needs to get the vaccination, but the question becomes how many people must in order to eradicate an infection? The basic reproductive number can be used to find out. In fact, in simple models one need only vaccinate $1 - \frac{1}{R_0}$ of the population in order for the infection to die out [28]. This gives a useful tool to health officials to determine how much of a vaccine to make each year for something like influenza. For vector-borne diseases, a classical result for R_0 is that to eradicate the disease, the vector population must be divided by R_0^2 [9]. So the basic reproductive number can provide more than just stability results, it can help health officials determine the best course of action for disease eradication.

There are other reproductive numbers that are helpful in modeling. While the basic reproductive number can quantify the transmissibility of a disease, the effective reproductive number, $R(t)$, is a time-dependent quantity that accounts for the popu-

lation's reduced susceptibility [13]. This is used when a population is assumed to be completely susceptible to an infection. It is the average number of secondary infections in a population made up of susceptible and non-susceptible individuals. Another reproductive number is the effective reproductive number, or R_E. This value gives the average number of secondary infections caused by a single infective, at a given susceptible fraction [13]. The replacement number, R, is defined to be the average number of secondary infections produced by a typical infective during the entire period of infectiousness [30]. It should be noted that after the infection has invaded a population and not everyone is susceptible then R is always less than R_0.

Another reproductive number that is useful in studying situations involving multiple interacting infections is the invasion reproductive number, (IRN), often denoted $\tilde{R}_i$ where i is the invading infection. Multiple cocirculating pathogens, whether different infections or different strains of the same infection, can result in co-infections, or in some cases competing infections. The IRN of one of the pathogens with respect to another or the others is defined as the average number of secondary infections caused by introducing one person infected with that pathogen into an environment where one or a combination of the other pathogen(s) is already at an endemic state [55]. It measures the ability of a pathogen to invade while the other pathogen is already at equilibrium. Most models that calculate these values only do so for two infections, but it is possible to consider multiple infections, though the models will be very complex. IRNs are associated with the same kind of threshold behavior as BRNs: if a pathogen's IRN is greater than 1 then the pathogen can invade even though the other pathogen has established itself at some endemic level within the population. The methods for finding invasion reproductive numbers are similar to those for basic reproductive numbers, only the system is assumed to be at an endemic equilibrium for one of the infections.

1.3 Seasonality

Mathematical models must be simple enough to analyze but complex enough to be biologically relevant. This is a difficult balance to maintain, as a completely biologically accurate model would most likely be so difficult to analyze that nothing could be gained from it. For ordinary differential equations one of the assumptions most people make is that all parameters of the system are constant. These systems are called autonomous systems. There is much theory for autonomous systems as they are simpler to analyze. The problem with these assumptions is the models are not as biologically accurate and so one can only obtain so much information from the results. To study the effects of seasonality on disease extinction one could consider parameters that vary with time. Such systems are called non-autonomous systems. These systems are able to capture more biological information but are much more difficult to analyze. One of the biggest differences for epidemic models between autonomous and non-autonomous is the calculation of the basic reproductive numbers. The methods, including the next-generation methods mentioned before, for autonomous systems do not necessarily transfer over for non-autonomous systems.

Many diseases exhibit seasonality [4]. For vector-borne diseases: malaria has a peak season during warm and rainy seasons, dengue hemorrhagic fever has peak rates during hot-dry and rain seasons, and West Nile Virus has human cases peak in summer and early fall in temperate regions [31, 52, 11]. Cholera and rotavirus have peaks during certain seasons throughout the year [43, 14]. Respiratory pathogens like measles and influenza also increase in their outbreaks during certain seasons of the year [20, 19]. Some models that have diseases with seasonality will only look at one season at a time in order to simplify the model, effectively losing that seasonality factor. Yet since seasonality plays such an important part in the transmission of these diseases it should somehow be incorporated into the models to see if it plays

a factor in the epidemics. This can be done in a variety of ways. Many modelling approaches use forced oscillators to show a wide range of dynamics. The simplest way to study seasonality in models is by making the transmission parameter periodic in time [18, 6]. Other parameters can also be made periodic, such as birth or death rates for those species that have mating seasons. This is not to say that seasonal forcing will work in all cases and indeed using seasonal forcing in models makes them much more complex and difficult to analyze.

Since R_0 depends on the transmission coefficient and most models incorporate seasonality by considering a time varying transmission, R_0 can be greatly affected by seasonality [4]. One idea to study how seasonality affects R_0 is to consider the long-time average of R_0 [54]. This however does not work in every model as there are cases where a time-averaged R_0 will predict the disease to die out yet simulations show it will persist [39]. So other methods have been necessary.

1.4 Outline

The rest of this work is laid out as follows. Chapter 2 will lay out the methods for calculating the basic reproductive number for autonomous and non-autonomous systems, specifically periodic systems. The techniques for both systems follow a similar pattern. There are two different quantities for periodic systems: R_T which is found using the time-average method and R_{LO} the linear operator method. These will be compared to determine when they agree in their expression for the BRN and how the model behaves when they do not. Sufficient conditions will then be identified for these two quantities to agree.

Chapter 3 will extend the linear operator method to calculate invasion reproductive numbers for periodic systems. The idea is to lay out a specific pattern to follow for a general periodic epidemic model with multiple interacting infections. Theorems

will be shown that the IRN does indeed hold the threshold behavior as before for autonomous systems.

Chapter 4 applies the methods of reproductive numbers to a single-host model of Chagas disease where two cocirculating strains of the parasite are competing for the same host resource. The context comes from the case of *Trypanosoma cruzi* strains circulating in the southeast United States, strain I and IV, where it has been observed that both strains persist at endemic levels within woodrats and so competitive exclusion does not seem to hold in this case. The idea is to see if seasonality can account for the observed copersistence of the strains. Basic reproductive numbers and invasion reproductive numbers will be calculated for both strains to determine conditions for the stability of equilibria.

CHAPTER 2

Methods for deriving the basic reproductive number for periodic epidemic systems

2.1 Introduction

As stated before, one of the main goals when studying epidemic models is to understand how the disease can be eradicated. This gives rise to a natural threshold as to whether an infection can invade and persist within a population. The basic reproductive number was defined as the expected number of secondary cases produced by a typical infected individual during its entire period of infectiousness in a completely susceptible population [16]. Mathematically the BRN gives a threshold value that is used to determine stability of a disease-free equilibrium. It was proven that if $R_0 < 1$ the disease-free equilibrium is locally asymptotically stable, but unstable if $R_0 > 1$. It should be noted that R_0 is a dimensionless quantity and not a rate.

This chapter is devoted to understanding how the BRN can be calculated for both autonomous and nonautonomous epidemic models. First, the focus will be on autonomous systems as those methods have been well flushed out and so just a recap for how next-generation methods are used to find the BRN for these systems. Then periodic systems will be introduced. There are two different methods to find the BRN and both will be presented. Then examples will be shown to understand when the methods agree in their expression for the BRN and when they are different. It will be shown that using linear operators gives the correct threshold behavior, but a theorem will be presented that shows when these two methods agree.

2.2 Methods for Calculating the Basic Reproductive Number

2.2.1 Autonomous Systems

In order to understand how the basic reproductive number (BRN) is calculated for non-autonomous systems, one must first understand the theory for autonomous systems. Consider the setting in [50] where a heterogeneous population, distinguishable by age, behavior, spatial position, and/or stage of disease, is grouped into n homogeneous compartments. Let $x = (x_1, \ldots, x_n)^t$, with each $x_i \geq 0$, be the number of individuals in each compartment. Sort the compartments so that the first m compartments represent infected individuals. Define $\mathbf{X}_s$ to be the set of all disease free states, that is $x_i = 0$, for $i = 1, ..., m$. It is important to distinguish new infections from all other changes in population. Let $\mathscr{F}_i(x)$ be the rate of new infections in compartment i, $\mathscr{V}_i^+(x)$ be the rate of transfer into compartment i by all other means, and $\mathscr{V}_i^-(x)$ be the rate of transfer out of compartment i. Each function is assumed to be twice differentiable. The disease transmission model then becomes:

$$\dot{x}_i = f_i(x) = \mathscr{F}_i(x) - \mathscr{V}_i(x), i = 1, ...n \tag{2.1}$$

where $\mathscr{V}_i = \mathscr{V}_i^- - \mathscr{V}_i^+$. In addition, these functions must satisfy assumptions (A1)-(A5) below. These assumptions assure the model is well posed and makes biological sense.

- (A1) If $x \geq 0$, then $\mathscr{F}_i, \mathscr{V}_i^+, \mathscr{V}_i^- \geq 0$ for $i = 1, ...n$
- (A2) If $x_i = 0$ then $\mathscr{V}_i^- = 0$. If $x \in \mathbf{X}_s$, then $\mathscr{V}_i^- = 0$ for $i = 1, ...m$
- (A3) $\mathscr{F}_i = 0$ if $i > m$
- (A4) If $x \in \mathbf{X}_s$ then $\mathscr{F}_i = 0$ and $\mathscr{V}_i^+ = 0$ for $i = 1, ...m$
- (A5) If $\mathscr{F}_i$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts, for $x_0 \in \mathbf{X}_s$

The last assumption states that there is a locally asymptotically stable disease-free equilibrium x_0, not necessarily unique, in the disease-free subspace $\mathbf{X}_s$. The matrix $Df(x_0)$ can thus be partitioned as new matrices and can be defined out of this. Define F and V and below:

$$F = \left[\frac{\partial \mathscr{F}_i}{\partial x_j}(x_0)\right] \qquad V = \left[\frac{\partial \mathscr{V}_i}{\partial x_j}(x_0)\right] \qquad 1 \leq i, j \leq m.$$

From Diekmann et al., the basic reproductive number is the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual [16]. To calculate R_0, consider the matrix FV^{-1}. The (i, k) entry of the product FV^{-1} is the expected number of new infections in compartment i produced by the infected individual originally introduced into compartment k. Following [16] this is called the next generation matrix for the model and:

$$R_0 = \rho(FV^{-1}) \tag{2.2}$$

where $\rho(A)$ denotes the spectral radius of a matrix A. The spectral radius ρ is the largest eigenvalue of the matrix. As shown in Diekmann et al. [16], R_0 can be used to study the stability of the disease-free equilibrium of the full system.

2.2.2 Floquet Theory

Before moving onto the methods for nonautonomous systems some background is needed for these types of dynamical systems. Consider the system:

$$\dot{x} = A(t)x, x \in \mathbb{R}^n \tag{2.3}$$

where $t \to A(t)$ is a T-periodic continuous matrix-valued function. A fundamental matrix of a system of n homogeneous ordinary differential equations is a matrix-valued function, $\Psi(t)$, whose columns are linearly independent solutions of the system. Floquet's theorem gives a canonical form for fundamental matrix solutions [10].

Theorem (Floquet's Theorem)**.** *If $\Psi(t)$ is a fundamental matrix solution of the T-periodic system 2.3, then, for all $t \in \mathbb{R}$,*

$$\Psi(t+T) = \Psi(t)\Psi^{-1}(0)\Psi(T). \tag{2.4}$$

In addition, there is a matrix B (which may be complex) such that

$$e^{TB} = \Psi^{-1}(0)\Psi(T) \tag{2.5}$$

and a T-periodic matrix function $t \to P(t)$ (which may be complex valued) such that $\Psi(t) = P(t)e^{tB}$ for all $t \in \mathbb{R}$. Also, there is a real matrix R and a real 2T-periodic matrix function $t \to Q(t)$ such that $\Psi(t) = Q(t)e^{tR}$ for all $t \in \mathbb{R}$.

This theorem gives a representation called a Floquet normal form for the fundamental matrix $\Psi(t)$. For a ω-periodic system define a monodromy matrix, $\Phi(t)$, to be the inverse of the fundamental matrix evaluated at the period ω. A matrix is a principal fundamental matrix if it is a fundamental matrix and there exists a t_0 such that $\Psi^{-1}(t_0) = I$. So if the solution to the ω-periodic system is a principal fundamental matrix, then the monodromy matrix is just $\Phi(t) = \Psi(\omega)$.

The problem becomes how these matrices are calculated. Most systems cannot be solved analytically, so numerical work must be done. The fundamental matrix is computed in terms of Taylor series, using the original matrix $A(t)$ to various powers. This can be done since the solution is of the form $e^{TB} = \Psi^{-1}(0)\Psi(T)$, by using the matrix exponential definition:

$$e^{tA} = \sum_{0}^{\infty} \frac{t^k}{k!}A^k = I + tA + \frac{t^2}{2!}A^2 + \frac{t^3}{3!}A^3 + \cdots . \tag{2.6}$$

2.2.3 Non-autonomous Systems

2.2.3.1 Time-Averaged Method

For non-autonomous systems the methods are more challenging. There are several methods used to calculate the BRN for non-autonomous systems. Some authors calculated it by replacing any time-varying parameters with their long time averages [39, 23, 53, 24, 34, 22]. To explain this method, some notation is needed. Denote the long-term average of a function as $\langle\cdot\rangle$, that is:

$$\langle\cdot\rangle = \lim_{t\to\infty} \frac{1}{t} \int_0^t \cdot \, d\tau \tag{2.7}$$

Using this method, one replaces the time-varying parameters with their long-term averages. The system then reduces to an autonomous system and the method laid out by van den Driessche and Watmough can be used. The autonomous system's BRN R_T is still calculated as the spectral radius of the matrix FV^{-1}. Many authors used this method to find R_T [39, 23, 53, 24, 34, 22]. Ma and Ma in their 2006 paper [39] gave many different models using this method. For most of the models they presented, the reproductive number found using this method was proved to have the same threshold behavior as expected for autonomous systems. However, this does not always work. The last model presented by Ma and Ma showed a case where R_T was above 1, but when the model was simulated using those parameters, the disease died out. So the time average approach seems to miss some behavior.

2.2.3.2 Linear Operator Method

It appears that there are cases where R_T will give conditions for the disease to persist, yet the system actually does eradicate the disease. Bacaër and Guernaoui [9] published a paper proposing a method to calculate the basic reproductive number for a model of cutaneous leishmaniasis using an approach which extends the linear oper-

ator method first defined by Diekmann et al. on autonomous systems, by adapting the next-generation operator method of van den Driessche and Watmough to periodic systems. They proved this reproductive number held the same threshold behavior for the model, but did not lay out an explicit formula for calculating it. Wang and Zhao [51] presented a theory of the basic reproductive number for a large class of periodic compartmental models that parallels Bacaër's method by extending the work of van den Driessche and Watmough. The method is laid out as follows.

Consider a setting similar to [50] where a heterogeneous population is grouped into n homogeneous compartments. In this model, certain parameters will be assumed to be ω-periodic, thus giving a non-autonomous system. Sort the compartments so that the first m represent infected classes. Consider again the set $\mathbf{X}_s$ to be all disease-free states, where now values in $\mathbf{X}_s$ can be disease-free periodic solutions and not just equilibria. Let $\mathscr{F}_i(t,x)$ be the input rate of newly infected individuals in the ith compartment, $\mathscr{V}_i^+(t,x)$ be the input rate of individuals by other means and $\mathscr{V}_i^-(t,x)$ be the rate of transfer out of compartment i. The model is then given by:

$$\frac{dx_i}{dt} = \mathscr{F}_i(t,x) - \mathscr{V}_i(t,x) = f_i(t,x), i = 1, ..., n \tag{2.8}$$

where $\mathscr{V}_i = \mathscr{V}_i^- - \mathscr{V}_i^+$. Similar to autonomous models, the following assumptions must be made. They again show the model is well posed and makes biological sense.

- (A1) For each $1 \leq i \leq n$, the functions $\mathscr{F}_i(t,x), \mathscr{V}_i^+(t,x)$, and $\mathscr{V}_i^-(t,x)$ are nonnegative and continuous on $\mathbb{R} \times \mathbb{R}_+^n$ and continuously differentiable with respect to x.
- (A2) There is a real number $\omega > 0$ such that for each $1 \leq i \leq n$, the functions $\mathscr{F}_i(t,x), \mathscr{V}_i^+(t,x)$, and $\mathscr{V}_i^-(t,x)$ are ω-periodic in t. (This is new for periodic models.)

- (A3) If $x_i = 0$ then $\mathscr{V}_i^- = 0$. If $x \in \mathbf{X}_s$, then $\mathscr{V}_i^- = 0$ for $i = 1, ...m$.
- (A4) $\mathscr{F}_i = 0$ if $i > m$.
- (A5) If $x \in \mathbf{X}_s$ then $\mathscr{F}_i = 0$ and $\mathscr{V}_i^+ = 0$ for $i = 1, ...m$.

In addition to these assumptions, two more must be verified, however, the next one (A6) is just the same as (A5) from the autonomous case. Assume the model has a disease-free periodic solution $x_0(t)$. It must be verified that $x_0(t)$ is linearly asymptotically stable in the disease-free subspace, $\mathbf{X}_s$. Define an $(n-m) \times (n-m)$ matrix

$$M(t) := \left(\frac{\partial f_i(t, x_0(t))}{\partial x_j} \right)_{m+1 \leq i,j \leq n}. \tag{2.9}$$

Let $\Phi_M(t)$ be the monodromy matrix of the linear ω-periodic system $\frac{dz}{dt} = M(t)z$. To verify the next assumption, one needs to show that the spectral radius of the monodromy matrix is less than one, or (A6) $\rho(\Phi_M(\omega)) < 1$.

For the next assumption, (A7), following the notation from [50], define two $m \times m$ matrices by

$$F(t) = \left[\frac{\partial \mathscr{F}_i(t, x_0(t))}{\partial x_j} \right]_{1 \leq i,j \leq m}, \qquad V(t) = \left[\frac{\partial \mathscr{V}_i(t, x_0(t))}{\partial x_j}(x_0) \right]_{1 \leq i,j \leq m}.$$

Let $Y(t, s), t \geq s$ be the evolution operator of the linear ω-periodic system $\frac{dy}{dt} = -V(t)y$. That is, for each $s \in \mathbb{R}$ the $m \times m$ matrix $Y(t, s)$ satisfies

$$\frac{d}{dt} Y(t, s) = -V(t)Y(t, s), \forall t \geq s, Y(s, s) = I \tag{2.10}$$

where I is the $m \times m$ identity matrix. The monodromy matrix $\Phi_{-V}(t)$ of the system then equals $Y(t, 0), t \geq 0$. The last assumption that must be verified is that the internal evolution of individuals in the infectious compartments is dissipative, and exponentially decays in many cases. So assume that (A7) $\rho(\Phi_{-V}(\omega)) < 1$. These assumptions are similar to van den Driessche and Watmough but with two new additions: (A2) which spcifies a ω-periodic environment (due to seasonality) and (A7) the infection will eventually die out if no new infections arise.

The theory for nonlinear autonomous systems has been well established for studying stability of equilibria. In 1960, the Hartman-Grobman theorem was proved showing that the local behavior of the system around a hyperbolic equilibrium point can be studied using the linearized system around the same point [7]. In 1975 this theorem was extended by Kenneth Palmer to non-autonomous systems [42]. This allows the use of the linearized system in (A6) to be used to study the stability of the disease-free solution.

Based on the assumptions (A1)-(A7), the basic reproductive number for the epidemic model can be calculated. Always assume the population is near the disease-free periodic state $x_0(t)$. By standard theory of linear periodic systems, [32], there exists a $K > 0$ and $\alpha > 0$ such that

$$\|Y(t,s)\| \leq Ke^{-\alpha(t-s)}, \forall t \geq s, s \in \mathbb{R}. \tag{2.11}$$

It then follows that

$$\|Y(t,t-a)F(t-a)\| \leq K\|F(t-a)\|e^{-\alpha a}, \forall t \in \mathbb{R}, a \in [0,\infty). \tag{2.12}$$

With the model being periodic, suppose that $\phi(s)$, which is ω-periodic in s, is the initial distribution of infectious individuals. Then $F(s)\phi(s)$ is the distribution of those infected who were introduced at time s. Given $t \geq s$, then $Y(t,s)F(s)\phi(s)$ gives the distribution of those infected individuals who were newly infected at time s and remain infected at time t. Then

$$\psi(t) := \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da \tag{2.13}$$

is the distribution of accumulative new infections at time t produced by all those infected individuals introduced at previous time to t.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^m$, with the max norm and the positive cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0, \forall t \in \mathbb{R}\}$. Now define a new linear operator $L : C_\omega \to C_\omega$ by

$$(L\phi)(t) = \int_0^\infty Y(t, t-a)F(t-a)\phi(t-a)da, \forall t \in \mathbb{R}, \phi \in C_\omega. \tag{2.14}$$

Call L the next infection operator, following the motivation of van den Driessche and Watmough, and then the spectral radius of L is given by:

$$R_{LO} := \rho(L) \tag{2.15}$$

for the periodic epidemic model.

Following the approach from [9], one can obtain another linear operator on C_ω, using the same notation as Wang and Zhao in their paper:

$$(\bar{L}\phi)(t) = \int_0^\infty F(t)Y(t, t-a)\phi(t-a)da = F(t)\int_0^\infty Y(t, t-a)\phi(t-a)da, \forall t \in \mathbb{R}, \phi \in C_\omega. \tag{2.16}$$

The spectral radius of $\bar{L}$, $\rho(\bar{L})$, was defined in [9] as the basic reproductive number. Wang and Zhao showed that the basic reproductive number for L and the basic reproductive number for $\bar{L}$ coincide, but that the kernels have different biological interpretations.

As before with autonomous systems, the question becomes does the basic reproductive number have the same threshold behavior of disease invasion, where if $R_0 < 1$ then the disease-free periodic solution is stable, while it is unstable when $R_0 > 1$. Wang and Zhao proved that indeed this is the case, but in order to characterize and calculate R_0 for periodic systems they needed to take a different approach to actually calculate the BRN. The reason for this is that linear operators are difficult to work with, so they decided to approach it using Floquet theory instead.

Consider the linear ω-periodic equation

$$\frac{dw}{dt} = \left[-V(t) + \frac{F(t)}{\lambda}\right] w, t \in \mathbb{R} \tag{2.17}$$

with parameter $\lambda \in (0, \infty)$. Let $W(t, s, \lambda), t \geq s, s \in \mathbb{R}$ be the evolution operator of the system (4.9) on $\mathbb{R}^m$. Wang and Zhao showed that the linear operator $W(t, s, \lambda)$ is positive in $\mathbb{R}^m$ for each $t \geq s, s \in \mathbb{R}$. The Perron-Frobenius theorem implies that $\rho(W(\omega, 0, \lambda))$ is an eigenvalue of $W(\omega, 0, \lambda)$ with a nonnegative eigenvector. This gives the following theorems from [51]:

Theorem (2.1). *i. If $\rho(W(\omega, 0, \lambda)) = 1$ has a positive solution λ_0, then λ_0 is an eigenvalue of L, and hence $R_0 > 0$.*

ii. If $R_0 > 0$, then $\lambda = R_0$ is the unique solution of $\rho(W(\omega, 0, \lambda)) = 1$.

iii. $R_0 = 0$ if and only if $\rho(W(\omega, 0, \lambda)) < 1 \ \forall \lambda > 0$.

Theorem (2.2). *i. $R_0 = 1$ if and only if $\rho(\Phi_{F-V}(\omega)) = 1$*

ii. $R_0 > 1$ if and only if $\rho(\Phi_{F-V}(\omega)) > 1$

iii. $R_0 < 1$ if and only if $\rho(\Phi_{F-V}(\omega)) < 1$

Thus the disease-free solution, $x_0(t)$, is asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

These results show that to find the basic reproductive number, one needs to find the monodromy matrix, $\Phi_{F-V}(t)$ of the system, (4.9) and evaluate it at the period, ω. Then find the spectral radius of $\Phi_{F-V}(\omega)$ and solve the equation $\rho(\Phi_{F-V}(\omega)) = 1$ for λ. This λ is the basic reproductive number R_0. The threshold behavior for the disease-free solution can then be studied. In many cases, it is not possible to find the monodromy matrix analytically. In these cases numerical work will have to be done to find the BRN, as will be outlined in the final section of the chapter.

2.3 Examples

In order to see how these methods are used, consider the following sequence of simple models. The goal is to understand how the time-average method relates to the linear operator method. Beginning with the simplest epidemic model examples with one infected class, periodic models are developed that build in complexity to determine when the expressions for R_T and R_{LO} are the same. For each set of models, one parameter is varied with time in the first case and then the model is generalized to consider all parameters to be time-varying.

2.3.1 Single Infected Class: Seasonal Infection

Consider a model with one infected class and one susceptible class where the susceptible population gets infected at a rate $\beta(t)$. They die of natural mortality μ and the infection is cleared at a rate of γ. This system is shown below:

$$\begin{aligned} \frac{dI}{dt} &= \beta(t)\frac{SI}{N} - (\mu+\gamma)I \\ \frac{dS}{dt} &= \mu N + \gamma I - \beta(t)\frac{SI}{N} - \mu S \end{aligned} \tag{2.18}$$

where $\beta(t) \geq 0 \ \forall t$, and $\exists t_\beta \in (0,\omega) : \beta(t_\beta) > 0$ and assumed to be piecewise continuous and ω-periodic. One can calculate $\mathscr{F}$ and $\mathscr{V}$ as:

$$\mathscr{F}(t) = \begin{bmatrix} \beta(t)\frac{SI}{N} \\ 0 \end{bmatrix}, \mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} (\mu+\gamma)I \\ \beta(t)\frac{SI}{N} + \mu S - (\mu N + \gamma I) \end{bmatrix}.$$

Verification of (A1)-(A5) for both methods is simple from observation of the vectors $\mathscr{F}$ and $\mathscr{V}$. The model has a disease-free equilibrium, $(0, N_0)$, where N_0 is the initial condition of the population. For the linear operator method, (A6) must be verified. To do this, one must find $M(t)$:

$$M(t) := -\mu. \tag{2.19}$$

Solving the system $\frac{dz}{dt} = M(t)z$ in this case yields the principal fundamental solution, $\Psi(t) = e^{-\mu t}$, since $\Psi^{-1}(0) = I$ where I is the identity matrix. The monodromy matrix evaluated at the period ω is then $\Phi_M(\omega) = e^{-\mu\omega}$and clearly (A6) is true.

Now one needs to define $F(t)$ and $V(t)$. These are both evaluated at the disease-free equilibrium:

$$\begin{aligned} F(t) &= \beta(t) \\ V(t) &= \mu + \gamma. \end{aligned} \tag{2.20}$$

Now (A7) must be verified, which requires looking at the system below:

$$\frac{dy}{dt} = -(\mu + \gamma)y. \tag{2.21}$$

Again this system gives the principal fundamental matrix and so one need only consider the monodromy matrix evaluated at the period. This is $\Phi_{-V}(\omega) = e^{-(\mu+\gamma)\omega}$, and clearly (A7) holds.

Now to calculate the basic reproductive number, consider the time-average method first. To use this replace the time-varying function in F and V with the long-time average; in this case the only function is $\langle\beta(t)\rangle$. Since this is a periodic function, the long time average becomes $\langle\beta\rangle = \frac{1}{\omega}\int_0^\omega \beta(t)dt$. Now calculate FV^{-1} which is:

$$FV^{-1} = \frac{\frac{1}{\omega}\int_0^\omega \beta(t)dt}{\mu + \gamma} = \frac{\langle\beta\rangle}{\mu + \gamma}. \tag{2.22}$$

The spectral radius of this is just the expression itself and so:

$$R_T = \frac{\langle\beta\rangle}{\mu + \gamma}. \tag{2.23}$$

To characterize R_0 using the linear operator method, consider the following ω-periodic equation:

$$\frac{dw}{dt} = \left[-(\mu + \gamma) + \frac{\beta(t)}{\lambda}\right] w, t \in \mathbb{R} \tag{2.24}$$

which has fundamental solution:

$$w(t) = exp\left(\frac{1}{\lambda}\int_0^t \beta(s)ds - (\mu+\gamma)t\right). \tag{2.25}$$

Then the monodromy matrix is defined as before, and the goal is to find λ_0 such that $\rho(\Phi_{F-V}(\omega)) = 1$, which happens exactly when the exponent in $w(t)$ equals 0. This yields:

$$R_{LO} = \lambda_0 = \frac{\frac{1}{\omega}\int_0^\omega \beta(t)dt}{\mu+\gamma} = \frac{\langle\beta\rangle}{\mu+\gamma}. \tag{2.26}$$

So in this case the two methods produce the same result, and $R_T = R_{LO} = R_0$.

2.3.2 Single Infected Class: General Case

Consider the system as before except now all parameters are considered to be time-varying:

$$\begin{aligned}\frac{dI}{dt} &= \beta(t)\frac{SI}{N} - (\mu(t)+\gamma(t))I \\ \frac{dS}{dt} &= \mu(t)N + \gamma(t)I - \beta(t)\frac{SI}{N} - \mu(t)S\end{aligned} \tag{2.27}$$

where $\beta(t) \geq 0\ \forall t$, and $\exists t_\beta \in (0,\omega) : \beta(t_\beta) > 0$, $\mu(t) \geq 0\ \forall t$, and $\exists t_\mu \in (0,\omega) : \mu(t_\mu) > 0$, and $\gamma(t) \geq 0\ \forall t$, and $\exists t_\gamma \in (0,\omega) : \gamma(t_\gamma) > 0$ and all are assumed to be piecewise continuous and periodic. One can calculate $\mathscr{F}$ and $\mathscr{V}$ as:

$$\mathscr{F}(t) = \begin{bmatrix} \beta(t)\frac{SI}{N} \\ 0 \end{bmatrix}, \mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} (\mu(t)+\gamma(t))I \\ \beta(t)\frac{SI}{N} + \mu(t)S - (\mu(t)N + \gamma(t)I) \end{bmatrix}.$$

Verification of (A1)-(A5) for both methods is simple from observation of the vectors $\mathscr{F}$ and $\mathscr{V}$. The model has a disease-free equilibrium, $(0, N_0)$, where N_0 is the initial condition of the population. For the linear operator method, (A6) must be verified. To do this, one must find $M(t)$:

$$M(t) := -\mu(t). \tag{2.28}$$

Solving the system $\frac{dz}{dt} = M(t)z$ in this case yields the principal fundamental matrix, $\Psi(t)$, since $\Psi^{-1}(0) = I$ where I is the identity matrix. The monodromy matrix evaluated at the period is then $\Phi_M(\omega) = exp\left(-\int_0^\omega \mu(t)dt\right)$ and clearly (A6) is true.

Define $F(t)$ and $V(t)$, both of which are evaluated at the disease-free equilibrium:

$$\begin{aligned} F(t) &= \beta(t) \\ V(t) &= \mu(t) + \gamma(t). \end{aligned} \tag{2.29}$$

Now (A7) must be verified, which requires looking at the system below:

$$\frac{dy}{dt} = -(\mu(t) + \gamma(t))y. \tag{2.30}$$

Again this system gives the principal fundamental matrix and so one need only consider the monodromy matrix evaluated at the period. This is $\Phi_{-V}(\omega) = exp\left(-\int_0^\omega(\mu(t) + \gamma(t))\right)$, and clearly (A7) holds.

Consider again the time-average method first. Now replace $\beta(t), \mu(t)$, and $\gamma(t)$ with their long-time averages and calculate FV^{-1} which is:

$$FV^{-1} = \frac{\frac{1}{\omega}\int_0^\omega \beta(t)dt}{\frac{1}{\omega}\int_0^\omega(\mu(t) + \gamma(t))dt} = \frac{\langle\beta\rangle}{\langle\mu + \gamma\rangle}. \tag{2.31}$$

The spectral radius of this is just the expression itself and so:

$$R_T = \frac{\langle\beta\rangle}{\langle\mu + \gamma\rangle}. \tag{2.32}$$

To characterize R_0 using the linear operator method, consider the following ω-periodic equation:

$$\frac{dw}{dt} = \left[-(\mu(t) + \gamma(t)) + \frac{\beta(t)}{\lambda}\right] w, t \in \mathbb{R} \tag{2.33}$$

which has fundamental solution:

$$w(t) = exp\left(\frac{1}{\lambda}\int_0^t \beta(s)ds - \int_0^t(\mu(s) + \gamma(s))ds\right). \tag{2.34}$$

Then the monodromy matrix is defined as before, and the goal is to find λ_0 such that $\rho(\Phi_{F-V}(\omega)) = 1$, which happens exactly when the exponent in $w(t)$ equals 0. This yields:

$$R_{LO} = \lambda_0 = \frac{\frac{1}{\omega}\int_0^\omega \beta(t)dt}{\frac{1}{\omega}\int_0^\omega (\mu(t)+\gamma(t))dt} = \frac{\langle\beta\rangle}{\langle\mu+\gamma\rangle} \tag{2.35}$$

So in this case the two methods produce the same result again: $R_T = R_{LO} = R_0$.

2.3.3 Two Infected Classes

Now consider the case with two infected classes, similar to a two strain virus that has the same host. The susceptible class gets infected with the first infection by $\beta_1(t)$ and with the second infection by $\beta_2(t)$ and there are assumed to be no coinfections. The infection is cleared at rates γ_1 and γ_2. Consider the system:

$$\begin{aligned}
\frac{dI_1}{dt} &= \beta_1(t)\frac{SI_1}{N} - (\mu+\gamma_1)I_1 \\
\frac{dI_2}{dt} &= \beta_2(t)\frac{SI_2}{N} - (\mu+\gamma_2)I_2 \\
\frac{dS}{dt} &= \mu N + \gamma_1 I_1 + \gamma_2 I_2 - \left(\beta_1(t)\frac{SI_1}{N} + \beta_2(t)\frac{SI_2}{N}\right) - \mu S
\end{aligned} \tag{2.36}$$

where the same assumptions hold as before for $\beta_1(t)$, and $\beta_2(t)$. Then $\mathscr{F}$ and $\mathscr{V}$ are:

$$\mathscr{F}(t) = \begin{bmatrix} \beta_1(t)\frac{SI_1}{N} \\ \beta_2(t)\frac{SI_2}{N} \\ 0 \end{bmatrix}, \mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} (\mu+\gamma_1)I_1 \\ (\mu+\gamma_2)I_2 \\ \beta_1(t)\frac{SI_1}{N} + \beta_2(t)\frac{SI_2}{N} + \mu S - (\mu N + \gamma_1 I_1 + \gamma_2 I_2) \end{bmatrix}.$$

Verification of (A1)-(A5) for both methods is simple from observation of the vectors $\mathscr{F}$ and $\mathscr{V}$. The model has a disease-free equilibrium, $(0, 0, N_0)$, with N_0 being the initial population size. For the linear operator method, (A6) must be verified with:

$$M(t) := -\mu. \tag{2.37}$$

Solving the system $\frac{dz}{dt} = M(t)z$ in this case yields the principal fundamental matrix. The monodromy matrix evaluated at the period ω is then $\Phi_M(\omega) = e^{-\mu\omega}$and clearly (A6) is true.

Define $F(t)$ and $V(t)$:

$$F(t) = \begin{bmatrix} \beta_1(t) & 0 \\ 0 & \beta_2(t) \end{bmatrix}, V(t) = \begin{bmatrix} \mu+\gamma_1 & 0 \\ 0 & \mu+\gamma_2 \end{bmatrix}.$$

Now (A7) must be verified, which requires looking at the system below:

$$\frac{dy}{dt} = \begin{bmatrix} -(\mu+\gamma_1) & 0 \\ 0 & -(\mu+\gamma_2) \end{bmatrix} y$$

Solving gives the fundamental matrix:

$$\Psi_{-V}(t) = \begin{bmatrix} e^{-(\mu+\gamma_1)t} & 0 \\ 0 & e^{-(\mu+\gamma_2)t} \end{bmatrix}.$$

Clearly $\Psi_{-V}^{-1}(0) = I$, and so the monodromy matrix is the principal fundamental matrix evaluated at the period ω. Then the spectral radius of the monodromy matrix is

$$\rho(\Phi_{-V}(\omega)) = \max_j (exp\left(-(\mu+\gamma_j)\omega\right)) < 1, j = 1, 2. \tag{2.38}$$

So (A7) is satisfied.

Using the time-average method calculate FV^{-1} which is:

$$FV^{-1} = \begin{bmatrix} \frac{\langle\beta_1\rangle}{\mu+\gamma_1} & 0 \\ 0 & \frac{\langle\beta_2\rangle}{\mu+\gamma_2} \end{bmatrix}.$$

The spectral radius of this is then:

$$R_T = \rho(FV^{-1}) = \max_i \left\{ \frac{\langle\beta_i\rangle}{\mu+\gamma_i}, i = 1, 2 \right\}. \tag{2.39}$$

For the linear operator method, consider the following ω-periodic system:

$$\begin{aligned} \frac{dw_1}{dt} &= \left[-(\mu+\gamma_1) + \frac{\beta_1(t)}{\lambda} \right] w_1 \\ \frac{dw_2}{dt} &= \left[-(\mu+\gamma_2) + \frac{\beta_2(t)}{\lambda} \right] w_2 \end{aligned} \tag{2.40}$$

which has fundamental matrix:

$$\Psi_{F-V}(t) = \begin{bmatrix} exp\left(\frac{1}{\lambda}\int_0^t \beta_1(s)ds - (\mu+\gamma_1)t\right) & 0 \\ 0 & exp\left(\frac{1}{\lambda}\int_0^t \beta_2(s)ds - (\mu+\gamma_2)t\right) \end{bmatrix}.$$

The monodromy matrix is as defined before, so solve for λ_0 such that $\rho(\Phi_{F-V}(\omega)) = 1$, which happens exactly when the exponent equals 0. This yields:

$$R_{LO} = \lambda_0 = \max_i \left\{ \frac{\langle \beta_i \rangle}{\mu + \gamma_i}, i = 1, 2 \right\} \tag{2.41}$$

and again $R_T = R_{LO} = R_0$.

2.3.4 Two Infected Classes: General Case

Now for the generalized form of the previous system. Consider the system:

$$\begin{aligned} \frac{dI_1}{dt} &= \beta_1(t)\frac{SI_1}{N} - (\mu(t) + \gamma_1(t))I_1 \\ \frac{dI_2}{dt} &= \beta_2(t)\frac{SI_2}{N} - (\mu(t) + \gamma_2(t))I_2 \\ \frac{dS}{dt} &= \mu(t)N + \gamma_1(t)I_1 + \gamma_2(t)I_2 - \left(\beta_1(t)\frac{SI_1}{N} + \beta_2(t)\frac{SI_2}{N}\right) - \mu(t)S \end{aligned} \tag{2.42}$$

where the same assumptions hold as before for $\beta_1(t), \beta_2(t), \mu(t), \gamma_1(t)$ and $\gamma_2(t)$. Then $\mathscr{F}$ and $\mathscr{V}$ are:

$$\mathscr{F}(t) = \begin{bmatrix} \beta_1(t)\frac{SI_1}{N} \\ \beta_2(t)\frac{SI_2}{N} \\ 0 \end{bmatrix},$$

.

$$\mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} (\mu(t) + \gamma_1(t))I_1 \\ (\mu(t) + \gamma_2(t))I_2 \\ \beta_1(t)\frac{SI_1}{N} + \beta_2(t)\frac{SI_2}{N} + \mu(t)S - (\mu(t)N + \gamma_1(t)I_1 + \gamma_2(t)I_2) \end{bmatrix}$$

Verification of (A1)-(A5) for both methods is simple from observation of the vectors $\mathscr{F}$ and $\mathscr{V}$. The model has a disease-free equilibrium, $(0, 0, N_0)$, with N_0 being the initial population size. For the linear operator method, (A6) must be verified with:

$$M(t) := -\mu(t). \tag{2.43}$$

Solving the system $\frac{dz}{dt} = M(t)z$ in this case yields the principal fundamental matrix. The monodromy matrix evaluated at the period ω is then $\Phi_M(\omega) = exp\left(-\int_0^\omega \mu(t)dt\right)$ and clearly (A6) is satisfied.

Define $F(t)$ and $V(t)$ as follows:

$$F(t) = \begin{bmatrix} \beta_1(t) & 0 \\ 0 & \beta_2(t) \end{bmatrix}, V(t) = \begin{bmatrix} \mu(t) + \gamma_1(t) & 0 \\ 0 & \mu(t) + \gamma_2(t) \end{bmatrix}.$$

Now (A7) must be verified, which requires looking at the system below:

$$\frac{dy}{dt} = \begin{bmatrix} -(\mu(t) + \gamma_1(t)) & 0 \\ 0 & -(\mu(t) + \gamma_2(t)) \end{bmatrix} y$$

Solving gives the fundamental matrix:

$$\Psi_{-V}(t) = \begin{bmatrix} exp\left(-\int_0^t (\mu(s) + \gamma_1(s))ds\right) & 0 \\ 0 & exp\left(-\int_0^t (\mu(s) + \gamma_2(s))ds\right) \end{bmatrix}.$$

Clearly $\Psi_{-V}^{-1}(0) = I$, and so the monodromy matrix is the principal fundamental matrix evaluated at the period ω. Then the spectral radius of the monodromy matrix is

$$\rho(\Phi_{-V}(\omega)) = \max_j \left(exp\left(-\int_0^\omega (\mu(t) + \gamma_j(t))dt\right)\right) < 1, j = 1, 2 \tag{2.44}$$

So (A7) is satisfied.

Using the time-average method calculate FV^{-1} which is:

$$FV^{-1} = \begin{bmatrix} \frac{\langle \beta_1 \rangle}{\langle \mu + \gamma_1 \rangle} & 0 \\ 0 & \frac{\langle \beta_2 \rangle}{\langle \mu + \gamma_2 \rangle} \end{bmatrix}.$$

The spectral radius of this is then:

$$R_T = \rho(FV^{-1}) = \max_i \left\{ \frac{\langle \beta_i \rangle}{\langle \mu + \gamma_i \rangle}, i = 1, 2 \right\} \tag{2.45}$$

For the linear operator method, consider the following ω-periodic system:

$$\begin{aligned} \frac{dw_1}{dt} &= \left[-(\mu(t) + \gamma_1(t)) + \frac{\beta_1(t)}{\lambda} \right] w_1 \\ \frac{dw_2}{dt} &= \left[-(\mu(t) + \gamma_2(t) + \frac{\beta_2(t)}{\lambda} \right] w_2 \end{aligned} \tag{2.46}$$

which has fundamental matrix:

$$\Psi_{F-V}(t) = \begin{bmatrix} e^{\left(\frac{1}{\lambda}\int_0^t (\beta_1(s)ds - \int_0^t (\mu(s)+\gamma_1(s))ds\right)} & 0 \\ 0 & e^{\left(\frac{1}{\lambda}\int_0^t (\beta_2(s)ds - \int_0^t (\mu(s)+\gamma_2(s))ds\right)} \end{bmatrix}.$$

The monodromy matrix is as defined before, so solve for λ_0 such that $\rho(\Phi_{F-V}(\omega)) = 1$, which happens exactly when the exponent equals 0. This yields:

$$R_{LO} = \lambda_0 = \max_i \left\{ \frac{\langle \beta_i \rangle}{\langle \mu + \gamma_i \rangle}, i = 1, 2 \right\} \tag{2.47}$$

and again $R_T = R_{LO} = R_0$.

2.3.5 Modified Vector-Host Model: Version 1

Consider a modified vector-host model in which vectors get infected by other vectors at a rate $\beta_v(t)$ and hosts get infected by vectors at a rate $\beta_h(t)$. Vectors die at a rate $\mu_v(t)$ and hosts die at a rate of $\mu_h(t)$. The infection is cleared by hosts at a rate $\gamma(t)$. The system then becomes:

$$\begin{aligned} \frac{dI_v}{dt} &= \beta_v(t)\frac{S_v I_v}{N_v} - \mu_v(t) I_v \\ \frac{dI_h}{dt} &= \beta_h(t)\frac{S_h I_v}{N_h} - (\mu_h(t) + \gamma(t)) I_h \\ \frac{dS_v}{dt} &= \mu_v(t) N_v - \beta_v(t)\frac{S_v I_v}{N_v} - \mu_v(t) S_v \\ \frac{dS_h}{dt} &= \mu_h(t) N_h + \gamma(t) I_h - \beta_h(t)\frac{S_h I_v}{N_h} - \mu_h(t) S_h \end{aligned} \tag{2.48}$$

where the same assumptions hold as before for $\beta_v(t), \beta_h(t), \mu_v(t), \mu_h(t)$ and $\gamma(t)$. Then $\mathscr{F}$ and $\mathscr{V}$ are:

$$\mathscr{F}(t) = \begin{bmatrix} \beta_v(t)\frac{S_v I_v}{N_v} \\ \beta_h(t)\frac{S_h I_v}{N_h} \\ 0 \\ 0 \end{bmatrix},$$

$$\mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} \mu_v(t) I_v \\ (\mu_h(t) + \gamma(t)) I_h \\ \beta_v(t)\frac{S_v I_v}{N_v} + \mu_v(t) S_v - \mu_v(t) N_v \\ \beta_h(t)\frac{S_h I_v}{N_h} + \mu_h(t) S_h - \mu_h(t) N_h - \gamma_v(t) I_h \end{bmatrix}.$$

Verification of (A1)-(A5) for both methods is simple from observation of the vectors $\mathscr{F}$ and $\mathscr{V}$. The model has a disease-free equilibrium, $(0, 0, N_v, N_h)$, where N_v and N_h are the initial conditions. For the linear operator method, (A6) must be verified with:

$$M(t) = \begin{bmatrix} -\mu_v(t) & 0 \\ 0 & -\mu_h(t) \end{bmatrix}.$$

Solving the system $\frac{dz}{dt} = M(t)z$ in this case yields the principal fundamental matrix:

$$\Psi_M(t) = \begin{bmatrix} exp\left(-\int_0^t \mu_v(s)ds\right) & 0 \\ 0 & exp\left(-\int_0^t \mu_h(s)ds\right) \end{bmatrix}.$$

Clearly $\Psi_M^{-1}(0) = I$ and thus the monodromy matrix is the principal fundamental matrix evaluated at the period:

$$\Phi_M(\omega) = \begin{bmatrix} exp\left(-\int_0^\omega \mu_v(t)dt\right) & 0 \\ 0 & exp\left(-\int_0^\omega \mu_h(t)dt\right) \end{bmatrix}$$

and clearly (A6) is satisfied.

Define $F(t)$ and $V(t)$ as follows:

$$F(t) = \begin{bmatrix} \beta_v(t) & 0 \\ \beta_h(t) & 0 \end{bmatrix}, V(t) = \begin{bmatrix} \mu_v(t) & 0 \\ 0 & \mu_h(t) + \gamma(t) \end{bmatrix}.$$

Now (A7) must be verified:

$$\frac{dy}{dt} = \begin{bmatrix} -\mu_v(t) & 0 \\ 0 & -(\mu_h(t) + \gamma(t)) \end{bmatrix} y.$$

Solving gives the fundamental matrix:

$$\Psi_{-V}(t) = \begin{bmatrix} exp\left(-\int_0^t \mu_v(s)ds\right) & 0 \\ 0 & exp\left(-\int_0^t (\mu_h(s) + \gamma(s))ds\right) \end{bmatrix}.$$

Clearly $\Psi_{-V}^{-1}(0) = I$, and so the monodromy matrix is as defined above. Then the spectral radius of the monodromy matrix is

$$\rho(\Phi_{-V}(\omega)) = \max\left(exp\left(-\int_0^\omega \mu_v(t)dt\right), exp\left(-\int_0^\omega (\mu_h(t) + \gamma_j(t))dt\right)\right) < 1. \tag{2.49}$$

So (A7) is satisfied.

Using the time-average method calculate FV^{-1} which is:

$$FV^{-1} = \begin{bmatrix} \frac{\langle \beta_v \rangle}{\langle \mu_v \rangle} & 0 \\ 0 & 0 \end{bmatrix}.$$

The spectral radius of this is then:

$$R_T = \rho(FV^{-1}) = \frac{\langle \beta_v \rangle}{\langle \mu_v \rangle}. \tag{2.50}$$

For the linear operator method, consider the following ω-periodic system:

$$\frac{d\mathbf{w}}{dt} = \begin{bmatrix} \frac{\beta_v(t)}{\lambda} - \mu_v(t) & 0 \\ \frac{\beta_h(t)}{\lambda} & -(\mu_h(t) + \gamma(t)) \end{bmatrix} \mathbf{w}$$

which has fundamental matrix:

$$\Psi_{F-V}(t) = \begin{bmatrix} exp\left(\frac{1}{\lambda}\int_0^t(\beta_v(s)ds - \int_0^t \mu_v(s)ds\right) & 0 \\ f(t) & exp\left(-\int_0^t(\mu_h(s)+\gamma(s))ds\right) \end{bmatrix}$$

where:

$$f(t) = exp\left(-\int_0^t(\mu_h(s)+\gamma(s))ds\right)\left(\frac{1}{\lambda}\int_0^t \beta_h(s)exp\left(\frac{1}{\lambda}\int_0^t \beta_v(\tau)d\tau + \int_0^t(\mu_h(\tau)+\gamma(\tau)-\mu_v(\tau))d\tau\right)ds\right)$$

It can be shown that $\Psi_{F-V}(0) = I$ so the monodromy matrix is the fundamental matrix evaluated at the period, ω. Solve for λ_0 such that $\rho(\Phi_{F-V}(\omega)) = 1$, which happens exactly when the exponent for the first entry, the only diagonal entry that includes a λ, equals 0. This yields:

$$R_{LO} = \lambda_0 = \frac{\langle\beta_v\rangle}{\langle\mu_v\rangle} \tag{2.51}$$

and so they agree in their expression and $R_T = R_{LO} = R_0$.

2.3.6 Modified Vector-Host Model: Version 2

Consider the system as before with the added infection of hosts by other hosts at a rate $\beta_h(t)$ and hosts get infected by vectors at a rate $\beta_{vh}(t)$. The system is below:

$$\begin{aligned}
\frac{dI_v}{dt} &= \beta_v(t)\frac{S_vI_v}{N_v} - \mu_v(t)I_v \\
\frac{dI_h}{dt} &= \beta_{vh}(t)\frac{S_hI_v}{N_h} + \beta_h(t)\frac{S_hI_h}{N_h} - (\mu_h(t)+\gamma(t))I_h \\
\frac{dS_v}{dt} &= \mu_v(t)N_v - \beta_v(t)\frac{S_vI_v}{N_v} - \mu_v(t)S_v \\
\frac{dS_h}{dt} &= \mu_h(t)N_h + \gamma(t)I_h - \beta_{vh}(t)\frac{S_hI_v}{N_h} - \beta_h(t)\frac{S_hI_h}{N_h} - \mu_h(t)S_h
\end{aligned} \tag{2.52}$$

where the same assumptions hold as before for $\beta_v(t), \beta_{vh}(t), \beta_h(t), \mu_v(t), \mu_h(t)$ and $\gamma(t)$. Then $\mathscr{F}$ and $\mathscr{V}$ are:

$$\mathscr{F}(t) = \begin{bmatrix} \beta_v(t)\frac{S_v I_v}{N_v} \\ \beta_{vh}(t)\frac{S_h I_v}{N_h} + \beta_h(t)\frac{S_h I_v}{N_h} \\ 0 \\ 0 \end{bmatrix},$$

$$\mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} \mu_v(t) I_v \\ (\mu_h(t) + \gamma(t)) I_h \\ \beta_v(t)\frac{S_v I_v}{N_v} + \mu_v(t) S_v - \mu_v(t) N_v \\ \beta_{vh}(t)\frac{S_h I_v}{N_h} + \beta_h(t)\frac{S_h I_v}{N_h} + \mu_h(t) S_h - \mu_h(t) N_h - \gamma_v(t) I_h \end{bmatrix}.$$

Verification of (A1)-(A5) for both methods is simple from observation of the vectors $\mathscr{F}$ and $\mathscr{V}$. The model has a disease-free equilibrium, $(0, 0, N_v, N_h)$, where N_v and N_h are the initial conditions. For the linear operator method, (A6) must be verified with:

$$M(t) = \begin{bmatrix} -\mu_v(t) & 0 \\ 0 & -\mu_h(t) \end{bmatrix}.$$

Solving the system $\frac{dz}{dt} = M(t)z$ in this case yields the principal fundamental matrix:

$$\Psi_M(t) = \begin{bmatrix} exp\left(-\int_0^t \mu_v(s)ds\right) & 0 \\ 0 & exp\left(-\int_0^t \mu_h(s)ds\right) \end{bmatrix}.$$

Clearly $\Psi_M^{-1}(0) = I$ and thus the monodromy matrix is the principal fundamental matrix evaluated at the period:

$$\Phi_M(\omega) = \begin{bmatrix} exp\left(-\int_0^\omega \mu_v(t)dt\right) & 0 \\ 0 & exp\left(-\int_0^\omega \mu_h(t)dt\right) \end{bmatrix}$$

and clearly (A6) is satisfied.

Define $F(t)$ and $V(t)$ as follows:

$$F(t) = \begin{bmatrix} \beta_v(t) & 0 \\ \beta_{vh}(t) & \beta_h(t) \end{bmatrix}, V(t) = \begin{bmatrix} \mu_v(t) & 0 \\ 0 & \mu_h(t) + \gamma(t) \end{bmatrix}.$$

Now (A7) must be verified:

$$\frac{dy}{dt} = \begin{bmatrix} -\mu_v(t) & 0 \\ 0 & -(\mu_h(t) + \gamma(t)) \end{bmatrix} y$$

Solving gives the fundamental matrix:

$$\Psi_{-V}(t) = \begin{bmatrix} exp\left(-\int_0^t \mu_v(s)ds\right) & 0 \\ 0 & exp\left(-\int_0^t (\mu_h(s) + \gamma(s))ds\right) \end{bmatrix}.$$

Clearly $\Psi_{-V}^{-1}(0) = I$, and so the monodromy matrix is as defined above. Then the spectral radius of the monodromy matrix is

$$\rho(\Phi_{-V}(\omega)) = \max\left(exp\left(-\int_0^\omega \mu_v(t)dt\right), exp\left(-\int_0^\omega (\mu_h(t) + \gamma_j(t))dt\right)\right) < 1. \tag{2.53}$$

So (A7) is satisfied.

Using the time-average method calculate FV^{-1} which is:

$$FV^{-1} = \begin{bmatrix} \frac{\langle \beta_v \rangle}{\langle \mu_v \rangle} & 0 \\ 0 & \frac{\langle \beta_h \rangle}{\langle \mu_h + \gamma \rangle} \end{bmatrix}.$$

The spectral radius of this is then:

$$R_T = \rho(FV^{-1}) = max\left\{\frac{\langle \beta_v \rangle}{\langle \mu_v \rangle}, \frac{\langle \beta_h \rangle}{\langle \mu_h + \gamma \rangle}\right\}. \tag{2.54}$$

For the linear operator method, consider the following ω-periodic system:

$$\frac{d\mathbf{w}}{dt} = \begin{bmatrix} \frac{\beta_v(t)}{\lambda} - \mu_v(t) & 0 \\ \frac{\beta_{vh}(t)}{\lambda} & \frac{\beta_h(t)}{\lambda} - (\mu_h(t) + \gamma(t)) \end{bmatrix} \mathbf{w}$$

which has fundamental matrix:

$$\Psi_{F-V}(t) = \begin{bmatrix} exp\left(\frac{1}{\lambda}\int_0^t(\beta_v(s)ds - \int_0^t \mu_v(s)ds\right) & 0 \\ f(t) & exp\left(\frac{1}{\lambda}\int_0^t \beta_{vh}(s)ds - \int_0^t(\mu_h(s)+\gamma(s))ds\right) \end{bmatrix}$$

where:

$f(t) = exp\left(\frac{1}{\lambda}\int_0^t \beta_h(s)ds - \int_0^t(\mu_h(s)+\gamma(s))ds\right) \times$
$\left(\frac{1}{\lambda}\int_0^t \beta_{vh}(s) exp\left(\frac{1}{\lambda}\int_0^t(\beta_v(\tau) - \beta_h(\tau)d\tau + \int_0^t(\mu_h(\tau)+\gamma(\tau)-\mu_v(\tau))d\tau\right)ds\right)$

It can be shown that $\Psi_{F-V}(0) = I$ so the monodromy matrix is the fundamental matrix evaluated at the period, ω. Solve for λ_0 such that $\rho(\Phi_{F-V}(\omega)) = 1$, which happens exactly when the exponent for diagonal entries equals 0. This yields:

$$R_{LO} = \lambda_0 = max\left\{\frac{\langle\beta_v\rangle}{\langle\mu_v\rangle}, \frac{\langle\beta_h\rangle}{\langle\mu_h+\gamma\rangle}\right\} \tag{2.55}$$

and so they agree in their expression and $R_T = R_{LO} = R_0$.

2.3.7 Vector-Host Model

Consider the system:

$$\begin{aligned} \frac{dI_v}{dt} &= \beta_v(t)\frac{S_v I_h}{N_v} - \mu_v I_v \\ \frac{dI_h}{dt} &= \beta_h(t)\frac{S_h I_v}{N_h} - (\mu_h+\gamma)I_h \\ \frac{dS_v}{dt} &= \mu_v N_v - \beta_v(t)\frac{S_v I_h}{N_v} - \mu_v S_v \\ \frac{dS_h}{dt} &= \mu_h N_h + \gamma I_h - \beta_h(t)\frac{S_h I_v}{N_h} - \mu_h S_h \end{aligned} \tag{2.56}$$

where the same assumptions hold as before for $\beta_v(t)$, and $\beta_h(t)$. Then $\mathscr{F}$ and $\mathscr{V}$ are:

$$\mathscr{F}(t) = \begin{bmatrix} \beta_v(t)\frac{S_v I_v}{N_v} \\ \beta_h(t)\frac{S_h I_v}{N_h} \\ 0 \\ 0 \end{bmatrix}, \mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} \mu_v I_v \\ (\mu_h+\gamma)I_h \\ \beta_v(t)\frac{S_v I_h}{N_v} + \mu_v S_v - \mu_v N_v \\ \beta_h(t)\frac{S_h I_v}{N_h} + \mu_h S_h - \mu_h N_h - \gamma I_h \end{bmatrix}.$$

Verification of (A1)-(A5) for both methods is simple from observation of the vectors $\mathscr{F}$ and $\mathscr{V}$. The model has a disease-free equilibrium, $(0, 0, N_v, N_h)$, where N_v and N_h are the initial population sizes. For the linear operator method, (A6) must be verified with:

$$M(t) = \begin{bmatrix} -\mu_v & 0 \\ 0 & -\mu_h \end{bmatrix}.$$

Solving the system $\frac{dz}{dt} = M(t)z$ in this case yields the principal fundamental matrix which gives the monodromy as this matrix evaluated at the period:

$$\Phi_M(t) = \begin{bmatrix} e^{-\mu_v t} & 0 \\ 0 & e^{-\mu_h t} \end{bmatrix}$$

and clearly (A6) is satisfied.

Define $F(t)$ and $V(t)$ as follows:

$$F(t) = \begin{bmatrix} 0 & \beta_v(t) \\ \beta_h(t) & 0 \end{bmatrix}, V(t) = \begin{bmatrix} \mu_v & 0 \\ 0 & \mu_h + \gamma \end{bmatrix}.$$

Now (A7) must be verified:

$$\frac{dy}{dt} = \begin{bmatrix} -\mu_v & 0 \\ 0 & -(\mu_h + \gamma) \end{bmatrix} y.$$

Solving gives the principal fundamental matrix and so the monodromy matrix is:

$$\Phi_{-V}(\omega) = \begin{bmatrix} e^{-\mu_v \omega} & 0 \\ 0 & e^{-(\mu_h+\gamma)\omega} \end{bmatrix}$$

and again (A7) is satisfied.

Using the time-average method calculate FV^{-1} which is:

$$FV^{-1} = \begin{bmatrix} 0 & \frac{\langle \beta_v \rangle}{\langle \mu_v \rangle} \\ \frac{\langle \beta_h \rangle}{\langle \mu_h + \gamma \rangle} & 0 \end{bmatrix}.$$

The spectral radius of this is then:

$$\rho(FV^{-1}) = \sqrt{\frac{\langle\beta_v\rangle\langle\beta_h\rangle}{\mu_v(\mu_h+\gamma)}} \tag{2.57}$$

For the linear operator method, consider the following ω-periodic system:

$$\frac{d\mathbf{w}}{dt} = \begin{bmatrix} -\mu_v & \frac{\beta_v(t)}{\lambda} \\ \frac{\beta_h(t)}{\lambda} & -(\mu_h+\gamma) \end{bmatrix} \mathbf{w}$$

Now this system is difficult to solve, so consider the case where $\beta_v(t), \beta_h(t)$ are square-wave functions:

$$\beta_v(t) = \begin{cases} a_v & : 0 < t < \tau \\ b_v & : \tau < t < \omega \end{cases} \tag{2.58}$$

$$\beta_h(t) = \begin{cases} a_h & : 0 < t < \tau \\ b_h & : \tau < t < \omega \end{cases} \tag{2.59}$$

So when $0 < t < \tau$ the system becomes:

$$\frac{d\mathbf{w}}{dt} = \begin{bmatrix} -\mu_v & \frac{a_v}{\lambda} \\ \frac{a_h}{\lambda} & -(\mu_h+\gamma) \end{bmatrix} \mathbf{w}$$

which has eigenvalues:

$$r_{1,2} = -\frac{1}{2}\left\{(\mu_h+\gamma+\mu_v) \pm \sqrt{(\mu_h+\gamma-\mu_v)^2 + \frac{4a_va_h}{\lambda^2}}\right\}. \tag{2.60}$$

All quantities in the radical are > 0 so the radicand $> 0, \forall\lambda \in \mathbb{R}$. In this case the fundamental matrix is:

$$\Psi_a(t) = \begin{bmatrix} \frac{a_v}{\lambda}e^{r_1t} & (\mu_h+\gamma+r_2)e^{r_2t} \\ (\mu_v+r_1)e^{r_1t} & \frac{a_h}{\lambda}e^{r_2t} \end{bmatrix}.$$

Doing the same thing for the interval $\tau < t < \omega$ gives:

$$\Psi_b(t) = \begin{bmatrix} \frac{b_v}{\lambda} e^{q_1(t-\tau)} & (\mu_h + \gamma + q_2) e^{q_2(t-\tau)} \\ (\mu_v + q_1) e^{q_1(t-\tau)} & \frac{b_h}{\lambda} e^{q_2(t-\tau)} \end{bmatrix}$$

where

$$q_{1,2} = -\frac{1}{2} \left\{ (\mu_h + \gamma + \mu_v) \pm \sqrt{(\mu_h + \gamma - \mu_v)^2 + \frac{4 b_v b_h}{\lambda^2}} \right\}. \tag{2.61}$$

For the entire interval of interest, $0 < t < \omega$, the solution becomes:

$$\Psi(t) = \begin{cases} \Psi_a(t) \Psi_a^{-1}(0) & : 0 < t \leq \tau \\ \Psi_b(t) \Psi_b^{-1}(\tau) \Psi_a(\tau) \Psi_a^{-1}(0) & : \tau < t \leq \omega \end{cases} \tag{2.62}$$

The monodromy matrix is then:

$$\Phi_{F-V}(\omega) = \Psi(\omega) \tag{2.63}$$

Getting an explicit solution is challenging as it requires finding each piece in the solution for the entire interval then multiplying those matrices together for the final solution. It can be done, and once it is, the real difficulty comes when trying to find the spectral radius of the monodromy matrix, $\Phi_{F-V}(\omega)$. The eigenvalues for this matrix are difficult expressions so finding the largest eigenvalue, the spectral radius, becomes even more challenging. It can also be done but when trying to solve the spectral radius for a λ_0 such that $\rho(\Phi_{F-V}(\omega)) = 1$, the result is a transcendental equation and so work from here must be done numerically. For the set of parameters in Table 4.1, the equation $\rho(\Phi_{F-V}(\omega)) = 1$ is solved numerically in Mathematica and graphed as a function of τ where $0 < \tau < \omega$. This gives a graph for R_{LO}. For comparison, R_T is also graphed as a function of τ. The results are shown in Figure 2.1:

Table 2.1. Parameter values for (2.56)

Parameter	Value
a_h	0.7875
b_h	1.7325
a_v	2.3625
b_v	0.7875
μ_h	1
μ_v	1
γ	1

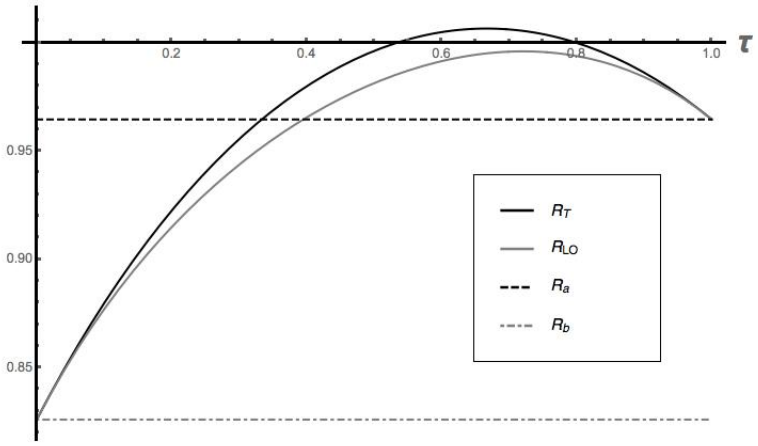

Figure 2.1. Graphs of (2.56) that shows R_T (black) and R_{LO} (gray) for varying values of τ. The dashed and dotdashed lines represent the basic reproductive numbers of the autonomous systems where $\beta_j = a_j$ $(\tau = \omega)$ and $\beta_j = b_j$ $(\tau = 0)$.

The graph clearly shows that the time average method produces a reproductive number that goes above 1 while the linear operator method always stays below 1. So clearly they are predicting different disease behaviors for a certain range of τ values. To see how the system behaves for the given set of parameters, simulations are run

in Matlab to see the end time result. Figure 2.2 below shows this:

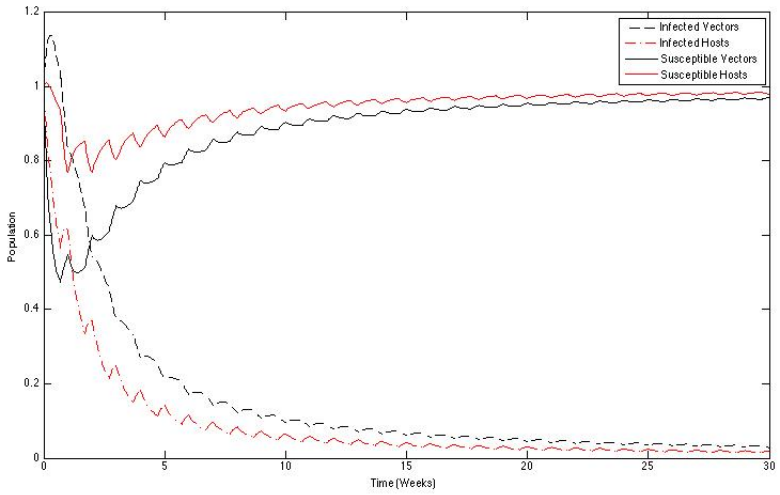

Figure 2.2. Simulation of (2.56) for the set of parameters in which $R_{LO} < 1 < R_T$, shows the disease-free equilibrium to be stable.

So the disease actually dies out over time given the parameters used to get Figure 2.1. It would seem that the time average method actually overestimates the disease transmission risk in this case. So why then did the other models agree in their expression, yet this simple model does not? This would seem to suggest that R_T is not the correct R_0 for the system but that R_{LO} is.

2.4 Theorem

So when do the expressions for R_T and $R_{LO} = R_0$ agree? In their paper [51], Wang and Zhao proved that for models where the $F(t)$ and $V(t)$ matrices are constant or diagonal, the two methods would produce the same expression for R_0. However, this result can extend further. In looking at the examples, one can notice that with

all the models that agree for the methods, the matrices $F(t)$ and $V(t)$ are either diagonal or triangular. This leads to the following theorem.

Theorem 1. *Consider an n-dimensional ω-periodic system with m infected classes. If the $m \times m$ matrices $F(t)$ and $V(t)$ are triangular of the same form, that is they are both upper or lower triangular, then the time-average method for calculating R_0 gives the same expression as the linear operator method.*

To prove this a theorem is needed from [48].

Theorem (2.5)**.** *If $A(t)$ is a periodic lower triangular matrix function*

$$\begin{pmatrix} a_{11}(t) & 0 & \cdots & 0 \\ a_{21}(t) & a_{22}(t) & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots \\ a_{n1}(t) & a_{n2}(t) & \cdots & a_{mm}(t) \end{pmatrix}$$

then the characteristic multipliers of the system $\dot{X} = A(t)X$ are given by $exp\left(\int_0^\omega a_{11}(t)dt\right), exp\left(\int_0^\omega a_{22}(t)dt\right), \cdots, exp\left(\int_0^\omega a_{mm}(t)dt\right)$, and a set of Floquet exponents are given by

$$\frac{1}{\omega}\int_0^\omega a_{11}(t)dt, \frac{1}{\omega}\int_0^\omega a_{22}(t)dt, \cdots, \frac{1}{\omega}\int_0^\omega a_{mm}(t)dt. \tag{2.64}$$

The result holds for upper triangular matrices as well. Now to the proof of Theorem 1.

Proof. Suppose without loss of generality that they are lower triangular matrices, that is:

$$F(t) = \begin{pmatrix} a_{11}(t) & 0 & \cdots & 0 \\ a_{21}(t) & a_{22}(t) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ a_{n1}(t) & a_{n2}(t) & \cdots & a_{mm}(t) \end{pmatrix}$$

$$V(t) = \begin{pmatrix} b_{11}(t) & 0 & \cdots & 0 \\ b_{21}(t) & b_{22}(t) & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ b_{n1}(t) & b_{n2}(t) & \cdots & b_{mm}(t) \end{pmatrix}$$

For the time average method replace each of the functions in the matrix with their long time-average and calculate the matrix FV^{-1}:

$$FV^{-1} = \begin{pmatrix} \frac{\langle a_{11} \rangle}{\langle b_{11} \rangle} & 0 & \cdots & 0 \\ * & \frac{\langle a_{22} \rangle}{\langle b_{22} \rangle} & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ * & * & \cdots & \frac{\langle a_{mm} \rangle}{\langle b_{mm} \rangle} \end{pmatrix}$$

Since the eigenvalues sit on the diagonal, the factors $*$ below the diagonal will not matter in the calculation of the spectral radius. The spectral radius is then:

$$R_T = \max \left\{ \frac{\langle a_{11} \rangle}{\langle b_{11} \rangle}, \frac{\langle a_{22} \rangle}{\langle b_{22} \rangle}, \cdots, \frac{\langle a_{mm} \rangle}{\langle b_{mm} \rangle} \right\} \tag{2.65}$$

For the linear operator method consider the system:

$$\frac{dw}{dt} = \left[-V(t) + \frac{F(t)}{\lambda} \right] w, t \in \mathbb{R} \tag{2.66}$$

The matrix for this system is lower triangular and so using Theorem 2.5 from [48] the eigenvalues are the exponents of the integrals of the entries on the diagonals. The diagonal entries are:

$$\frac{1}{\lambda} \int_0^\omega (a_{ii}(t) - b_{ii}(t))\, dt, 1 \leq i \leq m. \tag{2.67}$$

When this equation is solved for the spectral radius it gives the max of all the expressions. Then this is solved for λ_0 equal to 1. Doing so gives an expression for R_0:

$$R_{LO} = \max \left\{ \frac{\langle a_{11} \rangle}{\langle b_{11} \rangle}, \frac{\langle a_{22} \rangle}{\langle b_{22} \rangle}, \cdots, \frac{\langle a_{mm} \rangle}{\langle b_{mm} \rangle} \right\} \tag{2.68}$$

and so the two methods agree in their expression for R_0 $\square$

Notice this condition is a sufficient one. There may be cases where they agree in their expression but the matrices are not triangular. The time-average method is much easier to implement in these systems as finding FV^{-1} is easier than having to solve the system (4.9). However, since R_{LO} is the correct expression for R_0 to use the time-average method, the system must be in the form of these special matrices. This does give a nice way to find R_0 for these periodic systems.

The case of one infected class is a special case since the solution for (4.9) would be a scalar. This is a special case of the theorem since scalar systems are trivially diagonal or triangular. This says that no matter how complicated the compartmentalization of the model, if the infected class is homogeneous the long-term average determines persistence. So it allows the use of the time-average method instead of the linear operator method and the expression for the basic reproductive number will always be the same.

It should be noted that it is not always the case that the time-average R_T will overestimate the disease transmission risk. Wang and Zhao in [51] found an example where the time-averaged system underestimates the disease transmission risk. Many more examples were given in [8] of the time average system overestimating or underestimating the disease transmission risk.

Now that there is a precise way to calculate the basic reproductive number for periodic systems, the next step is to extend this method to invasion reproductive numbers. For autonomous systems, the methods were similar to methods to calculate the BRN, so it would seem trying to extend the linear operator method, now that it is shown to be the correct method, is the best course of action. First, a guideline for

calculating numerically the BRN when an explicit form of the fundamental matrix cannot be found is presented.

2.5 Numerical Methods

The previous examples highlighted ways in which the different methods could be applied and when they agreed and disagreed in their representation of the BRN. All the example were either triangular and thus the time-average method could be used, or in the case of the last example, an explicit matrix was found for the fundamental solution matrix of the system. However, in most cases, this cannot be done. The systems that (4.9) produces typically cannot be solved by hand and so numerical methods must be used to try and find the BRN. In fact even in the last example, since the fundamental matrix had λ in it, in order to find the BRN a transcendental equation must be solved. This had to be done numerically and so an explicit expression for the BRN could not be found. In general, an explicit expression for any BRN using the linear operator method cannot be found, and so numerical work must be done.

Generally when solving a system of ordinary differential equations, all that is wanted is a single solution to understand what the system does for a given set of parameters. For the linear operator method for finding a BRN this is not enough. One must find a fundamental matrix, which means that for an n-dimensional system, one must find n linear independent solutions. Each solution can be found in multiple ways, but first one must determine that each solution is indeed linearly independent from the others. For this one needs only to ensure that each initial condition is linearly independent from the others. The easiest way to do this is to use a standard basis, where each initial condition is just a unit vector of the appropriate size. This guarantees, at least algebraically, that the solutions will be linearly independent.

As stated before, the solutions can be found in multiple ways. For a given value of λ, the solutions are found using some numerical method. This could be something as simple as Runge-Kutta methods or even Euler's method. These of course only produce approximations of the solution, and thus can at least give an approximation of the fundamental matrix as well. Once the solutions have been found, the next step is to build the fundamental matrix, $\Psi(t)$, with each column being a solution. The fundamental matrix depends on λ and so to find it, λ is fixed. This matrix is then evaluated at the period and to use the linear operator method the maximum eigenvalue is found, $\rho(\Psi(\omega))$. The BRN is then the root λ of $\rho(\Psi(\omega)) - 1$. To find this value of λ use some root finding method, the easiest being the bisection method.

Though this does not explicitly give a formula for finding the BRN numerically using the linear operator method, it does give some guidelines for how it can be done. One must choose the numerical techniques they deem best for finding the fundamental matrix.

CHAPTER 3

Invasion reproductive numbers for periodic epidemic models

The basic reproductive numbers from the last chapter are useful tools in studying epidemics. They give conditions on when a disease-free equilibrium is stable or unstable. Unfortunately many infections persist endemically in affected populations. When they do it is important to understand when, if ever, other infections can invade this system. These invasions could have multiple effects on the population. One possibility when coinfection is not possible is competitive exclusion since these pathogens are competing for the same resource, susceptible individuals, it could be that one pathogen holds an advantage and will thus win the competition over the other pathogen. However, there is also the case both pathogens could co-persist at endemic levels within the population.

In order to study these scenarios, invasion reproductive numbers (IRNs), often denoted $\tilde{R}_i$ where i is the invading infection, are used. Using this notation the set of resident infections is made implicit. The IRN of one pathogen with respect to another or the others is defined as the average number of secondary infections caused by introducing one person infected with that pathogen into an environment where the given combination of other pathogen(s) is already at an endemic state [55]. These are often used in studies where competitive exclusion exists [55, 44] and they measure the ability of a pathogen to invade while other pathogens are already at equilibrium. However, one can define a different IRN, $\tilde{R}_0$, where each invading strain is joined into one category and not distinguished from each other. Then $\tilde{R}_0$ is the expected number of secondary cases one infected individual with some infection not resident

in the population produces in a population where all (and only) infections assumed to be resident are present. It measures the ability of pathogens to invade while other pathogens are already at equilibrium without distinguishing which pathogen is actually able to invade.

Most models that calculate these values only do so for two infections [55, 44, 15], that is for a system with k infections where $k = 2$ the resident infection is implicit. It is possible, however, to consider multiple infections, though the models will be very complex. When $k > 2$, the resident infections must be made explicit. IRNs are associated with the same kind of threshold behavior as BRNs: if a pathogen's IRN is greater than 1 then the pathogen can invade even though the other pathogen has established itself at some endemic level within the population. The methods for finding invasion reproductive numbers are similar to those for basic reproductive numbers, only the system is assumed to be at an endemic equilibrium for at least one of the infections.

In those cases where the number of infections in the populations is greater than 2, one will not be able to distinguish between which infection or infections are indeed successfully invading when $\tilde{R}_0 > 1$, where $\tilde{R}_0$ is calculated with each possible invading infection joined together. Individual IRNs would need to be calculated in these scenarios to see if the results can be related to each other. In the examples that follow, only one resident infection and one invading infection are considered.

As stated before, most studies that use IRNs only calculate them for two infections, and even then only do so for their own particular models. It is because of this that there has been no explicit formula or guide to follow when calculating invasion reproductive numbers. In the case of autonomous models, many follow the methods of van den Driessche and Watmough [50] by extending their methods for the basic reproductive number to models involving more than one infection. This will be done

in the following section. For nonautonomous cases it becomes a little more difficult, as it was in calculating BRNs for these models. One can extend similar results by using the time-average method and replace each periodic parameter in the system with its long-time average. This reduces to an autonomous model and the methods described below can be used. This was done in [41] for an non-autonomous multi-strain SIS epidemic model. As in the case for BRNs, however, this will not always give the true threshold value. First what will be done is to show the extension of the methods for calculating BRNs for autonomous models to calculating IRNs for those same models. Then the next section will extend the methods originated by Bacäer and elaborated by Wang and Zhao [51] for BRNs to IRNs to obtain the same results for nonautonomous systems.

3.1 Autonomous systems

3.1.1 ${}_A\tilde{R}_0$

Consider a similar setup to van den Driessche and Watmough [50]. Let $x = (x_1, ..., x_n)^t$, with each $x_i \geq 0$, be the number of individuals in each compartment. Assume that there are k different infections, either multiple strains of the same infection or competing infections of different types, and let $A \subseteq \{1, ..., k\}$ be a subset of these infections where each infection in A is resident within the population. By using this approach, an exploitation can be made in the fact that the first step in next generation operator methods is epidemiological. This allows the reclassification of resident infections to be considered non-infected. Now one can calculate the invasion reproductive number of all the infections not in A with respect to all the infections in A, that is, the IRN of A_c where A_c denotes the complement of A in $\{1, \ldots, k\}$. This invasion reproductive number will be denoted as ${}_A\tilde{R}_0$. In order to do so, a reclassifi-

cation is done as to what constitutes an infection. The IRN is calculated for the set of infections $j \in A_c$ and so only those classes with such infection, including single and co-infected classes, are considered to be infected. The invasion reproductive number is the expected number of secondary cases one infected individual with some infection $j \in A_c$ produces in a population where all (and only) infections in A are resident.

The compartments are then arranged so that the first m compartments correspond to infected individuals with infections from A_c. Define $\mathbf{E}_{A_c}$ to be the set of all A_c-infection free states, that is,

$$\mathbf{E}_{A_c} = \{x \geq 0 | x_i = 0, i = 1, ..., m\}. \tag{3.1}$$

Let $\mathscr{F}_i(x)$ be the rate of new infections in compartment i, $\mathscr{V}_i^+(x)$ be the rate of transfer into compartment i by all other means, and $\mathscr{V}_i^-(x)$ be the rate of transfer out of compartment i. Assume that each function is continuously differentiable at least twice in each variable. Now the model becomes:

$$\dot{x}_i = f_i(x) = \mathscr{F}_i(x) - \mathscr{V}_i(x), i = 1, ..., n, \tag{3.2}$$

where $\mathscr{V}_i = \mathscr{V}_i^- - \mathscr{V}_i^+$. In addition, these functions need to satisfy the following assumptions:

- (A1) If $x \geq 0$, then $\mathscr{F}_i, \mathscr{V}_i^+, \mathscr{V}_i^- \geq 0$ for $i = 1, ...n$
- (A2) If $x_i = 0$ then $\mathscr{V}_i^- = 0$. If $x \in \mathbf{E}_{A_c}$, then $\mathscr{V}_i^- = 0$ for $i = 1, ...m$
- (A3) $\mathscr{F}_i = 0$ if $i > m$
- (A4) If $x \in \mathbf{E}_{A_c}$ then $\mathscr{F}_i = 0$ and $\mathscr{V}_i^+ = 0$ for $i = 1, ...m$
- (A5) If $\mathscr{F}_i$ is set to zero, then all eigenvalues of $Df(x_0)$ have negative real parts, for some A-endemic equilibrium, $x_0 \in \mathbf{E}_{A_c}$

For (A3), no new invading infections can happen in those classes that are considered non-infected classes. (A4) states that if the system is at a state free of infections in

A_c, then it will stay that way. The last assumption, (A5), states that there exists a stable endemic equilibrium of the system in the absence of any new infections. In order for this to be true, one must assume that the basic reproductive number for that particular infection is greater than 1. This guarantees that the endemic equilibrium exists. This allows the matrix $Df(x_0)$ to be partitioned using the following lemma.

Lemma 1. *Assume $R_0 > 1$. If $x_0 \in \boldsymbol{E}_{A_c}$ is an equilibrium free of infections in A_c of (3.2) and $f_i(x)$ satisfies (A1)-(A5), then the derivatives $D\mathscr{F}(x_0)$ and $D\mathscr{V}(x_0)$ are partitioned as*

$$D\mathscr{F}(x_0) = \begin{pmatrix} F & 0 \\ 0 & 0 \end{pmatrix}, D\mathscr{V}(x_0) = \begin{pmatrix} V & 0 \\ J_3 & J_4 \end{pmatrix}$$

where F and V are the $m \times m$ matrices defined by

$$F = \left[\frac{\partial \mathscr{F}_i}{\partial x_j}(x_0)\right] \qquad V = \left[\frac{\partial \mathscr{V}_i}{\partial x_j}(x_0)\right] \qquad 1 \leq i, j \leq m.$$

Further, F is non-negative, V is a non-singular M-matrix and all eigenvalues of J_4 have positive real part.

Proof is similar to [50]. The difference here in the Lemma is that it requires $R_0 > 1$ in the hypothesis. This is important to distinguish between a disease-free equilibrium and an A_c-free equilibrium. By requiring that $R_0 > 1$ then the disease-free equilibrium can never be stable.

Now the invasion reproductive number can be calculated. The goal here is to see if the extension of the method for the BRN will give the same threshold behavior for the IRN for some A_c-infection free equilibrium. That is, if $R_0 > 1$ and ${}_A\tilde{R}_0 < 1$, then the A_c-infection free equilibrium, x_0, is stable, but if ${}_A\tilde{R}_0 > 1$ then it is unstable. Recall that the invasion reproductive number is the expected number of secondary cases one infected individual with some infection $j \in A_c$ produces in a population

where all (and only) infections in A are resident. This definition can be interpreted by looking at the entries of FV^{-1}. Thus we can mathematically define ${}_A\tilde{R}_0$ as:

$$ {}_A\tilde{R}_0 = \rho(FV^{-1}) \tag{3.3}$$

where $\rho(A)$ is the spectral radius of the matrix A. This leads to the following theorem.

Lemma 2. *Consider the disease transmission model given by* (3.2) *with* $f(x)$ *satisfying conditions (A1)-(A5). Assume* $R_0 > 1$. *If* x_0 *is an* A_c*-infection free equilibrium of the model, then* x_0 *is locally asymptotically stable if* ${}_A\tilde{R}_0 < 1$, *but unstable if* ${}_A\tilde{R}_0 > 1$, *where* ${}_A\tilde{R}_0$ *is defined before.*

Proof is done in a similar way to [50], the differences being epidemiologically as described above where only those infections from A_c are considered infected.

The only issue with this method is that it loses the ability to distinguish among each infection invading. All the theorem states is that if some infection from A_c invades then the A_c-infection free equilibrium is unstable. However, each individual infection $j \in A_c$ has an invasion reproductive number. In fact, one can define this IRN, ${}_A\tilde{R}_j$, as the number of secondary infections which one infected individual with infection j produces in a population where all (and only) infections in A are present. To use this definition to study stability, one would need to calculate the individual IRN for each infection $j \in A_c$. The theorem for this procedure would be similar to the theorem above except the equilibrium would be stable if $\max_j({}_A\tilde{R}_j) < 1$ and unstable if $\max({}_A\tilde{R}_j) > 1$. This is difficult to prove in that it involves comparison of eigenvalues of matrices and submatrices. In order to find out which infection does invade in the case where ${}_A\tilde{R}_0 > 1$, what will be calculated is the individual infection IRN ${}_A\tilde{R}_j$ by making assumptions about other infections other than j that are not resident within the population.

3.1.2 Calculating infection j invasion reproductive numbers, ${}_A\tilde{R}_j$

The limitation of the overall invasion reproductive number is that it does not distinguish which pathogen(s) can invade successfully if indeed ${}_A\tilde{R}_0 > 1$. To address this consider only one infection, i.e. $j \in A_c$, invading at a time. The question in deriving ${}_A\tilde{R}_j$ then becomes what to do with those infections which are not resident but are also not invading. There are two ways to address this. The first is to consider them to be non-infected classes. This creates a set up similar to before. In fact, the method as described above is the same except that the matrices F and V would only be smaller since it is assumed that only one infection can invade. Since the other classes are now considered to be not infected, they are moved to the bottom of the model similar to the infections assumed to be resident. The procedure is followed as outlined above and this will give some expression for the IRN of infection j.

The other way to define a single-infection invasion reproductive number is to consider all the infections not resident nor invading as not part of the system. This reduces the original system by setting aside those equations and considering the smaller system with only the invading infection and the resident infections. The classes for co-infection involving those infections are also not considered. This means that the system is of smaller dimension; thus the equilibrium stability is in a smaller subspace than the original system. The method is done in the same way as before and stability results hold for ${}_A\tilde{R}_j < 1$ and unstable for ${}_A\tilde{R}_j > 1$, but for the smaller subspace equilibrium. The question is, does this relate to the original space E_{A_c}? The main thing that can be said is that if ${}_A\tilde{R}_j > 1$ then the instability of the A_c-infection free equilibrium in the smaller system will indeed relate back to the original system. If it is unstable in the smaller subspace then it is unstable in the larger space. This would mean that indeed infection j can invade and is at least one of the invading strains

if there are others. However, if ${}_A\tilde{R}_j < 1$ then yes the smaller subspace system has a stable equilibrium but in the context of the original system not much can be said. This does show that infection j cannot invade and so if ${}_A\tilde{R}_0 > 1$ then one or more of the other infections are invading and not infection j.

If one only cares about the stability of a given endemic equilibrium then ${}_A\tilde{R}_0$ is sufficient for that, but if one wishes to determine specifically which infection(s) can invade, then ${}_A\tilde{R}_j$ can be derived for every single possible invading strain to find out which one is causing the instability of the A-endemic equilibrium of the original system. What was done here was to describe two ways to calculate ${}_A\tilde{R}_j$, by considering those infections not resident and not invading as part of the system or not. However, which method is best for calculating ${}_A\tilde{R}_j$ is still open to discussion. It appears both methods give the same result and so it may be that each system must be studied on a case by case basis to determine which method will be better served for finding some expression for ${}_A\tilde{R}_j$. This will require more work to be done in the future.

3.1.3 Example

Consider the following model in which 2 infections spread through a population. Susceptibles become infected when coming into contact with an individual with infection one or two at a rate β_1, β_2 respectively. These infections are cleared at a rate of γ_1, γ_2 respectively as well. There is a mortality rate for all classes of μ. In this example it is also assumed that coinfection can occur. In this case, an infected individual with infection 1 can come in contact with an someone infected with infection 2 and will move into the coinfection class. k_1 and k_2 are multipliers that represent

the influence of a primary infection on the rate of (or susceptibility to) coinfection. This leads to the following system:

$$\begin{aligned}
\frac{dI_1}{dt} &= \beta_1 S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - k_1\beta_2 I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_1)I_1 + \gamma_2 I_{12} \\
\frac{dI_2}{dt} &= \beta_2 S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - k_2\beta_1 I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_2)I_2 + \gamma_1 I_{12} \\
\frac{dI_{12}}{dt} &= k_1\beta_2 I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) + k_2\beta_1 I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_1+\gamma_2)I_{12} \\
\frac{dS}{dt} &= \mu N + \gamma_1 I_1 + \gamma_2 I_2 - (\beta_1 S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) + \beta_2 S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right)) - \mu S
\end{aligned} \tag{3.4}$$

Assume that infection 2 is resident within the population. Then the equations are reordered so that only those classes considered to be infected are at the beginning. In this example that would be classes I_1 and I_{12}. The system when this is done will be:

$$\begin{aligned}
\frac{dI_1}{dt} &= \beta_1 S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - k_1\beta_2 I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_1)I_1 + \gamma_2 I_{12} \\
\frac{dI_{12}}{dt} &= k_1\beta_2 I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) + k_2\beta_1 I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_1+\gamma_2)I_{12} \\
\frac{dI_2}{dt} &= \beta_2 S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - k_2\beta_1 I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_2)I_2 + \gamma_1 I_{12} \\
\frac{dS}{dt} &= \mu N + \gamma_1 I_1 + \gamma_2 I_2 - (\beta_1 S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) + \beta_2 S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right)) - \mu S
\end{aligned} \tag{3.5}$$

Then $\mathscr{F}$ and $\mathscr{V}$ are:

$$\mathscr{F} = \begin{bmatrix} \beta_1 S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) \\ k_2\beta_1 I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) \\ 0 \\ 0 \end{bmatrix},$$

$$\mathscr{V} = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} k_1\beta_2 I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) + (\mu+\gamma_1)I_1 - \gamma_2 I_{12} \\ (\mu+\gamma_1+\gamma_2)I_{12} - k_1\beta_2 I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) \\ k_2\beta_1\frac{I_1 I_2}{N} + (\mu+\gamma_2)I_2 - \beta_2 S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - \gamma_1 I_{12} \\ \beta_1 S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) + \beta_2 S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) + \mu S - \mu N - \gamma_1 I_1 - \gamma_2 I_2 \end{bmatrix}.$$

Verification of (A1)-(A5) is simple from observation of the matrices. Since it is assumed that infection 2 is resident within the population, there exists an endemic equilibrium, $(0, 0, I_2^*, S^*)$, when $R_2 > 1$. The system is assumed to be at this equilibrium.

Define $F(t)$ and $V(t)$ as follows:

$$F = \begin{bmatrix} \beta_1 \frac{S^*}{N} & \beta_1 \frac{S^*}{N} \\ k_2\beta_1 \frac{I_2^*}{N} & k_2\beta_1 \frac{I_2^*}{N} \end{bmatrix}, V = \begin{bmatrix} k_1\beta_2 \frac{I_2^*}{N} + \mu + \gamma_1 & -\gamma_2 \\ -k_1\beta_2 \frac{I_2^*}{N} & \mu + \gamma_1 + \gamma_2 \end{bmatrix}.$$

The eigenvalues of the matrix FV^{-1} are:

$$\left\{0, \frac{\beta_1(N + I_2^*(k_2 - 1))}{(\mu + \gamma_1)N}\right\} \tag{3.6}$$

and ${}_A\tilde{R}_0 = \rho(FV^{-1})$.

In this example, ${}_A\tilde{R}_0$ is really just ${}_2\tilde{R}_1$ or $\tilde{R}_1$, since infection 2 is the only resident infection. It should be noted that ${}_1\tilde{R}_2$ can be calculated in an analogous way by assuming that infection 1 is resident. The only differences in the final value will be that 1 and 2 will be switched in each subscript. $\tilde{R}_1$ ends up being a weighted average among the susceptibles and the already infected.

3.2 Nonautonomous Systems

3.2.1 ${}_A\tilde{R}_0$

For nonautonomous systems, the same methods described for the basic reproductive number will be extended to invasion reproductive numbers. The first method would be to try a time-average method. The system could be changed to an autonomous system by simply using the long-time averages for the parameters that are varying with time [41]. By doing this, each periodic parameter is now just some constant, and this reduces the nonautonomous system to an autonomous system. The method described for autonomous systems above can now be used and an expression

for the IRN can be found as $\rho(FV^{-1})$. Unfortunately, as in the BRN case, this will not always yield the correct value for the IRN since it may overestimate or underestimate the capability of the invading infections. The rest of this chapter will focus on extending the linear operator method to calculate IRNs for nonautonomous systems. As in the basic reproductive number methods described before, it will be shown that this linear operator method will indeed produce the correct expression for the invasion reproductive number. So from here on, ${}_A\tilde{R}_T$ will represent the time-average IRN whereas ${}_A\tilde{R}_0$ will represent the linear operator IRN.

Consider a setup similar to [51] where a heterogeneous population is grouped into n homogeneous compartments. There are parameters of the system that are assumed to be ω-periodic and so this is a non-autonomous system. Assume that there are k different infections and let $A \subseteq \{1, ..., k\}$ be a subset of these infections where each infection in A is again assumed to be resident within the population. This again allows for the use of the exploitation in the fact that the first step in linear operator methods is epidemiological as was done in the autonomous case. Since the first steps here are epidemiological, one can reclassify the resident infections as non-infected. Now one can calculate the invasion reproductive number of all infections not in A, that is $\forall j \in A_c$ where A_c is considered to be A complement. The IRN is calculated for infections in A_c and so only those classes with these infections, including single and co-infected classes, are considered to be infected.

The compartments are then arranged so that the first m compartments correspond to infected individuals with infections from A_c. Consider again the set $\mathbf{E}_{A_c}$ to be all A_c-free states, where now values in $\mathbf{E}_{A_c}$ can be periodic solutions and not just equilibria. Let $\mathscr{F}_i(t, x)$ be the input rate of newly infected individuals in the ith

compartment, $\mathscr{V}_i^+(t,x)$ be the input rate of individuals by other means and $\mathscr{V}_i^-(t,x)$ be the rate of transfer out of compartment i. The model is then given by:

$$\frac{dx_i}{dt} = \mathscr{F}_i(t,x) - \mathscr{V}_i(t,x) = f_i(t,x), i = 1, ..., n \tag{3.7}$$

where $\mathscr{V}_i = \mathscr{V}_i^- - \mathscr{V}_i^+$. Similar to autonomous models, the following assumptions must be made. They again show the model is well posed and makes biological sense. Assumptions (A1), (A3), (A4), and (A5) correspond to assumptions (A1)-(A4) of the autonomous case. The only new one here is (A2) which states that there are periodic coefficients in the system.

- (A1) For each $1 \leq i \leq n$, the functions $\mathscr{F}_i(t,x), \mathscr{V}_i^+(t,x)$, and $\mathscr{V}_i^-(t,x)$ are nonnegative and continuous on $\mathbb{R} \times \mathbb{R}_+^n$ and continuously differentiable with respect to x.
- (A2) There is a real number $\omega > 0$ such that for each $1 \leq i \leq n$, the functions $\mathscr{F}_i(t,x), \mathscr{V}_i^+(t,x)$, and $\mathscr{V}_i^-(t,x)$ are ω-periodic in t.
- (A3) If $x_i = 0$ then $\mathscr{V}_i^-(t,x) = 0$. If $x \in \mathbf{E}_{A_c}$, then $\mathscr{V}_i^-(t,x) = 0$ for $i = 1, ...m$.
- (A4) $\mathscr{F}_i(t,x) = 0$ if $i > m$.
- (A5) If $x \in \mathbf{E}_{A_c}$ then $\mathscr{F}_i(t,x) = 0$ and $\mathscr{V}_i^+(t,x) = 0$ for $i = 1, ...m$.

In addition to these assumptions, two more must be verified. These are separated because the systems that need to be solved for them are nonautonomous and thus require new conditions based on monodromy matrices. The first assumption, (A6), is similar to (A5) in the autonomous case. Assume the model has an A_c-infection free periodic solution $x_0(t)$. Define an $(n-m) \times (n-m)$ matrix

$$M(t) := \left(\frac{\partial f_i(t, x_0(t))}{\partial x_j} \right)_{m+1 \leq i,j \leq n}. \tag{3.8}$$

Let $\Phi_M(t)$ be the monodromy matrix of the linear ω-periodic system $\frac{dz}{dt} = M(t)z$. It must be verified that $x_0(t)$ is linearly asymptotically stable in the A_c-infection free

subspace, $\mathbf{E}_{A_c}$. To do this one need to show that the spectral radius of the monodromy matrix is less than one, or (A6) $\rho(\Phi_M(\omega)) < 1$.

Following the notation from [50], define two $m \times m$ matrices by

$$F(t) = \left[\frac{\partial \mathscr{F}_i(t, x_0(t))}{\partial x_j}\right]_{1\le i,j\le m}, \qquad V(t) = \left[\frac{\partial \mathscr{V}_i(t, x_0(t))}{\partial x_j}(x_0)\right]_{1\le i,j\le m}.$$

Let $Y(t,s), t \ge s$ be the evolution operator of the linear ω-periodic system $\frac{dy}{dt} = -V(t)y$. That is for each $s \in \mathbb{R}$ the $m \times m$ matrix $Y(t,s)$ satisfies

$$\frac{d}{dt}Y(t,s) = -V(t)Y(t,s), \forall t \ge s, Y(s,s) = I \tag{3.9}$$

where I is the $m \times m$ identity matrix. The monodromy matrix $\Phi_{-V}(t)$ of the system then equals $Y(t,0), t \ge 0$. The last assumption that must be verified is that the internal evolution of individuals in the infectious compartments is dissipative, and exponentially decays in many cases. So assume that (A7) $\rho(\Phi_{-V}(\omega)) < 1$.

The theory for nonlinear autonomous systems has been well established for studying stability of equilibria. In 1960, the Hartman-Grobman thereom was proved showing that the local behavior of the system around a hyperbolic equilibrium point can be studied using the linearized system around the same point [7]. In 1975 this theorem was extended by Kenneth Palmer to non-autonomous systems [42]. This allows the use of the linearized system in (A6) to be used to study the stability of the j-infection free solution.

Based on the assumptions (A1)-(A7), the invasion reproductive numbers for the epidemic model can be analyzed. Always assume the population is near the A_c-infection free periodic state $x_0(t)$. By standard theory of linear periodic systems, [32], there exists a $K > 0$ and $\alpha > 0$ such that

$$\|Y(t,s)\| \le Ke^{-\alpha(t-s)}, \forall t \ge s, s \in \mathbb{R}. \tag{3.10}$$

It then follows that

$$\|Y(t,t-a)F(t-a)\| \leq K\|F(t-a)\|e^{-\alpha a}, \forall t \in \mathbb{R}, a \in [0,\infty). \tag{3.11}$$

With the model being periodic, suppose that $\phi(s)$, which is ω-periodic in s, is the initial distribution of infectious individuals. Then $F(s)\phi(s)$ is the distribution of those infected who were introduced at time s. Given $t \geq s$, then $Y(t,s)F(s)\phi(s)$ gives the distribution of those infected individuals who were newly infected at time s and remain infected at time t. Then

$$\psi(t) := \int_{-\infty}^{t} Y(t,s)F(s)\phi(s)ds = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da \tag{3.12}$$

is the distribution of accumulative new infections at time t produced by all those infected individuals introduced at previous time to t. Recall that infectious here means infectious only with respect to infection j.

Let C_ω be the ordered Banach space of all ω-periodic functions from $\mathbb{R}$ to $\mathbb{R}^m$, with the max norm and the positive cone $C_\omega^+ := \{\phi \in C_\omega : \phi(t) \geq 0, \forall t \in \mathbb{R}\}$. Now define a new linear operator $L : C_\omega \to C_\omega$ by

$$(L\phi)(t) = \int_{0}^{\infty} Y(t,t-a)F(t-a)\phi(t-a)da, \forall t \in \mathbb{R}, \phi \in C_\omega. \tag{3.13}$$

Call L the next infection operator, following the motivation of van den Driessche and Watmough, and then the spectral radius of L is given by:

$$_A\tilde{R}_j := \rho(L) \tag{3.14}$$

for the periodic epidemic model.

As before with autonomous systems, the question becomes does the invasion reproductive number hold the same threshold behavior for stability of the A_c-infection free equilibrium? First a simplification needs to be done. Using the linear operator can prove difficult, so generally one can use an equivalent system to find the IRN.

Consider the linear ω-periodic equation

$$\frac{dw}{dt} = \left[-V(t) + \frac{F(t)}{\lambda}\right] w, t \in \mathbb{R} \tag{3.15}$$

with parameter $\lambda \in (0, \infty)$. Let $W(t, s, \lambda), t \geq s, s \in \mathbb{R}$ be the evolution operator of the system (3.15) on $\mathbb{R}^m$. Wang and Zhao showed that the linear operator $W(t, s, \lambda)$ is positive in $\mathbb{R}^m$ for each $t \geq s, s \in \mathbb{R}$. The Perron-Frobenius theorem implies that $\rho(W(\omega, 0, \lambda))$ is an eigenvalue of $W(\omega, 0, \lambda)$ with a nonnegative eigenvector. This gives the following theorems from [51]:

Theorem (2.1). *i. If $\rho(W(\omega, 0, \lambda)) = 1$ has a positive solution λ_0, then λ_0 is an eigenvalue of L, and hence ${}_A\tilde{R}_0 > 0$.*

ii. If ${}_A\tilde{R}_0 > 0$, then $\lambda = {}_A\tilde{R}_0$ is the unique solution of $\rho(W(\omega, 0, \lambda)) = 1$.

iii. ${}_A\tilde{R}_0 = 0$ if and only if $\rho(W(\omega, 0, \lambda)) < 1 \ \forall \lambda > 0$.

Theorem (2.2). *i. ${}_A\tilde{R}_0 = 1$ if and only if $\rho(\Phi_{F-V}(\omega)) = 1$*

ii. ${}_A\tilde{R}_0 > 1$ if and only if $\rho(\Phi_{F-V}(\omega)) > 1$

iii. ${}_A\tilde{R}_0 < 1$ if and only if $\rho(\Phi_{F-V}(\omega)) < 1$

Thus the A_c-free solution, $x_0(t)$, is asymptotically stable if ${}_A\tilde{R}_0 < 1$ and unstable if ${}_A\tilde{R}_0 > 1$.

Proofs of these theorems are similar to [51]. These results show that to find the invasion reproductive number, one needs to find the monodromy matrix, $\Phi_{F-V}(t)$ of the system (3.15) and evaluate it at the period, ω. Then find the spectral radius of $\Phi_{F-V}(\omega)$ and solve the equation $\rho(\Phi_{F-V}(\omega)) = 1$ for λ. This λ is the overall invasion reproductive number ${}_A\tilde{R}_0$. The threshold behavior for the A_c-free solution can then be studied. In many cases, it is not possible to analytically find the monodromy matrix. In these cases numerical work, described in section 3.2.4, will have to be done to find the IRN.

One other issue is the method of using the time-average rather than this linear operator method. As in the case of the nonautonomous basic reproductive number, there are cases where both methods would agree in their expression for ${}_A\tilde{R}_0$. In fact the theorem can be extended here for the IRN.

Theorem 2. *Consider an n-dimensional ω-periodic system with m infected classes. If the $m \times m$ matrices $F(t)$ and $V(t)$ are triangular of the same form, that is they are both upper or lower triangular, then the time-average method for calculating the invasion reproductive number gives the same expression as the linear operator method. That is ${}_A\tilde{R}_T = {}_A\tilde{R}_0$.*

The case of one invading infection is a special case. One needs to be careful when trying to apply the theorem in this case. Notice that this theorem says that the matrices $F(t)$ and $V(t)$ must be triangular of the same form. If there is only one infected class when dealing with the single invading infection, then the matrices are trivially triangular and so the methods will agree. This would occur if there were no coinfection classes. If however, there are coinfection classes then the matrices $F(t)$ and $V(t)$ will be $m \times m$ matrices and thus must be triangular of the same form to be able to use each method to achieve the same expression for ${}_A\tilde{R}_0$. An example will be given later to show that indeed not every model will allow for both methods to produce the same result, just as in the BRN case.

3.2.2 Calculating infection j IRNs for nonautonomous models, ${}_A\tilde{R}_j$

As in the autonomous case, the limitation of the overall invasion reproductive number is that it does not distinguish which pathogen(s) can invade successfully if indeed ${}_A\tilde{R}_0 > 1$. To address this consider only one infection, i.e. $j \in A_c$, invading at a time. The question in deriving ${}_A\tilde{R}_j$ then becomes what to do with those infections which are not resident but are also not invading. There are two ways to address this.

The first is to consider them to be non-infected classes. This creates a set up similar to before. In fact, the method as described above is the same except that the matrices $F(t)$ and $V(t)$ would only be smaller since it is assumed that only one infection can invade. Since the other classes are now considered to be not infected, they are moved to the bottom of the model similar to the infections assumed to be resident. The procedure is followed as outlined above and this will give some expression for the IRN of infection j.

The other way to define a single-infection invasion reproductive number is to consider all the infections not resident nor invading as not part of the system. This reduces the original system by setting aside those equations and considering the smaller system with only the invading infection and the resident infections. The classes for co-infection involving those infections are also not considered. This means that the system is of smaller dimension; thus the equilibrium stability is in a smaller subspace than the original system. The method is done in the same way as before and stability results hold for ${}_A\tilde{R}_j < 1$ and unstable for ${}_A\tilde{R}_j > 1$, but for the smaller subspace equilibrium. The question is, does this relate to the original space E_{A_c}? The main thing that can be said is that if ${}_A\tilde{R}_j > 1$ then the instability of the A_c-infection free equilibrium in the smaller system will indeed relate back to the original system. If it is unstable in the smaller subspace then it is unstable in the larger space. This would mean that indeed infection j can invade and is at least one of the invading strains if there are others. However, if ${}_A\tilde{R}_j < 1$ then yes the smaller subspace system has a stable equilibrium but in the context of the original system not much can be said. This does show that infection j cannot invade and so if ${}_A\tilde{R}_0 > 1$ then one or more of the other infections are invading and not infection j.

This again gives other ways to determine which infection(s) specifically can invade, in the case when ${}_A\tilde{R}_0 > 1$. As before, both methods appear to give the same

result when discussing instability of the A-endemic equilibrium. This will require further work which will be done in a later study.

3.2.3 Example

Consider the following model where two infections are spread through a population. In this model susceptibles become infected with infection 1 or 2 by coming in contact with infected individuals from those population at a rate of $\beta_1(t), \beta_2(t)$ respectively. The infections are cleared at a rate γ_1, γ_2. Again it is assumed that infection 2 is resident in the population. Cross-immunity is assumed between the infections. This leads to the following system:

$$\begin{aligned}
\frac{dI_1}{dt} &= \beta_1(t)\frac{SI_1}{N} - (\mu+\gamma_1)I_1 \\
\frac{dI_2}{dt} &= \beta_2(t)\frac{SI_2}{N} - (\mu+\gamma_2)I_2 \\
\frac{dS}{dt} &= \mu N + \gamma_1 I_1 + \gamma_2 I_2 - (\beta_1(t)\frac{SI_1}{N} + \beta_2(t)\frac{SI_2}{N}) - \mu S
\end{aligned} \tag{3.16}$$

Then $\mathscr{F}$ and $\mathscr{V}$ are:

$$\mathscr{F}(t) = \begin{bmatrix} \beta_1(t)\frac{SI_1}{N} \\ 0 \\ 0 \end{bmatrix},$$

$$\mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} (\mu+\gamma_1)I_1 \\ (\mu+\gamma_2)I_2 - \beta_2(t)\frac{SI_2}{N} \\ \beta_1(t)\frac{SI_1}{N} + \beta_2(t)\frac{SI_2}{N} + \mu S - \mu N - \gamma_1 I_1 - \gamma_2 I_2 \end{bmatrix}.$$

Verification of (A1)-(A5) is simple from observation of the matrices. There exists an endemic periodic solution $(0, 0, I_2^*(t), S^*(t))$ when $R_2 > 1$, that is the basic reproductive number with respect to infection 2.

For the verification of (A6), consider the system where infection 1 is not present:

$$\begin{aligned} \frac{dI_2}{dt} &= \beta_2(t)\frac{SI_2}{N} - (\mu+\gamma_2)I_2 \\ \frac{dS}{dt} &= \mu N + \gamma_2 I_2 - \beta_2(t)\frac{SI_2}{N} - \mu S \end{aligned} \tag{3.17}$$

This has been studied before in [41, 29, 56]. In fact, [41] shows that if $R_2 > 1$ then the periodic endemic solution is stable. Define the following vectors $F(t)$ and $V(t)$ as follows:

$$\begin{aligned} F(t) &= \beta_1(t) \\ V(t) &= \mu + \gamma_1. \end{aligned} \tag{3.18}$$

For verification of (A7) consider the system:

$$\frac{dy}{dt} = -(\mu+\gamma_1)y. \tag{3.19}$$

This system gives the principal fundamental matrix and so one need only consider the monodromy matrix evaluated at the period. This is $\Phi_{-V}(\omega) = e^{-(\mu+\gamma)\omega}$, and clearly (A7) holds.

As defined above there are two methods to calculate the IRN. First consider the system given by the time average of the infection rates which in this case is $\langle\beta_1(t)\rangle$. Since the system is now autonomous, one can use the method described for autonomous systems above and need only calculate FV^{-1} which is:

$$FV^{-1} = \frac{\frac{1}{\omega}\int_0^\omega \beta(t)dt}{\mu+\gamma_1} = \frac{\langle\beta\rangle}{\mu+\gamma_1}. \tag{3.20}$$

The spectral radius of this is just the equation itself and so:

$$\tilde{R}_{1T} = \frac{\langle\beta_1\rangle}{\mu+\gamma_1}. \tag{3.21}$$

To characterize ${}_2\tilde{R}_1$ using the linear operator method, consider the following ω-periodic equation:

$$\frac{dw}{dt} = \left[-(\mu+\gamma_1) + \frac{\beta_1(t)}{\lambda}\right] w, t \in \mathbb{R} \tag{3.22}$$

which has fundamental solution:

$$w(t) = exp\left(\frac{1}{\lambda}\int_0^t \beta_1(s)ds - (\mu+\gamma_1)t\right). \tag{3.23}$$

Then the monodromy matrix is defined as before, and the goal is to find λ_0 such that $\rho(\Phi_{F-V}(\omega)) = 1$, which happens exactly when the exponent in $w(t)$ equals 0. This yields:

$${}_2\tilde{R}_1 = \lambda_0 = \frac{\frac{1}{\omega}\int_0^\omega \beta_1(t)dt}{\mu+\gamma_1} = \frac{\langle\beta\rangle}{\mu+\gamma_1}. \tag{3.24}$$

So in this case the time averaged IRN, $\tilde{R}_T$ has the same expression as the linear operator IRN, $\tilde{R}_0$. In reference to Theorem 2, the matrices $F(t)$ and $V(t)$ are trivially triangular since they consist of a single element. Thus the methods should agree in their expression. It should be stated again that this will not always be the case.

3.2.4 Numerical Analysis

The previous example gave a nice introduction into how this method works and can be applied. However, in the literature most periodic dynamical systems cannot be solved outright. Therefore very few have been able to come up with an explicit formula for ${}_A\tilde{R}_0$. This is the same issue that arises in the calculation of the basic reproductive number for non-autonomous systems. For these systems, numerical analysis must be done.

There are very few procedures in the literature to actually numerically calculate these IRNs. Some systems might be able to be solved up to some point before numerical work has to be implemented. As in the calculations of the BRNs of the last chapter, an example was given where the fundamental matrix $\Psi(t)$ was found, but solving for the monodromy matrix's eigenvalues proves rather challenging. Most times a transcendental equation must be solved and this just cannot be done by hand typically. An example will be worked in this section which illustrates this method.

In the literature, many focus attention on their particular model, solving for ${}_A\tilde{R}_0$ numerically, then using this information for sensitivity analysis with respect to some parameter in the system. Only one paper [47] gives some sort of outline for calculating this. In their paper, Safi et al. list steps for computing the basic reproductive number for non-autonomous systems, but the procedure can be applied for IRNs as well since the methods produce similar systems to solve.

First (A6) and (A7) must be verified. To do this one needs to solve the systems (3.8) and (3.9). The difficult part becomes that these systems come from a linearization about the endemic equilibrium, which could be periodic. In order to use the numerical methods to find the fundamental matrix, this periodic solution must be numerically approximated. For a given set of parameters, the system is run by using initial conditions where only the resident infections are present, e.g. setting all invading infection initial conditions to 0. Once the periodic solution is approximated it can be used to find the fundamental matrix as described before.

For the system (3.15), more work must be done. First let $W(t, \lambda)$ be the standard fundamental matrix. For a given set of parameters, since the IRN is being calculated and not the BRN, this system is linearized about the endemic equilibrium. Again this solution must be approximated in some way to program it into the calculations. Once that is done, a value of λ must be given. This is an initial guess. Using this value of λ, the matrix $W(\omega, \lambda)$ is numerically computed using some standard integrator to generate the necessary linearly independent solutions to (3.15) using standard basis vectors as respective initial condition vectors. Then the spectral radius $\rho(W(\omega, \lambda))$ is calculated. Last use a root finding method to find the zero of $f(\lambda) = \rho(W(\omega, \lambda)) - 1$ for a given value of λ. Adjust this value of λ in a particular way until the root is found.

3.2.4.1 Numerical Example

Consider the example given in calculating the IRN for autonomous systems in which 2 infections spread through a population. In order to make this a non-autonomous system, let the infection rates $\beta_1(t), \beta_2(t)$ be periodic functions. These infections are cleared at rates γ_1, γ_2 respectively. Mortality rate of μ for all classes. It is also assumed that coinfection can occur. k_1 and k_2 represent multipliers of the influence of a primary infection on the coinfection. The system is then:

$$\begin{aligned}
\frac{dI_1}{dt} &= \beta_1(t)S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - k_1\beta_2(t)I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_1)I_1 + \gamma_2 I_{12} \\
\frac{dI_2}{dt} &= \beta_2(t)S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - k_2\beta_1(t)I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_2)I_2 + \gamma_1 I_{12} \\
\frac{dI_{12}}{dt} &= k_1\beta_2(t)I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) + k_2\beta_1(t)I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_1+\gamma_2)I_{12} \\
\frac{dS}{dt} &= \mu N + \gamma_1 I_1 + \gamma_2 I_2 - \beta_1(t)S\left(\frac{I_1}{N}-\frac{I_{12}}{N}\right) + \beta_2(t)S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - \mu S
\end{aligned} \tag{3.25}$$

Assume that infection 2 is resident within the population. Then the equations are reordered so that only those classes considered to be infected are at the beginning. In this example that would be classes I_1 and I_{12}. The system when this is done will be:

$$\begin{aligned}
\frac{dI_1}{dt} &= \beta_1(t)S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - k_1\beta_2(t)I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_1)I_1 + \gamma_2 I_{12} \\
\frac{dI_{12}}{dt} &= k_1\beta_2(t)I_1\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) + k_2\beta_1(t)I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_1+\gamma_2)I_{12} \\
\frac{dI_2}{dt} &= \beta_2(t)S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right) - k_2\beta_1(t)I_2\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) - (\mu+\gamma_2)I_2 + \gamma_1 I_{12} \\
\frac{dS}{dt} &= \mu N + \gamma_1 I_1 + \gamma_2 I_2 - (\beta_1(t)S\left(\frac{I_1}{N}+\frac{I_{12}}{N}\right) + \beta_2(t)S\left(\frac{I_2}{N}+\frac{I_{12}}{N}\right)) - \mu S
\end{aligned} \tag{3.26}$$

Then $\mathscr{F}$ and $\mathscr{V}$ are:

$$\mathscr{F} = \begin{bmatrix} \beta_1(t)S\left(\frac{I_1}{N} + \frac{I_{12}}{N}\right) \\ k_2\beta_1(t)I_2\left(\frac{I_1}{N} + \frac{I_{12}}{N}\right) \\ 0 \\ 0 \end{bmatrix},$$

$$\mathscr{V} = \mathscr{V}^- - \mathscr{V}^+ = \begin{bmatrix} k_1\beta_2(t)I_1\left(\frac{I_2}{N} + \frac{I_{12}}{N}\right) + (\mu+\gamma_1)I_1 - \gamma_2 I_{12} \\ (\mu+\gamma_1+\gamma_2)I_{12} - k_1\beta_2(t)I_1\left(\frac{I_2}{N} + \frac{I_{12}}{N}\right) \\ k_2\beta_1(t)\frac{I_1 I_2}{N} + (\mu+\gamma_2)I_2 - \beta_2(t)S\left(\frac{I_2}{N} + \frac{I_{12}}{N}\right) - \gamma_1 I_{12} \\ \beta_1(t)S\left(\frac{I_1}{N} + \frac{I_{12}}{N}\right) + \beta_2(t)S\left(\frac{I_2}{N} + \frac{I_{12}}{N}\right) + \mu S - \mu N - \gamma_1 I_1 - \gamma_2 I_2 \end{bmatrix}.$$

Verification of (A1)-(A5) is simple from observation of the matrices. Since it is assumed that infection 2 is resident within the population, there exists an endemic periodic solution, $(0, 0, I_2^*(t), S^*(t))$, when $R_2 > 1$. This was shown to be true in [41] and thus (A6) is verified. The system is assumed to be at this periodic solution. Define the 2×2 matrices $F(t)$ and $V(t)$ as follows:

$$F = \begin{bmatrix} \beta_1(t)\frac{S^*(t)}{N} & \beta_1(t)\frac{S^*(t)}{N} \\ k_2\beta_1(t)\frac{I_2^*(t)}{N} & k_2\beta_1(t)\frac{I_2^*(t)}{N} \end{bmatrix}, V = \begin{bmatrix} k_1\beta_2(t)\frac{I_2^*(t)}{N} + \mu + \gamma_1 & -\gamma_2 \\ -k_1\beta_2(t)\frac{I_2^*(t)}{N} & \mu+\gamma_1+\gamma_2 \end{bmatrix}.$$

(A7) must be verified for each value of τ since changing τ changes the periodic solution. If $\tau = 0$ or $\tau = \omega$ then the system is autonomous and the verification is done. However, if $\tau \in (0, \omega)$ then the periodic endemic solution must be found for each value of τ. For the purposes here, (A7) will be verified for a particular value of $\tau = 0.5$. In this case the system:

$$\frac{dy}{dt} = -V(t)y \tag{3.27}$$

must be solved. For the parameters given in Table 3.2, the fundamental matrix is numerically approximated using linearly independent initial conditions so that the

final matrix has linearly independent solutions. Once this is done, the maximum eigenvalue of $\Phi_{-V}(\omega)$ can be found. Doing this gives $\rho(\Phi_{-V}(\omega)) = 0.288$ which is less than 1 and (A7) is verified.

To characterize ${}_2\tilde{R}_1$, consider the following system:

$$\frac{dw}{dt} = \left[-V(t) + \frac{F(t)}{\lambda}\right] w, t \in \mathbb{R}. \tag{3.28}$$

Unfortunately this system is difficult to solve. In order to simplify things define the square-wave β functions as follows:

$$\beta_1(t) = \begin{cases} a_1 & : 0 < t < \tau \\ b_1 & : \tau < t < \omega \end{cases} \tag{3.29}$$

$$\beta_2(t) = \begin{cases} a_2 & : 0 < t < \tau \\ b_2 & : \tau < t < \omega \end{cases} \tag{3.30}$$

This produces a system where the fundamental matrix can be found for each interval since each system will then be autonomous. However, finding ${}_2\tilde{R}_1$ must be done numerically. It should be noted that this can be done for ${}_1\tilde{R}_2$ and the procedure is analogous, with only the subscripts changed in each case.

First a special case of the model. If $k_1 = k_2 = 1$, then the model can be reduced in some sense. An interesting thing happens in this case in that even though the $F(t)$ and $V(t)$ matrices are not triangular, both the time-average method and the linear operator method end up producing the same result. To see how, one must make a simplification in the model. If the two infected classes and what are considered the two susceptible classes are added together, then the model will be the following:

$$\begin{aligned} \frac{d(I_1 + I_{12})}{dt} &= \frac{\beta_1(t)}{N}(I_2 + S)(I_1 + I_{12}) - (\mu + \gamma_1)(I_1 + I_{12}) \\ \frac{d(I_2 + S)}{dt} &= \mu N + \gamma_1(I_1 + I_{12}) - \frac{\beta_1(t)}{N}(I_2 + S)(I_1 + I_{12}) - \mu(I_2 + S) \end{aligned} \tag{3.31}$$

This produces a trivially triangular system that represents the original system and so the theorem from before can be applied so that the methods agree in their expression for the IRN. This is just the same as in the autonomous example with the time-average for the periodic solution and the transmission functions defined above.

The methods described in the previous chapter can be used here but there is an issue. Before, the calculations were for the basic reproductive number which is evaluated at the disease-free solution. Here the endemic solution is used. Unfortunately it cannot be found by hand. What must be done is to run the system out for initial conditions where the resident infection does not exist, i.e. $I_1 = 0$ and $I_{12} = 0$. Then one must find a way to approximate the solution after the system stabilizes so that it can be used when calculating the IRN. In the case of the example above with square-wave infection rates, the endemic periodic solution ends up being approximately piecewise linear. For a fixed value of τ, the system is run to determine what the periodic solution is. This is then programmed into Mathematica to determine the different values of the IRNs. For each value of τ a new periodic solution must be found and programmed into Mathematica to find the value of the IRN. Since this must be done for every value of τ, the curve it produces will not necessarily be smooth. Evenly spaced values of τ were used so that the graph could be pieced together. The time-average IRN can be used to determine if the same behavior is established. The results are shown in Figure 3.1. The same can be done for $\tilde{R}_2$. The results are shown in Figure 3.2. The parameter values used to determine the graphs are in Table 3.1.

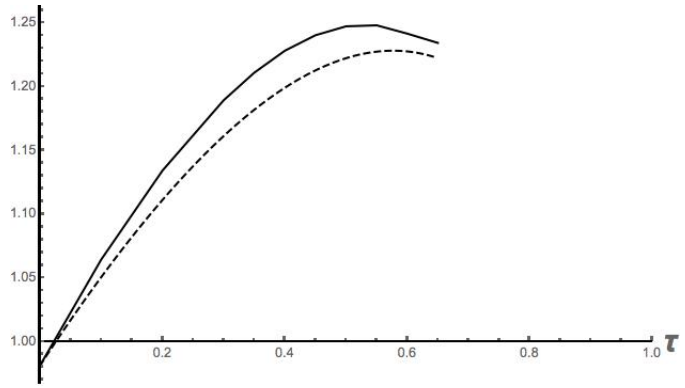

Figure 3.1. Graphs of system (3.25) with (3.28,3.29) that show $\tilde{R}_{1T}$ (dashed) and $\tilde{R}_{1LO}$ (solid) for varying values of τ.

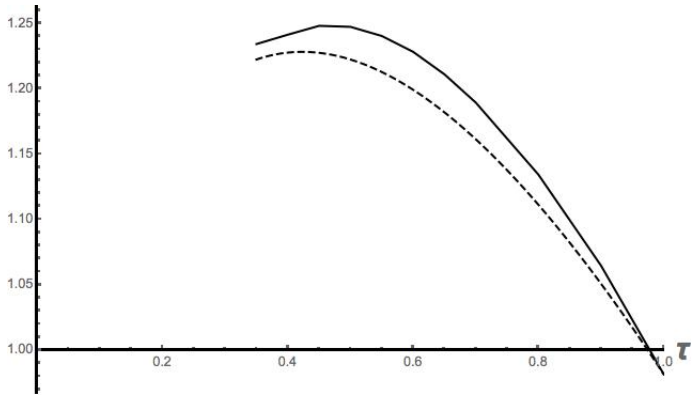

Figure 3.2. Graphs of system (3.25) with (3.28,3.29) that show $\tilde{R}_{2T}$ (dashed) and $\tilde{R}_{2LO}$ (solid) for varying values of τ.

In Figure 3.1, the graph only extends to $\tau = 0.65$ because $R_2 = 1$ at this value. For $\tau > 0.65$, $R_2 < 1$, violating (A5), and hence $\tilde{R}_1$ is undefined. Pathogen 1's ability to invade when $\tau > 0.65$ is held constant at R_1 independent of τ, since there is no pathogen 2 endemic equilibrium to invade in those cases, only the DFE. The reverse holds in Figure 3.2, where (by the symmetry in the parameter values used) for $\tau < 0.35$, $R_1 < 1$, so $\tilde{R}_2$ is undefined, and pathogen 2's ability to invade is measured

instead by R_2, since the only equilibrium it can invade is the DFE. Since $k_1 = k_2 = 2$ in these examples, the primary infections facilitate secondary ones and the pathogens can invade more easily, as in the case when $R_2 = 1$ suddenly and $\tilde{R}_1 > 1$ there. Thus pathogen 1 can invade more easily when $R_2 > 1$ than when $R_2 < 1$. In fact, in this example, the time-average method and the linear operator method for calculating BRNs produces the same expression and so the BRNs are indeed equal to 1 at those endpoints.

Picking a value of τ where each IRN is greater than one should give co-existence. In Figure 3.3 one can clearly see this is the case for $\tau = 0.5$. If the parameters were changed to show only one pathogen's IRN to be greater than 1 then the simulation would then show that the corresponding infection is able to invade and persist within the population.

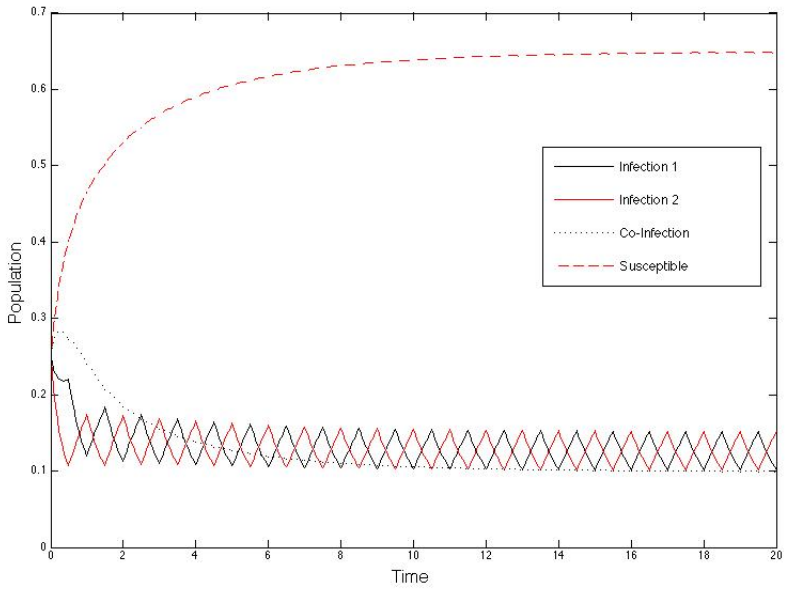

Figure 3.3. Simulation of system (3.25) with (3.28,3.29) for a set of parameters in which $\tilde{R}_1, \tilde{R}_2 > 1$.

Parameter	Value	Units
a_1	2	1/time
b_1	1	1/time
a_2	1	1/time
b_2	2	1/time
μ	1	1/time
γ_1	.35	1/time
γ_2	.35	1/time
k_1	2	
k_2	2	
ω	1	time

Table 3.1. Parameter values for (3.25), Figures 3.1, 3.2, and 3.3

Parameter	Value	Units
a_1	1.5	1/time
b_1	.5	1/time
a_2	.5	1/time
b_2	1.5	1/time
μ	1	1/time
γ_1	.35	1/time
γ_2	.35	1/time
k_1	2	
k_2	2	
ω	1	time

Table 3.2. Parameter values for (3.25) and Figure 3.4

Having shown values for certain parameters, what will be done now is to fix the parameters to get a graph that will show regions of parameter space where each infection will win and when there can be co-existence. To do this a new parameter must be included into the system in order to separate the mean amplitude (long-term average) from the periodic variability. Fixing a_1 and a_2 in the range of $(0, \frac{\omega}{\tau})$, define now the following for b_i:

$$b_i = \frac{\omega - a_i\tau}{\omega - \tau}, i = 1, 2. \tag{3.32}$$

Now attach to the original transmission rates a new parameter, $\tilde{\beta}_j, j = 1, 2$. Then the transmission rates become:

$$\beta_j(t) = \tilde{\beta}_j \begin{cases} a_j & : 0 < t < \tau \\ b_j & : \tau < t < \omega \end{cases} \tag{3.33}$$

These $\tilde{\beta}_j$ parameters, which now give the mean values for the $\beta_j(t)$, will be used as proxies for the BRNs to generate a graph illustrating the different infection outcomes in terms of the BRNs.

To produce the graphs, one must seek $\tilde{\beta}_1, \tilde{\beta}_2$ that make their corresponding IRN equal to 1. Take for example $\tilde{R}_1$. For all $\tilde{\beta}_2$ that make $R_2 > 1$, find the periodic solution $E_2(\tilde{\beta}_2) = \{(S(t), I_2(t)), 0 \leq t < \omega\}$. Use this to find the value of $\tilde{\beta}_1$ for which $\tilde{R}_1(\tilde{\beta}_1, \tilde{\beta}_2, E_2(\tilde{\beta}_2)) = 1$. When the $\tilde{\beta}_1$ and $\tilde{\beta}_2$ have been found, graph $(R_1(\tilde{\beta}_1), R_2(\tilde{\beta}_2))$ using a list plot command and connect. The other example is analogous with only subscripts changing. In the resulting graph, shown in Figure 3.4, the time-average curves were included for comparison (note the BRNs are identical in this model for the time-average and linear operator methods). The parameter values used to generate the graph are given in Table 3.2.

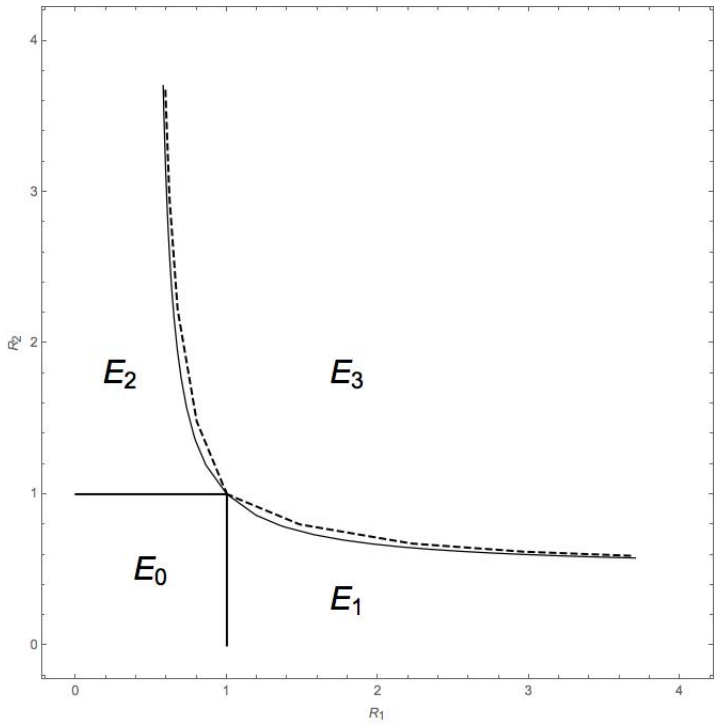

Figure 3.4. Graph showing 4 regions representing different behaviors of the system. E_0 is disease-free, E_1 is only infection 1 prevalent, E_2 is only when infection 2 is prevalent, and E_3 is coinfection. The dashed line is the linear operator method and the solid line is the time-average method.

As seen in Figure 3.4, the time-average will always overestimate the coinfection risk. So it appears, periodicity makes coinfection less likely. The linear operator method is still the correct method and must be used to estimate the infection risk for the model. If $\tilde{\beta}_1 = 1.07$ and $\tilde{\beta}_2 = 1.85$, the time-average predicts co-existence with IRN values of $\tilde{R}_{1T} = 1.00681$ and $\tilde{R}_{2T} = 1.01177$, and the linear operator method has values of $\tilde{R}_{1LO} = 0.861499$ and $\tilde{R}_{2LO} = 1.40866$. The BRNs at these values are $R_1 = 0.792593$ and $R_2 = 1.37037$. If the system is run for those parameters, infection 2 will persist while infection 1 dies out.

3.3 Conclusion

The methods for calculating basic reproductive numbers in both autonomous and nonautonomous epidemic models have been extended in a natural way to calculate invasion reproductive numbers. These IRNs give a way to determine stability of endemic equilibrium by determining whether certain competing infections can invade populations when there are already infections resident there.

For autonomous systems, the work of van den Driessche and Watmough was used by exploiting the fact that the first steps for the method are epidemiological and not mathematical. In the same way the methods of Wang and Zhao and Bacäer were extended for non-autonomous systems. In these systems generally one cannot get an explicit formula for the IRN and so one must approximate the IRNs numerically. Examples were shown throughout to give an idea of how the methods are used and techniques to help evaluate them in the case numerical work is done.

Now that these methods for calculating different reproductive numbers, both basic and invasion, have been discussed, the question becomes in what way are these helpful in certain models. These reproductive numbers might be used in models with seasonality where competing infections occur. One such disease is Chagas disease

where competing strains of the parasite occur in different host patterns and competitive exclusion does not hold in certain cases. The next chapter will explore this type of model to see if seasonality can account for this co-persistence.

CHAPTER 4

Seasonality in a two-strain model for sylvatic *T. cruzi* transmission

4.1 Introduction

There are many diseases which exhibit seasonal behavior [4]. Vector-borne diseases like malaria and dengue hemorrhagic fever have peak rates during warm, dry rainy season. Influenza seems to be a common topic each year as vaccines are given during peak seasons for the transmission of the virus [31, 52, 11]. Typically when modeling seasonal diseases, only peak transmission season is considered, so as to simplify the model. In order to incorporate seasonality, forced oscillators are generally used to show a wide range of dynamics. Early models used seasonality in the transmission dynamics, by varying the transmission with time [18, 6]. While many parameters can be made periodic within the model to account for different biological factors, including these things within models makes them difficult to analyze.

This study focuses on how seasonality affects a model with multiple strains of a parasite. In [3], Alfaro-Murillo et al. were studying an SIR model for influenza that incorporates seasonality in the transmission rate. They considered multiple strains of the infection. Using cosine waves in their transmission they suggested the seasonal variation might be responsible for observed patterns in influenza including higher frequency of disease recurrence in tropical regions than in the temperate regions.

Kamo and Sasaki in [33] created a multi-strain SIR model with seasonal transmission dynamics. They determined that the behavior of the multi-strain epidemiological dynamics critically depends on the coefficients of cross-immunity defined for

each pair of sub-types. They state that seasonality is clearly important in echovirus epidemics.

Ahna et al. [2] developed a two-strain model for bacterial species. They account for seasonality within the birth rate and death rate. The strains were clustered into three genetically close groups. They determined that if two strains are genetically similar, they are also epidemiologically similar in that they induce some cross-immunity in the hosts, but if they are genetically less similar, then they induce less cross-immunity in the hosts.

Aguiara et al. in [1] studied a two-strain model of Dengue fever using seasonality in the transmission parameters. They integrated the use of numerical bifurcation analysis and time series analysis techniques for the study of the long-term dynamics of the non-autonomous system. They state that seasonal forcing is essential in order to be able to reproduce signals of a yearly cycle in dengue incidence.

This study will focus on a two-strain model of Chagas disease. *Trypanosoma cruzi* is a protozoan parasite responsible for millions of infections of Chagas disease in Latin America. There have been a few cases reported in humans in the United States, but it is the sylvatic cycles that maintain the parasite, with vectors moving towards more populated areas in search of new food sources [36]. This chapter will focus on the sylvatic transmission of the disease between hosts and vectors. It will focus on hosts such as raccoons and woodrats. The two vectors associated with these hosts in the southern United States are *T. sanguisuga* and *T. gerstaeckeri*. Both vectors are associated with raccoons while only *T. gerstaeckeri* is associated with woodrats.

There are two different strains of *T. cruzi* commonly found in the U.S. Strains of *T. cruzi* have been classified as being one of six types, I-VI. In the U.S., only two types have been known to persist, types I and IV. Both of the hosts that are discussed

in the chapter, raccoons and woodrats, have been known to be associated with strains I and IV of the parasite.

Infection with a strain of *T. cruzi* has been shown to give hosts cross-immunity against infection from other strains. This naturally gives rise to a competition between strains for access to hosts and vectors. The single host-model of Kribs-Zaleta and Mubayi [36] predicts competitive exclusion, but there are reports that both strains are endemic within woodrats [12]. It appears that to a lesser extent, both strains have been observed in raccoons as well [45]. One of the possible explanations for two different strains being prevalent in the populations could have to do with different hosts living in close proximity to each other. In [35], Kribs and Mitchell developed multihost models which showed that spillover from other cycles such as opossums can account for trace prevalence of an otherwise losing strain, such as that seen in raccoons, but not at the roughly equal levels observed in some south Texas woodrat populations.

For this study, the model from [36] will be extended to incorporate seasonality. Seasonality can be incorporated into many of the model's parameters. The simplest approach is to just use seasonality in the transmission terms, specifically the vector transmission rate. Strain IV appears to be better adapted to vertical transmission [25], and may even be better at oral transmission, while strain I appears to be better at stercorarian transmission. This leads to a theory that strains adapted to different means of transmission may be better suited for different peak seasons depending on when hosts are numerous or scarce [49]. So if strain IV is better adapted at vertical transmission, it might do better in the spring, during a breeding season for hosts while strain I might fare better in winter when hosts are less likely to forage or move dens. Then techniques from the previous chapters will be used to find the basic and

the invasion reproductive numbers to determine whether seasonality may explain the observed co-persistence.

4.2 Seasonal Transmission Model

Kribs and Mubayi [36] created a single-host model to describe competition between *T. cruzi* I and IV (denoted strains 1 and 2 in the model). First, a summary of the model will be given and then the extensions to include the seasonal dynamics.

There are three modes of infections to hosts: vertical transmission, stercorarian, and predation. These could all be affected by seasonality. With vertical transmission, only female hosts are considered where it is assumed a proportion $p_j (j = 1, 2)$ of hosts infected with strain j give birth to infected young. Vectors obtain blood meals from infected hosts, and the rate at which that vector gets is infected is c_{vj}, while the rate that an infected vector infects a host is c_{hj} for strain type $j = 1, 2$. For predation, a portion of hosts ρ_j that consume an infected vector become infected with strain j.

For their model, Kribs and Mubayi used contact-based rates with piecewise linear (Holling type I) saturation [37, 38]. In the model Q is defined as the vector-host population density ratio, $Q = N_v/N_h$. The contact rates are defined as follows:

$$\begin{aligned} c_{hj}(Q) &= \beta_{hj} \min(\frac{Q}{Q_v}, 1) \\ c_{vj}(Q) &= \beta_{vj} \min(\frac{1/Q}{1/Q_v}, 1) = \beta_{vj} \min(\frac{Q_v}{Q}, 1) \\ E_h(Q) &= H \min(\frac{Q}{Q_v}, 1) \end{aligned} \tag{4.1}$$

with maximum values $\beta_{hj}, \beta_{vj} (j = 1, 2)$ and H respectively.

All of these infection rates could be affected by seasonality. Stercorarian infection rates could be affected if the vectors suspend development due to unfavorable conditions. This would mean they feed less, thus transmitting the disease less. During mating season for hosts, the vertical transmission rates could be higher. Also during

Table 4.1. Variables and notation for sylvatic *T. cruzi* transmission model

Variable	Meaning	Units
$S_h(t)$	Density of uninfected hosts	hosts/area
$I_{h1}(t)$	Density of hosts infected with *T. cruzi* I	hosts/area
$I_{h2}(t)$	Density of hosts infected with *T. cruzi* IV	hosts/area
$S_v(t)$	Density of uninfected vectors	vectors/area
$I_{v1}(t)$	Density of vectors infected with *T. cruzi* I	vectors/area
$I_{v2}(t)$	Density of vectors infected with *T. cruzi* IV	vectors/area
Q	Vector-host population ratio (N_v/N_h)	vectors/host
$c_{hj}(Q, Q_v)$	Strain j stercorarian infection rate	1/time
$c_{vj}(Q, Q_v)$	Strain j vector infection rate	1/time
$E_h(Q, Q_h)$	Per-host Predation rate	vectors/host/time

periods of higher activity for hosts, or when other food is less plentiful, they could feed on insects more, thus increasing the predation rate.

The total host density is $N_v = S_v + I_{v1} + I_{v2}$, and the same for total vector density, N_v. The total vector birth rate, b_v, is

$$b_v(N) = r_v N(1 - N/K_v), \tag{4.2}$$

and same for host birth rate, b_h. h here represents either woodrats (W) or raccoons (R) and v is *T. sanguisuga* (S) or *T. gerstaeckeri* (G). The previous model gives rise to the following equations:

Table 4.2. Parameter definitions for woodrat/*T. gerstaeckeri* cycles, with values taken from [36].

Parm.	Definition	Units	Value
r_h	Growth rate for hosts	per year	1.8
r_v	Growth rate for vectors	per year	100
μ_h	Natural mortality rate of hosts	per year	1
μ_v	Natural mortality rate of vectors	per year	.562
N_h^*	(Equilibrium) host population density	hosts/acre	9.3
K_h	Carrying capacity for hosts	hosts/acre	21
N_v^*	(Equilibrium) vector population density	vectors/acre	128
K_v	Carrying capacity for vectors	vectors/acre	129
Q_h	Threshold vector-host density ratio for predation	vectors/host	10
Q_v	Threshold vector-host density ratio for bloodmeals	vectors/host	100
β_{h1}	Strain 1 stercorarian infection rate	per year	10.125
β_{h2}	Strain 2 stercorarian infection rate	per year	5.805
β_v	Vector infection rate	per year	1.59
p_1	Strain 1 vertical transmission proportion	dimensionless	0.05
p_2	Strain 2 vertical transmission proportion	dimensionless	0.1
H	(Maximum) per-host predation rate	vec/host/year	1
ρ	Estimated proportion of hosts infected after consuming a vector infected with strain 1	hosts/vector	0.177

$$
\begin{aligned}
S_h'(t) &= \left(1 - \frac{p_1 I_{h1}(t) + p_2 I_{h2}(t)}{N_h}\right) b_h N_h(t) - \left[c_{h1}(Q(t)) + \rho_1 E_h(Q(t))\right] S_h(t) \frac{I_{v1}(t)}{N_v(t)} \\
&\quad - \left[c_{h2}(Q(t)) + \rho_2 E_h(Q(t))\right] S_h(t) \frac{I_{v2}(t)}{N_v(t)} - \mu_h S_h(t) \\
I_{h1}'(t) &= p_1 \frac{I_{h1}(t)}{N_h} b_h(N_h) + \left[c_{h1}(Q(t)) + \rho_1 E_h(Q(t))\right] S_h(t) \frac{I_{v1}(t)}{N_v(t)} - \mu_h I_{h1}(t) \\
I_{h2}'(t) &= p_2 \frac{I_{h2}(t)}{N_h} b_h(N_h) + \left[c_{h2}(Q(t)) + \rho_2 E_h(Q(t))\right] S_h(t) \frac{I_{v2}(t)}{N_v(t)} - \mu_h I_{h2}(t) \\
S_v'(t) &= b_v(N_v(t)) - c_{v1}(Q(t)) S_v(t) \frac{I_{h1}(t)}{N_h} - c_{v2}(Q(t)) S_v(t) \frac{I_{h2}(t)}{N_h} - \mu_v S_v(t) \\
&\quad - E_h(Q(t)) N_h \frac{S_v(t)}{N_v(t)} \\
I_{v1}'(t) &= c_{v1}(Q(t)) S_v(t) \frac{I_{h1}(t)}{N_h} - \mu_v I_{v1}(t) - E_h(Q(t)) N_h \frac{I_{v1}(t)}{N_v(t)} \\
I_{v2}'(t) &= c_{v2}(Q(t)) S_v(t) \frac{I_{h2}(t)}{N_h} - \mu_v I_{v2}(t) - E_h(Q(t)) N_h \frac{I_{v2}(t)}{N_v(t)}
\end{aligned}
\tag{4.3}
$$

The autonomous model of [36] exhibits competitive exclusion, as it was shown that at most one strain's IRN can exceed 1 ($\tilde{R}_i > 1 \Rightarrow \tilde{R}_j < 1$). To investigate whether

periodicity in general can explain (exhibit) co-persistence in this model, periodicity will be introduced into just a single parameter, for the vector transmission rates c_{vj}.

Without any time variation in the demographic parameters, the demographics go to a unique globally asymptotically stable equilibrium (with N_h^*, N_v^*), and the model simplifies, as in [36]. To simplify the model, introduce the following notation:

$$\begin{aligned}
\tilde{\beta}_{hj} &= c_{hj}(Q^*) + \rho_j E_h(Q^*), (j = 1, 2) \\
\tilde{\beta}_{vj} &= c_{vj}(Q^*), (j = 1, 2) \\
\tilde{\mu}_v &= \mu_v + E_h(Q^*)/Q^* \\
Q^* &= N_v^*/N_h^*
\end{aligned} \tag{4.4}$$

To include the periodicity, redefine the vector transmission rates as follows:

$$\tilde{\beta}_{vj}(t) = c_{vj}(Q^*) \begin{cases} a_j & : 0 < t < \tau \\ b_j(a) & : \tau < t < \omega \end{cases} \tag{4.5}$$

for $(j = 1, 2)$. Define $b_j(a) = \frac{\omega - a_j \tau}{\omega - \tau}$ where ω is the period which for this model is 1 year and τ is the length of the first season. This framework makes the time-average value the same regardless of $a_j \in [0, 1]$.

4.3 Basic reproductive numbers

Rearrange the system so that only infected classes are at the beginning. This produces the system below:

$$
\begin{aligned}
I'_{h1}(t) &= p_1 \frac{I_{h1}(t)}{N_h^*} b_h(N_h^*) + \tilde{\beta}_{h1} S_h(t) \frac{I_{v1}(t)}{N_v^*} - \mu_h I_{h1}(t) \\
I'_{h2}(t) &= p_2 \frac{I_{h2}(t)}{N_h^*} b_h(N_h^*) + \tilde{\beta}_{h2} S_h(t) \frac{I_{v2}(t)}{N_v^*} - \mu_h I_{h2}(t) \\
I'_{v1}(t) &= \tilde{\beta}_{\mathbf{v1}}(\mathbf{t}) S_v(t) \frac{I_{h1}(t)}{N_h^*} - \tilde{\mu}_v I_{v1}(t) \\
I'_{v2}(t) &= \tilde{\beta}_{\mathbf{v2}}(\mathbf{t}) S_v(t) \frac{I_{h2}(t)}{N_h^*} - \tilde{\mu}_v I_{v2}(t) \\
S'_h(t) &= \left(1 - \frac{p_1 I_{h1}(t) + p_2 I_{h2}(t)}{N_h^*}\right) b_h N_h^* - \tilde{\beta}_{h1} S_h(t) \frac{I_{v1}(t)}{N_v^*} \\
&\quad - \tilde{\beta}_{h2} S_h(t) \frac{I_{v2}(t)}{N_v^*} - \mu_h S_h(t) \\
S'_v(t) &= b_v(N_v^*) - \tilde{\beta}_{\mathbf{v1}}(\mathbf{t}) S_v(t) \frac{I_{h1}(t)}{N_h^*} - \tilde{\beta}_{\mathbf{v2}}(\mathbf{t}) S_v(t) \frac{I_{h2}(t)}{N_h^*} - \tilde{\mu}_v S_v(t)
\end{aligned}
\tag{4.6}
$$

For the basic reproduction numbers, define the matrices $\mathscr{F}(t)$ and $\mathscr{V}(t)$ as follows:

$$
\mathscr{F}(t) = \begin{bmatrix}
\tilde{\beta}_{h1} S_h(t) \frac{I_{v1}}{N_v^*} + p_1 \mu_h I_{h1}(t) \\
\tilde{\beta}_{h2} S_h(t) \frac{I_{v2}}{N_v^*} + p_2 \mu_h I_{h2}(t) \\
\tilde{\beta}_{v1}(t) S_v(t) \frac{I_{h1}}{N_h^*} \\
\tilde{\beta}_{v2}(t) S_v(t) \frac{I_{h2}}{N_h^*} \\
0 \\
0
\end{bmatrix},
$$

$\mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ =$

$$\begin{bmatrix} \mu_h I_{h1}(t) \\ \mu_h I_{h2}(t) \\ \tilde{\mu}_v I_{v1}(t) \\ \tilde{\mu}_v I_{v2}(t) \\ \tilde{\beta}_{h1} S_h(t) \frac{I_{v1}(t)}{N_v^*} + \tilde{\beta}_{h2} S_h(t) \frac{I_{v2}(t)}{N_v^*} + \mu_h S_h(t) - \left(1 - \frac{p_1 I_{h1}(t) + p_2 I_{h2}(t)}{N_h^*}\right) b_h N_h^* \\ \tilde{\beta}_{v1}(t) S_v(t) \frac{I_{h1}(t)}{N_h^*} + \tilde{\beta}_{v2}(t) S_v(t) \frac{I_{h2}(t)}{N_h^*} + \tilde{\mu}_v S_v(t) - b_v(N_v^*) \end{bmatrix}.$$

Verification of (A1)-(A5) is simple from observation of the matrices. For (A6), consider the matrix given by:

$$M(t) = \begin{bmatrix} -\mu_h & 0 \\ 0 & -\tilde{\mu}_v \end{bmatrix}.$$

Solving the autonomous system $\frac{dz}{dt} = Mz$ in this case yields the principal fundamental matrix and since it is diagonal, $\rho(\Psi_M) < 1$ and (A6) is satisfied.

Define $F(t)$ and $V(t)$ as follows:

$$F(t) = \begin{bmatrix} p_1\mu_h & 0 & \tilde{\beta}_{h1} & 0 \\ 0 & p_2\mu_h & 0 & \tilde{\beta}_{h2} \\ \tilde{\beta}_{v1}(t) & 0 & 0 & 0 \\ 0 & \tilde{\beta}_{v2}(t) & 0 & 0 \end{bmatrix}, V(t) = \begin{bmatrix} \mu_h & 0 & 0 & 0 \\ 0 & \mu_h & 0 & 0 \\ 0 & 0 & \tilde{\mu}_v & 0 \\ 0 & 0 & 0 & \tilde{\mu}_v \end{bmatrix}.$$

To verify (A7), the system $\frac{dy}{dt} = -V(t)y$ must be solved. This is an autonomous system and produces a diagonal fundamental matrix, and it is clear that (A7) is satisfied.

The BRNs must be found numerically by solving system:

$$\frac{dw}{dt} = \left[-V(t) + \frac{F(t)}{\lambda}\right] w, t \in \mathbb{R} \tag{4.7}$$

to get a fundamental matrix $\Psi(t,\lambda)$. This matrix is then used to solve for λ such that $\rho(\Psi(\omega,\lambda))=1$. This is done using the methods described in previous chapters. Explicit forms for the autonomous case are given in [36].

4.4 Invasion reproductive numbers

For the strain 1 invasion reproductive number, assume that strain 2 is resident within the population. Rearrange the order of the equations so that only those infected classes with strain 1 are at the top.

$$\begin{aligned}
I'_{h1}(t) &= p_1\frac{I_{h1}(t)}{N_h^*}b_h(N_h^*)+\tilde{\beta}_{h1}S_h(t)\frac{I_{v1}(t)}{N_v^*}-\mu_h I_{h1}(t)\\
I'_{v1}(t) &= \tilde{\beta}_{\mathbf{v1}}(\mathbf{t})S_v(t)\frac{I_{h1}(t)}{N_h^*}-\tilde{\mu}_v I_{v1}(t)\\
I'_{h2}(t) &= p_2\frac{I_{h2}(t)}{N_h^*}b_h(N_h^*)+\tilde{\beta}_{h2}S_h(t)\frac{I_{v2}(t)}{N_v^*}-\mu_h I_{h2}(t)\\
I'_{v2}(t) &= \tilde{\beta}_{\mathbf{v2}}(\mathbf{t})S_v(t)\frac{I_{h2}(t)}{N_h^*}-\tilde{\mu}_v I_{v2}(t)\\
S'_h(t) &= \left(1-\frac{p_1I_{h1}(t)+p_2I_{h2}(t)}{N_h}\right)b_hN_h^*-\tilde{\beta}_{h1}S_h(t)\frac{I_{v1}(t)}{N_v^*}\\
&\quad -\tilde{\beta}_{h2}S_h(t)\frac{I_{v2}(t)}{N_v^*}-\mu_hS_h(t)\\
S'_v(t) &= b_v(N_v^*)-\tilde{\beta}_{\mathbf{v1}}(\mathbf{t})S_v(t)\frac{I_{h1}(t)}{N_h^*}-\tilde{\beta}_{\mathbf{v2}}(\mathbf{t})S_v(t)\frac{I_{h2}(t)}{N_h^*}-\tilde{\mu}_vS_v(t)
\end{aligned}\tag{4.8}$$

Define the matrices $\mathscr{F}(t)$ and $\mathscr{V}(t)$ as follows:

$$\mathscr{F}(t)=\begin{bmatrix}\tilde{\beta}_{h1}S_h(t)\frac{I_{v1}}{N_v^*}+p_1\mu_hI_{h1}(t)\\ \tilde{\beta}_{v1}(t)S_v(t)\frac{I_{h1}(t)}{N_h^*}\\ 0\\ 0\\ 0\\ 0\end{bmatrix},$$

$\mathscr{V}(t) = \mathscr{V}^- - \mathscr{V}^+ =$

$$\begin{bmatrix} \mu_h I_{h1}(t) \\ \tilde{\mu}_v I_{v1}(t) \\ \mu_h I_{h2}(t) - p_2 \frac{I_{h2}(t)}{N_h^*} b_h(N_h^*) - \tilde{\beta}_{h2} S_h(t) \frac{I_{v2}(t)}{N_v^*} \\ \tilde{\mu}_v I_{v2}(t) - \tilde{\beta}_{v2}(t) S_v(t) \frac{I_{h2}}{N_h^*} \\ \tilde{\beta}_{h1} S_h(t) \frac{I_{v1}(t)}{N_v^*} + \tilde{\beta}_{h2} S_h(t) \frac{I_{v2}(t)}{N_v^*} + \mu_h S_h(t) - \left(1 - \frac{p_1 I_{h1}(t) + p_2 I_{h2}(t)}{N_h^*}\right) b_h N_h^* \\ \tilde{\beta}_{v1}(t) S_v(t) \frac{I_{h1}(t)}{N_h^*} + \tilde{\beta}_{v2}(t) S_v(t) \frac{I_{h2}(t)}{N_h^*} + \tilde{\mu}_v S_v(t) - b_v(N_v^*) \end{bmatrix}.$$

Verification of (A1)-(A5) is simple from observation of the matrices. To verify the other assumptions, define the periodic endemic solution, $(0, 0, I_{h2}^*(t), I_{v2}^*(t), S_h^*(t), S_v^*(t))$. Verification of (A6) is difficult. The matrix $M(t)$ is defined as follows:

$$M(t) = \begin{bmatrix} \frac{p_2 b_h}{N_h^*} - \mu_h & \tilde{\beta}_{h2} \frac{S_h^*(t)}{N_v^*} & \tilde{\beta}_{h2} \frac{I_{v2}^*(t)}{N_v^*} & 0 \\ \tilde{\beta}_{v2}(t) \frac{S_v^*(t)}{N_h^*} & -\tilde{\mu}_v & 0 & 0 \\ -\frac{p_2 b_h}{N_h^*} & -\tilde{\beta}_{h2} \frac{S_h^*(t)}{N_v^*} & -\tilde{\beta}_{h2} \frac{I_{v2}^*(t)}{N_v^*} - \mu_h & 0 \\ -\tilde{\beta}_{v2}(t) \frac{S_v^*(t)}{N_h^*} & 0 & 0 & -\tilde{\beta}_{v2}(t) \frac{I_{h2}^*(t)}{N_h^*} - \tilde{\mu}_v \end{bmatrix}$$

To verify (A6), the system $\frac{dz}{dt} = Mz$ must be solved, but it must be done for every value of τ since changing τ changes the periodic solution. If $\tau = 0$ or $\tau = \omega$ then the system is autonomous and the verification is done. However, if $\tau \in (0, \omega)$ then the periodic endemic solution must be found for each value of τ. For the purposes here, (A6) will be verified for a particular value of $\tau = 0.5$. For the parameters given in Table 4.2, the fundamental matrix is numerically approximated using linearly independent initial conditions so that the final matrix has linearly independent solutions. Once this is done, the maximum eigenvalue of $\Phi_{-V}(\omega)$ can be found. Doing this gives $\rho(\Phi_M(\omega)) = 0.0452$ which is less than 1 and (A6) is verified. Define $F(t)$ and $V(t)$ as follows:

$$F(t) = \begin{bmatrix} p_1 \mu_h & \tilde{\beta}_{h1} \frac{S_h^*(t)}{N_v^*} \\ \tilde{\beta}_{v1}(t) \frac{S_v^*(t)}{N_h^*} & 0 \end{bmatrix}, V(t) = \begin{bmatrix} \mu_h & 0 \\ 0 & \tilde{\mu}_v \end{bmatrix}.$$

To verify (A7) notice that $V(t)$ is diagonal and thus (A7) is done. The IRNs must be found numerically by solving system:

$$\frac{dw}{dt} = \left[-V(t) + \frac{F(t)}{\lambda}\right] w, t \in \mathbb{R} \tag{4.9}$$

to get a fundamental matrix $\Psi(t, \lambda)$. Then the monodromy matrix is found and then used to solve for λ such that $\rho(\Phi(\omega, \lambda)) = 1$.

4.5 Results

The goal of this chapter is to determine if co-persistence is possible when vector transmission rates are periodic. Using the simple square wave of (4.5), the boundaries of $\tilde{R}_j = 1$ are graphed as functions of R_j using the mean transmission values $\tilde{\beta}_{vj}$ as proxies for R_j as described in the previous chapter. Using the set of parameters given in Tables 4.1 and 4.2, and the periodic vector transmission rates of $a_1 = 1.96, a_2 = 0.04$ with $\omega = 1, \tau = 0.5$, the first step in finding $\tilde{R}_j$ is to find the periodic strain-i-endemic ($i \neq j$) solution as this is needed for the matrices $F(t)$ and $V(t)$ in order to solve the system (4.9). This is done by solving the system in Matlab for initial conditions where only the resident infection exists. Once this is numerically calculated, (4.9) is solved using Mathematica to find the fundamental matrix for a given value of λ. This is done using linearly independent initial conditions to ensure that the matrix consists of linearly independent solutions and that it is a principal fundamental matrix. Then the IRN is the value of lambda for which $\rho(\Phi(\omega, \lambda)) = 1$ The results are shown in Figure 4.1.

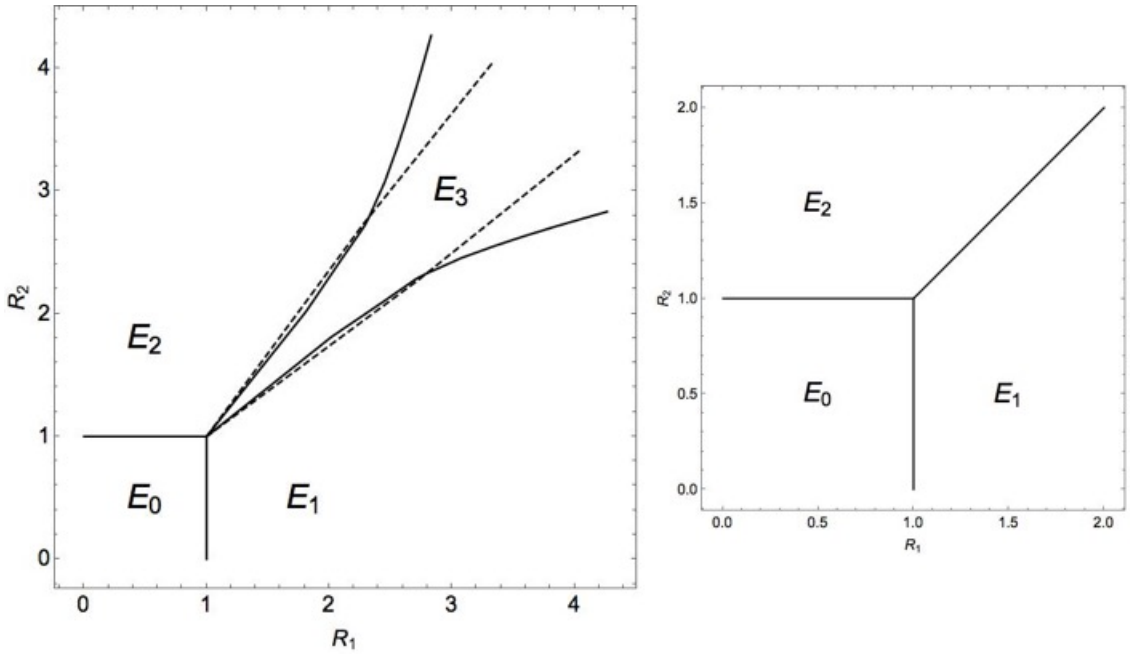

Figure 4.1. Left graph showing 4 regions representing different behaviors of the system in terms of the BRN/IRN threshold curves ($R_j = 1, \tilde{R}_j = 1, j = 1, 2$) for mild and extreme periodic variation in the vector transmission rates, $\tilde{\beta}_{vj}(t)$. E_0 is disease-free, E_1 is only strain 1 prevalent, E_2 is only strain 2 prevalent, and E_3 is co-persistence. The dashed line is for $a_1 = b_2 = 1.2$ and $a_2 = b_1 = 0.8$ and the solid line is for $a_1 = b_2 = 1.96$ and $a_2 = b_1 = 0.04$. The right figure is for the autonomous system, where $\tilde{R}_1$ and $\tilde{R}_2$ coincide and thus co-persistence is not possible.

The autonomous single host model of [36] predicted competitive exclusion. The graph above shows that if the scaling factors a and $b(a)$ approach 1, the graph closes up, and thus will be the same as in the autonomous case. Running the system for the same parameters with the values closer to 0 and 2 as in the graph above gives the result in Figures 4.2 and 4.3.

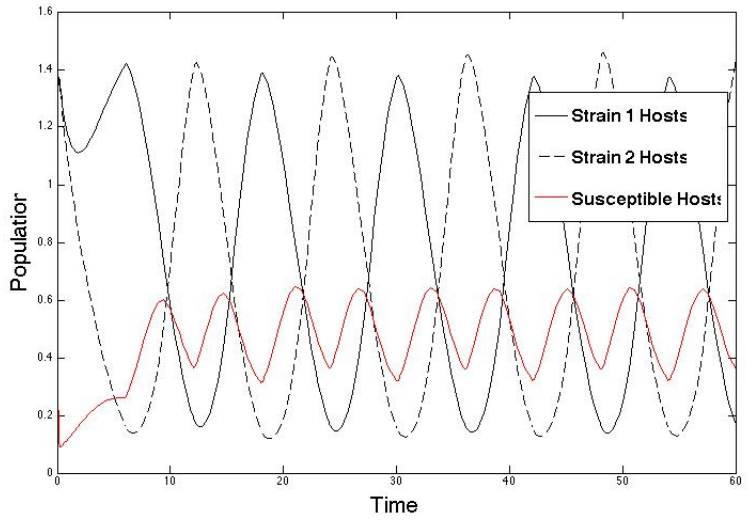

Figure 4.2. Simulation of system (4.3) for the host classes showing co-persistence between strains.

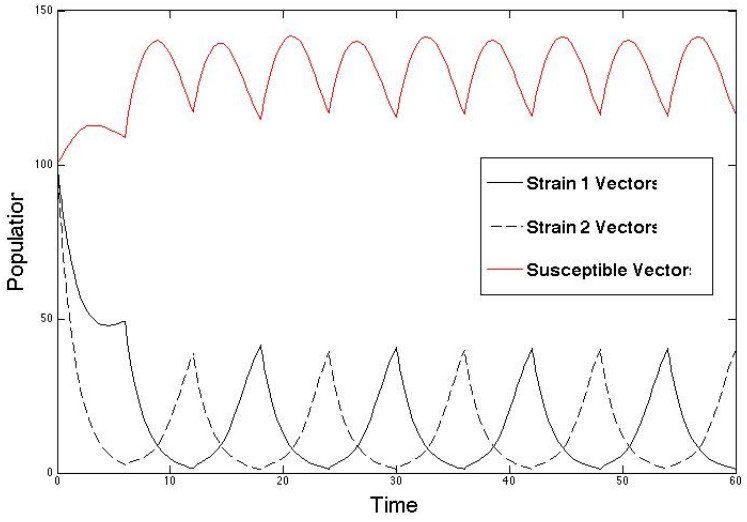

Figure 4.3. Simulation of system (4.3) for the vector classes showing co-persistence between strains.

4.6 Discussion

As seen in Figure 4.1, seasonality in the vector infection rate is sufficient to explain co-persistence of the two strains of the parasite. There could be other parameters in which seasonality could open up co-persistence. The values used for the simulations all fall within the ranges given in [36] except for the vector transmission rates. It does appear that for any values on opposite sides of 1 for the vector transmission seasonal scaling parameters, there are values of the other model parameters (in particular the BRNs) for which co-persistence will happen, though more work will need to be done in the future to determine what particular values will give the desired result.

This appears to suggest that it is possible for one strain to do better than the other at certain times of the year, and vice versa, in the south Texas woodrat populations where co-persistence has been observed. As stated before, strain 2 has been shown to be better adapted to vertical transmission, and thus could have an advantage in the spring when hosts produce [25]. As observed by Kribs and Mubayi [36], strain 1 is more adapted to stercorarian infection, and can win competition in woodrats under the right conditions.

It would appear from the model that in places with strong seasonal variations in climate (temperature, precipitation, etc.), there is a much larger parameter space than in places where those seasonal variations are milder, in which co-persistence is possible. These wide seasonal variations create scenarios where a pathogen can establish enough of a dominance during its peak season to survive long enough to not be driven out by another pathogen capable of surviving under different seasonal conditions. As those seasonal variations get weaker, the pathogen may not be able to thrive long enough to prevent any invading pathogens from driving it out. This suggests a potential link between seasonal variability and genetic diversity within

pathogens. A pathogen's ability to survive (via diversity) could be higher in regions with large seasonal climate changes where that pathogen has a strong adaptation towards those seasonal variations.

In this model, it appears that co-persistence is only possible under periodicity. In the last chapter, an example was given that showed co-persistence is less likely under periodicity. The difference between the models is that the infection modeled in the last chapter allowed for (and even fostered) coinfection while the strains of the Chagas model exhibit cross-immunity. Coinfection could allow for the strain not adapted for those seasons where the resident strains thrive to persist long enough that the resident strain is not able to survive outside its peak season. So the invading infection is able to establish itself enough during the resident infection's peak season to eventually drive the resident infection out. Further work is needed to study the relationship between coinfection and seasonality's effect on co-persistence and whether this holds in more broad terms.

Further work needs to be done to determine those parameters in the Chagas model in which seasonality matters. Host and vector demographics vary seasonally, which can be included in the model with host/vector birth and death rates, and thus there would be no demographic equilibrium, but rather an asymptotically periodic demographic state. Here the model only considered seasonality in the vector transmission rate. The minimal seasonality allows co-persistence while varying multiple parameters could actually lead to competitive exclusion. This model does provide a new explanation for the observed co-persistence of the strains in the wild.

CHAPTER 5

Conclusion

The purpose of this dissertation was to discuss and apply ways to calculate reproductive numbers for nonautonomous epidemic systems. For the basic reproductive number, the method crafted by Bacaër[9] and extended by Wang and Zhao [51] was shown. The time-average method was also given, as it seems like a natural way to calculate BRNs for these systems. It is also significantly simpler (you can actually write down the expressions, whereas with the linear operator method one can never do so). However, as shown by Ma and Ma it does not always give the correct threshold behavior [39]. Many examples were given showing times when the time-average method and the linear operator method agree in their expression for the BRN. Wang and Zhao showed that if the $F(t)$ and $V(t)$ matrices are constant or diagonal, then the methods agree in their expression. This dissertation proved in a theorem that the agreement can be extended to triangular matrices. One special case shown was when there is only a single infected class. In this case, the two methods always agree as the system will be trivially triangular. Numerical results were shown for when the methods disagree. For instance, it was shown that the time-average method sometimes underestimates and sometimes overestimates outbreak risk. In those cases, simulations and graphs verified that the linear operator method gives the correct threshold behavior. A pseudocode was given to find the BRN in the case where it must be done numerically.

When discussing models with multiple infections, the invasion reproductive number is another useful tool to determine stability of an endemic periodic solution.

First the method was laid out for autonomous systems, extending van den Driessche and Watmough's method [50] to show that the same threshold behavior can be used for a periodic solution. The method was extended by exploiting the fact that the first step in next generation operator methods is epidemiological. This allowed for reclassification as to what was considered an infected class. Here, two different IRNs were shown, the first being the overall non-resident infections' ability to invade. The second IRN measured instead each individual infection's ability to invade in the case when the overall IRN is greater than 1. The next step was to extend this method for nonautonomous systems. Using the same methods as in the case for BRNs, the linear operator method was extended and shown to hold the same threshold behavior. An example was given that showed when the time-average method and the linear operator agreed in their expression, giving rise to an extension of the theorem from the previous chapter. This showed if the matrices $F(t)$ and $V(t)$ are triangular of the same form the methods would agree. A numerical example was given in which, for this particular case, seasonality led to a decreased chance of co-persistence. The same principle from the first chapter applies here in that the two methods agree in the case of a single invading infected class.

The last chapter was an application of the methods to a model of Chagas disease. The single-host model of Kribs and Mubayi [36] was used to include seasonality in the transmission parameters. The goal was to see if seasonality could explain why competitive exclusion does not hold in certain sylvatic cycles. For a set of biologically realistic parameters it does appear that seasonality can explain why the different strains are observed to be at endemic levels, especially within woodrat populations. Each strain's adaptation to a particular transmission pathway could give it an advantage during certain seasons of the year, allowing it to persist even during seasons in which it cannot infect at the same peak values. This also leads to pathogen diversity

as a function of the magnitude of seasonal variations. It appears that a wider seasonal variation can foster more scenarios of co-persistence whereas if the seasonal variation is narrow, co-persistence becomes less likely.

One issue with the linear operator method, though it does give the correct threshold behavior, is that it relies heavily on numerical work. Each periodic solution must be numerically found in order to compute the IRNs for those models with competing infections. The fundamental matrices must also be numerically computed. This can lead to tedious and time-consuming work as for each set of parameters, each of these things must be calculated and programmed to use. There is also the issue of verifying (A6) and (A7) for each model, which when they rely on the periodic solution, must be done each time a parameter is changed. This creates issues when wanting to do sensitivity analysis or understand the behavior of the reproductive numbers.

For the linear operator method, there is more work to be done for the IRNs. In the case where the overall IRN, ${}_A\tilde{R}_0 > 1$, it does not tell which infection(s) are in fact invading, only that something is persisting enough to cause unstability. More work needs to be done for the individual IRNs, ${}_A\tilde{R}_j$, in order to verify whether they show that if the endemic solution is unstable in the smaller subspace, this gives instability in the larger space. This requires a comparison of eigenvalues for submatrices that falls outside of the mathematical work of this dissertation. There is also the issue of determining whether all the individual IRNs being less than 1 implies that the overall IRN is less than 1. There could be scenarios where it might not, as in coinfection between resident and invading strains.

Further work needs to be done on the Chagas model to determine which source(s) of seasonality are the most significant in the population where co-persistence was observed. Another area for future research is the connection between coinfection and seasonality's impact on co-persistence. In the coinfection model, it appeared that sea-

sonality decreases the possibility of co-persistence in contrast to the *T. cruzi* model presented here. Further work needs to be done to study questions over whether vector vs. indirect transmission plays a role in the connection between coinfection and seasonality's impact on co-persistence. This leads to studies on the strength of coinfection dynamics and the strength of seasonal variation. Though periodicity complicates epidemiological models, it appears to create more biologically relevant dynamics. These can lead to impactful studies to determine the best way to prevent disease outbreaks.

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BIOGRAPHICAL STATEMENT

Christopher David Mitchell was born in Dallas, Texas, and grew up all over the DFW metroplex. In 2009, he began his undergraduate studies at The University of Texas at Arlington. He knew he wanted to study mathematics early on, but it was not until his involvement in an undergraduate research program called UTTER that he discovered his passion for mathematical epidemiology. He continued his graduate studies at UTA, working under his adviser, Christopher Kribs, on many different projects. He has applied epidemiological modeling techniques to study the growth of populations as diverse as honeybees and zombies, and has worked on a few projects dealing with Chagas disease. Christopher is happily married and has a beautiful son.