Guinea Worm Disease *(Dracunculiasis)*: Opening a mathematical can of worms!

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Introduction

Chapter 1

Abstract

This paper details an original continuous time ODE model describing a macroparasite infection known as guinea worm disease (GWD). In doing so, the modeling process, the steps involved and its iterative nature are presented forming a guide to infection modeling. Specific mathematical concepts utilized in model analysis including the *Next-Generation Operator* are discussed. A brief introduction to the biology of GWD is given, specifically the life cycles of the parasite (guinea worm) and the intermediate host (copepod). Symptoms and interventions are also highlighted. A detailed description of the original model is given, including parameters and a nondimensionalization. An algebraic solution to the disease-free equilibrium is found and a numerical stability analysis of the solution is conducted. The paper analyzes key parameters to determine effective combinations of intervention. Simulations of these various combinations are presented and analysis of their application to an endemic equilibrium of the GWD system is shown.

Chapter 2

Introduction & Motivation

Dracunculiasis, more generally called Guinea Worm Disease (GWD), is a serious problem in various countries in Africa. This macroparasite infection currently plagues adults and children. Intervention and prevention techniques have been implemented in these areas to significantly reduce outbreaks. In this paper we provide explanation of an original model describing the interactions among humans, copepods, and guinea worms. Both SEIS and SI infection models are used in this paper. In addition, we conduct a stability analysis of the disease-free equilibrium as well as simulate various intervention scenarios. The combination of larvicides, pipe filters and education proves to be a promising intervention. This paper not only describes the population and infection dynamics of the system, but also underscores the social implications of Guinea Worm Disease. The fact is that GWD is not just a disease of poverty but rather a cause of poverty due to the disability it causes.

According to the CDC, 966 cases of *Dracunculiasis* were reported from South Sudan, Chad, Mali, and Ethiopia as of August 2011 [20]. These countries are not the only areas affected over the past fifteen years. Cases have gone from 3.5 million per year in 1986 to fewer than 1,800 in 2010[20]. The disease is spread through contaminated drinking water. Contamination is in the form of a parasite, *Dracunculus medinensis*, that has developmental stages both inside a human host and inside a copepod host. It is transmitted to humans through the maturation of larvae into adult worms inside the body and is transmitted to copepods through ingestion of free-living larvae.

To determine how GWD spreads in a given region, we model the disease using a compartmental model. This model represents the three different populations; humans, copepods, and guinea worms, by partitioning the populations into different categories or compartments based on stages of infection and growth. Both the humans and copepods have susceptible and infectious stages. Guinea worms are either categorized as eggs or free-living larvae outside of the host. Using ordinary differential equations, we model the change in size of each compartment.

After we describe the model, there are some key issues we wish to explore. For example, we want to identify equilibrium values, characterize stability and understand dynamics. Both the disease-free and endemic equilibria are of particular interest. Determining the stability of these points gives insight into the global health implications caused by a GWD epidemic. Such insight is therefore used to help minimize the disruption of the lives of those afflicted with the disease.

Due to GWD's heath and economic effects, it is the goal of this project to describe the dynamics of guinea worms, copepods, and humans with an original model. A continuous time ODE model is used to study the biological and ecological consequences of these interactions. Intervention in the form of a larvicide, pipe filters, and education are simulated to determine effectiveness. Though the

World Health Organization had certified 187 countries and territories around the world as being free of GWD, as of August 2011, we suggest this to be too bold of a statement. Understanding of the system is useful to prevent reinfection, a possibility since there is no immunity to the disease [20].

The paper is structured in the following manner. In Chapter 3, we discuss the modeling process, the steps involved and its iterative nature. Next we describe the use of compartment models and present examples of different population and infection models. Chapter 4 details the mathematical concepts utilized in model analysis and provides examples with methodology. Chapter 5 highlights a key concept, the *Next-Generation Operator*. This is an essential method for stability analysis of our multi-infection model. The biology of GWD is presented in Chapter 6, specifically the life cycles of the guinea worm and copepods. Symptoms and interventions are also explained. Chapter 7 describes the model, parameters and a nondimensionalization of the model. Chapter 8 determines an algebraic solution to the disease-free equilibrium, goes through a numerical stability analysis of the solution and analyzes key parameters to determine effective combinations of intervention. In addition, we present simulations of these various combinations and apply them to an outbreak scenario or endemic equilibrium of the GWD system.

Part II

Mathematical Modeling

Chapter 3

Mathematical Modeling: Compartment Models

3.1 What is modeling?

Mathematical modeling provides a conceptual framework in which the researcher can tap into real systems and determine a particular description. Developing this description involves the ability to tell a physical or biological story using logic, notation, and mathematical techniques. Modeling is a process, rather an iterative process, that requires the repetition of a number of steps [3].

One begins this process with investigation of a real system. We outline important biological characteristics, translate these into the mathematical notation, sketch the model, and reinterpret the results mathematically then biologically. The methodology that many follow can be broken down into three stages: *(1) Formation Stage*, *(2) Solution State*, and *(3) Interpretation Stage*. Each stage has a number of steps that complete the progression. This progression is shown in Fig 2.1. These steps include the following [3].

(**i**) empirical observations
(**ii**) formalization of biological/physical model
(**iii**) development of mathematical model based on (ii)
(**iv**) formalization of statistical model
(**v**) model analysis
(**vi**) interpretation & comparison of (v) results with the real system
(**vii**) evaluation of insights gained

In the formulation stage, empirical observations (i) are made through experiments and data collection. The proper literature review is necessary to gain the knowledge required to detail the system as well as to understand the data and experimental results. For example, if the modeler wishes to describe the yearly population of flowers in a particular garden, data on the number of seeds and flowers per given area would be helpful information. Formalization of a biological/physical model (ii) involves detailing the various pathways, mechanisms, chemical reactions and different relationships of the system under observation. Creation of a mathematical model (iii) involves

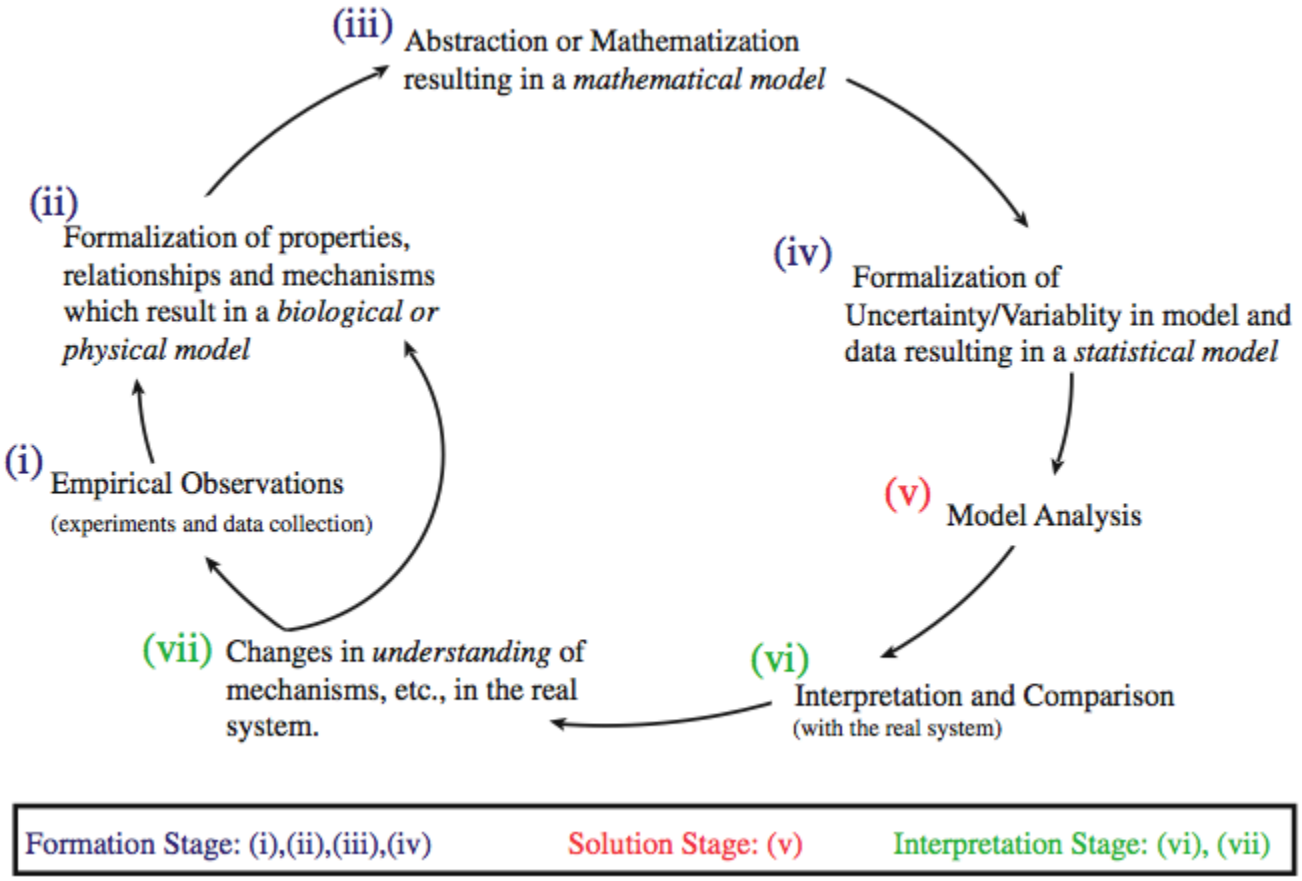

Figure 3.1: The Iterative Modeling Process [3].

differential equations with constraints and initial conditions that describe the biological/physical model. Lastly, formalization of a statistical model (iv) accounts for variability and uncertainty in the model and data. It is assumed that there is a certain amount of error in the model due to the nature of measurement and observations. In this paper, the original model presented does not include a statistical model or statistical analysis.

In the solution stage, model analysis (v) entails simulations, stability analysis, perturbation studies and perhaps parameter estimation and data fitting. This analysis is the modeler's tool to quantify the biological/physical system and research hypotheses.

The last stage is the interpretation stage. Interpretation and comparison (vi) verifies or refutes that the conclusions of the model analysis match the initial predictions. The result of this comparison leads to (vi) evaluation of insights gained. The comparisons help dictate the next step in the process. Many times, predictions are reworked and additional experiments are required. Other times, the mismatching leads to a simplification of the model or a call for more detail.

The ultimate question yet to be asked is, *What are the reasons for modeling?* It comes down to the fact that modelers can provide transparency, mechanism, and predictions. Modeling allows for the investigation of a complex system and increases the accessibility of understanding the system. In addition, manipulation of a system is more controlled and plausible through simulations. The modeler drives hypotheses and experimentation for further biological investigation of the system.

3.2 Compartment Models

Compartment models are used to describe the transport of materials, whether they be fluids, cells or populations in biological systems. The basic idea with compartment models is to describe a system as a number of compartments and to derive equations of mass-balance for each of these compartments [5]. A compartment model contains a number of compartments, each containing specific material that can be exchanged following a set of rules. Every compartment or box has a number of connections that lead to the box (inflows) and a number of arrows that lead from the box (outflows). Material either flows from one compartment to another, is added from the outside through a source, or removed through a drain or a sink [5]. A conservation law that allows the model for account for the material is used. Each compartment has a mathematical equation governed by a conservation law. The conservation laws dictate what flows in, out, and transfers from one compartment to the next. It is essential to note that one should not think of what enters and leaves each compartment as individual components that can be describe independently. On the contrary, it is the system that should be treated as a whole with well-mixed averages.

With these models there are limitations. Every system under investigation may not be suitable for a compartment model description. To determine if this method is viable, the modeler must ask the following questions. *Is the system closed? Is assuming homogeneity reasonable? Or rather, is the material in each compartment uniformly mixed? Is the balance equation accurate? Is the balance of mass relevant?* [5] The various answers to these questions dictate the usage and modification of a compartment model application.

One of the key aspects of a system the modeler must address is whether it is closed. The mass-balance equations used in compartment models are only correct if all material added and removed from the system is accounted for in the model. Many descriptions of phenomena guarantee this condition by assuming that the total amount of material is constant. In a real system, this is obviously not always the case. Next, the modeler must consider the homogeneity of the system. The use of compartment models is usually prefaced by the assumption that all material is well-mixed or homogeneous. This means that each unit of material is equally likely to be moved out of the compartment as either an outflow or a transition to another compartment. This assumption is not described in the equations, since only the total amount of material in each compartment is represented. All systems are not well-mixed. For example, any model involving a gradient would violate homogeneity. Each difference in concentration that makes up the gradient would need its own compartment or require explicit handling of space. The accuracy of the balance equation is questioned if all sources of material are not known. In real systems, some of the mass-balances are not known to the observer. Lastly, the modeler must consider if the balance of mass is relevant to the system. Depending on the system under observation, mass-balance may not be useful or capable of describing the system.

There are many phenomena that are commonly described with compartment models, including mixing problems, predator-prey dynamics, and the spread of disease and infection. Simple examples include the nonlinear continuous time SIS and SIRS infection models.

Example 1. *SIS model [12, p.1]*
Consider an infection that spreads throughout a population via contact where "healthy" individuals are susceptible to the infection (S) and "infectious" individuals (I) are capable of transmitting the infection.

To begin the modeling process, we will first describe the model in words.

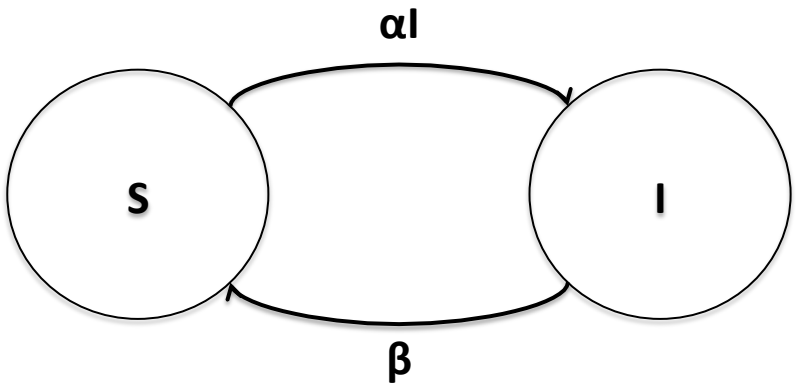

Figure 3.2: SIS model

change in S = gain from recovery - loss to infection
change in I = loss to recovery + gain from infection

Next, replace the words with symbols. The rate of change of S is represented with $\frac{dS}{dt}$. The "gain from recovery" term of the S equation is represented by βI. The "loss to infection" term is represented by αIS. Similarly, in the I equation the rate of change of I is stated as $\frac{dI}{dt}$ "loss to recovery" term is represented by αIS and the same term is used for the gain from infection as the loss to infection term of the S class. We can think of β as the leaving rate from the I compartment. Everything, in this model, that leaves one compartment enters another (i.e. it is a closed system). The resulting equations read as the following. *The rate of change of S is proportional to the number of individuals infected and the number of individuals recovered.* A similar argument holds for the I class. Since infection is only transmitted through contact with infectious hosts, we might expect that the rate that S individuals gain infection is proportional to the density of infectious individuals, I, and the density of susceptible individuals, S, with a constant of proportionality, α. The rate that S individuals recover is proportional to the number of infectious individuals leaving/recovering with a constant of proportionality β.

Thus, the following equations result

$$\begin{cases} \frac{dS}{dt} = \beta I - \alpha IS \\ \frac{dI}{dt} = -\beta I + \alpha IS \end{cases} \tag{3.1}$$

The following assumptions dictate how we treat the model. The total population is held constant. That is $\frac{dN}{dt} = \frac{dS}{dt} = \frac{dI}{dt} = 0$. Since N = S + I, the equation for S can be rewritten as $S = N - I$ and substituted into the I equation to form a one-dimensional nonlinear continuous time model.

$$\frac{dI}{dt} = \alpha I(N - I) - \beta I. \tag{3.2}$$

Therefore, we can write the model as $\frac{dI}{dt} = g(I) = \alpha I(N - I) - \beta I$. Though this is simplified, the model is still nonlinear. It is common practice in modeling, however, to linearize a model. That is provide an approximation of the model. To apply the method, we must first understand a linear model. The following example provides us with a platform onto which we can apply our techniques of analysis.

Let us use some numbers. Suppose 30 individuals become infected on day $d = 1$ and the length of the infection is 14 days. On day 14, we expect all 30 infected individuals will recover and become susceptible one again. We would expect $\frac{1}{14}$ of the individuals to recover each day. This means we would expect approximately 2 individuals to recover each day. Thus, the recovery rate β is $\frac{1}{14}$ per day and β has units of $\left(\frac{1}{\text{time}}\right)$.

To determine the units for α, let us consider the definition of the infection rate. It is considered the product of the number of contacts an individual has per unit of time and the probability of an infected individual infecting a susceptible divided by the total population. When multiplied by S, we have the probability that an individual will infect another individual. Then, multiplying by I, we have the number of individual infected by one unit of time.

For example, if we have 30 susceptible humans and introduced 5 infected individuals into the system. If an individual makes 1.5 contacts per day and for every 4 individuals in contact with an infected individual, 3 of them become infected, α will be defined as follows.

$$\begin{aligned}\alpha &= \left(\frac{1.5 \text{ contacts}}{\text{individual . day}}\right)\left(\frac{0.75 \text{ infected individuals}}{\text{contact}}\right)\left(\frac{1}{35 \text{ individuals}}\right) \\ &= 0.032\left(\frac{1}{\text{individual . day}}\right)\end{aligned}$$

So, if we have 30 susceptible individuals come into contact with 5 infected individuals, then approximately 5 individuals will become newly infected.

$$\begin{aligned}\alpha SI &= \left(\frac{0.032}{\text{individual . day}}\right)\left(30 \text{ susceptible individuals}\right)\left(5 \text{ infected individuals}\right) \\ &= 5\left(\frac{\text{individuals}}{\text{day}}\right)\end{aligned}$$

This means that the change of S or I due to infection is approximately $5\left(\frac{\text{individuals}}{\text{day}}\right)$.

Example 2. *A beaver farm*
In this example we study the population dynamics of beaver in a farm. We know that beavers have an inflow from birth and two outflows, one from death and one from harvesting.

change in N = gain from birth - loss to death - loss to harvesting

Let $N(t)$ denote the size of the beaver population at any time t. To derive to model we need to replace the contributions to the change the size of the beaver population. We will assume that both the birth and death rates are constant, that is a set number of beaver will enter and leave the system in a given time period. For the farmer to make money, P beavers must be harvested (and sold) every week. We represent the rate of change of N as $\frac{dN(t)}{dt}$ and replace "gain from birth" with $bN(t)$ as well as "loss to death" with $mN(t)$. Lastly, "loss to harvesting" is represented by P, a fixed number per year. The following model can be formed from the above substitutions. Thus, the rate of change from birth is proportional to the number of beavers and the constant of proportionality is b. Similarly, the rate of change from death is proportional to the number of beavers with a constant of proportionality, m (Fig 3.3).

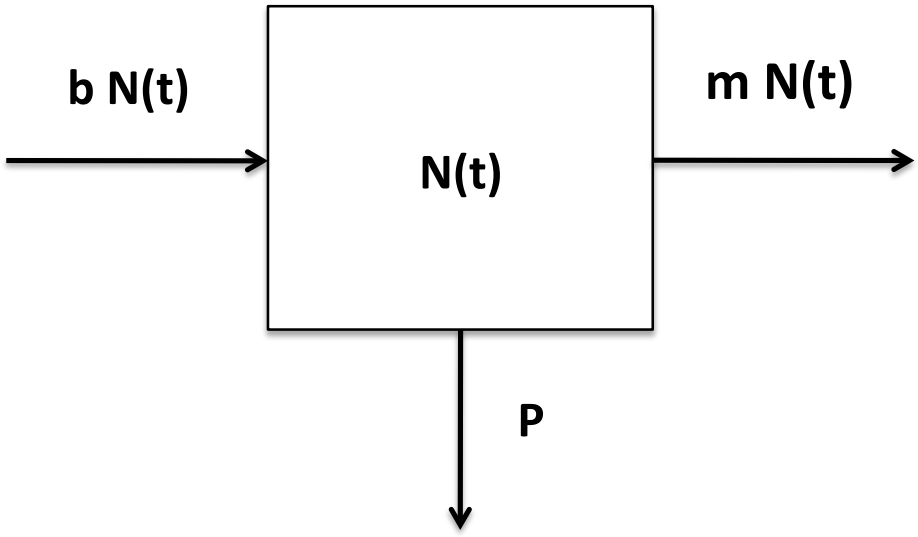

Figure 3.3: Compartment model describing beaver farm

Tracking the inflows and outflows, we can derive the following differential equation describing the population.

$$\frac{dN(t)}{dt} = bN(t) - mN(t) - P = (b-m)N(t) - P \tag{3.3}$$

Let us use some numbers. Suppose we have 300 beavers on the farm on day $t = 1$. The length of time for the birth of beavers is approximately 110 days. This means that on day 110, a new beaver enters the system. Approximately, 3 beavers are born each day in the given system. Thus, the birth rate, b, is $\frac{1}{\text{time}}$. Similarly, the length of time for the death of a beaver is approximately 15 years or 5,500 days. This means that the death rate m of beavers is $\frac{1}{5{,}500 \text{ days}}$ and is therefore very small relative to the birth rate. Lastly, the number of beavers sold per day is 5. This means that $P = \frac{5 \text{ beavers}}{\text{day}}$. Thus, the death rate is relatively small compared to the harvesting rate. The change of $N(t)$ from "loss" is due harvesting, not natural death.

This is a linear first order differential equation. Understanding the above linear example assists us with the linearization of a nonlinear continuous time model. This linearization is crucial to

successfully conduct a stability analysis.

Example 3. *SIRS model [12, pp.1-3]*
The SIRS model is used to describe the amount of susceptible, infected, recovered individuals in a population. This model is appropriate under the following assumptions: the population must be considered fixed/constant and the only way an individual can leave the susceptible group is to become infected. The only way an individual can leave the infected group is to recover from the disease/infection. Once an individual has recovered, the individual receives immunity. There is no inherited immunity and the member of the population mixes homogeneously (have similar interactions) with all other individuals. $S(t)$ is the number of susceptible individuals at time t, $I(t)$ is the number of infected individuals at time t and $R(t)$ is the number of recovered individuals at time t. N is the total population size and thus $N = S + I + R$. The total change in the population at any time is zero. Thus,

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0. \tag{3.4}$$

This implies a closed system. In this model, once an individual is infected and reaches the recovered class the individual acquires immunity. That is, the recovered do not become susceptible. The representation of the model is given in Figure 3.4 where q and r are positive constants such that q is the per capita infection rate and r is the per capita recovery rate. We define $\frac{1}{a}$ is the average length of time a recovered individual has immunity from the disease. Therefore, a is the rate that recovered individuals will return to the susceptible class.

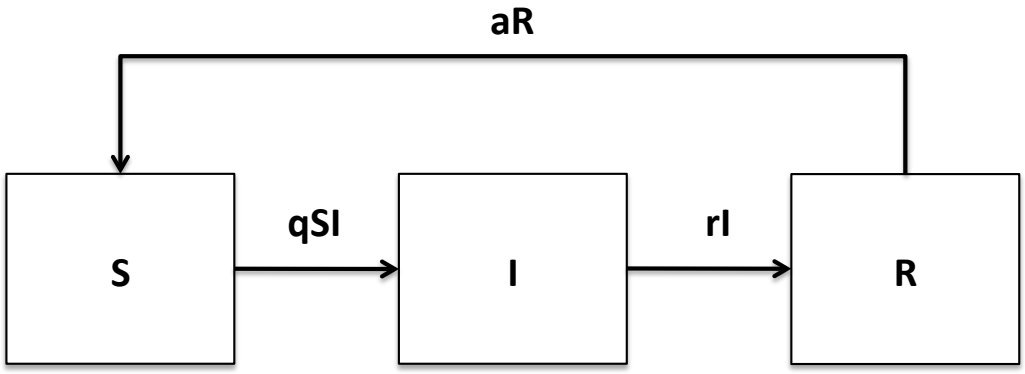

Figure 3.4: SIRS model

The number of individuals that become infectious depends on the size of the susceptible class and the number of individuals that recover only depends on the size of the infectious class. Below is the system of ordinary differential equations used to describe the biological system.

Table 3.1: SIS State Variables

$S(t)$	susceptible individuals
$I(t)$	infectious individuals
$R(t)$	recovered individuals

Table 3.2: SIS Parameters

q	infection rate $\left(\frac{1}{\text{individual . time}}\right)$
r	recovery rate $\left(\frac{1}{\text{time}}\right)$
a	loss of immunity rate $\left(\frac{1}{\text{time}}\right)$

$$\frac{dS}{dt} = -qSI + aR \tag{3.5}$$
$$\frac{dI}{dt} = qSI - rI \tag{3.6}$$
$$\frac{dR}{dt} = rI - aR \tag{3.7}$$

This example has one infected class. The next example incorporates two infected/diseased classes that are differentiated by the stage of infection.

Example 4. *SEIRS Model [10, p. 281]*
The SEIRS model is a modified version of the SIRS model. The model has similarities to Example 3. Both models have compartments for susceptible, infected, and recovered individuals , however, the SEIRS model has an additional infectious class. That is, an exposed or latently infected class represented by E. This means that individuals in this class are infected but not infectious. They can not spread infection to others through contact. In addition, the model does not have a constant population. This means that $\frac{dN}{dt} \neq 0$. The change in the total population is proportional to the birth rate of susceptible individuals and the death of the total population.

$$\frac{dN}{dt} = \lambda - \mu N$$

The model is described visually through Figure 2.5. The time spent latently infected is $\frac{1}{k}$, where k is the progression rate from exposed to infected. β is the effective contact rate and Λ is the recovery rate. $\frac{1}{r}$ is the duration of immunity before the individual becomes susceptible again.

The following equations represent the given system.

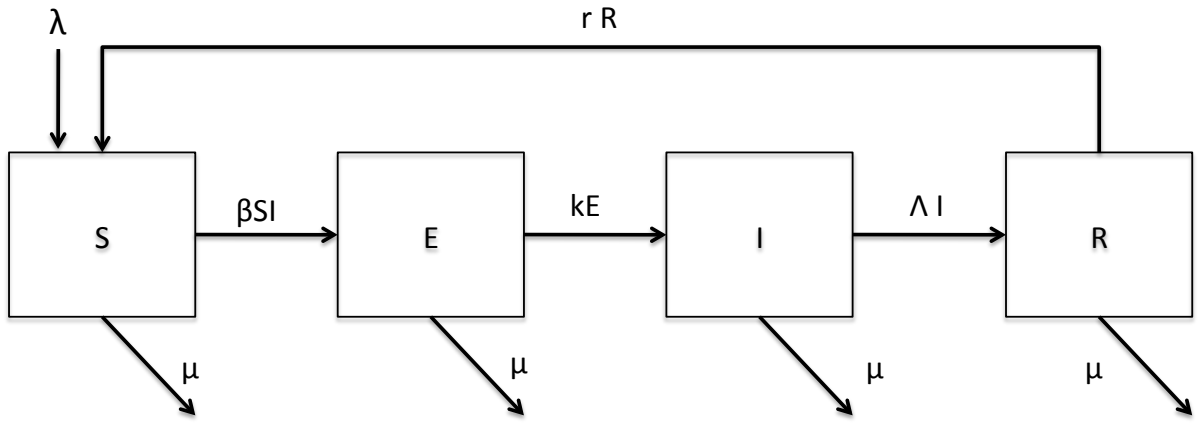

Figure 3.5: SEIRS model

$$\frac{dS}{dt} = \lambda - \beta SI + rR - \mu S \tag{3.8}$$

$$\frac{dE}{dt} = \beta SI - (\mu + k)E \tag{3.9}$$

$$\frac{dI}{dt} = kE - (\mu + \Lambda)I \tag{3.10}$$

$$\frac{dR}{dt} = \Lambda I - \mu R - rR \tag{3.11}$$

Table 3. Parameters	
λ	birth rate $\left(\frac{\text{individual}}{\text{time}}\right)$
β	infection rate $\left(\frac{1}{\text{individual . time}}\right)$
k	transition rate $\left(\frac{1}{\text{time}}\right)$
Λ	recovery rate $\left(\frac{1}{\text{time}}\right)$
r	loss of immunity rate $\left(\frac{1}{\text{time}}\right)$
μ	mortality rate $\left(\frac{1}{\text{time}}\right)$

The preceding examples will be revisited when discussing equilibrium points and stability.

Chapter 4

Important Mathematical Concepts & Applications

4.1 Equilibrium Points and Behavior of Linear Systems

In this section, we introduce some mathematical concepts that will be used to evaluate and analyze the models previously described. In mathematical modeling, long-term behavior of solutions to models is a main point of interest. Consider the following generic dynamical system.

Let $\frac{d\mathbf{X}}{dt} = f(\mathbf{X})$ where $\mathbf{X} = (X_1, \cdots, X_n)$ and

$$\begin{cases} \frac{dX_1}{dt} = f_1(X_1, X_2, \cdots, X_n) \\ \\ \frac{dX_2}{dt} = f_2(X_1, X_2, \cdots, X_n) \\ \\ \vdots \\ \\ \frac{dX_n}{dt} = f_n(X_1, X_2, \cdots, X_n) \end{cases} \tag{4.1}$$

is an n-dimensional system of differential equations.

Definition 1. Equilibrium point. *[4, p.5] An equilibrium point of the system of differential equations (3.1) is the value of the solution that is unchanging in time. Therefore,* $\mathbf{X}^* = (X_1^*, X_2^*, \cdots, X_n^*)$ *is an equilibrium point if* $f(X_1^*, X_2^*, \cdots, X_n^*) = 0$.

A solution that begins at an equilibrium point will remain at $\mathbf{X}^*$, since $X_1, X_2, \cdots, X_n$ will not change. Determining the stability of equilibria gives information about the long term behavior of the model.

Definition 2. Stable equilibrium point. *[4, p.84]* An equilibrium point $\mathbf{X}^*$ is a *stable equilibrium point or a sink* if any solution with initial condition sufficiently close to $\mathbf{X}^*$ is asymptotic to $\mathbf{X}^*$ as t increases. That is, if solutions "near" $\mathbf{X}^*$ approach $\mathbf{X}^*$ in time, then $\mathbf{X}^*$ is *locally stable* .

Definition 3. Unstable equilibrium point. *[4, p.84]* An equilibrium $\mathbf{X}^*$ is an *unstable equilibrium point or a source*if all solutions that start sufficiently close to $\mathbf{X}^*$ is asymptotic to $\mathbf{X}^*$ as t decreases. That is, if solutions "near" $\mathbf{X}^*$ diverge from $\mathbf{X}^*$ in time, it is *locally unstable.*

Theorem 1. *[4, pp.290, 305] Suppose $\mathbf{X}^*$ is an equilibrium point of the differential equation $\frac{d\mathbf{X}}{dt} = f(\mathbf{X})$ where f is a continuously differentiable function. Then,*

- if $f'(\mathbf{X}) < 0$, then $\mathbf{X}^*$ is a sink.
- if $f'(\mathbf{X}) > 0$, then $\mathbf{X}^*$ is a source.
- if $f'(\mathbf{X}) = 0$, then we need additional information to determine the type of $\mathbf{X}^*$.

Theorem 2. *[4, pp. 284,299]*
For a linear system of differential equations:

- *If the eigenvalues of the matrix all have negative real parts, then the equilibrium is a sink. If these eigenvalues are complex, then the sink is a spiral sink.*
- *If the eigenvalues of the matrix all have positive real parts, then the equilibrium is a source. If these eigenvalues are complex, then the source is a spiral source.*
- *If the eigenvalues of the matrix have both negative and positive real parts, then the equilibrium is a saddle.*

We can apply the above definitions and theorem to Example 4.1, our beaver problem in Section 3.2. First, we must determine the solution of the model. The particular solution can be found by determining the equilibrium solutions (2.5). That is

$$\frac{dN(t)}{dt} = (b-d)N^* - P = 0.$$

This implies that $N^* = \frac{P}{b-d}$. If we let the birth rate $b = 0.4$, the death rate $d = 0.015$ and $P = 150$, then we get the equilibrium solution $N^* = 6000$.

The general solution to the homogeneous equation

$$\frac{dN(t)}{dt} = (b-d)N(t)$$

is given by $N(t) = Ce^{(b-d)t}$ where C is an arbitrary constant that can be found by applying the initial conditions. We combine the particular solution of the inhomogeneous equation and the general solution of the homogeneous equation to get the following equation.

$$N(t) = Ce^{rt}, \qquad N(0) = 6000 \Rightarrow C = 6000$$

$$N(t) = 6000e^{rt}.$$

Theorem 3. *Assuming the the beaver birth rate is greater than the death rate* $(b > d)$, $N^* = \frac{P}{b-d}$ *is unstable.*

Proof. Let $N^* = \frac{P}{b-d}$ be the equilibrium solution of $f(N) = (b-d)N - P$. Since the derivative $f'(N) = b - d$, we know that $b > d$ and therefore $f'(N) > 0$. According to Theorem 1, N^* is unstable. □

A graph of this solution is also shown in Figure 4.1. Note that an initial population larger than the equilibrium population makes the population grow while an initial population smaller than the equilibrium population makes the population decrease in size. To the farmer, this means that it is very important that he/she monitors the size of the population and tries to keep it at 6000. Note in a real biological setting, birth and death rates vary. If the farmer monitors the birth and death rates weekly, this model could be used to compute how many beavers can be sold to keep a manageable population.

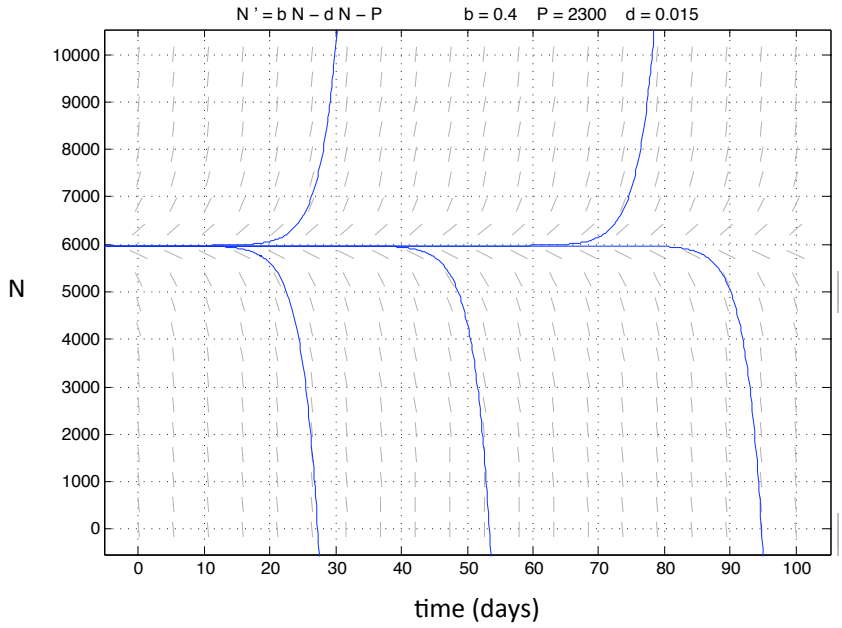

Figure 4.1: A beaver solution

4.2 Stability of Nonlinear Systems

The following examples and analysis are in reference to nonlinear systems.

Let us look at Example 1, our SIS model. Using (2.3), which we redefined as $g(I) = \alpha I(N-I) - \beta I$, we compute the equilibrium points defined as $g(I^*) = 0$. This calculation results in the trivial solution ($I^* = 0$) and the non-trivial solution $I^* = N - \frac{\beta}{\alpha}$.

Theorem 4. *Assuming $\alpha > \beta$, that is the infection rate is greater than the recovery rate, $I^* = N - \frac{\beta}{\alpha}$ is a sink.*

Proof. Let $I^* = N - \frac{\beta}{\alpha}$ be the non-trivial equilibrium point of the model $g(I) = \alpha I(N - I) - \beta I$. Taking the derivate of $g(I)$, we find that $g^{'}(I) = \alpha N - 2\alpha I - \beta$. Solving for the derivative at I^*, we find that $g^{'}(I^*) = \beta - \alpha N$. Given our assumption that $\alpha > \beta$, $g^{'}(I^*) < 0$ and therefore a stable sink. □

After graphing the solution Figure 4.2, we confirmed that $I^* = N - \frac{\beta}{\alpha}$ is stable as long as $\beta < N\alpha$.

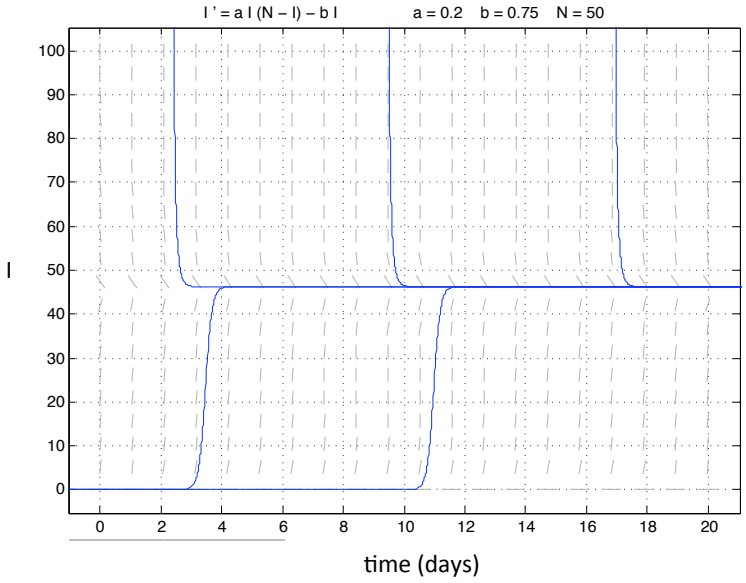

Figure 4.2: SIS solution

Definition 4. Global Stability. *[4, p.84] An equilibrium point is globally stable if all solutions converge to the equilibrium as $t \to \infty$.*

It follows that global stability implies local stability. To determine the local stability of the equilibrium point under analysis, we linearize the system.

For the system of equations in (3.1), the Jacobian matrix is defined to be the following $n \times n$ matrix.

$$\mathrm{J} = \begin{pmatrix} \frac{\partial f_1}{\partial X_1} & \frac{\partial f_1}{\partial X_2} & \cdots & \frac{\partial f_1}{\partial X_n} \\ \frac{\partial f_2}{\partial X_1} & \frac{\partial f_2}{\partial X_2} & \cdots & \frac{\partial f_2}{\partial X_n} \\ \vdots & \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial X_1} & \frac{\partial f_n}{\partial X_2} & \cdots & \frac{\partial f_n}{\partial X_n} \end{pmatrix}.$$

J is the matrix that represents the linearized system of (3.1)

Example 5. *[4, pp. 277-278]*

Consider the system

$$\frac{d\mathbf{Y}}{dt} = \mathbf{GY} \quad \textit{where} \quad \mathbf{G} = \begin{pmatrix} 8 & -11 \\ 6 & -9 \end{pmatrix}.$$

First, we compute the eigenvalues of $\mathbf{G}$ by finding the roots of the characteristic polynomial.

$$det(\mathbf{G} - \lambda I) = det \begin{pmatrix} 8-\lambda & -11 \\ 6 & -9-\lambda \end{pmatrix} = (8-\lambda)(-9-\lambda) + 66 = \lambda^2 + \lambda - 6 = 0.$$

The roots of this equation are $\lambda_1 = -3$ and $\lambda_2 = 2$, the eigenvalues of $\mathbf{G}$.

Next, we compute the eigenvectors. For $\lambda_1 = -3$, the equations that give the eigenvectors (x_1, y_1) are

$$\begin{cases} 8x_1 - 11y_{11} = -3x_1 \\ 6x_1 - 9y_{11} = -3y_1 \end{cases}$$

This means that any nonzero vector that lies along the line $y = x$ in the plane is an eigenvector for $\lambda_1 = -3$. We choose $V_1 = (1, 1)$. Therefore the solution is

$$\mathbf{Y_1(t)} = e^{-3t}\mathbf{V_1}$$

is a straight-line solution lying on the line $y = x$. As t increases, the solution approaches the origin.

Following similar steps, we can compute the eigenvectors that correspond to $\lambda_2 = 2$ that lie along the line $6x - 11y = 0$, specifically $\mathbf{V_2} = (11, 6)$. We get a straight-line solution

$$\mathbf{Y_2(t)} = e^{2t}\mathbf{V_2}$$

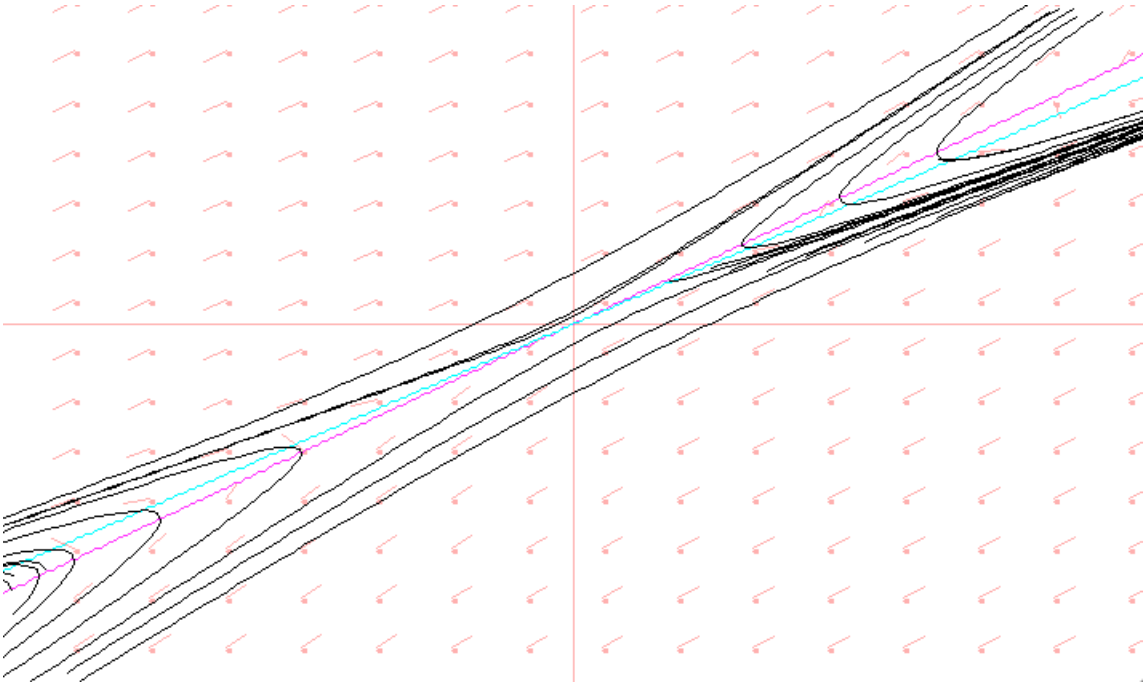

Figure 4.3: Saddle

that diverges away from the origin as t increases. Therefore, the general solution is

$$\mathbf{Y(t)} = k_1 e^{-3t}\mathbf{V_1} - k_2 e^{2t}\mathbf{V_2}.$$

where the straight-line solutions produce a phase portrait that displays a saddle (Fig 4.3).

Theorem 5. *[4, p. 323] Let $(X_1^*, X_2^*, \cdots, X_n^*)$ be an equilibrium point of an n-dimensional system of differential equations. If the eigenvalues of the Jacobian matrix J of this system evaluated at $(X_1^*, X_2^*, \cdots, X_n^*)$ all have negative real parts, then the equilibrium point is locally stable. If at least one of the characteristic roots has a positive real part, then the equilibrium point is unstable.*

The eigenvalues of the Jacobian matrix of a two-dimensional system are the roots of a quadratic characteristic equation. The following theorem specifies these conditions with respect to Theorem 5.

Theorem 6. *[4, p. 323] For a two-dimensional system of differential equations, let $\tau = tr(J) = a_{11} + a_{22}$ and $\Delta = det(J) = a_{11}a_{22} - a_{12}a_{21}$.*

1. *If $\Delta < 0$, then the fixed point is a saddle.*
2. *If $\Delta > 0$ and $\tau < 0$, then the fixed point is a sink.*

To clarify, Theorem 6 is utilized with two-dimensional nonlinear systems. Another useful calculation for infection models is the reproductive number, R_0, which is used to determine the stability of a disease.

Both the sink and saddle are different types of fixed points of two-dimensional systems dictated by the sign of $\tau = tr(J)$ and $\Delta = det(J)$ of the system's Jacobian, J. The $\tau\Delta$ - plane is determined by the graph of the parabola $\Delta = \frac{\tau^2}{4}$ on the $\tau\Delta$-plane. If $\tau^2 - 4\Delta = 0$ or if $\Delta = \frac{\tau^2}{4}$, we have repeated eigenvalues. Points above the parabola ($\Delta > \frac{\tau^2}{4}$) correspond to systems with complex eigenvalues. Points below the parabola ($\Delta < \frac{\tau^2}{4}$) correspond to systems with real eigenvalues. The following figure summarizes the different types of fixed points depending on specific conditions.

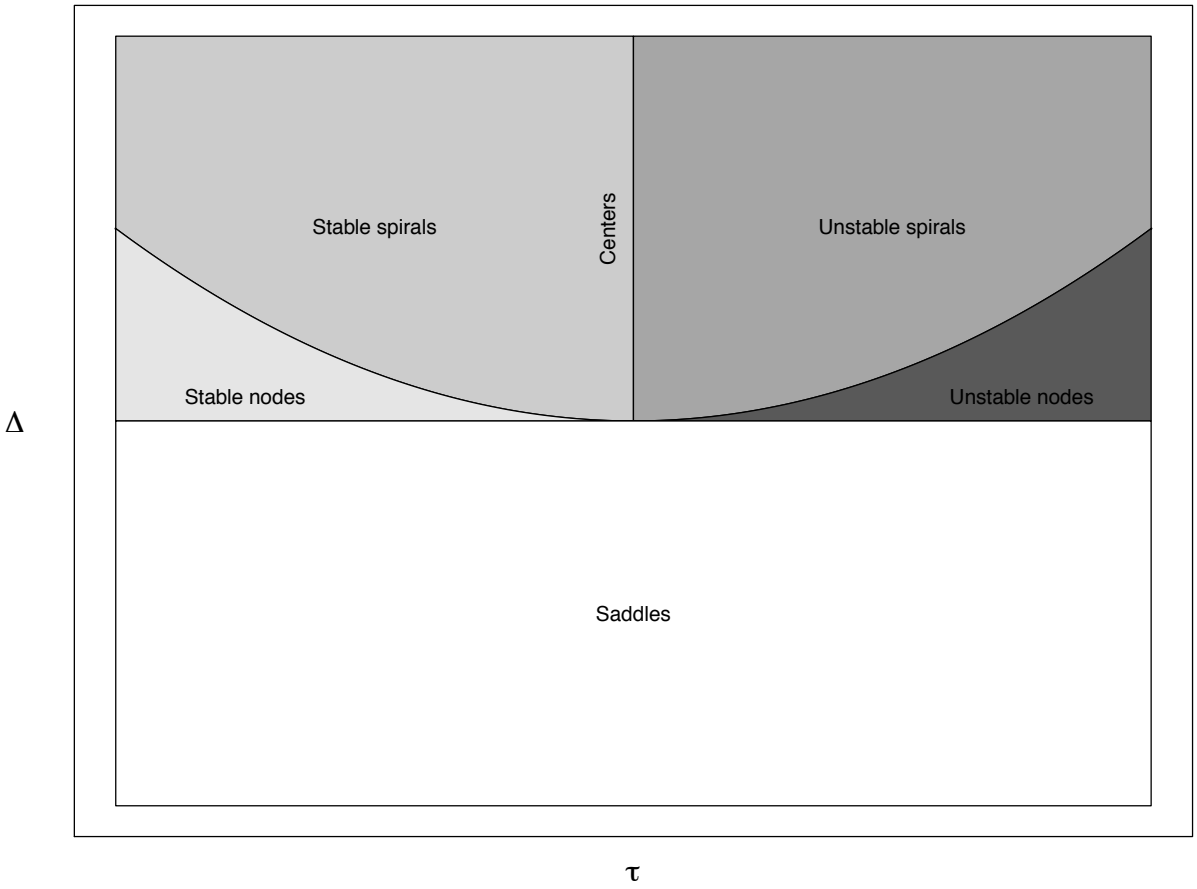

Figure 4.4: Trace-Determinant Plane

4.3 The Basic Reproductive Number : R_0

For epidemiology models, a quantity R_0, is derived to assess the stability of the disease free equilibrium. R_0 represents the number of secondary cases that are caused by a single infectious case introduced into a completely susceptible population [1]. When $R_0 < 1$, if a disease is introduced, there are insufficient new cases per case and the disease cannot invade the population. When $R_0 > 1$, the disease will become endemic.

Definition 5. Reproductive Number. *[11, p. 1]*
The reproductive number, R_0, is generally defined to be the number of secondary infections caused by one infectious person during the course of an infection in a susceptible population.

There are many interpretations but commonly it is a dimensionless number that takes into account transmissibility (the probability of infection given contact), the average rate of contact and the duration of infection. That is,

$$R_0 \propto \left(\frac{infection}{contact}\right)\left(\frac{contact}{time}\right)\left(\frac{time}{infection}\right) \propto (infection\ rate)(time\ spent\ infecting).$$

In general, $R_0 = \tau\ \bar{c}\ d$, where τ is transmissibility, $\bar{c}$ is the average rate of contact between a susceptible and an infected individuals and d is the duration of infection.

Theorem 7. *[14, p.2] The reproductive number of the SIRS model is $R_0 = \frac{qN}{r}$.*

Proof. Using the definitions and theorems above, we can conduct a stability analysis on Example 3. First, we must do a quick calculation of the reproductive number for the SIRS model. We know from Definition 5 that R_0 is essentially the infection rate multiplied by the time of infection. For our SIRS model, we assume a disease-free state. This means that $R_0 = 0$ and $I(0) << 1$ and therefore $N \approx S$. Thus,

$$R_0 = \frac{qN}{r} \tag{4.2}$$

□

Theorem 8. *[14, pp.2-5] The equilibrium points of the SIRS model are the disease free equilibrium $(N, 0, 0)$ and the endemic equilibrium point (I^*, R^*), where $I^* = \frac{qN-r}{q(1+\frac{r}{a})}$ and $R^* = \frac{r}{a}\frac{qN-r}{q(1+\frac{r}{a})}$. (I^*, R^*) exists if $R_0 > 1$.*

Proof. To determine the equilibrium points for the given system of equations, we set the system of equations equal to zero. For the disease-free equilibrium, we assume that the diseased classes are zero and $S = N$. To find (I^*, R^*), we reduce the system to two equations using a substitution based on our initial assumption $(S = N - I - 0)$. In doing so, the following system results.

$$\frac{dI}{dt} = q(N - r)I - qI^2 - qRI \tag{4.3}$$
$$\frac{dR}{dt} = rI - aR \tag{4.4}$$

Next, we set (3.3), (3.4) equal to zero and solve for R^*.

$$R^* = \frac{rI^*}{a} \tag{4.5}$$

Then substitution (3.5) into (3.3), we find the following expression for I^* and R^*.

$$I^* = \frac{qN - r}{q(1 + \frac{r}{a})} \tag{4.6}$$

$$R^* = \frac{r}{a}\frac{qN - r}{q(1 + \frac{r}{a})} \tag{4.7}$$

Given these equations and the fact that the populations and parameters are positive, (I^*, R^*) exists only if $qN - r > 0 \implies \frac{qN}{r} > 1$.

Substituting (3.2) into (3.6) & (3.7), we determine the following equations.

$$I^* = \frac{r(R_0 - 1)}{q(1 + \frac{r}{a})} \tag{4.8}$$

$$R^* = \frac{r^2}{a}\frac{R_0 - 1}{q(1 + \frac{r}{a})} \tag{4.9}$$

It is known that r, a, N and $q > 0$. Therefore the reproductive number $R_0 > 0$ and the point exists if $R_0 > 1$. □

To determine the local stability of the equilibrium points, we apply the linearization principle and calculate the Jacobian matrix J for this system. Let $\frac{dI}{dt} = f_1$ and $\frac{dR}{dt} = f_2$. Then taking the partial derivatives of the two-dimensional system, we get the following entries of the Jacobian matrix J.

$$a_{11} = \frac{\partial f_1}{\partial I} = qN - r - qR - 2qI \quad a_{12} = \frac{\partial f_1}{\partial R} = -qI$$

$$a_{21} = \frac{\partial f_2}{\partial I} = r \qquad\qquad a_{22} = \frac{\partial f_2}{\partial R} = -a$$

We can determine the stability for both the disease-free and endemic equilibria.

(1) Disease-Free Equilibrium: $I^* = R^* = 0$

Theorem 9. *[6, p.2] The disease-free equilibrium of the SIRS model is stable if* $R_0 < 1$ *and unstable if* $R_0 > 1$.

Proof. The Jacobian J of the SIRS model at the disease-free equilibrium has the following entries.

$$a_{11} = \frac{\partial f_1}{\partial I} = qN - r \quad a_{12} = \frac{\partial f_1}{\partial R} = 0$$

$$a_{21} = \frac{\partial f_2}{\partial I} = r \qquad a_{22} = \frac{\partial f_2}{\partial R} = -a$$

Using Theorem 6, we calculate both the $tr(J)$ and the $det(J)$.

$$tr(J) = qN - r - a \qquad det(J) = -qaN$$

We can substitute $R_0 = \frac{qN}{r}$, which results in $tr(J) = r(R_0 - 1) - q$ and $det(J) = -ar(R_0 - 1)$. This means that when $R_0 < 1$, $tr(J) < 0$ and $det(J) > 0$. According to Theorem 6, the above conditions dictate that the equilibrium is a sink and therefore stable. If $R_0 > 1$, $det(J) < 0$ and the equilibrium is a saddle and therefore unstable. □

(2) Endemic Equilibrium: $(I^*, R^*) \neq (0, 0)$

Theorem 10. *[6, p.3] The endemic equilibrium point is stable if* $R_0 > 1$.

Proof. The Jacobian J of the SIRS model at the endemic equilibrium has the following entries.

$$a_{11} = qN - r - \frac{r}{a}\frac{qN - r}{1 + \frac{r}{a}} - 2\frac{qN - r}{1 + \frac{r}{a}} \qquad a_{12} = -\frac{qN - r}{1 + \frac{r}{a}}$$

$$a_{21} = r \qquad a_{22} = -a$$

Next, we determine the $tr(J)$ and the $det(J)$. Substituting the above expressions, we find the following terms for both quantities.

$$tr(J) = a_{11} + a_{22} = qN - r - \frac{r}{a}\frac{qN - r}{1 + \frac{r}{a}} - 2\frac{qN - r}{1 + \frac{r}{a}} - a \tag{4.10}$$

$$det(J) = a_{11}a_{22} - a_{12}a_{21} = -qNa + ra + r\frac{qN - r}{1 + \frac{r}{a}} - 2a\frac{qN - r}{1 + \frac{r}{a}} \tag{4.11}$$

Substituting $R_0 = \frac{qN}{r}$ into 3.8 and 3.9, the following expressions were found.

$$tr(J) = \frac{-r(R_0 - 1) - a - r}{1 + \frac{r}{a}} \tag{4.12}$$

$$det(J) = \frac{ra(R_0 - 1)}{1 + \frac{r}{a}} \tag{4.13}$$

Since all parameters are positive, if $R_0 > 1$, $tr(J) < 0$, and $det(J) > 0$. According to Theorem 6, the endemic equilibrium point (I^*, R^*) is a sink and therefore stable. □

The calculation of the reproductive number and the stability analysis of Example 3 is relatively simple. A factor that contributes to this simplicity is that the model has only one diseased class. Other models have multiple levels of infection and different diseased classes. This fact complicates the reproductive number calculation. For a systematic way to calculate the secondary infections produced by an infection, we look to the *Next-Generation Operator*, a method that utilizes the spectral radius of a transmission matrix.

Chapter 5

Defining R_0 : The Next-Generation Operator

The basic reproductive number, R_0, as defined in Definition 5, Section 4.3, is applicable for a single "typical" infection. R_0 is typically found through the study and calculation of the eigenvalues of the Jacobian at the disease-free equilibrium. To account for multiple types of infected individuals, a different R_0 must be used. That is a reproductive number that describes a generation of infection. The *Next-Generation Operator* approach allows us to do this. The next-generation operator is given by the transmission matrix and R_0 is defined as the spectral radius of the transmission matrix.

Definition 6. Transmission matrix. *[10, pp.93-94]*
For n infectious populations, the transmission matrix $\mathbf{T}$ is an $n \times n$ matrix whose entries t_{ij} are the number of infections caused in a population i by an infective individual in population j.

Definition 7. Spectral radius. *[11, p. 94]*
The spectral radius of a matrix A, denoted $\rho(A)$, is defined to be the maximum of the absolute value of the eigenvalues of the matrix.

So for an $n \times n$ matrix with eigenvalues $\lambda_1, \lambda_2, \lambda_3, \ldots,$

$$\rho(A) = \max\{|\lambda_i| : 1 \leq i \leq n\}. \tag{5.1}$$

5.1 What is a Generation?

A generation in an infection model is a wave of secondary infection that flows from each previous infection [12]. In general, R_i denotes the reproduction number of the ith generation. The first generation of an epidemic is all the secondary infections that result from infectious contact with the index case, or generation zero. Thus, R_0 is the number of infections generated by generation zero. Calculation of the reproductive number, R_0, is evaluated at a disease-free state. That is, the infected/diseased classes are zero.

5.2 Method for determining the transmission matrix

We define the next-generation matrix or the transmission matrix as the square matrix $\mathbf{T}$ in which the ijth element of $\mathbf{T}$, t_{ij} is the expected number of infections of type i caused by a single infected individual of type j. The basic reproductive number is the *spectral radius* of $\mathbf{T}$, which is known as the dominant/maximum eigenvalue of $\mathbf{T}$. A useful property of $\mathbf{T}$ is that this matrix is non-negative. It is guaranteed that there will be a single, unique eigenvalue which is positive, real, and strictly greater than all the others. This eigenvalue is R_0.

To provide further detail of the method, consider the next-generation matrix $\mathbf{T}$ is defined as $\mathbf{T} = FV^{-1}$, where

$$F = \left[\frac{\partial F_i(x_0)}{\partial x_j}\right] \tag{5.2}$$

$$V = \left[\frac{\partial V_i(x_0)}{\partial X_j}\right] \tag{5.3}$$

Here, F_i describes the new infections, while V_i describes transfers of infections from one compartment to another. x_0 is the disease-free equilibrium state. The spectral radius, $\rho(\mathbf{T}) = \rho(FV^{-1})$, is the reproductive number R_0.

Example 6. To best illustrate this method, we will apply it to Example 4, our SEIRS model. We assume a disease-free state where $S = N$. We also assume that there is change in the total population. Thus, $N = \frac{\lambda}{\mu}$. This is an appropriate model for application of the next-generation operator, since there are two infected classes, E and I. To calculate the transmission matrix T, we must first identify the ways in which (1) new infections are 'born' and (2) individuals can move between compartments. In this example, there are two infective classes but one way for new infections to arise. If we look at the equations for E and I compartments, (2.9) and (2.10), we can represent the two-dimensional system in vector form and then separate the system into two matrices. F_i accounts for the new infections of the system and V_i accounts for the outflows and transfers from one compartment to another. We can deduce that the only source of new infection is from newly infected susceptible individuals represented by βSI. We can substitute our assumption for S to get $\frac{\beta\lambda I}{\mu}$.

$$\begin{pmatrix} \frac{dE}{dt} \\ \\ \frac{dI}{dt} \end{pmatrix} = \begin{pmatrix} -(\mu+k)E + \frac{\beta\lambda I}{\mu} \\ \\ kE + (\mu+\Lambda)I \end{pmatrix} \tag{5.4}$$

$$= \begin{pmatrix} \frac{\beta\lambda I}{\mu} \\ \\ 0 \end{pmatrix} - \begin{pmatrix} (\mu+k)E \\ \\ -kE + (\mu+\Lambda)I \end{pmatrix} \tag{5.5}$$

$$= F_i - V_i. \tag{5.6}$$

Thus, taking the partial derivatives of both F_i and V_i to get $\mathbf{F}$ and $\mathbf{V}$.

$$\mathbf{F} = \begin{pmatrix} 0 & \frac{\beta\lambda}{\mu} \\ 0 & 0 \end{pmatrix} \tag{5.7}$$

$$\mathbf{V} = \begin{pmatrix} (\mu + k) & 0 \\ -k & (\mu + \Lambda) \end{pmatrix}. \tag{5.8}$$

Next, we determine the inverse of $\mathbf{V}$, $\mathbf{V^{-1}}$and then calculate the transmission matrix $\mathbf{T}$.

$$\mathbf{V^{-1}} = \begin{pmatrix} \frac{1}{(\mu+k)} & 0 \\ \frac{k}{(\mu+k)(\mu+\Lambda)} & \frac{1}{(\mu+\Lambda)} \end{pmatrix}.$$

Thus, the transition matrix $\mathbf{T} = \mathbf{FV^{-1}}$ is given by the following matrix.

$$\mathbf{T} = \begin{pmatrix} \frac{-\beta\lambda k}{\mu(\mu+k)(\Lambda+\mu)} & \frac{\beta\lambda}{\mu(\Lambda+\mu)} \\ 0 & 0 \end{pmatrix}.$$

R_0 is the leading or maximum eigenvalue of the the transition matrix. This is simple, since we are dealing with a 2×2 matrix.

$$R_0 = \frac{\beta\lambda k}{\mu(k+\mu)(\Lambda+\mu)}. \tag{5.9}$$

It is important to note that the reproductive number in this case is the product of the rate of new exposures and new infections. This will be important to recall when calculating the reproduction number of the guinea worm model.

Part III

Guinea Worm Disease

Chapter 6

The Biology of Guinea Worm Disease

As previously discussed, GWD affects populations that are in contact with drinking water containing guinea worm larvae. As a result of improper filtration and water collection, this disease afflicts communities in remote parts of Africa that have contaminated drinking water sources. It is a vector transmitted infection in which copepods serve as an intermediary stage in the infection process. Infection is transferred through the ingestion of guinea worm larvae. The parasite that causes this disease is the nematode *Dracunculus medinensis* [6]. The nematode *D. medinensis* belongs to the order of Spirurida, which are tissue parasites that produce eggs containing larvae or release free larvae [14] (Fig 6.1). These free larvae require arthropods/copepods as intermediate hosts. Averaging 1 meter in length and only 1-2mm thick, the mature female guinea worm is considered one of the longest nematodes (Fig 6.2). These macroparasites fester in the abdominal tissues of the human host and then migrate to the skin's surface, forming a painful blister.

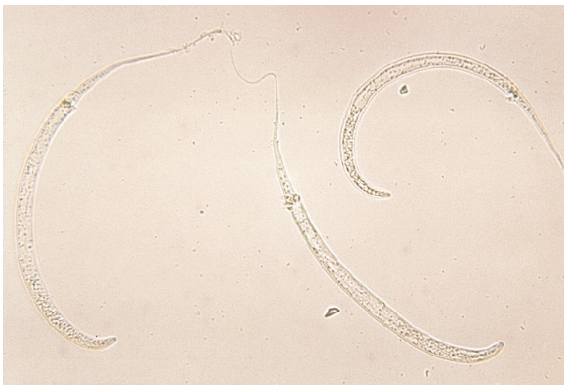

Figure 6.1: Guinea worm larvae [16].

Figure 6.2: Guinea worm in vial [8].

The life cycle of the parasite has three stages, one occurring in the water, one in the copepod, and one in the human (Fig 6.3). Infection is only caused by female worms. The path of infection is described as follows. The human drinks unfiltered well or pond water containing copepods that are infected with mature larvae (Fig 6.6). After ingestion, gastric juices in the human digest the infected copepod and worm larvae are released. Movement of the larvae to abdominal tissues occurs so they can grow and mate. Next, maturation occurs and female worms migrate towards skin's surface approximately 9-11 months after infection [6]. As a result, formation of blister occurs.

With time, the blister ruptures and the emerging female worm releases eggs into the water source, later hatching and becoming immature stage 1 larvae. Larvae are ingested by copepod and resist digestion. After 2 weeks, (two molts) stage 3 larvae have developed into infective/mature larvae.

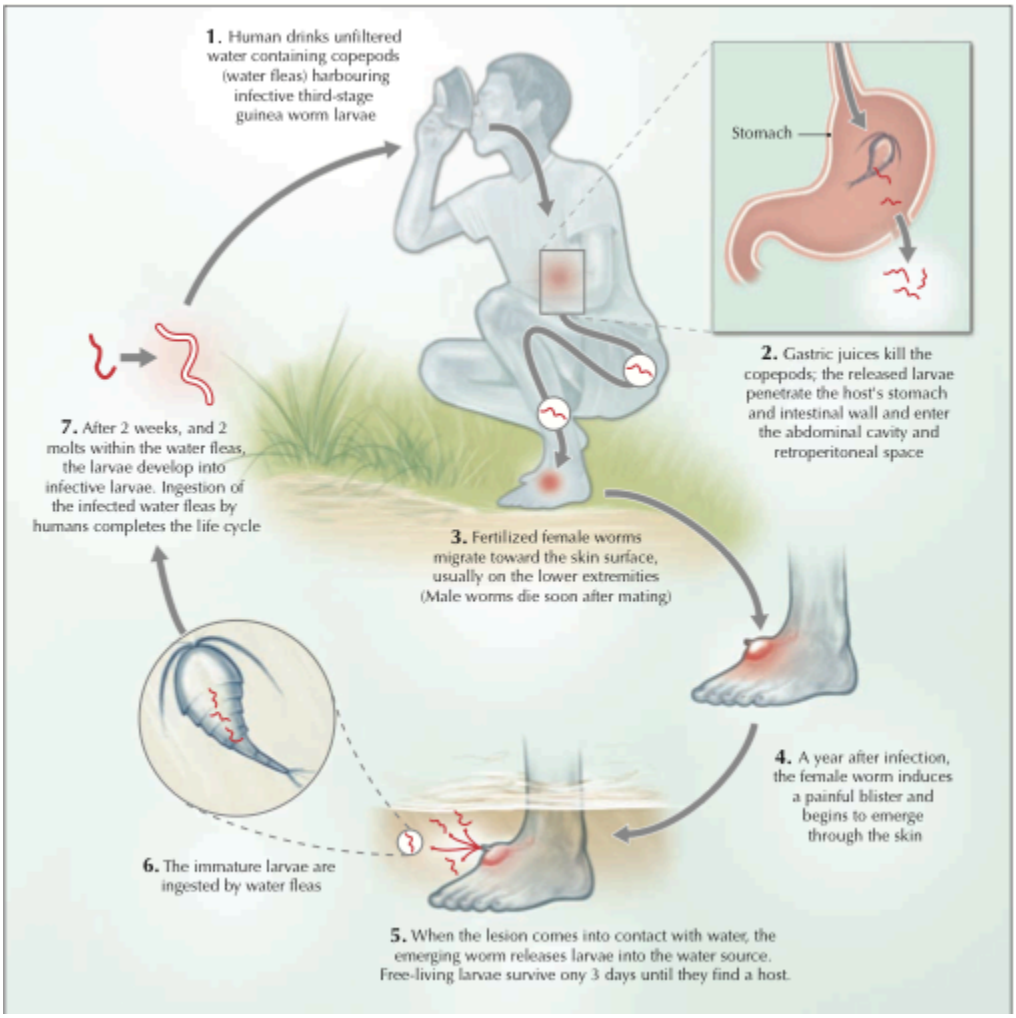

Figure 6.3: Life cycle of guinea worm [11].

The copepods, a group of small crustaceans, that transmit guinea worm disease are typically 1 to 2 millimeters (0.04 to 0.08 in) long, with a teardrop shaped body and large antennae [6] (Fig 6.5). The organism has four developmental stages: eggs, nauplius, copepodite, and adult (Fig 6.4). The larvae stages including nauplius and copepodite are of particular interest. The timing of this cycle must be in sync with the infection process. For our purposes, we ignore the different stages of larvae.

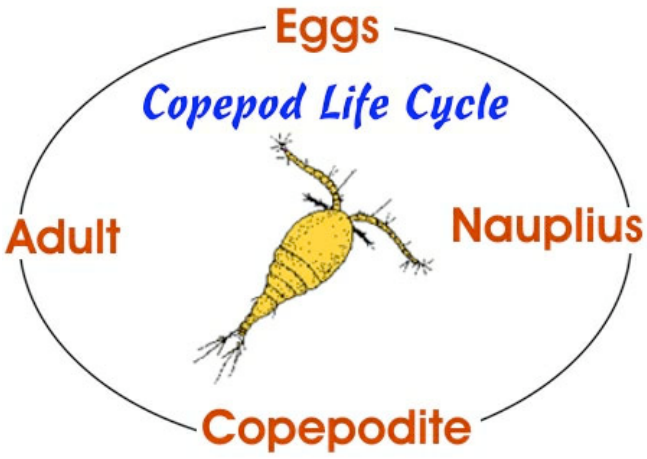

Figure 6.4: Cyclic copepod development [16].

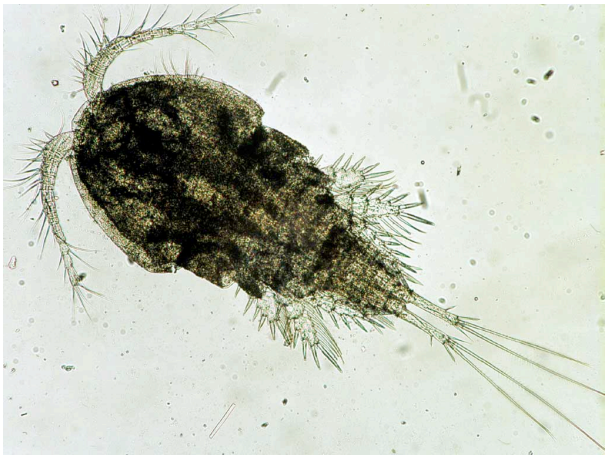

Figure 6.5: Fuzzy microscopic horseshoe crabs [8].

Figure 6.6: Infested copepod inducing death [16].

6.1 Symptoms & Interventions

One of the difficult aspects of the disease is the absence of symptoms until after infection. There are no symptoms until approximately 1 year after infection. The only indication is the blister on the surface of skin and the pain/burning sensation associated with it. Additionally, days before the worm exits the human host the patient develops a fever, swelling, and pain in the general area. The blister bursts within 24-72 hours and the worm emerges, leaving a wound that is susceptible to secondary infections [20]. Currently, there is no within-host treatment/cure. Several forms of prevention, however, have been introduced including pipe filters (reduces the number of copepods

consumed) and larvicides (reduces free living GW larvae in drinking water sources). A key component of decreasing guinea worm outbreaks is education. Awareness of the disease, its symptoms, and how it spreads could prevent people from going to the water while infected, decreasing the amount of eggs released into the water source.

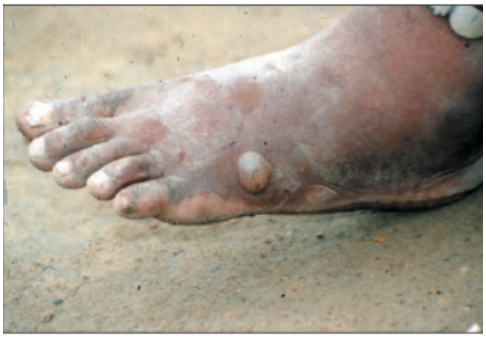

Figure 6.7: Foot blister induced by the female guinea worm in a person with dracunculiasis [15].

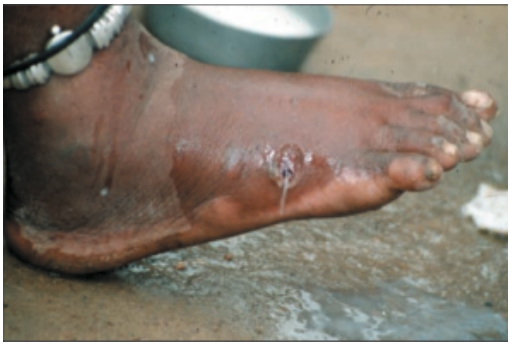

Figure 6.8: Guinea worm emerging from foot ulcer [19].

Using our knowledge of Guinea Worm Disease and the biological system it involves, we can create what is known as an ecological epidemiology model. This model not only seeks to understand the disease that afflicts the human population but also aims to grasp the population dynamics of the macroparasite and its intermediate host.

Chapter 7

A Model for Guinea Worm Disease

7.1 Introduction to the Model

This model incorporates the fact that exposed humans experience a period during which GWD is undergoing developmental stages in their bodies. During this time, humans are infected but not yet infectious. It is important to note that though copepods never recover from GWD, humans can recover, yet do not acquire any immunity. Thus, once the infectious humans recover, they are once again just as likely to become infected with the disease.

In this model, we represent the human population with a *SEI* model and the copepod population with an *SI* model. Humans become infected when guinea worm larvae that are released inside the body after consumption of contaminated drinking water. Since there is a slow maturation rate of the guinea worm within the host, the recovery rate is the reciprocal of the number of days it takes for the worm to leave the body after breaking through the skin's surface.

The model includes regular births and deaths of the human, copepod, and guinea worm populations. No human deaths occur due to GWD directly. Note that N_H and N_C are the total human and copepod populations. Unlike other models, the change in the total population of humans and copepods is not constant. The equations for these are given below.

$$N_H = S_H + E_H + I_H$$

$$\frac{dN_H}{dt} = b_H N_H \left(1 - \frac{N_H}{K_H}\right)$$

$$N_C = S_C + I_C$$

$$\frac{dN_C}{dt} = b_C N_C \left(1 - \frac{N_C}{K_C}\right).$$

To best describe the biological system, the model is broken down into three sections to address the human, copepod and guinea worm populations. As previously stated, the SEI infection model is used to describe the human population. The human population is described using logistic growth, $\frac{dN_H}{dt} = b_H N_H(1 - \frac{N_H}{K_H})$. The susceptible human compartment S_H gains individuals through births,

$b_H N_H$, and recovery from infection, rI_H. A loss of individuals is a result of natural death, $b_H N_H \frac{S_H}{K_H}$, and infection, $\epsilon_c \beta(I_C) S_H$. The infected human compartment E_H gains individuals through infection $\epsilon_c \beta(I_C) S_H$ and loses individuals when they become infectious ρE_H and to natural death $b_H N_H \frac{E_H}{K_H}$. Lastly, the infectious human compartment I_H gains individuals when infected individuals become infectious ρE_H and loses individuals when they die $b_H N_H \frac{I_H}{K_H}$ and recover rI_H.

Similarly, the copepod population is described using logistic growth. That is, $\frac{dN_C}{dt} = b_C N_C(1 - \frac{S_C}{K_C})$. Here we use a SI model. The susceptible copepod compartment S_C gains more individuals only through births, $b_C N_C$. Copepods cannot recover from infection. The population loses more copepods through natural death $b_C N_C \frac{S_C}{K_C}$, consumption by humans, $\beta(I_C) S_H$, and to infection by guinea worm larvae, $\epsilon_L \alpha(L) S_C$. The infected copepod compartment I_C gains individuals through infection, $\epsilon_L \alpha(L) S_C$, and loses more copepods through natural death, $\delta_C I_C$, and consumption by humans $\beta(I_C) S_H$.

The guinea worm population is represented by both eggs and larvae populations. The egg compartment E gains more individuals by the release of eggs from adult worms exiting human hosts, $\lambda_0 \lambda_1 I_H$. The population loses eggs through natural death, δE, and hatching into larvae, fE. We assume that the natural death rate of eggs is less than the hatching rate. That is $\delta < f$. The larvae compartment L gains more larvae by hatching and maturation, $f\sigma E$. Losses occur due to natural death, $\delta_L L$, and consumption of larvae by copepods, $\alpha(L)(S_C + I_C)$. The following system of equations describes the above events and interactions.

$$\frac{dS_H}{dt} = b_H N_H \left(1 - \frac{S_H}{K_H}\right) + rI_H - \epsilon_c \beta \left(\frac{I_C}{N_C + K_C'}\right) S_H \tag{7.1}$$

$$\frac{dE_H}{dt} = \epsilon_c \beta \left(\frac{I_C}{N_C + K_C'}\right) S_H - \rho E_H - b_H N_H \frac{E_H}{K_H} \tag{7.2}$$

$$\frac{dI_H}{dt} = \rho E_H - rI_H - b_H N_H \frac{I_H}{K_H} \tag{7.3}$$

$$\frac{dE}{dt} = \lambda_0 \lambda_1 I_H - \delta E - fE \tag{7.4}$$

$$\frac{dL}{dt} = f\sigma E - \delta_L L - \alpha \left(\frac{L}{L + K_L'}\right) N_C \tag{7.5}$$

$$\frac{dS_C}{dt} = b_C N_C \left(1 - \frac{S_C}{K_C}\right) - \epsilon_L \alpha \left(\frac{L}{L + K_L'}\right) S_C - \beta \left(\frac{S_C}{N_C + K_C'}\right) S_H \tag{7.6}$$

$$\frac{dI_C}{dt} = \epsilon_L \alpha \left(\frac{L}{L + K_L'}\right) S_C - \delta_C I_C - \beta \left(\frac{I_C}{N_C + K_C'}\right) S_H \tag{7.7}$$

Here $\beta(I_C)$ is the copepod consumption rate and $\alpha(L)$ is the larvae consumption rate.

$$\beta(I_C) = \beta \left(\frac{I_C}{N_C + K_C'}\right)$$
$$\alpha(L) = \alpha \left(\frac{L}{L + K_L'}\right).$$

These rates are dependent on the probability of ingesting an infected copepod or guinea worm larvae, resulting in infection.

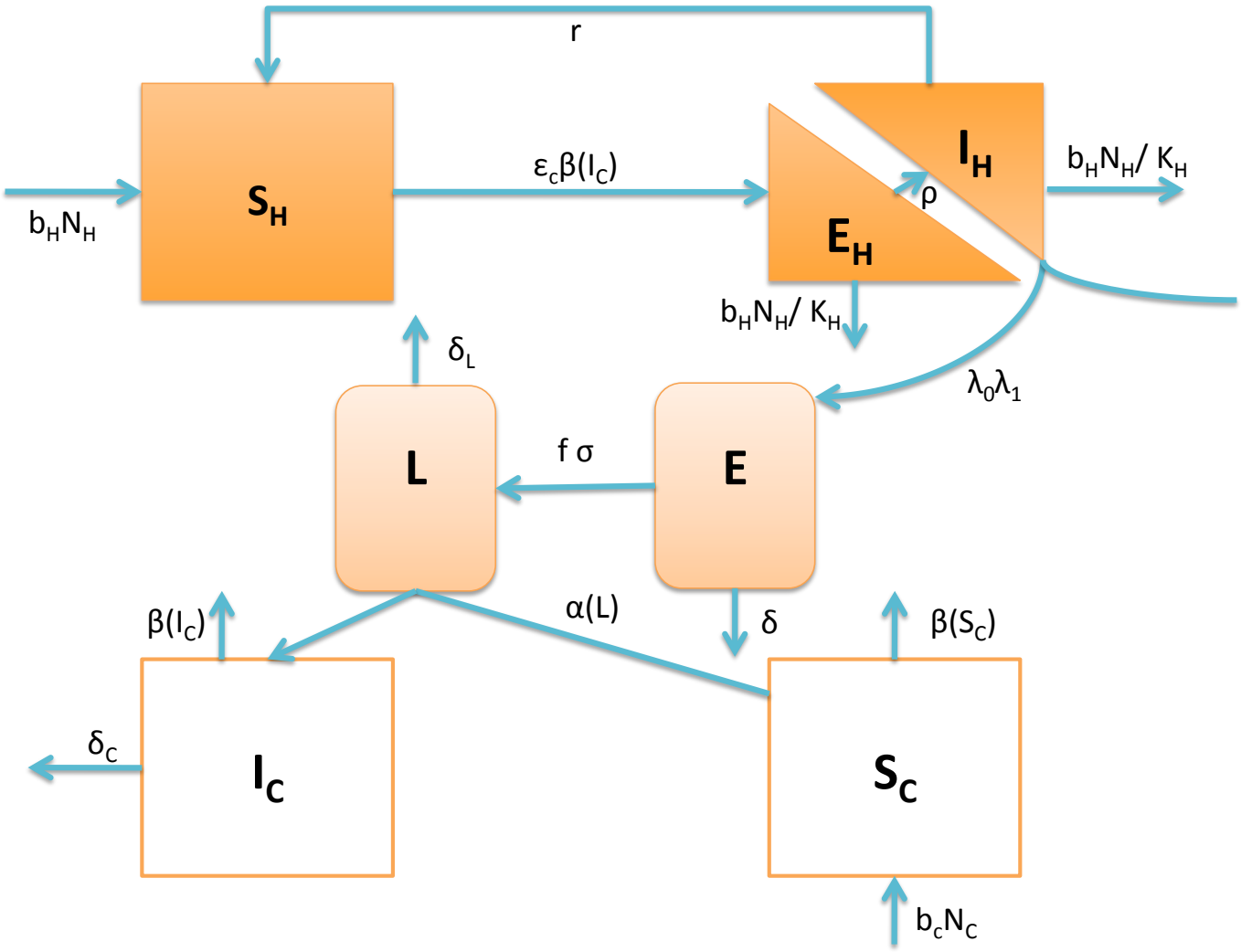

Figure 7.1: Compartment model

Table 7.1: State Variables

$S_H(t)$	susceptible humans
$E_H(t)$	latently infected humans
$I_H(t)$	infectious humans
$E(t)$	guinea worm eggs
$L(t)$	guinea worm larvae
$S_C(t)$	susceptible copepods
$I_C(t)$	infectious copepods

Table 7.2: Parameters

b_H	human birth rate $(\frac{1}{\text{time}})$
r	recovery rate $(\frac{1}{\text{time}})$
ϵ_c	human infection fraction $(\frac{\text{humans infected}}{\text{copepod}})$
β	copepod consumption rate $(\frac{\text{copepods consumed}}{\text{human} \cdot \text{time}})$
ρ	activation (infected to infectious) rate $(\frac{1}{\text{time}})$
λ_0	visitation rate $(\frac{\text{visits to the water}}{\text{time}})$
λ_1	egg release rate $(\frac{\text{eggs released}}{\text{human} \cdot \text{visit}})$
δ	natural death rate of eggs $(\frac{1}{\text{time}})$
f	hatching rate $(\frac{1}{\text{time}})$
σ	fraction of larvae surviving to stage 3 $(\frac{\text{larvae survived}}{\text{egg}})$
δ_L	natural death rate of larvae $(\frac{1}{\text{time}})$
α	larvae consumption rate $(\frac{\text{larvae consumed}}{\text{copepod} \cdot \text{time}})$
ϵ_L	copepod infection fraction $(\frac{\text{copepods infected}}{\text{larvae}})$
b_c	copepod birth rate $(\frac{1}{\text{time}})$
δ_c	natural death rate of copepods $(\frac{1}{\text{time}})$
$K_C^{'}$	copepod saturation constant (copepods)
$K_L^{'}$	larvae saturation constant (larvae)

7.2 Infection Rates

There are two infection rates in this model. One is the human infection rate. It is dependent upon the probability of consuming an infected copepod. The other is the copepod infection rate. It is dependent upon the number of larvae in the system. The rates are described below.

$$\epsilon_C \beta(I_C) = \epsilon_C \beta\left(\frac{I_C}{N_C + K_C^{'}}\right) \tag{7.8}$$

$$\epsilon_L \alpha(L) = \epsilon_L \alpha\left(\frac{L}{L + K_L^{'}}\right) \tag{7.9}$$

where ϵ_C is the probability of being infected, β is the copepod consumption rate and $\frac{I_C}{N_C+K_C^{'}}$ is the probability of consuming an infected copepod. $K_C^{'}$ is the copepod saturation term that saturates the copepod population. Similarly, ϵ_L is the probability that a copepod will be infected by a guinea worm larvae. α is the larvae consumption rate and $\frac{L}{L+K_L^{'}}$ is the saturated larvae population term. This indicates that the larvae consumption rate is dependent upon the number of larvae in the system.

7.3 Nondimensionalization

For simplicity, we utilize a nondimensionalization technique in which we scale the equations to be fractional quantities of the classes' "carrying capacities". We assign new variables for S_H, E_H, I_H, E, L, S_C, I_C with the following terms $\widetilde{S}_H$, $\widetilde{E}_H$, $\widetilde{I}_H$, $\widetilde{E}$, $\widetilde{L}$, $\widetilde{S}_C$ and $\widetilde{I}_C$. We get the following equations.

$$\widetilde{S}_H = \frac{S_H}{K_H}\ , \quad \widetilde{E}_H = \frac{E_H}{K_H}\ , \quad \widetilde{I}_H = \frac{I_H}{K_H} \tag{7.10}$$

$$\widetilde{E} = \frac{E}{K_E}\ , \quad \widetilde{L} = \frac{L}{K_L} \tag{7.11}$$

$$\widetilde{S}_C = \frac{S_C}{K_C}\ , \quad \widetilde{I}_C = \frac{I_C}{K_C} \tag{7.12}$$

This gives us seven dimensions for the fractional populations of the different classes. Additionally, we have to scale the initial assumptions, which include N_H and N_C as well as develop newly defined parameters for the now dimensionless system. Thus,

$$\widetilde{N}_H = \frac{N_H}{K_H} \tag{7.13}$$

$$\widetilde{N}_C = \frac{N_C}{K_C} \tag{7.14}$$

and

$$\widetilde{N}_H = \widetilde{S}_H + \widetilde{E}_H + \widetilde{I}_H \qquad \widetilde{N}_C = \widetilde{S}_C + \widetilde{I}_C.$$

Table 7.3: Dimensionless Parameters

$\omega_{HC} = \frac{K_H}{K_C}$	human/copepod carrying capacity ratio (*dimensionless*)
$\beta^{'} = \beta\omega_{HC}$	copepod consumption rate ($\frac{1}{\text{time}}$)
$K_E = \frac{K_H\lambda_0\lambda_1}{f}$	egg 'carrying capacity' (eggs)
$K_L = \frac{K_H\lambda_0\lambda_1}{\delta_L}$	larvae 'carrying capacity '(larvae)
$\alpha^{'} = \alpha(\frac{N_C K_C}{K_L})$	larvae consumption rate ($\frac{1}{\text{time}}$)
$\kappa_L = \frac{K_L^{'}}{K_L}$	larvae saturation constant (dimensionless)
$\kappa_L = \frac{K_C^{'}}{K_C}$	copepod saturation constant (dimensionless)

The following parameters used in the nondimensionalization.

Using the above equations and parameters, we nondimensionalize each differential equation of the model in the following manner. Let us define $\frac{d\widetilde{S}_H}{dt}$ as an example. By substituting (6.10), $\widetilde{S}_H$, into the derivative, we find

$$\begin{aligned}
\frac{d\widetilde{S}_H}{dt} &= \frac{d\frac{S_H}{K_H}}{dt} = \frac{1}{K_H}\left(\frac{dS_H}{dt}\right) \\
&= \frac{1}{K_H}[b_H N_H\left(1 - \frac{S_H}{K_H}\right) + rI_H - \epsilon_c\beta\left(\frac{I_C}{N_C + K_C^{'}}\right)S_H] \\
&= b_H\widetilde{N}_H(1 - \widetilde{S}_H) + r\widetilde{I}_H - \epsilon_c\beta\left(\frac{I_C}{N_C + K_C^{'}}\right)\widetilde{S}_H, \quad \text{by substituting (6.10) and (6.13).} \\
&= b_H\widetilde{N}_H(1 - \widetilde{S}_H) + r\widetilde{I}_H - \epsilon_c\beta\left(\frac{I_C}{K_C(\frac{N_C}{K_C} + \frac{K_C^{'}}{K_C})}\right)\widetilde{S}_H \\
&= b_H\widetilde{N}_H(1 - \widetilde{S}_H) + r\widetilde{I}_H - \epsilon_c\beta\left(\frac{\widetilde{I}_C}{\widetilde{N}_C + \kappa_C}\right)\widetilde{S}_H, \quad \text{by substituting } \kappa_C \text{ , (6.12) and (6.14).}
\end{aligned}$$

Continuing this process, we calculate each differential equation and obtain the following system of scaled equations.

$$\frac{d\widetilde{S}_H}{dt} = b_H\widetilde{N}_H(1-\widetilde{S}_H) + r\widetilde{I}_H - \epsilon_c\beta\left(\frac{\widetilde{I}_C}{\widetilde{N}_C+\kappa_C}\right)\widetilde{S}_H \tag{7.15}$$

$$\frac{d\widetilde{E}_H}{dt} = \epsilon_c\beta\left(\frac{\widetilde{I}_C}{\widetilde{N}_C+\kappa_C}\right)\widetilde{S}_H - \rho\widetilde{E}_H - b_H\widetilde{N}_H\widetilde{E}_H \tag{7.16}$$

$$\frac{d\widetilde{I}_H}{dt} = \rho\widetilde{E}_H - r\widetilde{I}_H - b_H\widetilde{N}_H\widetilde{I}_H \tag{7.17}$$

$$\frac{d\widetilde{E}}{dt} = f\widetilde{I}_H - (\delta+f)\widetilde{E} \tag{7.18}$$

$$\frac{d\widetilde{L}}{dt} = \delta_L\sigma\widetilde{E} - \delta_L\widetilde{L} - \alpha'\left(\frac{\widetilde{L}}{\widetilde{L}+\kappa_L}\right) \tag{7.19}$$

$$\frac{d\widetilde{S}_C}{dt} = b_C\widetilde{N}_C(1-\widetilde{S}_C) - \epsilon_L\alpha(\frac{\widetilde{L}}{\widetilde{L}+\kappa_L})\widetilde{S}_C - \beta'(\frac{\widetilde{S}_C}{\widetilde{N}_C+\kappa_C})\widetilde{S}_H \tag{7.20}$$

$$\frac{d\widetilde{I}_C}{dt} = \epsilon_L\alpha\left(\frac{\widetilde{L}}{\widetilde{L}+\kappa_L}\right)\widetilde{S}_C - \delta_C\widetilde{I}_C - \beta'\left(\frac{\widetilde{I}_C}{\widetilde{N}_C+\kappa_C}\right)\widetilde{S}_H \tag{7.21}$$

Equations (6.15 - 6.21) are used for calculation of the reproductive number, stability analysis and simulations. Without nondimensionalization, the differences in size of populations, rates, and time intervals cause great difficulty when calculating solutions to our system.

Chapter 8

Analysis and Results

Solving the equations (6.15-6.21) numerically, we can see how the system evolves over time. To simulate the seven-dimensional system, we used *MATLAB 7.12.0.635 (R2011a)*, specifically an ODE solver called *ode15s*. It is a stiff system solver with a low to medium order of accuracy. *ode15s* is a variable order solver based on the numerical differentiation formulas (NDFs) [17]. Optionally, it uses the backward differentiation formulas (BDFs, also known as Gear's method) that are usually less efficient. Like ode113, ode15s is a multistep solver. It is suggested to try ode15s when ode45 fails, or is very inefficient, and the problem is stiff, or when solving a differential-algebraic problem [18]. It is an ideal solver to use when the mass matrix or Jacobian is nonsingular and sparse. Our system's Jacobian is definitely sparse.

In Section 8.1 we calculate the system's disease-free equilibrium. We determine the reproductive number using the *Next-Generation Operator* in Section 8.2. After this calculation is computed, Section 8.4 shows bifurcation diagrams of our key parameters. Analysis is conducted to see how the stability of the disease-free equilibrium can change based on changes in these parameters. Lastly, in Section 8.5 we conduct a parameter analysis by looking at combinations of key parameters in hopes of developing simulation scenarios.

Using our results from the previous study, we illustrate dynamics below. Section 8.6 presents the results of simulations of an endemic equilibrium with no intervention. This scenario represents an epidemic, or worst case scenario. We believe that such a situation occurred in the early 80's, resulting in many relief efforts [20]. Section 8.7 shows results from simulations that represent the introduction of a larvacide to the water source of the system plagued by the epidemic. Lastly, Section 8.8 displays the results of simulations of the positive effects of educational intervention and pipe filters.

8.1 The Disease-Free Equilibrium

Theorem 11. *If one of the diseased classes ($\widetilde{E}_H$, $\widetilde{I}_H$, $\widetilde{E}$, $\widetilde{L}$, or $\widetilde{I}_C$) of an equilibrium point of the system (6.19-6.25) is zero, then all the diseased classes are zero.*

Proof. To examine an equilibrium point of the system, we must set the left-hand side of the equations (6.19-6.25) equal to zero. It is sufficient to show that if any one of the diseased classes is zero, then the others must also be zero. It is assumed that all model parameters and total fractional

populations $\widetilde{N}_H$, $\widetilde{N}_H$ are non-zero and positive. The susceptible populations are non-zero as well. Suppose $\widetilde{I}_H = 0$. Then from (6.16), we see that $\frac{d\widetilde{I}_H}{dt} = 0 = \rho\widetilde{E}_H$. Since $\rho > 0$, this implies that $\widetilde{E}_H = 0$. Similarly, when $\widetilde{E}_H = 0$ the equation (6.18) tells us that $\frac{d\widetilde{E}_H}{dt} = 0 = \epsilon_C\beta\frac{\widetilde{I}_C}{\widetilde{N}_C+\kappa_C}\widetilde{S}_H$. Since $\widetilde{S}_H > 0$, this implies that $\epsilon_C\beta\frac{\widetilde{I}_C}{\widetilde{N}_C+\kappa_C} = 0 \Rightarrow \epsilon_C\beta\widetilde{I}_C = 0$. We know from our assumptions that $\epsilon_C\beta > 0$. Thus, $\widetilde{I}_C = 0$. Using this result, we find from equation (6.21) that $\frac{d\widetilde{I}_C}{dt} = 0 = \epsilon_L\alpha\frac{\widetilde{L}}{\widetilde{L}+\kappa_L}\widetilde{S}_C$. We know that $\widetilde{S}_C > 0$ and therefore $\epsilon_L\alpha\frac{\widetilde{L}}{\widetilde{L}+\kappa_L} = 0 \Rightarrow \widetilde{L} = 0$, since $\epsilon_L\alpha > 0$. Lastly, equation (6.19) shows that $\frac{d\widetilde{L}}{dt} = 0 = \delta_L\sigma\widetilde{E}$. Since $\delta_L\sigma > 0 \Rightarrow \widetilde{E} = 0$. Thus, if $\widetilde{I}_H = 0$, then $\widetilde{E}_H = 0$ if and only if $\widetilde{E} = \widetilde{L} = \widetilde{I}_C = 0$. Hence, if any one of the diseased classes is zero, then all disease classes are zero. □

Theorem 12. *Assuming $b_C > \kappa_C >> \beta'$, the system of equations (6.19-6.25) has exactly one disease-free equilibrium (dfe) point x_{dfe} = ($\widetilde{N}_H$, 0, 0, 0, 0, $\widetilde{N}_C$, 0) where,*

$$\widetilde{N}_H^* = 1 \tag{8.1}$$

$$\widetilde{N}_C^* = \frac{(b_c - b_c\kappa_C) + \sqrt{(b_c + b_c\kappa_C)^2 - 4b_c\beta'}}{2b_c} \tag{8.2}$$

Proof. To verify that x_{dfe} is an equilibrium point of the model, we check that the left-hand side of equations (6.19-6.25) are all zero at x_{dfe}. Next, we must check that this is the only dfe equilibrium point. Since we are only considering the disease-free equilibrium point we must have $\widetilde{E}_H = \widetilde{I}_H = \widetilde{E} = \widetilde{L} = \widetilde{I}_C = 0$. This means that the total human and copepod populations are susceptible. That is, $\widetilde{N}_H = \widetilde{S}_H$ and $\widetilde{N}_C = \widetilde{S}_C$. Thus, $\frac{d\widetilde{N}_H}{dt} = \frac{d\widetilde{S}_H}{dt}$ and $\frac{d\widetilde{N}_H}{dt} = \frac{d\widetilde{S}_H}{dt}$. So, we need only to replace $\widetilde{N}_H$ for $\widetilde{S}_H$ and solve equation (6.19) for all possible solutions by setting $\frac{d\widetilde{N}_H}{dt} = 0$. A similar argument is used for $\widetilde{S}_C$.

To consider x_{dfe}, set the right hand side of modified (6.19) equal to zero. This results in the following equality. $0 = b_H\widetilde{N}_H(1 - \widetilde{N}_H)$. This implies that $\widetilde{N}_H^* = 0$ or $\widetilde{N}_H^* = 1$. Since we assume that $\widetilde{N}_H$ is positive, $\widetilde{N}_H^* = 1$. Using this result, we set modified equation (6.24) equal to zero and use the quadratic formula to get $\widetilde{N}_C^* = 0$ or $\widetilde{N}_C^* = \frac{(b_c-b_c\kappa_C)+\sqrt{(b_c+b_c\kappa_C)^2-4b_c\beta'}}{2b_c}$. From our assumptions, it is known that $\sqrt{(b_c + b_c\kappa_C)^2 - 4b_c\beta'} > 0$, since $(b_c + b_c\kappa C)^2 > 4b_C\beta'$ and $4b_C\beta' < 1$. We know $4b_C\beta' < 1$ because $\beta' = \beta\frac{K_H}{K_C}$ is a fractional copepod consumption rate. The consumption rate β is already small and the fractional carrying capacity $\frac{K_H}{K_C} << 1$. So, we can assume that $b_C\beta' << 1 \Rightarrow 4b_C\beta' < 1$. Thus, if $\widetilde{N}_C > 0$, there is only one equilibrium value for $\widetilde{N}_C$, $\widetilde{N}_C^* = \frac{(b_c-b_c\kappa_C)+\sqrt{(b_c+b_c\kappa C)^2-4b_c\beta'}}{2b_c}$. Hence, the only disease-free equilibrium point is x_{dfe} = ($\widetilde{N}_H^*$, 0, 0, 0, 0, $\widetilde{N}_C^*$, 0). □

8.2 The Reproductive Number

As discussed in Chapter 4, the next-generation operator is used to calculate the reproductive number R_0 of a system. This number is used to determine the stability of the disease-free equilibrium of the system ($\widetilde{N}_H$, 0, 0, 0, 0, $\widetilde{N}_C$, 0) from Theorem 12.

To compute R_0, we express the model equations in vector form as the difference between the rate of new infection in each infected compartment, F_i, and the rate of transfer between each infected compartment, V_i. For this case, the only compartments involved are latently infected humans, infectious humans, eggs, larvae and infected copepods. Recall, this calculation is done at x_{dfe} and therefore $\widetilde{S}_H = \widetilde{N}_H^*$ and $\widetilde{S}_H = \widetilde{N}_H^*$ and all diseased classes are zero. Thus we have,

$$\frac{d}{dt}\begin{bmatrix} \widetilde{E}_H \\ \widetilde{I}_H \\ \widetilde{E} \\ \widetilde{L} \\ \widetilde{I}_C \end{bmatrix} = F_i - V_i = \begin{bmatrix} \epsilon_C\beta\left(\frac{\widetilde{I}_C}{\widetilde{N}_C^*+\kappa_C}\right)\widetilde{S}_H \\ 0 \\ f\widetilde{I}_H \\ 0 \\ \epsilon_L\alpha\left(\frac{\widetilde{L}}{\widetilde{L}+\kappa_L}\right)\widetilde{S}_C \end{bmatrix} - \begin{bmatrix} \rho\widetilde{E}_H \\ r\widetilde{I}_H - \rho\widetilde{E}_H \\ (\delta+f)\widetilde{E} \\ \delta_L\widetilde{L} + \alpha'\left(\frac{\widetilde{L}}{\widetilde{L}+\kappa_L}\right) - \delta_L\alpha\widetilde{E} \\ \beta'\left(\frac{\widetilde{I}_C}{\widetilde{N}_C^*+\kappa_C}\right)\widetilde{S}_H \end{bmatrix}.$$

Next, we calculate the corresponding Jacobian matrices about the disease free equilibrium of the system. Thus, substitute $\widetilde{S}_H = \widetilde{N}_H^*$ and $\widetilde{S}_H = \widetilde{N}_H^*$. Recall, $\widetilde{E}_H = \widetilde{I}_H = \widetilde{E} = \widetilde{L} = \widetilde{I}_C = 0$.

$$\mathbf{F} = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\epsilon_C\beta\widetilde{N}_H^*}{\widetilde{N}_H^*+\kappa_C} \\ 0 & 0 & 0 & 0 & 0 \\ 0 & f & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{\epsilon_L\alpha\widetilde{N}_C^*}{\kappa_L} & 0 \end{bmatrix} \quad \text{and} \quad \mathbf{V} = \begin{bmatrix} \rho & 0 & 0 & 0 & 0 \\ -\rho & r & 0 & 0 & 0 \\ 0 & 0 & \delta+f & 0 & 0 \\ 0 & 0 & -\delta_L\alpha & \delta_L + \frac{\alpha'}{\kappa_L} & 0 \\ 0 & 0 & 0 & 0 & \frac{\beta'\widetilde{N}_H^*}{\widetilde{N}_C^*+\kappa_C} \end{bmatrix}.$$

By taking the inverse of the matrix $\mathbf{V}$, we find

$$\mathbf{V^{-1}} = \begin{bmatrix} \frac{1}{\rho} & 0 & 0 & 0 & 0 \\ \frac{1}{r} & \frac{1}{r} & 0 & 0 & 0 \\ 0 & 0 & \frac{1}{\delta+f} & 0 & 0 \\ 0 & 0 & \frac{\delta_L\alpha}{(\delta+f)(\delta_L+\frac{\alpha'}{\kappa_L})} & \frac{1}{\delta_L+\frac{\alpha'}{\kappa_L}} & 0 \\ 0 & 0 & 0 & 0 & \frac{\widetilde{N}_C^*+\kappa_C}{\beta'\widetilde{N}_H^*} \end{bmatrix}.$$

The basic reproductive number for the system is calculated as the spectral radius of the next generation matrix $\mathbf{T} = \mathbf{FV^{-1}}$.

$$\mathbf{T} = \begin{bmatrix} 0 & 0 & 0 & 0 & \frac{\epsilon_C}{\omega_{HC}} \\ 0 & 0 & 0 & 0 & 0 \\ \frac{f}{r} & \frac{f}{r} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \frac{\epsilon_L\alpha^2\widetilde{N}_H^*\delta_L}{\kappa_L(\delta+f)(\delta_L+\frac{\alpha'}{\kappa_L})} & \frac{\epsilon_L\alpha\widetilde{N}_C^*}{\kappa_L\delta_L+\alpha'} & 0 \end{bmatrix}.$$

Taking the maximum eigenvalue, we find that

$$R_0 = \sqrt[3]{\frac{\epsilon_C \; K_C \; f \; \epsilon_L \; \alpha^2 \; \lambda_0 \; \lambda_1}{r \; (\delta + f) \; \left(\frac{\delta_L K'_L}{\widetilde{N}^*_C} + \alpha K_C \right)}} \tag{8.3}$$

$$\text{where} \quad \widetilde{N}^*_C = \frac{(b_c - b_c\kappa_C) + \sqrt{(b_c + b_c\kappa_C)^2 - 4b_c\beta'}}{2b_c}. \tag{8.4}$$

We know in general that if $R_0 < 1$, the x_{dfe} of our system is stable. Similarly, if $R_0 > 1$, the x_{dfe} of our system is unstable. In the next section, we consider these relationships of R_0 to determine parameter ranges for three key parameters; λ_0, β, and δ_L that maintain stability.

Using the parameter values found in Table 8.1, we numerically found the disease-free equilibrium as shown in Fig. 8.1. The results show that the disease is not present in the human and copepod populations and the guinea worm population is nearly extinct in the given time period.

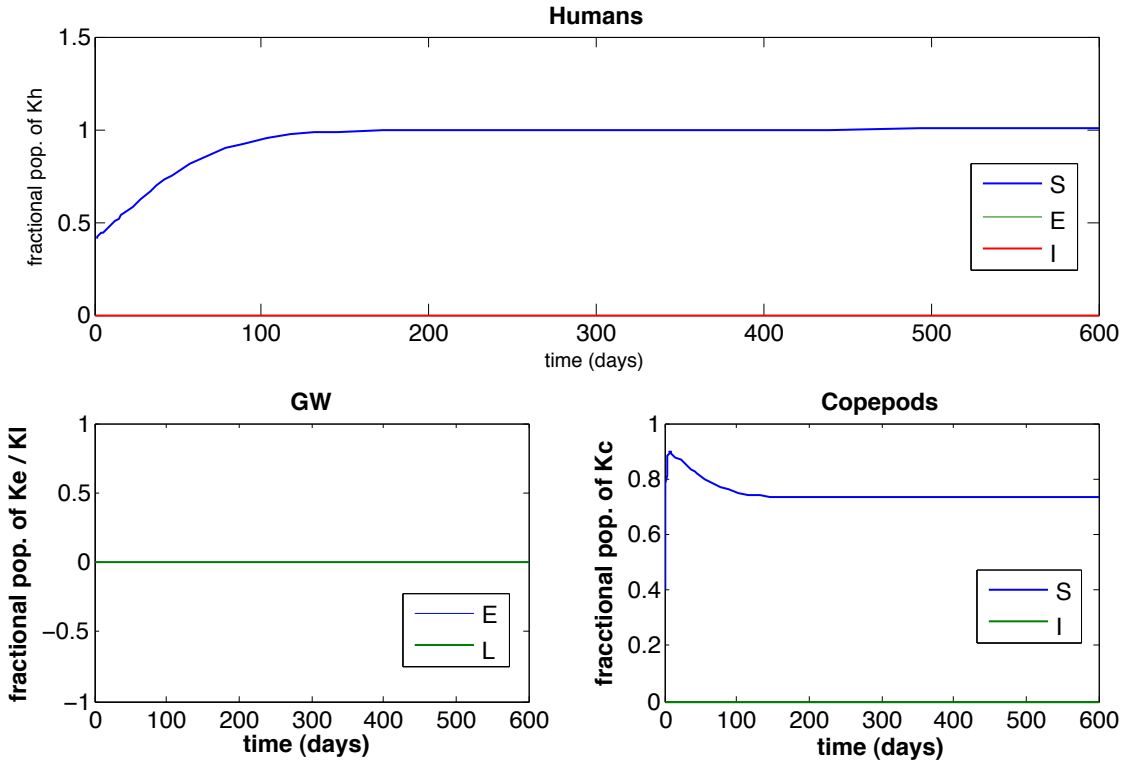

Figure 8.1: Disease-Free Equilibrium

These parameter values are used later to conduct stability analysis involving our reproductive number, R_0.

Table 8.1: Disease-Free Parameter Values

$r = 0.072$	$\epsilon_C = 0.44$
$\beta = 3$	$\rho = 0.0027$
$\lambda_0 = 0.001$	$\lambda_1 = 25000$
$\delta = 0.01$	$f = 0.072$
$\sigma = 0.2$	$\delta_L = 2.5$
$\alpha = 0.1$	$\epsilon_L = 0.1$
$b_C = 1$	$\delta_C = 1$
$K_L^{'} = 5000$	$b_H = 0.033$
$K_C^{'} = 2000$	$K_C = 10000$
$K_H = 500$	

8.3 Endemic Equilibrium

Similarly, we simulated an endemic equilibrium using parameter values found in Table 8.2. The results show that disease is present in the system in the human, guinea worm, and copepod populations.

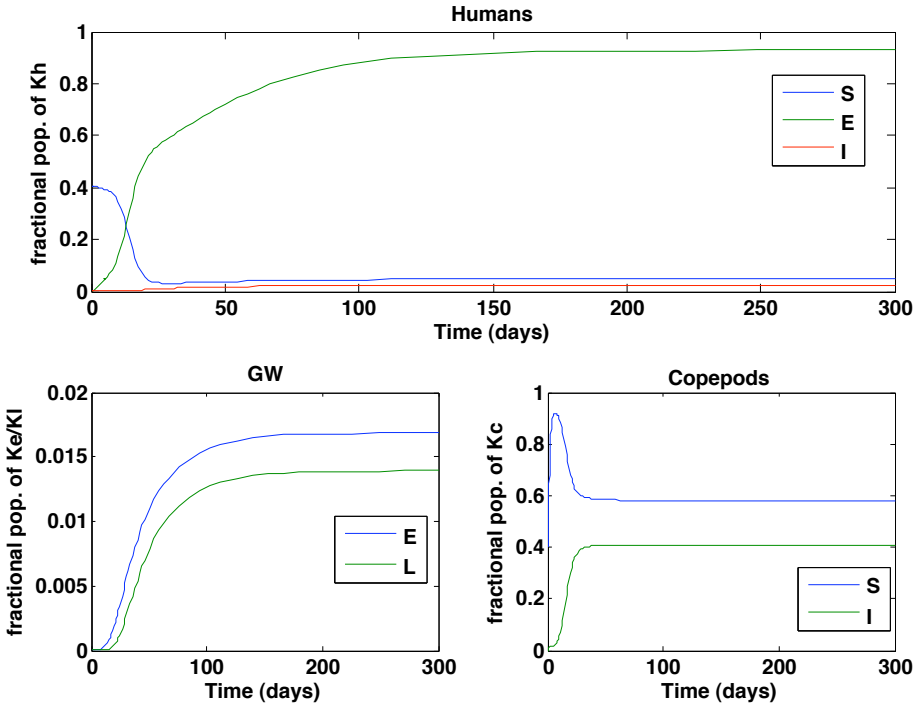

Figure 8.2: Endemic Eq: $\lambda_0 = 0.05$, $\beta = 3$, $\delta_L = 2.5$

Table 8.2: Endemic Parameter Values

$r = 0.072$	$\epsilon_C = 0.667$
$\beta = 3$	$\rho = 0.0027$
$\lambda_0 = 0.05$	$\lambda_1 = 25000$
$\delta = 0.03$	$f = 0.072$
$\sigma = 0.9$	$\delta_L = 0.25$
$\alpha = 0.8$	$\epsilon_L = 0.9$
$b_C = 1$	$\delta_C = 1$
$K_L^{'} = 5000$	$b_H = 0.033$
$K_C^{'} = 2000$	$K_C = 10000$
$K_H = 500$	

8.4 Bifurcation Diagrams

Consider the three forms of intervention discussed in Section 6.1. We identify specific parameters that would apply these interventions to the model. The first intervention parameter is λ_0. This is the water source visitation rate. Education is the intervention represented by a decrease in this parameter. By decreasing the number of times an individual visits the water source, there is a smaller chance of infection. Our analysis describes that x_{dfe} is stable if $\mathbf{0 < \lambda_0 < 0.0038}$.

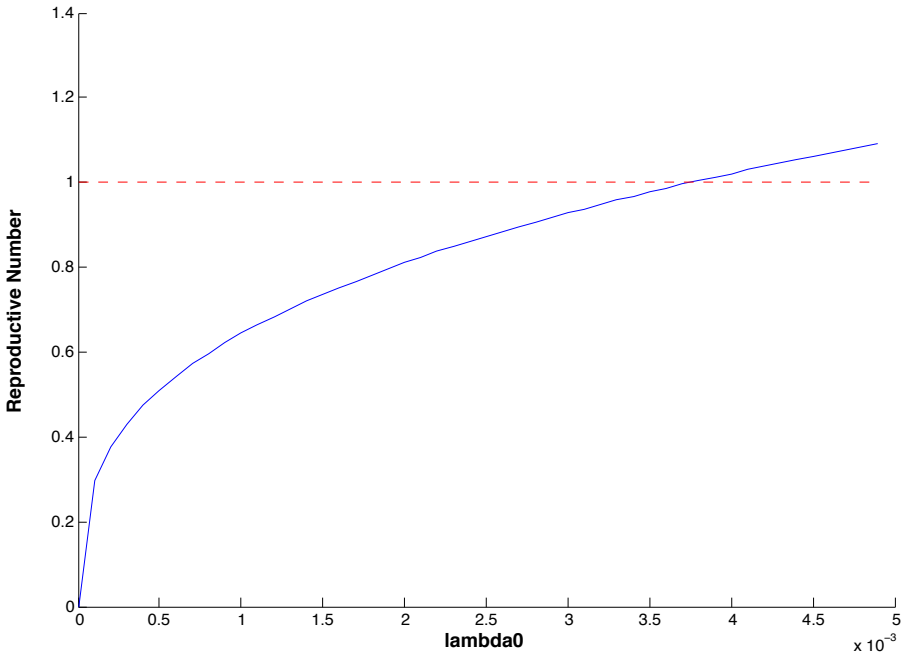

Figure 8.3: Education: Intervention parameter λ_0

Similarly, our second intervention parameters is β. This is the copepod consumption rate. Pipe

filters are represented by a decrease in this parameter. By decreasing the number of copepods consumed per day, the probability of infection is decreased. Our analysis describes that x_{dfe} is stable if $\mathbf{0} < \beta < \mathbf{78}$.

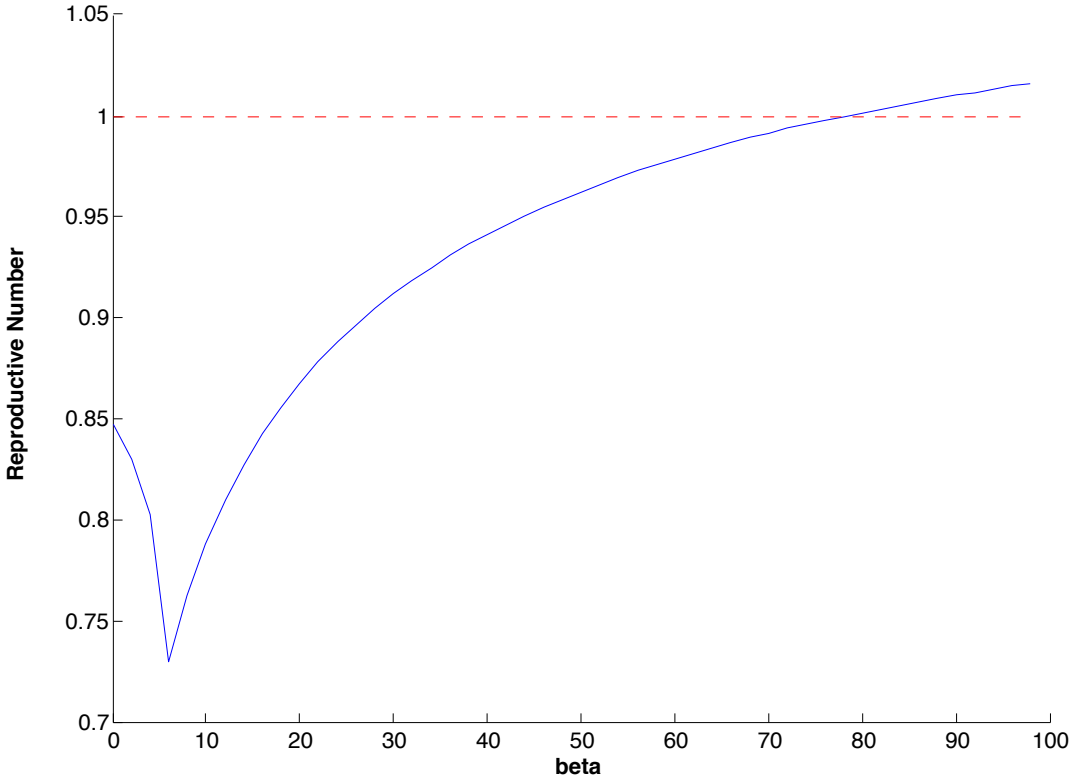

Figure 8.4: Pipe Filters: Intervention parameter β

Lastly, the third intervention parameter is δ_L. This is the larvae death rate. Larvicides are represented by an increase in this parameter. By increasing the death of free-living larvae, the probability of copepod infection as well as human infection decreases. Our analysis describes that x_{dfe} is stable if $\mathbf{0.25} < \delta_{\mathbf{L}}$ (Fig 8.5).

The results from this analysis provided base parameter values for which we use to test combinations of these parameters. It is the goal to construct intervention scenarios from our findings.

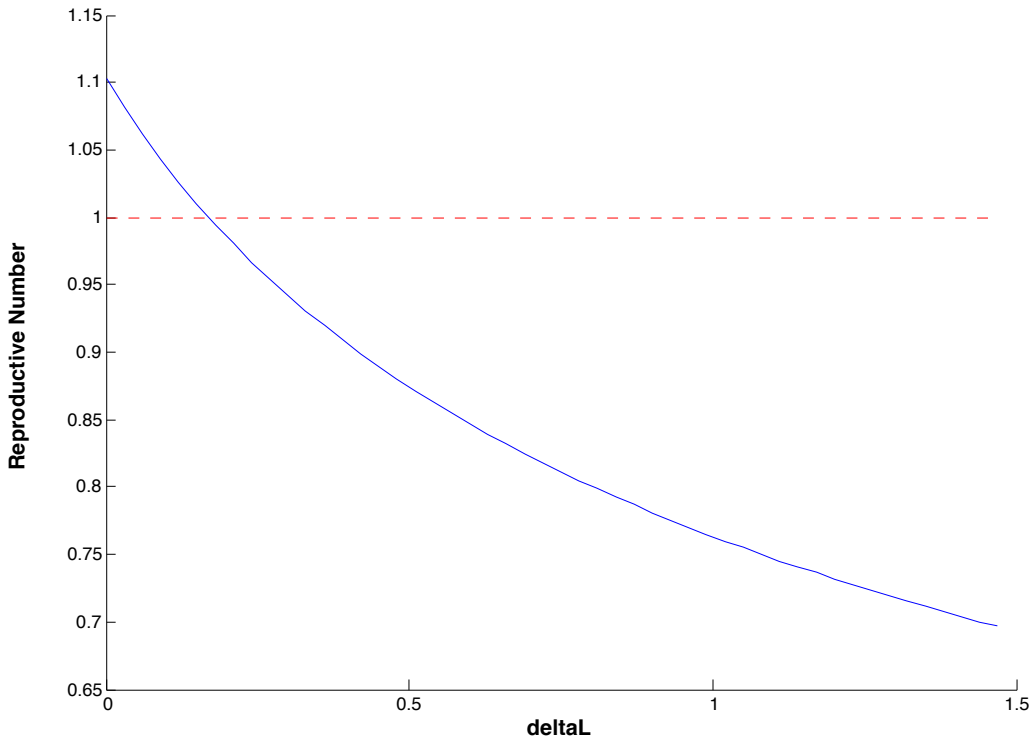

Figure 8.5: Larvicide: Intervention parameter δ_L

8.5 Parameter Analysis

To assist in developing simulation scenarios, we look at different combinations of our intervention parameters and observe the effects they have on the solutions of different compartments.

From Figure 8.6 we see that the combination of education (λ_0) and larvicide (δ_L) is not necessarily the most effective course of action. We find that there is a significant reduction in the egg compartment E but there is little effect on the infected copepod compartment I_C. Figure 8.7 highlights that though the combination of pipe filters (β) and larvicide (δ_L) significantly reduces the infected copepod compartment I_C, there is still a high fraction of infected humans E_H. Figure 8.8 confirms that the combination of pipe filters (β) and education (λ_0) are effective at reducing the infected compartments.

This analysis leads to three simulations that describe intervention scenarios. The first scenario excludes intervention to provide a base line. The next two scenarios incorporate a larvicide alone and the combination of education and pipe filters.

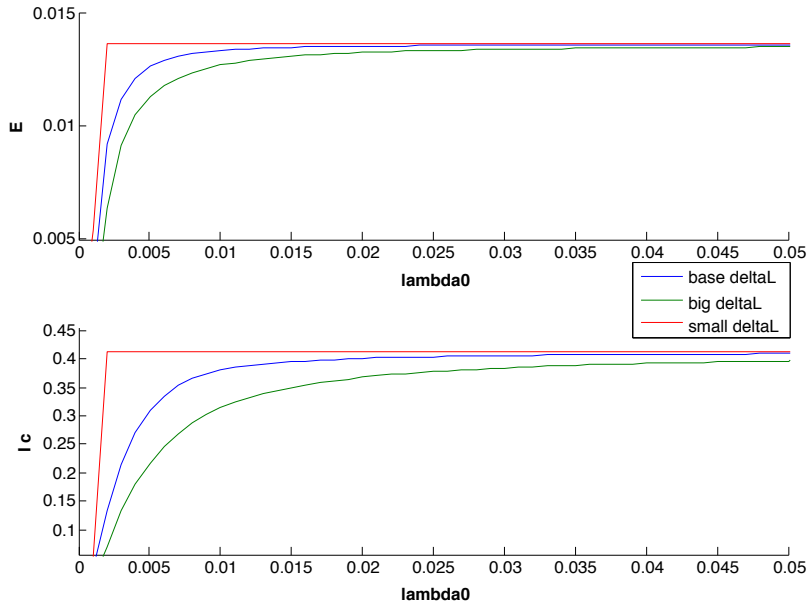

Figure 8.6: Combined effects of λ_0 and δ_L: δ_L = (small, base, big) = (0.0001, 0.25, 5)

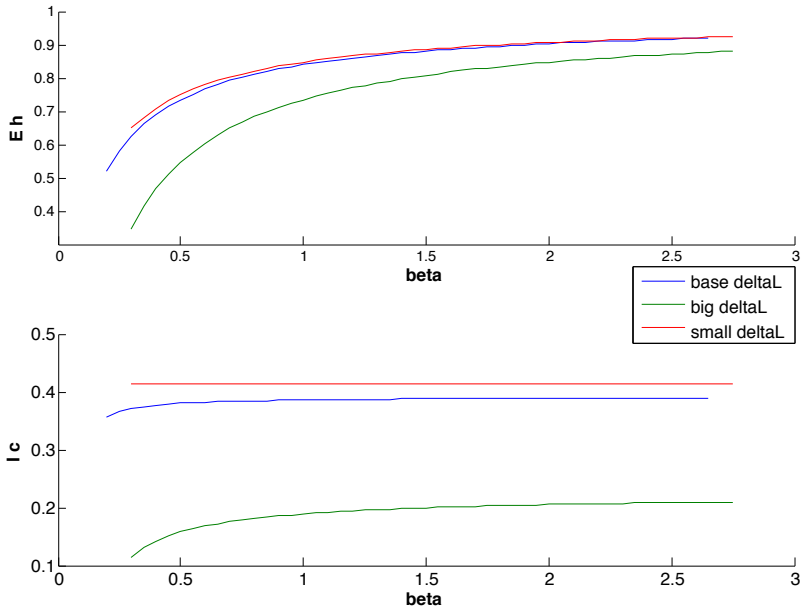

Figure 8.7: Combined effects of β and δ_L: δ_L = (small, base, big) = (0.0001, 0.25, 5)

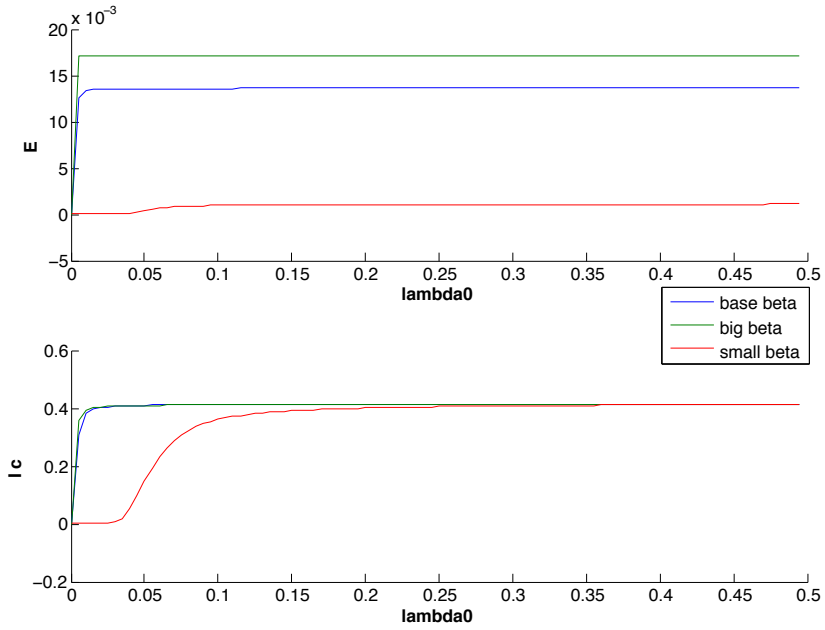

Figure 8.8: Combined effects of λ_0 and β: β = (small, base, big) = (0.01, 0.5, 5)

8.6 Scenario 1: No Intervention

An endemic equilibrium is simulated with experimentally determined parameters and initial conditions. The following parameters where used to simulate the epidemic. $\lambda_0 = 0.001$, $\beta = 3$, $\delta_L = 2.5$. Additional values can be found in Table 8.2. The system contained fractional populations of each class (See Fig. 8.9). These parameter values produce a sudden outbreak of GWD.

Based on our results, we find that there is a high fractional population of guinea worm eggs and larvae as well as infected humans and copepods. Thus, the system is guinea worm ridden. Recall that the compartments contain fractional populations of the carrying capacity.

8.7 Scenario 2: Introduction of a Larvicide

Introduction of larvicide, a water treatment that reduces the number of copepods in the given sample, was simulated by increasing the natural larvae death rate ($\delta_L = 450$) and using the initial parameter values listed in Table 7. With the decreased larvae compartment, change is seen over a 1000 day time interval in the infected human compartment. In addition, there is a decrease in infected copepods (See Fig. 8.8). Increasing the death further is quite unrealistic, since that larvicide at high concentrations in the water is likely to affect other organisms in the environment. Other combinations of intervention must be explored.

The results show that though the water treatment is effective, it must be an annual procedure. The guinea worm eggs and larvae are significantly reduced for about a year until around day 400, when the populations begin to grow again. This shows the endemic equilibrium has pseudo stability.

It also highlights the necessity of annual water treatments. Though manageable, the deleterious effects to other populations within the water source as well as on land may outweigh the benefits. Thus, it is necessary to find an alternative combination of interventions.

8.8 Scenario 3: Introduction of Education & Pipe Filters

Education about the disease and the avoidance of the water source is simulated by decreasing the water source visitation rate λ_0. The pipe filters are simulated by decreasing the copepod consumption rate. The probability of ingesting an infected copepod is the same but the number of copepods ingested per day is much less. β is reduced. The new values of the two parameters are $\lambda_0 = 0.01$ and $\beta = 0.4$. Similar to Section 8.6 and 8.7, we use the initial parameter values in Table 7. We found the following results (See Fig. 8.11).

It is shown that with the combination of pipe filters and education, the egg and larvae compartments are decreased to zero as well as the infected copepod compartment. This, in turn, reduced the infected and infectious human compartments significantly, proving to be a successful method of intervention. Thus, education and pipe filters is the viable intervention combination and can replace the use of a larvicide.

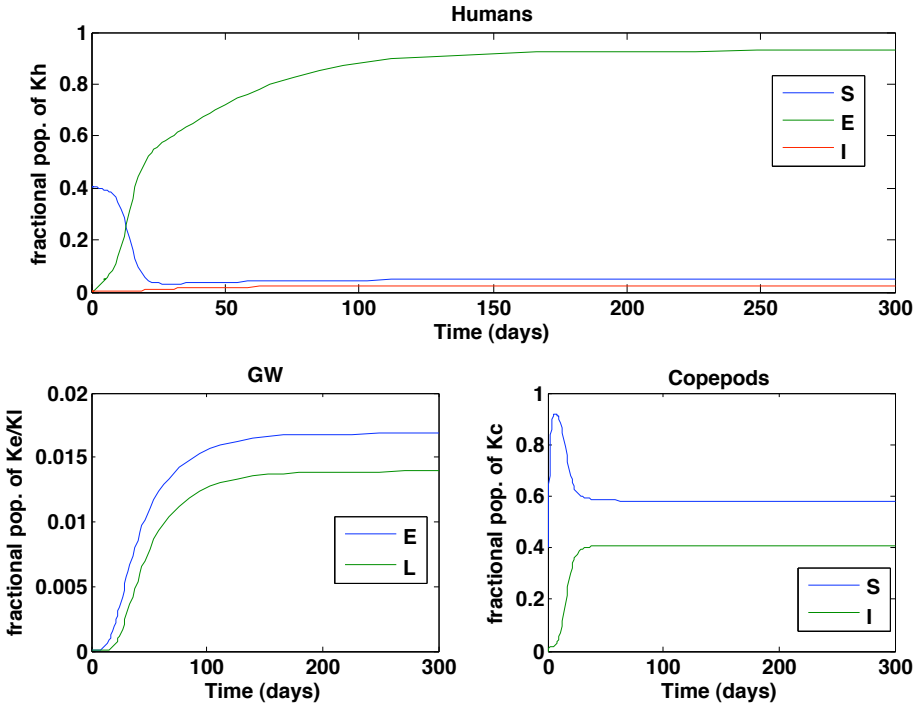

Figure 8.9: Scenario 1: $\lambda_0 = 0.05$, $\beta = 3$, $\delta_L = 2.5$

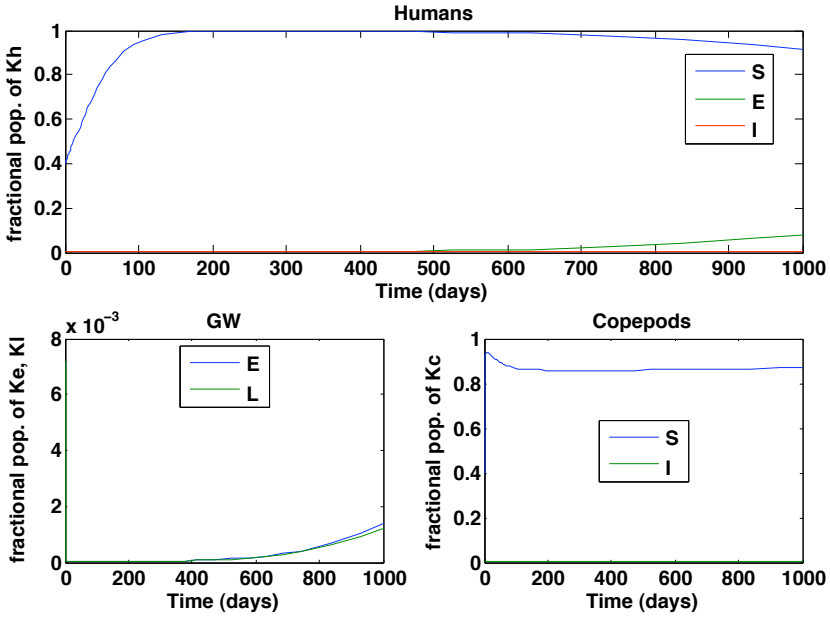

Figure 8.10: Scenario 2: $\lambda_0 = 0.05$, $\beta = 3$, $\delta_{\mathbf{L}} = \mathbf{450}$

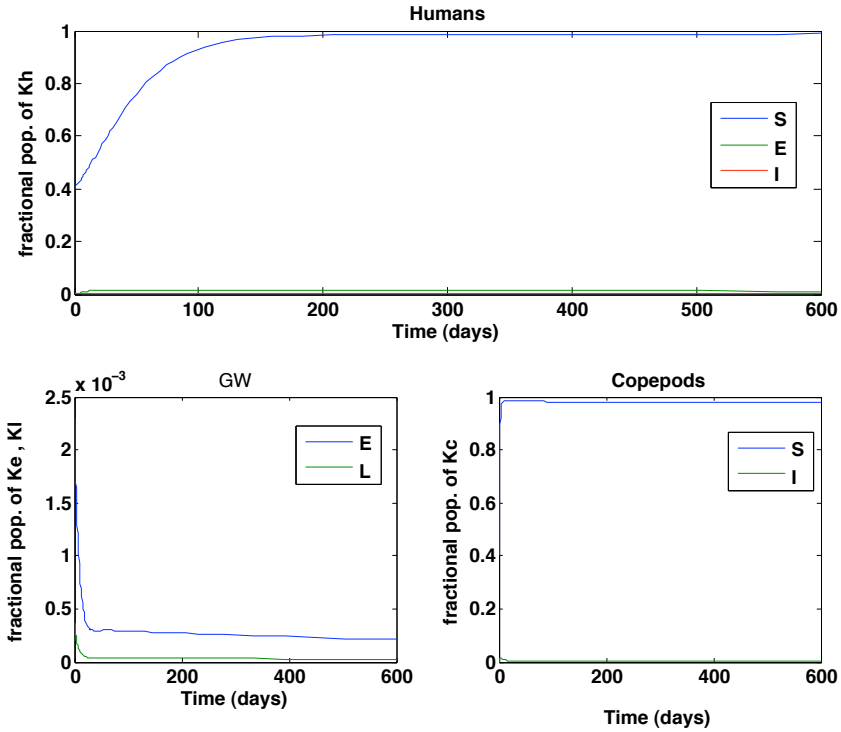

Figure 8.11: Scenario 3: $\lambda_{\mathbf{0}} = \mathbf{0.01}$, $\beta = \mathbf{0.4}$, $\delta_L = 0.25$

Part IV

Conclusion and Explanation

Chapter 9

Conclusion

The global campaign to eradicate Guinea Worm Disease began in 1980 at the U.S. Centers for Disease Control and Prevention (CDC). Guinea Worm Disease (GWD) eradication was targeted as an ideal indicator of success for the United Nations 1981-1990 International Drinking Water Supply and Sanitation Decade (IDWSSD) because the disease could only be transmitted through contaminated drinking water. A year later, GWD eradication was adopted as a sub-goal of the IDWSSD [20]. Though many view the disease as virtually absent, nothing is certain and there is always the potential of an outbreak. The creation of this model as well as the stability and numerical analysis conducted proved useful for multiple reasons. It confirms that the current efforts of relief organizations are warranted and working. We found that the continued use of pipe filters and education is needed to ensure the stability of the disease-free state. If necessary, an annual larvicide may be used to increase larvae death. The main result of this model is the intervention parameter value intervals. Keeping values within these intervals allows the system to remain disease-free. In a way, this model is a warning to public health officials that a high level of attention is necessary to prevent future outbreaks.

On the other hand, this model can be viewed as a tool for the fledgling modeler. It presents the modeling process as cyclic and stresses the importance of reinterpretation and modification. It highlights compartmental modeling of diseases and the methodology of sketching a mathematical model from a biological description. Multiple techniques including nondimensionalization and the *Next-Generation Operator* are detailed. Lastly, stability and parameter analysis is described to assist with interpretation. Overall, this paper is a user guide for modelers interested in ecological epidemiology models.

Future areas of study include conducting a more in depth sensitivity analysis. Many of these parameters can not be estimated directly from existing research. Latin hypercube sampling could be used to test the sensitivity of the model to each input parameter. This approach has been successfully applied in the past to many other disease models. Latin hypercube sampling is a stratified sampling technique that creates sets of parameters by sampling for each parameter according to a predefined probability distribution [10]. In addition, some complexities of the system including the copepod's multiple larvae stages have been omitted from this model. An attempt to incorporate the time component of these stages into the model could prove beneficial.

With any type of modeling we always have the risk that the behavior observed mathematically does not translate to real-world situations. This original model provides a basis for examining the GWD host-macroparasite interactions and allots for modification and reinterpretation.

Chapter 10

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