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Numerical Solution of Stochastic Differential Equations with an Application to an Inhalation Anthrax Model

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To the Graduate Council:

I am submitting herewith a thesis written by Kacy Savannah Aslinger entitled "Numerical Solution of Stochastic Differential Equations with an Application to an Inhalation Anthrax Model." I have examined the final electronic copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Mathematics.

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Numerical Solution of Stochastic Differential Equations with an Application to an Inhalation Anthrax Model

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I dedicate this thesis to my parents.

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Abstract

A protocol for transforming deterministic models into stochastic models and analyzing them is presented. This protocol is applied to a deterministic model previously presented to model inhalation anthrax in the lungs. A numerical method is applied to the stochastic model and results are analyzed.

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Chapter 1

Introduction

This chapter introduces random variables, other basic probability concepts, as well as Brownian Motion (also known as a Wiener Process) which are necessary for stochastic calculus. Then stochastic calculus is introduced so that we can use it to solve a system of stochastic ordinary differential equations via the Euler-Maruyama scheme, which will be introduced in Chapter 2.

1.1 Basic Probability and Random Variables

To begin with basic probability, start with a set Ω of outcomes called the sample space, $\mathcal{A}$ a $\sigma - algebra$ of the subsets of Ω, and a probability measure denoted $\mathbb{P}$. A probability measure is a funtion $\mathbb{P} : \mathcal{A} \longrightarrow [0, 1]$ which assigns probabilities to events, and $\mathbb{P}(\Omega) = 1$ Durrett (2010). The collective $(\Omega, \mathcal{A}, \mathbb{P})$ is called a probability space. Random variables provide information about experiments that we can observe. They are defined as such:

Definition 1. *(Gard (1988)) A function $X : \Omega \to \mathbb{R}$ is a random variable if and only if $X^{-1}(-\infty, a] = \{\omega : X(\omega) \leq a\} \in \mathcal{A}$ for all real a.*

Some simple examples of a random variable are the outcome of a coin toss and the outcome of rolling a die. In terms of a die roll, Ω, the set of all possible outcomes,

is $\{1, 2, 3, 4, 5, 6\}$. $\mathcal{A}$ is a $\sigma - algebra$ of the subsets of Ω, or a collection of all the subsets of Ω. Considering a single outcome, $\mathbb{P}(X = 2)$ refers to the probability that our roll of the die results in a 2, and presuming that our die is fair, all outcomes have the same probability of $\frac{1}{6}$.

The expected value, also known as the mean, of a random variable X is denoted $\mathbb{E}(X)$. For the purposes of this paper, we shall only consider the continuous case in which $\mathbb{E}(X) = \int xp(x)dx$ where $p(x)dx$ is the probability that X takes its values in the interval $(x, x + dx)$ Kloeden and Platen (1999). In other words, $p(x)$ is equivalent to $\mathbb{P}(X = x)$. Note that the expected value of a random variable may or may not be finite. We also consider the "measure of spread" about the mean (called the variance), given by $Var(X) = \mathbb{E}(X^2) - (\mathbb{E}(X))^2$ Kloeden and Platen (1999).

A probability distribution that will appear in the definition of Brownian Motion (and the only specific distribution that will be mentioned) is a bell-shaped distribution called the Normal Distribution. Its density function is given by $p(x) = \frac{1}{\sqrt{2\pi}\sigma} e^{\frac{(x-\mu)^2}{2\sigma^2}}$, and it produces random variables with expected value μ and variance σ^2. If a random variable X follows the normal distribution, we write $X \sim N(\mu, \sigma^2)$. The standard normal distribution has mean zero and variance one.

Now, we'll introduce the concept of independence. Intuitively, two events are independent if they do not depend on one another. Two random variables are independent if $\mathbb{P}(X_1 \text{ and } X_2) = \mathbb{P}(X_1) \times \mathbb{P}(X_2)$. This definition can be extended to an arbitrary number of random variables.

Stochastic processes are functions of two variables, t and ω where t represents a discrete instant of time and ω is an element of Ω. In the context of this thesis, we shall only consider the notation that denotes a sample path (or trajectory). Thus, for each fixed $\omega \in \Omega$, $X(., \omega)$ corresponds to a real valued (or n-vector-valued) function defined on an arbitrary set and can be written as $X(., \omega) : T \to \mathbb{R}$ where T is a time set. Gard (1988),Kloeden and Platen (1999). An example of a stochastic process is a Wiener process, also known as Brownian Motion, which will be defined in the next section.

1.2 Brownian Motion

The majority of this section comes from Higham (2001) unless otherwise noted. The history of how Brownian motion was discovered can be found in Karatzas and Shreve (1991). It is random movement, and its applications are extensive including random perturbations in physical, biological, economic, and management systems Karatzas and Shreve (1991). The mathematician Wiener provided the first existence proof of Brownian motion, thus it is often referred to as the Wiener process.

Definition 2. *Higham (2001) A Standard Brownian motion, or standard Wiener process, over* $[0, T]$ *is a random variable* $W(t)$ *that depends continuously on* $t \in [0, T]$ *and satisfies the following three conditions:* 1. $W(0) = 0$ *(with probability* 1*)*

2. *For* $0 \leq s < t \leq T$ *the random variable given by the increment* $W(t) - W(s)$ *is normally distributed with mean zero and variance* $t - s$*, written* $W(t) - W(s) \sim N(0, t - s)$.

3. *For* $0 \leq s < t < u < v \leq T$*, the increments* $W(t) - W(s)$ *and* $W(v) - W(u)$ *are independent.*

One can simulate Brownian motion where $W(t)$ is specified at discrete time values. On a computer, the random numbers generated are not truly random but can be made to resemble random numbers in most properties and are called pseudo-random numbers Kloeden and Platen (1999). For the purposes of our study of Brownian motion, we use the MATLAB function `randn` which produces independent pseudo-random numbers from the $N(0, 1)$ distribution.

1.3 Stochastic Integrals

As mentioned above, Brownian motion has various applications. Various physical and biological systems, classically modeled by deterministic differential equations, can be more satisfactorily modeled if random effects in the physical phenomena are taken into consideration Gard (1988). Consider an ordinary differential equation

$\frac{dx}{dt} = F(t,x)$. This can be replaced with a random differential equation $\frac{dx}{dt} = F(t,x,y)$ where $y = y(t)$ represents some stochastic input (randomness in the system) Gard (1988). Such a problem is usually written in the form:

$$\begin{cases} dX(t) = f(X,t)dt + g(X,t)dW(t) \\ X(0) = X_0. \end{cases}$$

Formally, the solution of the initial value problem is obtained by the following:

$$X(t) = X_0 + \int_0^t f(X,s)ds + \int_0^t g(X,s)dW$$

Evans (2013).

The problem with this solution is that we do not have representation for the integral $\int_0^t g(X,s)dW$. In traditional calculus, when first learning integration, we approximate the integral (of a suitable function g) with the Riemann sum. The left-hand Riemann sum is given by

$$\sum_{j=0}^{N-1} g(t_j)(t_{j+1} - t_j).$$

Similarly, the stochastic integral can be approximated. The "left-hand" sum

$$\sum_{j=0}^{N-1} g(t_j)(W(t_{j+1}) - W(t_j))$$

is known as the Itô integral. In traditional calculus, the Riemann sum can be calculated in a number of ways, the left-hand sum, the right-hand sum, and the middle or midpoint sum. The Stratonovich integral in stochastic calculus uses the midpoint sum given by

$$\sum_{j=0}^{N-1} g\left(\frac{t_j + t_{j+1}}{2}\right)(W(t_{j+1}) - W(t_j)).$$

We compute these integrals in MATLAB by first creating a discretized Brownian path over a given interval. Then, to compute Itô's integral for $\int W dW$ (where W represents the Brownian path), we sum the elements of the Brownian path multiplied elementwise by the Brownian increments Higham (2001).

The question of which integral we should use naturally arises. The answer depends on how we intend the Brownian motion to approximate the real noise process and on how the stochastic differential equation itself approximates the real situation being modeled. In general, many biological systems (since intrinsically discrete in time, state, or both) utilize Itô's integral Kloeden and Platen (1999). Therefore, in this thesis, we will be utilizing Itô's integral in our numerical methods.

Chapter 2

Numerical Methods for Solving Stochastic Differential Equations

In this chapter, we will introduce Euler's Method for deterministic ordinary differential equations as seen in any standard numerical analysis text book. Then we will introduce the basics of the Euler-Maruyama scheme for stochastic ordinary differential equations which is one of the simplest time discrete approximations of an Itô process. Finally, we will dicuss the stability of the Euler-Maruyama scheme.

2.1 Euler's Method for Deterministic ODEs

The entirety of this section is derived from Burden and Faires (2001). Consider a well-posed initial-value problem

$$\frac{dy}{dt} = f(t, y), \quad a \leq t \leq b, \quad y(a) = \alpha.$$

Approximations to y, named w_i, are generated at mesh points in the interval $[a, b]$, which are equally distributed throughout the interval. The distance between the points is called the step size and is given by $h = \frac{b-a}{N}$. The simplest approximation

is produced by Euler's method:

$$w_{i+1} = w_i + hf(t_i, w_i)$$

for each $i = 0, 1, \ldots, N-1$ with the initial condition $w_0 = \alpha$, where $w_i \approx y(t_i)$. The mesh points are selected by the following equation:

$$t_i = a + ih$$

for each $i = 0, 1, 2, \ldots, N$ where N is a positive integer.

Euler's method is an explicit, first order method, and its error is expected to grow in no worse than linearly in h Burden and Faires (2001).

2.2 Euler-Maruyama method

For the Euler-Maruyama method, we will consider the stochastic initial value problem

$$dX(t) = f(X(t))dt + g(X(t))dW(t)$$

with $X(0) = X_0$ (X_0 is a random variable) and $0 \leq t \leq T$. Before applying a numerical method to the initial value problem, we first discretize the time interval by letting $\Delta t = T/L$ for some positive integer L and $\tau_j = j\Delta t$ Higham (2001). Note that $X(\tau_j)$ will be approximated by X_j. The Euler-Maruyama method is given by

$$X_j = X_{j-1} + f(X_{j-1})\Delta t + g(X_{j-1})(W(\tau_j) - W(\tau_{j-1}))$$

for $j = 1, 2, \ldots, L$. Note that taking $g = 0$ and X_0 constant yields the deterministic case which reduces to Euler's method given in the previous section Higham (2001).

2.2.1 The Brownian Bridge

Now we will implement the Euler-Maruyama method on a stochastic differential equation for which the solution is known. Consider the Brownian Bridge, given by

$$\begin{cases} dB = -\frac{B}{1-t}dt + dW \quad (0 \leq t \leq 1) \\ B(0) = 0 \end{cases}$$

with its solution

$$B(t) = (1-t)\int_0^t \frac{1}{1-s}dW \quad (0 \leq t \leq 1).$$

Evans (2013)

Implementing the Euler-Maruyama method in MATLAB on the stochastic differential equation and plotting it against the exact solution for the given Brownian path W, we get the results shown in Figure 2.1:

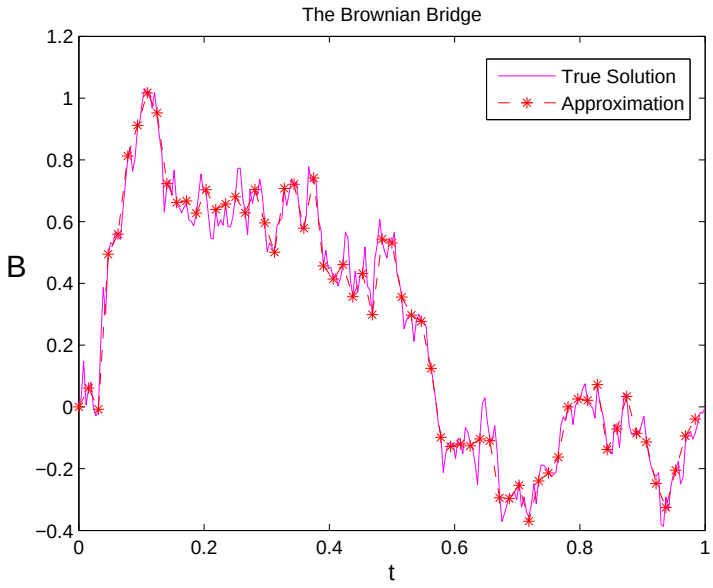

Figure 2.1: The Brownian Bridge
The Brownian Bridge true solution compared to its Euler-Maruyama method approximation.

2.3 The Convergence of Numerical Methods

Now that a numerical method for approximating a stochastic ordinary differential equation has been given, the convergence of the method is explored. Since $X(\tau_n)$ and X_n are random variables, we must measure their difference in an alternative way. We do this using the expected value. In general, if there exists a constant C such that

$$\mathbb{E}\left(|X_n - X(\tau)|\right) \leq C\Delta t^{\gamma}$$

for any fixed $\tau = n\Delta t \in [0, T]$ and Δt sufficiently small, then the method is said to have strong order of convergence equal to γ, which measures the rate at which the mean of the error decays as $\Delta t \to 0$ Higham (2001). The Euler-Maruyama method has a strong order of convergence of $\gamma = 0.5$ Kloeden and Platen (1999). An alternative to strong convergence is weak convergence, which measures the rate of decay of the error of the means. If there exists a constant C such that for all functions p in some class

$$\left|\mathbb{E}\left(p(X_n)\right) - \mathbb{E}\left(p(X(\tau))\right)\right| \leq C\Delta t^{\gamma}$$

at any fixed $\tau = n\Delta t \in [0, T]$ and Δt sufficitently small, then we say the the method has a weak order of convergence equal to γ Higham (2001). The Euler-Maruyama usually converges with weak order of $\gamma = 1$ Kloeden and Platen (1999).

Chapter 3

Numerical Methods

In this chapter, we will construct a protocol for creating and finding numerical solutions of stochastic models and for evaluating the results.

3.1 Converting Deterministic to Stochastic

As stated in Chapter 1, various physical and biological systems can be "more satisfactorily modeled" by adding randomness into the system Gard (1988). We start with a deterministic model consisting of ordinary differential equations. Stochasticity can be added into a system of partial differential equations, but this thesis focuses on ordinary differential equations. Next, decide where to introduce randomness into the system. One could potentially transform any rate or variable into a stochastic rate or variable, respectively, but the randomness of the parameter chosen needs to make sense within the system. Randomness could also be added into the system by merely adding a stochastic source term to an equation or a set of equations. We will assume that our new random variable is part of a Brownian Motion (or a Wiener process). Once randomness is added into the system, the new stochastic differential equation or equations needs to be put into the general form of stochastic differential equations given in Chapter 1, noting that in the general form, the equations are linear with respect to Brownian Motion. This can be achieved by linearization around the

random component. The last thing to do before trying to find a numerical solution to the new stochastic system is identify results in the deterministic case that we want to study. Some possibilities include the final values of the components of the model, the maximum value of components of the model, the time that they reach their maximum, and so on.

3.2 Solving the system of SDEs

For the purposes of this thesis, we will presume the convergence of the solution of the stochastic differential equations. We then decide which numerical method to apply to the now stochastic model. The Euler-Maruyama method described in Chatper 2 is the method that we'll use in this thesis; however, there are various other methods. The Milstein scheme, different order Strong Taylor Schemes, Itô-Taylor and Stratonovich-Taylor Approximations, are just a few of the methods listed in Kloeden and Platen (1999). All of the methods listed are explicit methods like the Euler-Maruyama; however, each method has a higher strong order of convergence than the Euler-Maruyama method. The lowest order of strong convergence for the methods listed is $\gamma = 1$ which is the strong order of convergence for the Milstein method. After adding stochasticity to the model, note that the entire system may not be stochastic. Some of the equations may still be deterministic even if they depend on a random variable from the other parts. In that case, we can choose a method to solve the deterministic portion of the system and combine that method with the stochastic method chosen to obtain a numerical solution. We then do multiple runs of code with different random seeds so that we have results from various sample paths and collect the desired results. As a general rule, the number of runs completed is related to the error in that the error is roughly one over the square root of the number of runs. Last, we analyze the results obtained from the system of stochastic differential equations and compare them to the results obtained by the deterministic system.

3.3 Summary of the Protocol

To summarize the given protocol, we begin with a deterministic model. We then decide which parameter or variable should become stochastic and replace it with a random variable. Once the term is replaced with the random variable, we need to make sure that the new stochastic equation is in the general form so that we can find a numerical solution of the system of equations. Before we find the numerical solution, we need to identify results in the deterministic model that we would like to study. We will assume convergence of the solution of the stochastic differential equations and choose a numerical method to apply to the model. After finding the numerical solution, we analyze the results obtained from the system of stochastic differential equations and compare them to the results obtained by the deterministic system.

Chapter 4

The Model

4.1 The Deterministic Inhalation Anthrax Model

In this chapter, we introduce the model presented in "Modeling the host response to inhalation anthrax" Day et al. (2011). Then we apply the protocol established in Chapter 3 to transform it into a stochastic model, implement a numerical method on the stochastic representation, and interpret the results. The full details of an inhalation anthrax infection and the construction of the model are described in Day et al. (2011), while the main ideas are introduced here. We start with three entities in the lung: free anthrax spores (denoted by S), a type of immune cell in the lung known as alveolar phagocytes (denoted by A), and alveolar host cells (denoted by H) which are alveolar phagocyes that have engulfed spores. When an initial load of spores is inhaled in the lung, the spores are absorbed by the alveolar phagocytes by a given rate, k_2, and trasformed into alveolar host cells. The alveolar host cells then migrate out of the lung by the rate k_3. The first subsystem relating these entities we consider is given by:

$$\begin{cases} \frac{dA}{dt} = -k_2SA + s_A - \mu_A A \\ \frac{dS}{dt} = -k_2SA \\ \frac{dH}{dt} = \frac{k_2SA}{n_S} - k_3H \end{cases}$$

and following the paper, we assume that the equation for A is in the quasi-steady state to arrive at the formula for A : $A = \frac{s_A}{k_2S+\mu_A}$. This reduces the subsystem to

$$\begin{cases} \frac{dS}{dt} = -\frac{k_2Ss_A}{k_2S+\mu_A} \\ \frac{dH}{dt} = \frac{\frac{k_2Ss_A}{k_2S+\mu_A}}{n_S} - k_3H. \end{cases}$$

Now we consider the immune system response within the lymph node with a second subsystem:

$$\begin{cases} \frac{dE}{dt} = s_E - \mu_E E - k_1 B_e E \\ \frac{dB_e}{dt} = k_3 n_B H + k_5 B_e(1 - \frac{B_e}{B_{emax}}) - k_6 E B_e - \frac{k_8 N B_e}{1+\frac{T_A}{c_{t1}}} \\ \frac{dN}{dt} = \frac{k_9 B_e E N_0}{1+\frac{T_A}{c_{t2}}} + \frac{k_{10} N N_0}{1+\frac{T_A}{c_{t3}}} - \mu_N N \\ \frac{dT_A}{dt} = k_4 \frac{B_e}{c_{tb}+B_e} - \mu_{T_A} T_A \end{cases} \tag{4.1}$$

where E represents resident immune cells, B_e represents extracellular bacteria, N represents neutrophils, and T_A represents anthrax toxins Day et al. (2011). The resident immune cells have a source term and a death term, but they also decay in relation to the extracellular bacteria. The first term of the extracellular bacteria equation is a source term due to host cells (H) releasing bacteria into the extra cellular environment. B_e grows logistically and is killed off by resident immune cells and neutrophils. The neutrophils are activated by extracellular bacteria and already activated neutrophils. They have a natural death rate of μ_N. The anthrax toxins are produced by the extracellular bacteria and decay at a rate of μ_{T_A}.

4.2 The Stochatic Inhalation Anthrax Model

Following the protocol given in Chapter 3. We choose to investigate the parameter k_2, which represents the rate at which resident lung phagocytes (or host cells), H, phagocytose anthrax spores. We will replace it with a random variable, $k_2 + c\eta$ where c is a constant and η is a normal random variable with mean 0 and variance 1. We choose to vary this rate because it is an estimated rate, and there is not any guarantee that this rate should be constant. Also it could be that variation in the phagocytosis rate may change downstream events including the final outcome. Subsystem one now becomes a system of stochastic differential equations is given by:

$$\begin{cases} \frac{dS}{dt} = -\frac{(k_2+c\eta)Ss_A}{(k+c\eta)S+\mu_A} \\ \frac{dH}{dt} = \frac{\frac{(k_2+c\eta)Ss_A}{(k_2+c\eta)S+\mu_A}}{n_S} - k_3H \end{cases} . \tag{4.2}$$

Note that Subsystem two (Equation 4.1) remains deterministic since the only component from Subsystem one that is feeding into it is H. Now we implement methods to approximate a solution to this stochastic model.

4.3 Numerical Methods

Note that (4.2) is not linear in the random variable. In order to implement the Euler-Maruyama method on this system of stochastic differential equations, it must first be linearized. We multiply the S equation by $\frac{(k_2S+\mu_A)-c\eta S}{(k_2S+\mu_A)-c\eta S}$ and arrive at the following system (after dropping out the η^2 term), in which η becomes dW:

$$\begin{cases} dS = -\frac{k_2Ss_A}{k_2S+\mu_A}dt - \frac{cSs_A\mu_A}{(k_2+\mu A)^2}dW \\ dH = \frac{k_2Ss_A}{n_S(k_2S+\mu_A)}dt + \frac{cSs_A\mu_A}{n_S(k_2+\mu A)^2}dW - k_3Hdt. \end{cases}$$

For the purpose of this thesis, we will assume that the system of equations does have a solution and that we can approximate it using the Euler-Maruyama method.

Since the only equations that involve the stochastic rate are the first two equations in the system, we will only apply the Euler-Maruyama method to that portion of the system. Subsystem two does not include the stochastic growth rate, only H. Thus H can be interpolated and our time steps put into a vector so that we can apply a built-in MATLAB ode solver to the submodel. The time steps are placed in a vector so that we can control the time steps used in the ode solver. Due to stiffness issues with the system, we used `ode23s` to solve the system of equations in the submodel. The results are listed and discussed in Chapter 5.

4.4 Results to Observe

Following the protocol in Chapter 3, we identify results that we would like to study. The first results to study are the effects that the stochasticity have on H, as it is the main stochastic term. We observe the maximum value of H with various values of c (of the form $c = k_2 \times x$) and varying spore loads and compare those results to the values obtained in the deterministic case. We also observe the overall trend of H and compare that to H in the deterministic case. H affects the entire system, so we will observe the overall trend of of the extracellular bacteria B_e and the neutrophils N as the levels of these entities indicate survival and death scenarios. We ran our code 1000 times for each value of c to observe these trends.

Chapter 5

Results and Conclusions

5.1 Deterministic Results

Before we start analyzing stochastic results, we observe results from the deterministic case. In Chapter 4, we listed results that we wanted to study. The first entities to observe are the host cells. The graph of H is shown in Figure 5.1 with an initial spore load of 4000, where it attains a maximum of 1302. After H attains its maximum, it decreases toward zero as time continues.

The graph of H for a spore load of 2×10^7 has a similar shape and trend, but the maximum attained is 5.64×10^6. Next, we observe the trend of the extracellular bacteria (B_e) and the neutrophils (N). Continued elevated levels of both B_e and N indicate a death scenario, while a survival scenario is indicated by decreasing levels of both B_e and N Day et al. (2011). Figures 5.2 and 5.3 indicate life and death scenarios, respectively, in the deterministic case. In the survival scenario, we start with an initial spore load of 4000; and in the death scenario, we start with an initial spore load of 2×10^7. In the following sections, we observe the effects of the stochasticity on the system. In particular, we study for various values of c the maximum values of H, the overall trend of H, and the distinction between the life and death scenarios.

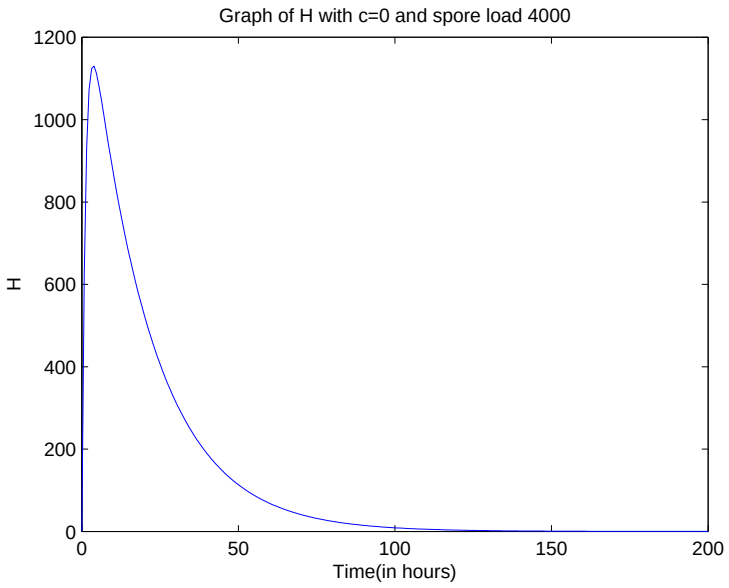

Figure 5.1: Host Cells
Host cells in the deterministic case and initial spore load of 4000.

5.2 Effects on H

One of the first things to look at in this stochastic model when analyzing results is the effect that the stochastics have on H, or the host cells. As observed in the Section 5.1, Figure 5.1 shows the graph of H including the deterministic case and with an initial spore load of 4000. We see that when using $c = \frac{k_2}{5}$ in Figure 5.4, while H is varying with the realizations, the overall behavior of H does not change.

It is difficult to see the differences in the different realizations of H because the graphs are similar enough that it is difficult to distinguish the lines, so Figure 5.5 and Figure 5.6 use boxplots that show the median values (indicated by the line in the middle of each box) as well as the first and third quartiles (the top and bottom of each box, respectively) for the maximum value of H with initial spore loads of 4000 and 2×10^7, respectively. Outliers of the maximum values of H are indicated by a + sign. In the deterministic case for initial spore loads of 4000 and 2×10^7 and various values of c, the maximum number of host cells is around 1130 and 5.64×10^6 respectively. In the case that the initial spore load is set at 4000, we see that the median values

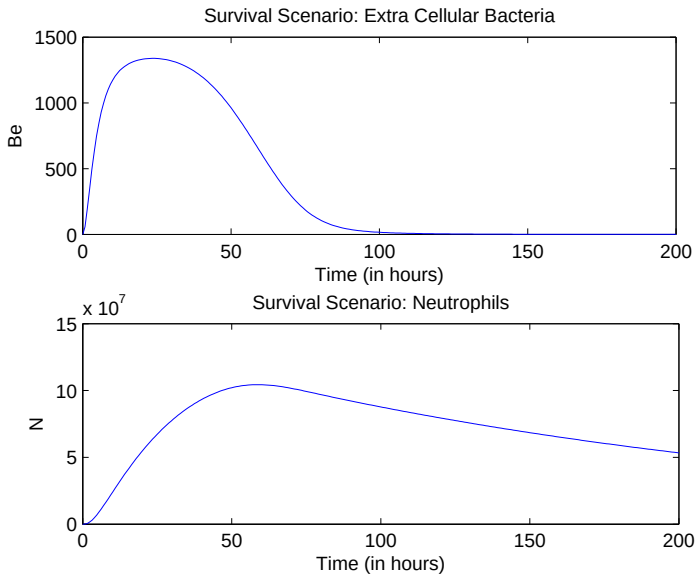

Figure 5.2: Extracellular bacteria and neutrophils in a survival scenario, with an initial spore load of 4000 in the deterministic case.

of the maximum number of host cells remain around the maximum value from the deterministic case, although as c becomes closer to k_2, the median value increases (as shown in Figure 5.7) as well as the variance (as shown in Figure 5.8). We see the same type of growth in the median value of the maximum values of the host cells as well as the variance for an initial spore load of 2×10^7 (Figure 5.9 and Figure 5.10 respectively). Note that in Figure 5.7 and Figure 5.9 that the scaling on the y-axis is narrow. For an initial spore load of 4000, doubling c from $\frac{k_2}{10}$ to $\frac{k_2}{5}$ yields a ratio in the median of the maximum number of host cells of 1.0057 and a slope of 64.7890, where the slope indicates the type of growth of the median value; and doubling c once more to $\frac{2k_2}{5}$ yields a ratio in the median of the maximum number of host cells of 1.0226 and a slope of 129.0285. We also observe the same differences in c with an initial spore load of 2×10^7. Doubling c from $\frac{k_2}{10}$ to $\frac{k_2}{5}$ yields a ratio of 1.0057, and doubling c once more to $\frac{2k_2}{5}$ yields a ratio of 1.0189. We now observe the slope of the variance of the maximum values of the host cells, where the slope indicates the type of growth of in the variance. For an initial spore load of 4000, the slope between $c = \frac{k_2}{10}$ and $c = \frac{k_2}{5}$ is 3.6803×10^3. The slope between $c = \frac{k_2}{5}$ and $c = \frac{2k_2}{5}$ is 1.2493×10^4. For an initial

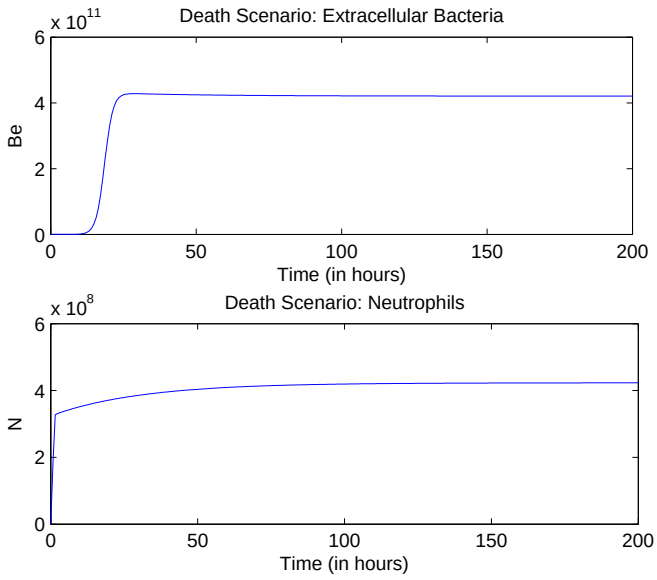

Figure 5.3: Extracellular bacteria and neutrophils in a death scenario, with an initial spore load of 2×10^7 in the deterministic case.

spore load of 2×10^7, the slope between $c = \frac{k_2}{10}$ and $c = \frac{k_2}{5}$ is 8.2815×10^{10}. The slope between $c = \frac{k_2}{5}$ and $c = \frac{2k_2}{5}$ is 1.8460×10^{11}.

5.3 Effects on Survivor Results

Now we want to examine the results that we get using the results of the stochastic system in the lymph node sub-model (Subsystem 2, equation (4.1)). In Day et al. (2011), the authors indicate with a high number of extracellular bacteria and neutrophils, the subject will die. To obtain a death scenario in the deterministic case, the initial spore count needs to be at 4240 or greater from our runs of the model. The authors start their death scenario at an initial spore count of 4500. For the results given, we used $c = \frac{k_2}{5}$ as it has the one of the largest variances out of the values that we used ($c = \frac{3k_2}{5}$ made the extracellular bacteria numbers drop below zero during some code runs). We see in Figure 5.11 that with an initial spore load of 4000, that the subject survives. If we increase the initial spore load to 4200 and even 4225, the graph still indicates that the subject survives. Any spore load before 4240

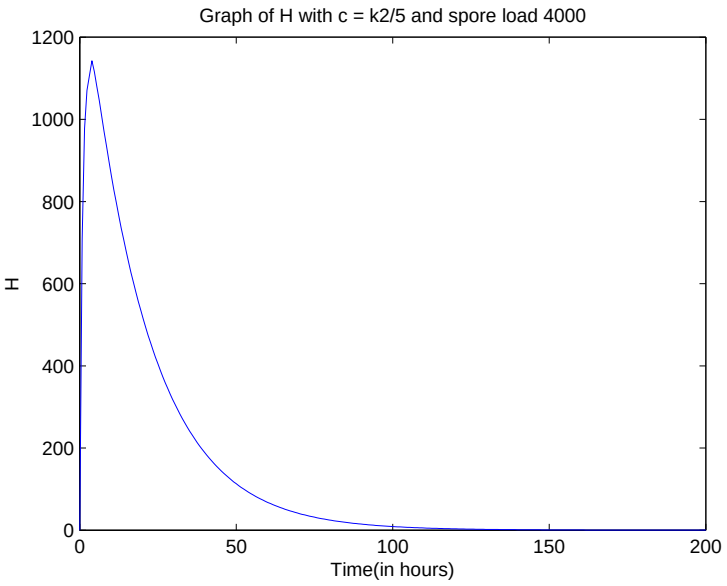

Figure 5.4: Graph of H
Graph of H with $c = \frac{k_2}{5}$ and initial spore load of $4,000$.

indicates a survival scenario. With an initial spore load of 4240 though, as shown in Figure 5.15, the subject dies as it also does in the deterministic case. Therefore, the stochasticity does not have a much of an impact, if any impact at all, on the system for an initial spore load of 4240.

Now for an initial spore load of 2×10^7 and various values of c, we will study the end values of extracellular bacteria. Observing the end value of the extracellular bacteria for 1000 runs, $c = \frac{k_2}{100}$ and an initial spore load of 2×10^7, we see that only 47.2% of the end values are greater than that of the determinisitic case. The difference, however, is so small that none of the end values in these runs yields a value that is greater than 1.01 times the end value of the deterministic case. Increasing c to $c = \frac{k_2}{5}$, 48% of the end values are greater than that of the deterministic case. Similar to the $c = \frac{k_2}{100}$ case, none of the end values are greater than 1.01 times the end value of the deterministic case. We see similar results for $c = \frac{2k_2}{5}$ and $c = \frac{3k_2}{5}$. To conclude, increasing the variance on k_2 does not have an impact that is different

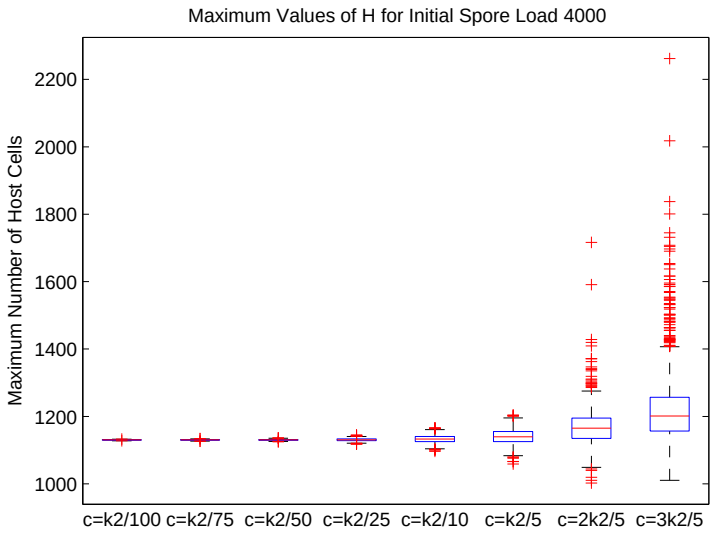

Figure 5.5: Distribution of the Maximum Value of H
Boxplot for varying values of c and initial spore load of 4000.

Table 5.1: Comparison of Extracellular Bacteria End Values

C-Value	% $\geq$ Deterministic	Maximum Value
0	—	5.642×10^6
$\frac{k_2}{100}$	47.2	5.657×10^6
$\frac{k_2}{5}$	48	6.037×10^6
$\frac{2k_2}{5}$	47.8	6.668×10^6
$\frac{3k_2}{5}$	41	8.419×10^6

than in the deterministic case. This could be because this system is stable enough that perturbing k_2 does not have a large effect on the survivalship scenario.

5.4 Future Directions

The protocol established in Chapter 3 worked well for this deterministic biological model. We were able to add stochasticity to the model, solve the system numerically, and analyze the results. An improvement to the protocol could address the issue of varying more than one parameter at once. While perturbing k_2 did not have

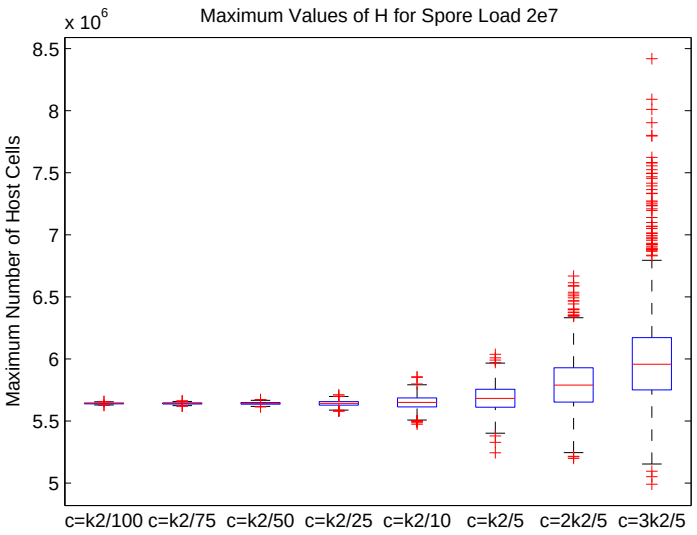

Figure 5.6: Distribution of the Maximum Value of H
Boxplot for varying values of c and initial spore load of 2×10^7.

any drastic effects on the results, there are other possible parameters that could be varied, such as n_b. This parameter is the number of bacteria (on average) inside a host cell after migrating to the MLN and after anthrax spores have germinated, become vegetative bacteria and grown intracellularly before lysing the cell Day et al. (2011). This is also an average estimated value, and the true value could vary in an unknown way. Another possible scenario is to add a stochastic term to one or more of the equations and then analyze survivalship scenarios.

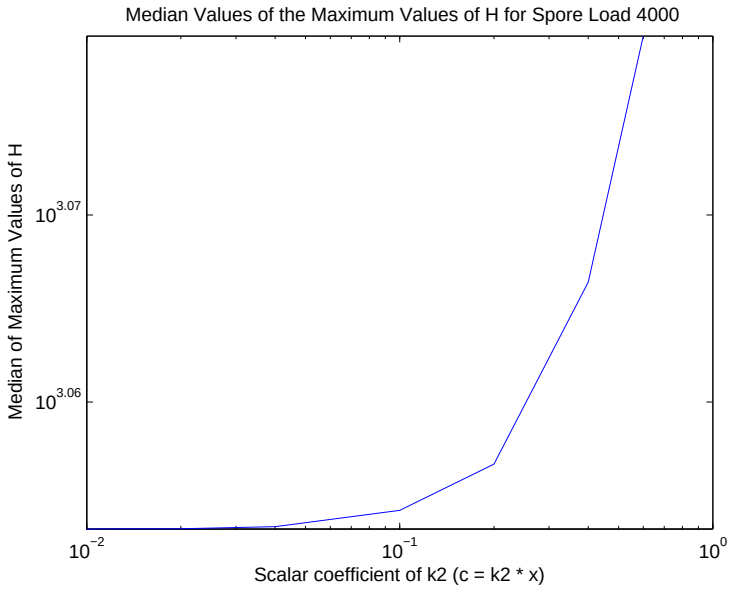

Figure 5.7: Median Values of the Maximum Values of H
Initial spore load of 4000

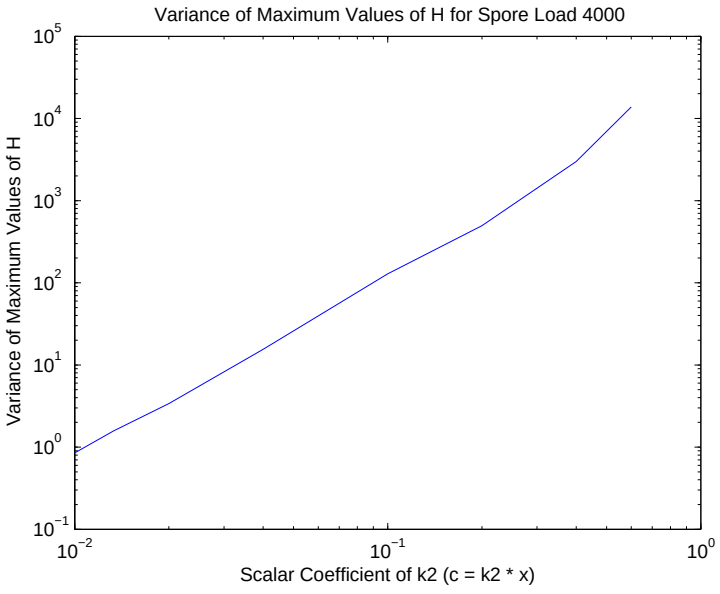

Figure 5.8: Variance of the Maximum Values of H
Initial spore load of 4000

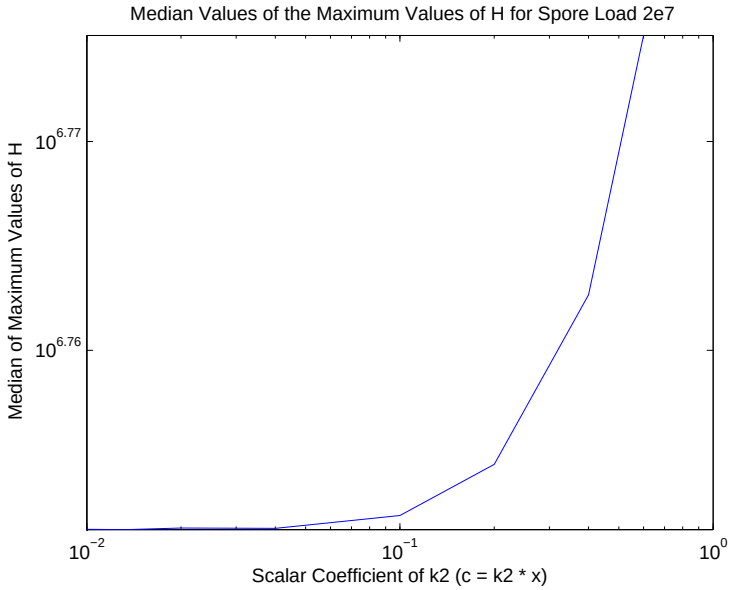

Figure 5.9: Median Values of the Maximum Values of H
Initial spore load of 2×10^7

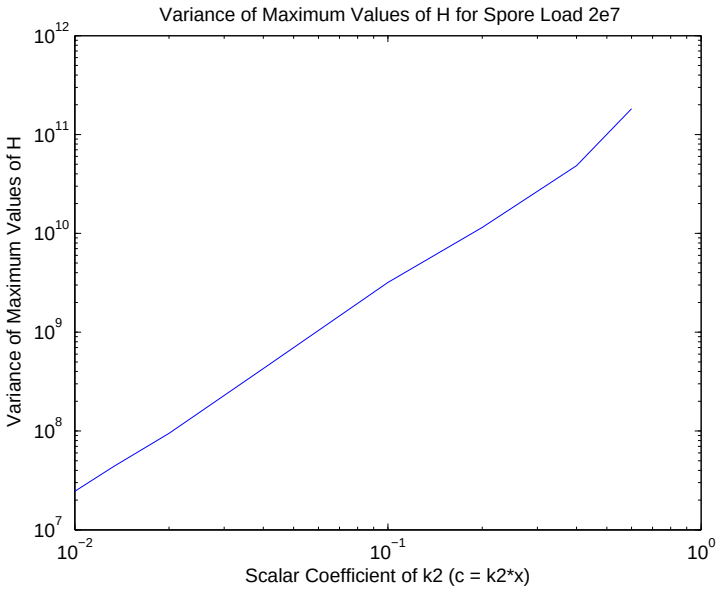

Figure 5.10: Variance of the Maximum Values of H
Initial spore load of 2×10^7

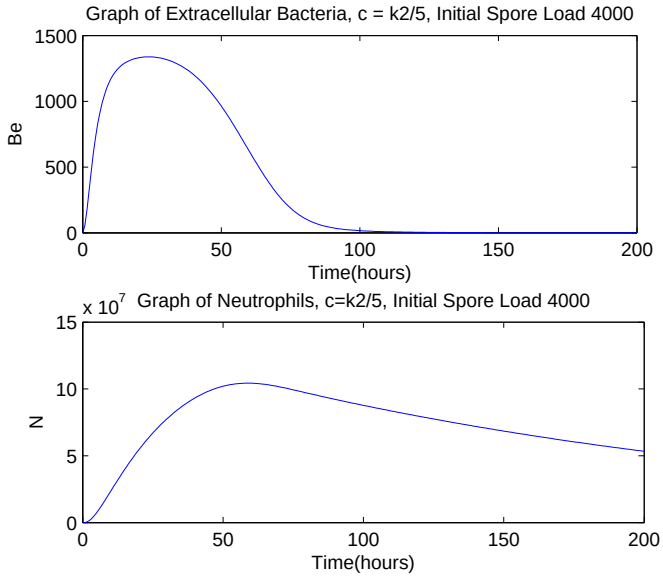

Figure 5.11: Extracellular bacteria and neutrophils with $c = \frac{k_2}{5}$ and initial spore load of 4000.

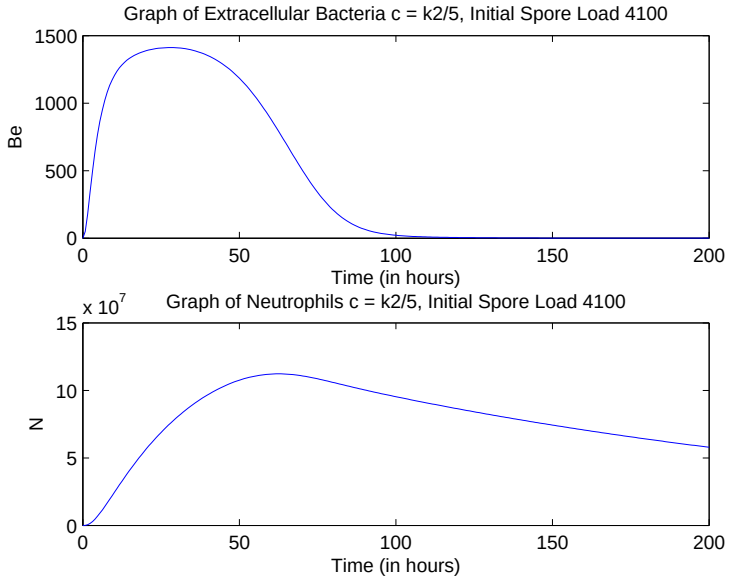

Figure 5.12: Extracellular bacteria and neutrophils with $c = \frac{k_2}{5}$ and initial spore load of 4100.

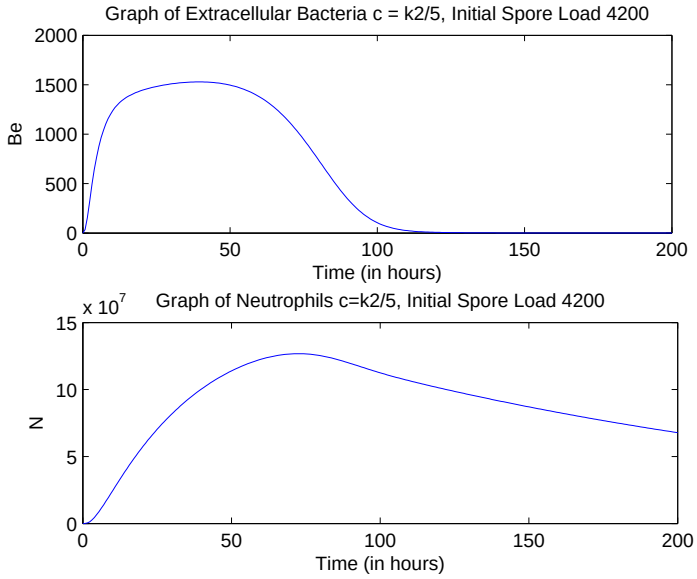

Figure 5.13: Extracellular bacteria and neutrophils with $c = \frac{k_2}{5}$ and initial spore load of 4200.

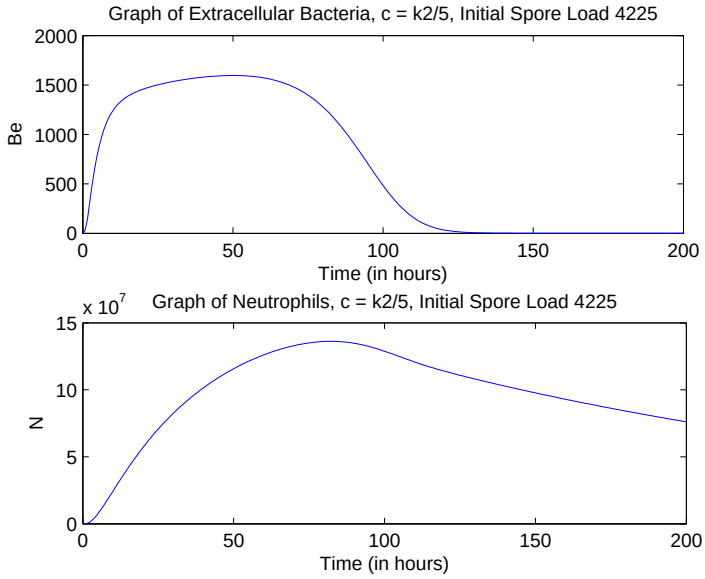

Figure 5.14: Extracellular bacteria and neutrophils with $c = \frac{k_2}{5}$ and initial spore load of 4225.

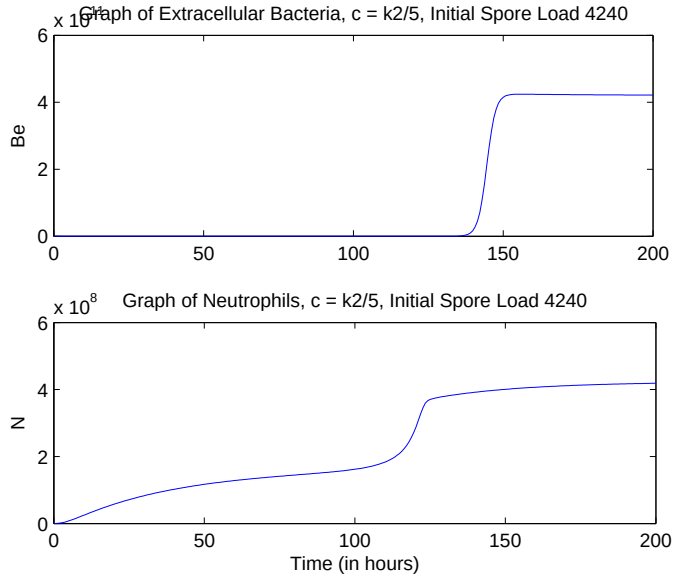

Figure 5.15: Extracellular bacteria and neutrophils with $c = \frac{k_2}{5}$ and initial spore load of 4240.

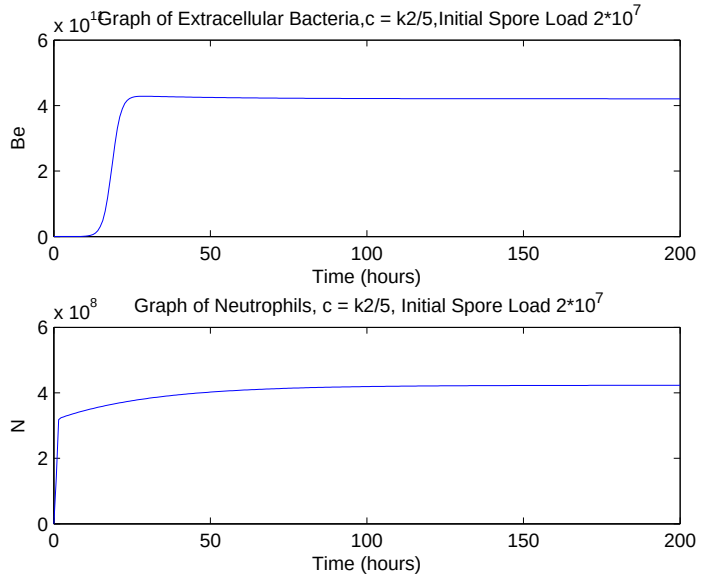

Figure 5.16: Extracellular bacteria and neutrophils with $c = \frac{k_2}{5}$ and initial spore load of 2×10^7.

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Vita

Kacy Aslinger was born and raised in East Tennessee where she attended school, rode horses, and participated in the school band. She graduated from Roane County High School in 2007 and furthered her education and the University of Tennessee. In the spring of 2011, she graduated from the University of Tennessee with a Bachelor of Science Degree in Mathematics. After taking a year off from school, Kacy decided to come back to the University of Tennessee to pursue a Master of Science Degree. During part of her time at the university, she worked as a Graduate Teaching Associate.