The Journal of Undergraduate Research

Volume 5 *Journal of Undergraduate Research, Volume 5: 2007*

Article 9

2007

Modeling Immune Response to Bacterial Infection

Carla Roth
South Dakota State University

Modeling Immune Response to Bacterial Infection

Author: Carla Roth
Faculty Sponsor: Dr. Matt Biesecker
Department: Mathematics

INTRODUCTION

Mathematical models have begun to play an important role in the study of biology. We will examine this role further by analyzing a specific model of the innate immune system's response to a bacterial infection. Beginning with the biological background of the model, we will move into an explanation of a specific model of this situation followed by a critique of the model and future work to be done with the topic.

The human body faces invasion from infectious agents including viruses and bacteria on a daily basis [6]. The human body in turn has various defense systems in place to counteract the daily threat from infectious agents and foreign material trying to enter the body's otherwise sterile environment. When an infectious agent first enters the body, the body's sensory systems alert its own cells known as host cells to the presence of the foreign material. The sensors then aid in guiding other host cells to the location of the infectious agent and initiating the process of destroying the foreign material. This form of defense against infectious agents plays a major role in the body's innate immunity [5]. Innate immunity is inborn and its effectiveness is independent of whether or not the body has been previously exposed to a given infectious agent [6].

Working with the body's innate immunity, the adaptive immune response specializes in recognizing particular infectious agents and developing specific antibodies to destroy them. While the innate immunity's defenses take action when foreign material gains access to the body despite the material's makeup, the reaction of the adaptive immune response is dependent upon whether or not the body has encountered the specific infectious agent before and if so, how many times the body has encountered it [5].

After being exposed to an infectious agent, the adaptive immune response works to produce antibodies to help recognize and destroy that specific type of infectious agent within the body. The adaptive immune response in turn becomes more efficient in destroying specific infectious agents after it has been exposed to the agents. The down side is that recognizing infectious agents and producing specific antibodies takes time. During this time the infectious agents may cause damage to the body or even death [5].

Due to the amount of time the adaptive immune response requires and its complex nature, we will focus on the innate immunity's response to a bacterial infection and specifically on its two major components: neutrophils and macrophages. Neutrophils and macrophages are both phagocytes, cells that specialize in destroying foreign material via ingestion. Macrophages and neutrophils circulate throughout the body ingesting foreign particles they encounter. In the case of an infection, damaged cells or macrophages that

have ingested foreign particles will release specific chemical signals within the body called cytokines to recruit the help of other phagocytes. One of the body's primary reactions to an infection, inflammation aides in the process of containing and destroying an infection [5].

Neutrophils possess a vital role during early inflammation. Produced in the bone marrow, neutrophils live for only 8 to 20 hours, while neutrophils recruited to fight an infection in the tissue undergo chemical changes that allow them to live for several days. Although neutrophils are short-lived, they still remain a dominant player in the innate immune response and account for 40 to 60 percent of the white blood cells found in the body. During an infection, the concentration of the neutrophils can increase up to tenfold to help fight off the infection [3].

Contrary to the short-lived neutrophils, macrophages live for weeks to months. Also produced in the bone marrow, blood monocytes experience changes as they leave the bloodstream and enter the body's tissues as macrophages. While in the tissue, macrophages may undergo changes to become active macrophages. Active macrophages have an increased killing power and are able to more easily recognize and digest foreign material. Macrophages play a role in both the innate immune response and the adaptive immune response recognizing and destroying foreign material [5]. We will focus solely on the macrophages role in the body's innate immune response.

We will now move on to explore a mathematical model of this situation presented in the paper "Release kinetics and cell trafficking in relation to bacterial growth explain the time course of blood neutrophils and monocytes during primary Salmonella infection." In a recent paper Takumi, Garssen, et al, make use of both their own and others' experimental data to create a system of differential equations to model the effects a bacterial infection has on neutrophil and macrophage concentrations [7]. The authors use the model to calculate the probability that the infected host's innate immune responses are overrun and the host becomes ill [7]. The following is an explanation and listing of the differential equations involved in this model. Note all of the individual terms and parameters in the equations are positive, B represents the concentration of bacteria, and capitalized letters represent concentrations that vary over time whereas lowercase letters represent constant values. A formal listing of the parameters used, their meanings, and their values can be found in Appendix A.

Equations (1) and (2) below model the individual concentrations of the neutrophils in the blood and in the tissue. Contrary to the neutrophils, macrophages possess three different states and equations (3), (4) and (5) represent the individual concentrations of the blood monocytes, tissue macrophages, and activated macrophages.

Rate of change of concentration of blood neutrophils = Rate of neutrophil release from bone marrow + Maximum neutrophil release rate in infection - Death rate of blood neutrophils - Migration rate of neutrophils from blood to tissue

$$\frac{d}{dt}N_b = s_1 + \frac{s_2 B^{n_1}}{h_1 + B^{n_1}} - d_1 N_b - \frac{k_1 N_b B^{n_2}}{h_2 + B^{n_2}} \quad (1)$$

Rate of change of concentration of tissue neutrophils = Migration rate of neutrophils from blood to tissue - Death rate of tissue neutrophils

$$\frac{d}{dt}N_t = \frac{k_1 N_b B^{n_2}}{h_2 + B^{n_2}} - d_2 N_t \quad (2)$$

Rate of change of concentration of blood monocytes = Rate of monocyte release from bone marrow + Rate of maximum monocyte release in infection - Death rate of blood monocytes - Migration rate of blood monocytes to tissue macrophages - Migration rate of blood monocytes to tissue macrophages in infection

$$\frac{d}{dt}M_b = s_3 + \frac{s_4 B^{n_3}}{h_3 + B^{n_3}} - d_3 M_b - k_2 M_b - \frac{k_3 M_b B^{n_4}}{h_4 + B^{n_4}} \quad (3)$$

Rate of change of concentration of tissue macrophages = Migration rate of blood monocytes to tissue macrophages + Migration rate of blood monocytes to tissue macrophages in infection - Death rate of tissue macrophages - Activation rate of tissue macrophages to activated macrophages in

$$\frac{d}{dt}M_t = k_2 M_b + \frac{k_3 M_b B^{n_4}}{h_4 + B^{n_4}} - d_4 M_t - cM_t B \quad (4)$$

Rate of change of concentration of activated macrophages = Activation rate of tissue macrophages to activated macrophages in infection - Death rate of activated macrophages

$$\frac{d}{dt}M_a = cM_t B - d_5 M_a \quad (5)$$

Rate of change of bacteria population = Growth rate of bacteria - Rate of phagocytosis by tissue neutrophils - Rate of phagocytosis by tissue macrophages - Rate of phagocytosis by activated macrophages

$$\frac{d}{dt}B = rB - z_1 N_t B - z_2 M_t B - z_3 M_a B \quad (6)$$

The relationship between the parameters and the concentration of the neutrophils and the macrophages is represented pictorially in Figure 1 (A) and (B). Within Figure 1 solid arrows represent the movement of phagocytes in the absence of infection and dashed arrows represent the movement of additional phagocytes that are present during an infection. Note a major difference between neutrophils and macrophages exists in that tissue macrophages possess a baseline source plus an additional source in the presence of an infection, as opposed to the tissue neutrophils where migration occurs only in the presence of an infection. Relating both the neutrophil and macrophage concentrations,

equation (6) introduces a per capita growth rate for the bacteria (r) along with per capita rates of phagocytosis for the neutrophils and macrophages. Note the rate of change of the bacterial concentration in equation (6) depends upon a single source and individual death terms for each type of phagocyte present at the sight of the infection.

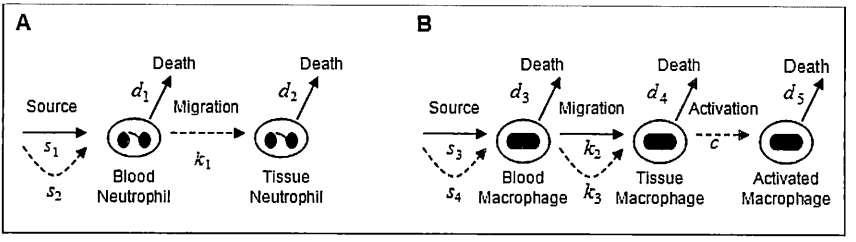

Figure 1

As an initial condition for the set of equations, we assume the bacteria concentration is equal to zero, such the $B(0)=0$. We consider this initial state a "healthy equilibrium" since it represents the case in which the body is free of harmful bacteria.

When $B(0)=0$, we assume the individual concentrations of neutrophils and macrophages are constant since no additional neutrophils or macrophages are being recruited in the absence of an infection. If the rates of change of the individual concentrations of neutrophils and macrophages are constant, then the rates of change of these concentrations are equal to zero. As a result, the left hand sides of equations (1) through (5) are equal to zero. With the left hand sides of equations (1) through (5) set equal to zero, we can solve the equations algebraically to determine the initial conditions of each variable while keeping in mind $B(0)=0$.

Thus, $N_b(0)=\frac{s_1}{d_1}$, $N_t(0)=0$, $M_b(0)=\frac{s_3}{d_3+k_2}$, $M_t(0)=\frac{k_3 s_3}{d_4(d_2+k_2)}$ and $M_a(0)=0$.

Note the initial concentrations of the tissue neutrophils and tissue macrophages align with the fact that tissue macrophages possess a baseline source and tissue neutrophils do not possess a baseline source as displayed in Figure 1 and equations (2) and (4).

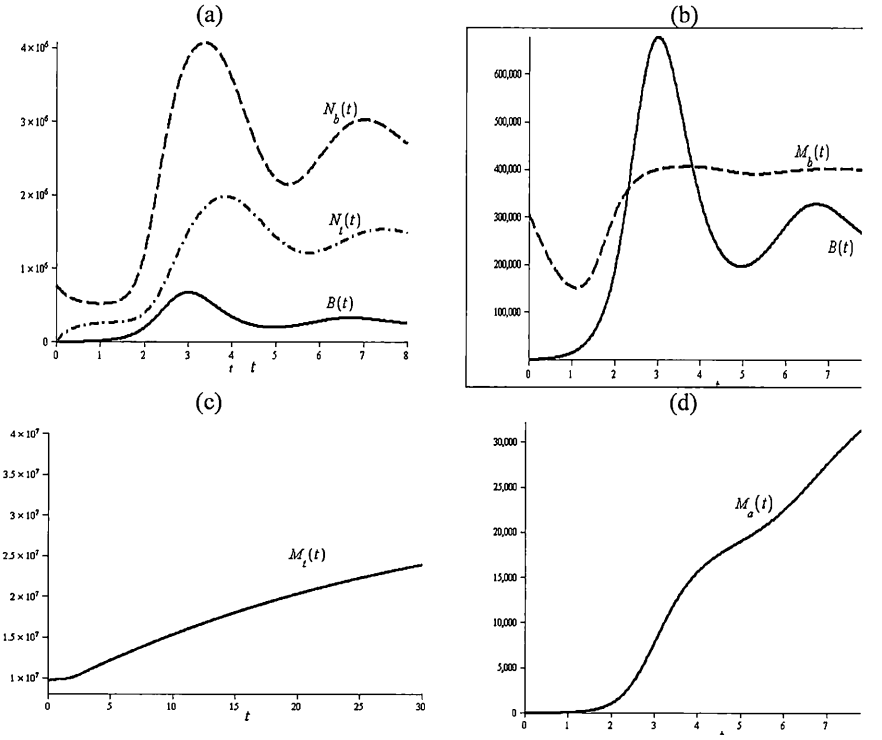

Figure 2. Numerical Solution of Equations (1)-(6)

Using parameter values as given in [7] (listed in Appendix A), a numerical solution to equations (1)-(6) is easily obtained. The graphs of the concentrations of bacteria, neutrophils and macrophages are then plotted over time. An initial value of B(0)=1000 was chosen. As can be seen in Figure 2a, an increase in the concentration of the bacteria is followed by an increase in the blood and tissue neutrophil concentrations, which results in a slight dip in the bacteria concentration. As time continues, the concentration of the bacteria begins to level off but stays above zero representing an unhealthy state. A similar relationship can exist with the blood monocytes and activated macrophages (See Figure 2b). The corresponding graph of tissue macrophages and activate tissue macrophages are displayed in Figures 2c and 2d.

Although the system of differential equations represented by equations (1) through (6) may accurately represent the innate immune response in specific situations, one will find various problems within the model upon further review. Analyzing the rate of change of the bacterial concentration as represented by equation (6), we discover given that a specific per capita growth rate of the bacteria, *r*, the bacteria may grow exponentially without bound. Bacteria cells multiply via binary fission; meaning a bacteria cell replicates all of its cell parts and then divides into two individual cells [5]. The time it

takes for a bacteria cell to duplicate itself depends upon the type of bacteria [5]. In general, a bacteria population can grow exponentially without bound given an unlimited amount of resources and space [5]. The current model allows for such an environment, whereas in the real world such an environment does not exist.

To analyze the possibility of unlimited exponential bacteria growth further we will prove the model allows for such a possibility as outlined in Proposition 1.

Proposition 1. *If* $r > z_1 N^* + \max(z_2, z_3) M^*$ *with*

$$N^* = \frac{k_1(s_1 + s_2)}{d_1 \cdot d_2} \text{ and } M^* = \frac{s_3 + s_4}{\min(d_3, d_4, d_5)},$$

then $B(t) \geq B(0)e^{r_0 t}$ *for some* $r_0 > 0$ [original to paper].

We will delay the proof of Proposition 1 until after a brief explanation of the processes involved in the proof. Proposition 1 states if the per capita growth rate for bacteria, r, is greater than an upper bound for the amount of bacteria being destroyed by all neutrophils and all macrophages, $z_1 N^* + \max(z_2, z_3) M^*$, for specific upper bounds on the concentration of neutrophils and macrophages, then the bacteria population is growing at a rate equal ~~than~~ exponential growth.

We will first show an upper bound exists for the concentration of both the neutrophils and the macrophages. Then we will use these upper bounds to establish the existence of a threshold value for r such that $\frac{d}{dt} B > 0$, the rate of change in the concentration of bacteria is greater than zero. Finally, we will use the threshold value for r to show $B(t) \geq B_0 e^{r_0 t}$ where $r_0 = r - z_1 N^* - z_3 M^*$. Note the upper bound values created, N^* and M^*, are crude upper bounds of the functions and lower maximum values may exist. The following lemma will be used within the proof of Proposition 1 to establish upper bounds for the neutrophil and the macrophage concentrations.

Lemma 1. *For a function* $z(t)$ *with* $z(0) > 0$ *and real numbers* $a, b > 0$:

1. *If* $\frac{dz}{dt} \geq bz$, *then* $z(t) \geq z(0)e^{bt}$ *for all* $t \geq 0$.
2. *If* $\frac{dz}{dt} \leq a - bz$ *with* $a > 0$ *and* $z(0) < \frac{a}{b}$, *then* $z(t) \leq \frac{a}{b}$ *for all* $t \geq 0$.

Proof of Lemma 1. Both statements will be proven using the well-known theorem if f, g are continuous and $f(w) \leq g(w)$ for all $w \in R$, then $\int_a^b f(w)\, dw \leq \int_a^b g(w)\, dw$ [1].

1. Let b be a real number such that $b > 0$. Assume $\frac{dz}{dt} \geq bz$ for some function $z(t)$. It follows from $\frac{dz}{dt} \geq bz$ that $\frac{dz}{dt}\frac{1}{z} \geq b$, which can be rewritten as $\frac{d}{dt}[\ln z(t)] \geq b$. Applying the theorem to the inequality $\frac{d}{dt}[\ln z(t)] \geq b$ results in

$\int_0^t \frac{d}{dt}[\ln z(t)]\,dt \geq \int_0^t b\,dt$. Then it follows $\ln z(t) - \ln z(0) = \ln\frac{z(t)}{z(0)} \leq bt$. Since $b > 0$, taking the exponential of each side of the inequality will still maintain the inequality. Hence, $e^{\ln[z(t)/z(0)]} \geq e^{r_0 t}$ and as a result $z(t) \geq z(0)e^{rt}$ for all $t \geq 0$.

2. Let a, b be real numbers such that $a > 0$ and $b > 0$. Assume $\frac{dz}{dt} \leq a - bz$ with $z(0) < \frac{a}{b}$ for some function $z(t)$. Then it follows from $\frac{dz}{dt} \leq a - bz$ that $\frac{dz}{dt} + bz \leq a$. Multiplying by an e^{bt} we obtain $e^{bt}\left(\frac{dz}{dt} + bz\right) \leq e^{bt}a$, which can be rewritten as $\frac{d}{dt}(e^{bt}z) \leq e^{bt}a$. Applying the theorem to $\frac{d}{dt}(e^{bt}z) \leq e^{bt}a$ we obtain $\int_0^t \frac{d}{dt}(e^{bt}z)\,dt \geq \int_0^t e^{bt}a\,dt$. As a result, $e^{bt}z(t) - e^0 z(0) \leq \frac{a}{b}(e^{bt} - 1)$. Multiplying the inequality by e^{-bt} results in $z(t) - z(0)e^{-bt} \leq \frac{a}{b} - \frac{a}{b}e^{-bt}$. Thus from $z(0) < \frac{a}{b}$ we obtain $z(t) \leq e^{-bt}(z(0) - \frac{a}{b}) + \frac{a}{b} \leq \frac{a}{b}$. Then it follows from $a > 0$ and $b > 0$ that $\frac{a}{b} > 0$, and as a result $z(t) \leq \frac{a}{b}$ for all $t \geq 0$. Q.E.D.

Proof of Proposition 1. To establish an upper bound for the neutrophil concentration, N^*, add the right hand sides of (1) and (2) which results in

$$\frac{d}{dt}(N_b + N_t) = s_1 + s_2\frac{B^{n_1}}{h_1 + B^{n_1}} - d_1 N_b - d_2 N_t$$
$$\leq s_1 + s_2 - \min(d_1, d_2)\cdot(N_b + N_t).$$

Let $N(t) = N_b(t) + N_t(t)$. Then by the second part of Lemma 1 with $a = s_1 + s_2$, $b = \min(d_1, d_2)$ and $z(t)=N(t)$ it follows that

$$N_t(t) \leq \mathrm{N}(t) \leq \frac{s_1 + s_2}{\min(d_1, d_2)}$$

for all $t \geq 0$. As a result $N^* = (s_1 + s_2)/\min(d_1, d_2)$ is an upper bound for the neutrophil concentration in the infected tissue.

To establish an upper bound for the macrophage concentration, M^*, add the right hand sides of (3), (4) and (5) which results in

$$\frac{d}{dt}(M_b + M_t + M_a) = s_3 + s_4\frac{B^{n_2}}{h_3 + B^{n_2}} - d_3 M_b - d_4 M_t - d_5 M_a$$
$$\leq s_3 + s_4 - \min(d_3, d_4, d_5)\cdot(M_b + M_t + M_a).$$

Let $M = M_b + M_t + M_a$. Then by the second part of Lemma 1 with $a=s_3+s_4$, $b = \min(d_3, d_4, d_5)$ and $z(t)=M(t)$ it follows that

$$M_a + M_t \le M(t) \le \frac{(s_3 + s_4)}{\min(d_3, d_4, d_5)}$$

for all $t \ge 0$. As a result $M^* = (s_3 + s_4)/\min(d_3, d_4, d_5)$ is an upper bound for the macrophage concentration in the infected tissue.

To establish a threshold value for r such that $\frac{d}{dt}B > 0$ we will first rewrite equation (6) as $\frac{d}{dt}B = B(r - z_1 N_t - z_2 M_t - z_3 M_a)$. Note $B(0)>0$ because a negative amount of bacteria is not possible and if no bacteria is present at time $t=0$, then the $B(t)=0$ for all $t \ge 0$. Then the established upper bounds for the neutrophil and macrophage concentrations imply

$$\frac{d}{dt}B \ge B(r - z_1 N^* - \max(z_2, z_3)M^*).$$

As a result $\frac{d}{dt}B > 0$ whenever $r > z_1 N^* + \max(z_2, z_3)M^*$. Now define

$$r_0 = r - z_1 N^* - \max(z_2, z_3)M^*.$$

Now assume that $r_0 > 0$ and we obtain

$$\frac{d}{dt}B = B(r - z_1 N_t - z_2 M_t - z_3 M_a)? \ge r_0 B > 0.$$

If $B(0) > 0$, by the first part of Lemma 1 with $b=r_0$ and $z(t)=B(t)$, it follows that $B(t)? \ge B(0)e^{r_0 t}$. Therefore, $B(t)$ is greater than exponential growth and the population of the bacteria grows at a rate equal to or greater than exponential growth. Q.E.D.

The proof of Proposition 1 mathematically outlines the possibility of unlimited bacteria growth within the current model. Given a specific per capita growth rate of the bacteria, r, the bacteria may grow exponentially without bound. This contradicts the real world situation in which numerous factors including the environment in which the bacteria resides affects the bacteria's growth. As a result for large per capita bacteria growth rates (large r), a model that considers a limited growth factor for the bacteria would more accurately reflect what occurs in the real world situation of bacterial infections. Combining the original growth term rB with a limiting growth factor $1-B/k$ for some constant k, would produce a source term of $rB(1-B/k)$ that more accurately represents the eventual leveling off of the exponentially growing bacteria population. To determine a precise value for k and to determine the effect the limiting growth factor will have on the accuracy of the model, future work will need to focus on how well the new model fits current data and for what bacteria growth rates the model holds true.

Another problem with the model exists within the parameter choices for the death rates of the blood and tissue neutrophils, d_1 and d_2 respectively. As previously explained, neutrophils in the tissue undergo chemical changes that allow them to live for several

days whereas neutrophils in the blood only live for 8 to 20 hours [3]. The current parameter choice of $d_1=d_2$ does not accurately represent the differences in the blood and tissue neutrophils' life spans. Changing the model by choosing death rates such that $d_1>d_2$ would more accurately reflect the biological nature of neutrophils. Future research is into the nature of neutrophils is necessary to determine accurate values for the separate death rates of blood and tissue neutrophils.

Further examination of equation (6) calls a different aspect of the model's biological nature into question. The killing term for the tissue neutrophils, z_1N_tB, allows for unbounded per capita phagocytic rates. This means as written, equation (6) allows for the possibility that a neutrophil can eat an infinite amount of bacteria. Research into the per capita phagocytic rate or killing rate of neutrophils has shown that a sigmoidal relation rather than linear relation exists between the per capita phagocytic rate of the neutrophils and the bacteria concentration [2]. As a result, the per capita phagocytic rate of neutrophils at first notably increases as the bacteria concentration increases and then begins to level off as the bacteria concentration continues to increase [2]. Thus the per capita phagocytic rate of neutrophils possesses a limit or a bound [2]. To accurately reflect the bound biology places on the neutrophil's per capita phagocytic rate, a limiting factor must be added to the killing term for tissue neutrophils in equation (6).

We propose a the following simplified model involving only bacteria and neutrophils that takes limited growth of bacteria and a bounded per capita phagocytic rate for neutrophils into account.

$$\frac{d}{dt}B = rB(1-B/K) - z\frac{B^m}{a^m+B^m}N_t \qquad (7)$$

$$\frac{d}{dt}N_b = s_1 + s_2\cdot\frac{B^{n_1}}{h_1+B^{n_1}} - d_1N_b - \frac{k_1B^{n_2}}{h_2+B^{n_2}}\cdot N_b \qquad (8)$$

$$\frac{d}{dt}N_t = \frac{k_1B^{n_2}}{h_2+B^{n_2}}\cdot N_b - d_2N_t. \qquad (9)$$

he differential equations for N_b and N_t are identical to equations (1) and (2). The ɔnstant z represents the maximum per capita phagocytic rate for tissue neutrophils ıd a is equal the bacterial concentration at which the phagocytic rate is half the ıaximum value. The upper limit for bacterial concentration is given by K. It is ıteresting to note that our model given by (7)-(9) yields bacterial concentrations (t) similar to the values obtained with the full model in equations (1)-(6). We ıoose parameter values for equations (7) and (8) as given in [7] and Appendix A. or equation (6) we let $K=10^9$ *c.f.u/ml* and estimated parameter values of $=1.14\times10^6$, $r=3.01$, $z=3.72$, and $m=1.20$ using a least squares fit to the ɔlution for the full model (1)-(6) derived by Takumi, Garssen, and others in [7].

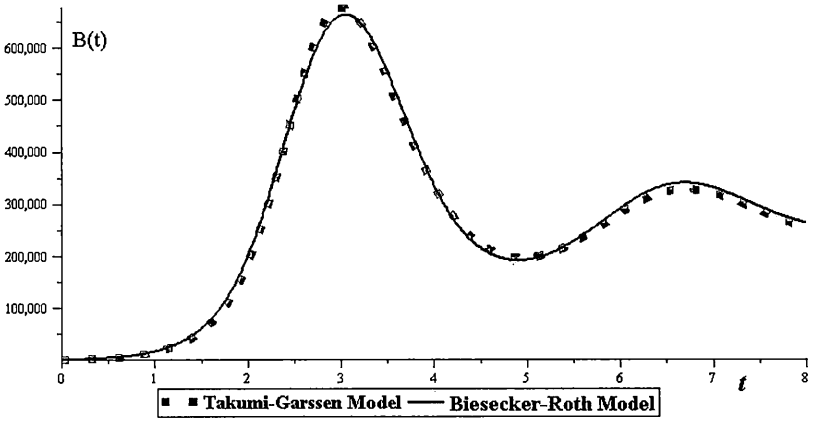

Figure 3. Numerical Solution of Equations (7)-(9)

Future work in this area could focus on determining an accurate bound for the per capita phagocytic rate of tissue neutrophils and calculating an accurate value for the constants a and m introduced in the limiting factor in equation (7). An investigation into the per capita phagocytic rates of the tissue and activated macrophages to determine whether or not introducing limiting factors is necessary could also be a focus of further research into this area. It would also be of interest to analyze the system of equations (7)-(9) to determine the number of equilibrium points and the stability of each equilibrium point.

BIBLIOGRAPHY

1. Bartle, R., D. Sherbert. Introduction to Real Analysis: Third Edition. New York: John Wiley & Sons, Inc., 2000.
2. Detilleux, J. "Neutrophils in the War Against Staphylococcus aureus: Predator-Prey Models to the Rescue." American Dairy Science Association 87 (2004):3716-3724.
3. Edwards, S. Biochemistry and Physiology of the Neutrophil. New York: Cambridge University Press, 1994.
4. Fagerström, T., P. Jagers, P. Schuster, E. Szathmary. "Biologists Put on Mathematical Glasses." Science 274 (1996): 2039-2049.
5. Nester, E., D. Anderson, C. Roberts, Jr., N. Pearsall, M. Nester, and D. Hurley. Microbiology: A Human Perspective. New York: McGraw Hill, 2004.
6. Roitt, I., P. Delves. Roitt's Essential Immunology. Oxford: Blackwell Science Ltd., 2001.
7. Takumi, K., J. Garssen, R. Jonge, W. Jong and A. Havelaar. "Release kinetics and cell trafficking in relation to bacterial growth explain the time course of blood neutrophils and monocytes during primary Salmonella infection." International Immunology 17 (2004): 85-93.

Appendix. Parameter Values from [7]

	Meaning	Value
r	Growth rate of bacteria	$3.1/day$
s_1	Rate of neutrophil release into blood (IOI)***	$1.6\times10^{6}\ cells/ml/day$
s_2	Max. rate of neutrophil release into blood during infection	$1.4\times10^{7}\ cells/ml/day$
s_3	Rate of monocyte release into blood (IOI)***	$3.0\times10^{5}\ cells/ml/day$
s_4	Max. rate of monocyte release into blood during infection	$8.0\times10^{5}\ cells/ml/day$
d_1	Neutrophil death rate in blood	$2.1/day$
d_2	Neutrophil death rate in tissue	$2.1/day$
d_3	Monocyte death rate in blood	$0.03/day$
d_4	Resting macrophage death rate in tissue	$0.03/day$
d_5	Activated macrophage death rate in tissue	$0.03/day$
k_1	Max. Neutro. migration rate from during infection	$1.1/day$
k_2	Monocyte migration rate from blood to tissue (IOI)***	$0.95/day$
k_3	Max. monocyte rate from blood to tissue due to infection	$1.7/day$
c	Activation rate of macrophages	$1.4\times10^{-9}\ c.f.u.^{**}/day$
z_1	Killing rate of neutrophils	$2.0\times10^{-6}\ ml/neut./day$
z_2	Killing rate of resting macrophages	$1.8\times10^{-9}\ ml/m\Phi^{*}/day$
z_3	Killing rate of activated macrophages	$8.6\times10^{-6}\ ml/m\Phi^{*}/day$
h_1	Constant for neutrophil release	2.1×10^{10}
h_2	Constant for neutrophil migration	6.0×10^{4}
h_3	Constant for monocyte release	3.2×10^{9}
h_4	Constant for monocyte migration	3000
n_1	Exponent for neutrophil release	1.9
n_2	Exponent for neutrophil migration	1.9
n_3	Exponent for monocyte release	2.0
n_4	Exponent for monocyte migration	1.1

*** (IOI) is an abbreviation for independent of infection.

** *c.f.u.*is an abbreviation for a colony forming unit.

* $m\Phi$ is an abbreviation for macrophage