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Using Partial Differential Equations to Model and Analyze the Treatment of a Chronic Wound With Oxygen Therapy Techniques

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Using Partial Differential Equations to Model and Analyze the Treatment of A Chronic Wound with Oxygen Therapy Techniques

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Honors College Graduate Distinction at Western Kentucky University

By

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ABSTRACT

Chronic wounds plague approximately 1.3-3 million Americans. The treatment of these wounds requires knowledge of the complex healing process of typical wounds. With a system of partial differential equations, this project attempts to model the intricate biological process and to describe oxygen levels, neutrophil and bacteria concentrations, and other biological parameters with respect to time and space. Analytical solutions for the model will be derived for various frames of time in the wound-healing process. The system of equations will be numerically solved using Matlab. Numerical simulations are performed to determine optimal treatment strategies for a chronic wound.

Keywords: Mathematical Modeling, Partial Differential Equations, Wound Healing

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PRESENTATIONS

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FIELDS OF STUDY

Major Field: Mathematics

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CHAPTER 1

INTRODUCTION

Chronic wounds are wounds that do not heal in the normal, orderly set of stages, and instead remain in a chronic inflammatory state. These long-lasting wounds are often linked with diseases such as diabetes. Approximately 1.3-3 million Americans are believed to be plagued with these unfortunate wounds per year; the United States spends about $5-10 billion annually addressing the problems associated with these wounds and researching how to treat them [10]. To better understand how doctors can treat chronic wounds, they must first know exactly what happens during the complex healing process of typical wounds.

A wound that successfully heals progresses through three sequential stages (inflammation, proliferation, and remodeling) and also in a predictable measure of time—typically 30 days or less. The first stage, inflammation, is the body's initial response to stop blood loss from the wounded area and is the activation of certain leukocytes called neutrophils [11]. During this time, usually within 24-to-48 hours after the injury, neutrophils arrive at the wound site and begin to remove foreign particles and bacteria and release proteins, called cytokines, that attract more white blood cells, which in turn become activated macrophages [11]. If the neutrophils are successful in removing the foreign particles and bacteria, as they often are in ordinary, normal healing wounds, then they are removed from the wound by either a form of "cellular death" called apoptosis or by macrophage phagocytosis, wherein activated macrophages—peaking anywhere from 48 to 96 hours after

the injury—"digest" the neutrophils [8]. Subsequently, the macrophages produce a new set of post-inflammatory cytokines and growth factors, beginning the formation of tissue that replaces the tender fibrin cloth that was initially created to stop blood loss [2, 5]. In chronic wounds, this inflammation stage is prolonged.

Chronic wounds are commonly caused by a type of "localized anemia" called ischemia, which impairs the process of healing by limiting the oxygen and nutrient supply in the tissue near the wound. As neutrophils, along with many other cells, process oxygen, they produce reactive oxygen species (ROS), which is toxic to bacteria [13]. If bacteria remain in the wound, infection can settle in, prolonging inflammation.

Mathematical models can mimic reality through the use of mathematical language. Mathematical theorems can be generalized to fit the specific problem at hand and draw broad conclusions. At the same time, modern day computers can easily provide numerical and specific conclusions for a model. Often real world experiments are costly, and sometimes impossible. Studying mathematical models can reduce the need for such experiments. For examples of other mathematical models and their analysis, see [3, 4, 6, 7, 14]. With regards to chronic wounds, both broad insights and numerical computations can easily lead to better treatments strategies for patients.

An ordinary differential equation (ODE) model was developed in [15]. In this paper, we modify several equations of the model proposed in [14]. We relate oxygen, neutrophils, and bacteria, considering their change over time and their spatial variation. By studying a partial-differential-equation (PDE) model, the spatial variation of these concentrations can be considered.

CHAPTER 2

MATHEMATICAL MODEL

The model focuses on the interaction during wound healing of three important species: oxygen, w; neutrophils, n; and bacteria, b. The wound is considered to be one-dimensional, with $x = 0$ located at the center of the radial wound site and $x = L$ located at the edge of the wound nearest healthy dermis. The equations of the model governing oxygen and neutrophil concentrations in the wound are motivated by the work done in [14] while the equation governing bacteria concentrations in the wound are motivated by [15] and are presented below.

Oxygen concentration $w(x,t)$:

$$\frac{\partial w}{\partial t} = D_w \frac{\partial^2 w}{\partial x^2} + \beta + \gamma G(t) - \lambda_{nw} n w - \lambda_{bw} b w - \lambda_w w \tag{1}$$

Oxygen concentrations are assumed to diffuse into the wound site from the wound edge at a constant rate D_w. Oxygen also diffuses in from below the wound region and we assume this creates a constant input of oxygen β. Oxygen therapy provides oxygen into the wound region in a time-dependent manner $G(t)$. Once in the wound site, oxygen is consumed by neutrophils and bacteria. The consumption of oxygen by the neutrophils and bacteria occurs at constant rates of λ_{nw} and λ_{bw}, respectively. Oxygen lost in any other fashion, unrelated to the neutrophils and bacteria, occurs at a constant rate of λ_w.

Neutrophil concentration $n(x,t)$:

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} + \chi_n \frac{\partial}{\partial x}\left(n \frac{\partial w}{\partial x}\right) + \frac{k_{in} k_{ni} b n g_n(\frac{w}{w_0})}{\lambda_{ni} n + \lambda_i}\left(1 - \frac{n}{n_0}\right) - \frac{\lambda_n \epsilon b_0 n}{\epsilon b_0 + b(1-\epsilon)} \quad (2)$$

The dominant movement of the neutrophils is a chemotactic response, in which the leukocytes detect the concentration gradient created by the diffusion of oxygen and move accordingly in to the wound. Neutrophils also diffuse in to the wound. However, the rate of diffusion relative to the neutrophils' chemotactic response is small. As bacteria proliferate in the wound, neutrophils are recruited into the wound site with an environmental carrying capacity of n_0. Neutrophil recruitment also depends on the total oxygen concentration in the wound by the function

$$g_n(\tfrac{w}{w_0}) = \begin{cases} 2(\frac{w}{w_0})^3 - 3(\frac{w}{w_0})^2 + 2, & \text{if } 0 \leq \frac{w}{w_0} \leq 1 \\ 1, & \text{otherwise} \end{cases}.$$

This direct correlation between the amount of bacteria in the wound and the neutrophil concentration also affects the removal of neutrophils from the wound. Neutrophils are removed from the wound through cellular apoptosis and by another leukocyte, macrophages, which arrive in the wound approximately 48 to 96 hours after injury. However, the rate of neutrophil removal is reduced due to the presence of bacteria in the wound.

Bacteria concentration $b(x,t)$:

$$\frac{\partial b}{\partial t} = k_b b\left(1 - \frac{b}{b_0}\right) - \frac{w}{K_w + w}\frac{\delta + k_{nr} n}{\lambda_{rb} b + \lambda_r} b - \lambda_b b \quad (3)$$

Bacteria are assumed to proliferate where it is initially concentrated (in this case at the center of the wound) at a rate of k_b. The wound has an environmental carrying capacity of b_0. Bacteria are removed by ROS, a natural byproduct of neutrophils' consumption of oxygen. Both an increase in oxygen levels and neutrophil concentrations within the wound site will contribute to the destruction of

bacteria. Other leukocytes enter the wound as time progresses and also create ROS. These leukocytes, such as macrophages, are assumed to be at a constant level δ. Thus, whenever there are bacteria in the wound, white blood cells are also present in the wound. Bacteria also die naturally at a linear rate λ_b.

Boundary and Initial Conditions

$$\left.\frac{\partial w}{\partial x}\right|_{x=0} = 0, w(L,t) = \zeta(L), w(x,0) = \zeta(x) \tag{4}$$

$$\left.\frac{\partial n}{\partial x}\right|_{x=0} = 0, n(L,t) = n_0 \mathrm{e}^{-\gamma_2 t}, n(x,0) = n_0 \left(\frac{x-L}{L}\right)^2 \mathrm{e}^{-\left(\frac{x-L}{\epsilon L}\right)^2} \tag{5}$$

$$\left.\frac{\partial b}{\partial x}\right|_{x=0} = \left.\frac{\partial b}{\partial x}\right|_{x=L} = 0, b(x,0) = b_0 \left(\frac{x}{L}\right)^2 \mathrm{e}^{-\left(\frac{L-x}{\epsilon L}\right)^2} \tag{6}$$

In equation (4), $\zeta(x) = \mathrm{sech}(\sqrt{\frac{\lambda_w}{D_w}})\cosh(0.8\sqrt{\frac{\lambda_w}{D_w}}x)$. The selection of $\zeta(x)$ and the conditions governing oxygen levels on the boundary are discussed in Chapter 4. Due to the symmetric nature of the problem, no-flux boundary conditions are needed to describe the oxygen, neutrophil, and bacteria concentrations at the center of the wound ($x = 0$). At $x = L$, the neutrophil concentration decays exponentially due to the transition of the neutrophils from the healthy dermis to the wounded area. Initially, neutrophil levels are at a normal level near the edge of the wound, and are negligible away from the wound edge. Bacteria neither enter nor leave the wound from the healthy skin at $x = L$, and thus no-flux conditions are used on this boundary as well.

To nondimensionalize equations (1)-(6), we let

$$\{x^*, t^*, w^*, n^*, b^*\} = \left\{\frac{x}{L}, \frac{D_w t}{L^2}, \frac{w}{w_0}, \frac{n}{n_0}, \frac{b}{b_0}\right\},$$
$$\{D_w^*, \beta^*, \lambda_{bw}^*, \lambda_{nw}^*, \lambda_w^*\} = \left\{1, \frac{L^2}{w_0 D_w}\beta, \frac{\lambda_{bw} b_0 L^2}{D_w}, \frac{\lambda_{nw} n_0 L^2}{D_w}, \frac{\lambda_w L^2}{D_w}\right\},$$
$$\{D_n^*, \chi_n^*, k_{ni}^*, \lambda_{ni}^*, \lambda_n^*, e^*\} = \left\{\frac{D_n}{D_w}, \frac{\chi_n w_0}{D_w}, \lambda_i \frac{L^2 b_0}{D_w} k_{in} k_{ni}, \frac{\lambda_{ni} n_0}{\lambda_i}, \lambda_n \frac{L^2}{D_w}, \frac{b_0(1-\epsilon)}{\epsilon b_0}\right\},$$
$$\{k_b^*, K_w^*, \delta^*, k_{nr}^*, \lambda_{rb}^*, \lambda_b^*\} = \left\{\frac{k_b L^2}{D_w}, \frac{K_w}{w_0}, \delta \frac{\lambda_r L^2}{D_w}, k_{nr} n_0 \frac{\lambda_r L^2}{D_w}, \frac{\lambda_{rb} b_0}{\lambda_r}, \lambda_b \frac{L^2}{D_w}\right\}.$$

where the asterisks denote dimensionless variables and parameters. Note that the choice of dimensionless parameters and variables is not unique. Removing the $*$ from the nondimensionalized variables and parameters for notational simplicity, equations (1)-(3) become

$$\frac{\partial w}{\partial t} = \frac{\partial^2 w}{\partial x^2} + \beta + \gamma G(t) - \lambda_{nw} n w - \lambda_{bw} b w - \lambda_w w, \tag{7}$$

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} + \chi_n \frac{\partial}{\partial x}\left(n \frac{\partial w}{\partial x}\right) + \frac{k_{ni} b n g_n(w)}{\lambda_{ni} n + 1}(1-n) - \frac{\lambda_n n}{eb+1}, \tag{8}$$

$$\frac{\partial b}{\partial t} = k_b b(1-b) - \frac{w}{K_w + w}\frac{\delta + k_{nr} n}{\lambda_{rb} b + 1} b - \lambda_b b, \tag{9}$$

and equations (4)-(6) become

$$\left.\frac{\partial w}{\partial x}\right|_{x=0} = 0, w(1,t) = \zeta(1), w(x,0) = \zeta(x), \tag{10}$$

$$\left.\frac{\partial n}{\partial x}\right|_{x=0} = 0, n(1,t) = \mathrm{e}^{-\gamma_2 t}, n(x,0) = x^2 \mathrm{e}^{-\left(\frac{1-x}{\epsilon}\right)^2}, \tag{11}$$

$$\left.\frac{\partial b}{\partial x}\right|_{x=0} = \left.\frac{\partial b}{\partial x}\right|_{x=L} = 0, b(x,0) = (1-x)^2 \mathrm{e}^{-\left(\frac{x}{\epsilon}\right)^2}. \tag{12}$$

CHAPTER 3

ANALYTICAL RESULTS

Analytical results can provide valuable insight to the biological implications of the model. First, the wound is examined without the presence of bacteria to provide a biological description for oxygen and neutrophil dynamics. Before finding solutions to the system, we examine the stability of the steady states, first without any spatial variation of the neutrophils and oxygen, and then with the spatial variation (i.e. diffusion of the oxygen and neutrophils and the chemotactic response of the neutrophils).

To begin our investigation of the system, we consider the ordinary differential equations satisfied by travelling wave solutions of equations (7)-(8) where b is assumed to be 0. Travelling waves arise frequently in the context of wound healing. Biologically, this implies that a wave front of cells move with a constant speed and constant shape. We assume there is a solution to each equation of the form $f(\psi)$, where $\psi = x + ct$, and c is the speed of propagation of the travelling waves. Without the presence of bacteria, letting $w(x,t) = f(\psi)$ and $n(x,t) = g(\psi)$, this reduces equations (7)-(9) to

$$cf' = f'' + \beta - \lambda_{nw} fg - \lambda_w f, \tag{13}$$

$$cg' = D_n g'' + \chi_n (gf')' - \lambda_n g, \tag{14}$$

where $'$ denotes the derivative with respect to ψ. To examine the steady states of

this system, (13)-(14) is transformed to a system of first order, nonlinear ordinary differential equations by setting $x_1 = f$, $x_2 = f'$, $x_3 = g$, and $x_4 = g'$. Removing the terms with spatial derivatives, substituting this change of variables into the system, and separating the derivatives to one side, we get a system of two ordinary differential equations.

$$\begin{aligned} x_1' &= \frac{\beta}{c} - \frac{\lambda_{nw}}{c} x_1 x_3 - \frac{\lambda_w}{c} x_1 \\ x_3' &= -\frac{\lambda_n}{c} x_3 \end{aligned} \tag{15}$$

Setting these derivatives equal to zero and solving for x_1 and x_3 we get the steady state $(x_1, x_3) = (\frac{\beta}{\lambda_w}, 0)$. The Jacobian for the system (15) (without spatial variation terms) is

$$\mathcal{J}(x_1, x_3) = \begin{bmatrix} -\frac{\lambda_{nw}}{c} x_3 - \frac{\lambda_w}{c} x_1 & -\frac{\lambda_{nw}}{c} \\ 0 & -\frac{\lambda_n}{c} \end{bmatrix}.$$

The eigenvalues of our evaluated Jacobian $\mathcal{J}(\frac{\beta}{\lambda_w}, 0)$ are $\{-\frac{\beta}{c}, -\frac{\lambda_n}{c}\}$. Because the real parts of the eigenvalues are negative, we conclude that the steady state $(\frac{\beta}{\lambda_w}, 0)$ is stable. The necessary condition that the real parts of the eigenvalues of the evaluated Jacobian be negative is clarified in Appendix B. Biologically, this implies that without bacteria in the system, the neutrophil concentration will tend to zero and the oxygen level in the wound will stabilize naturally to an average concentration of $\frac{\beta}{\lambda_w}$ when spatial variation is not considered.

Now we place the diffusion and chemotactic terms back into equations (15) and perform the same analysis to study the steady states of the unmodified system. Substituting x_1, x_2, x_3, and x_4 in to the system, and separating the derivatives to one side, we have the following system.

$$\begin{aligned} x_1' &= x_2 \\ x_2' &= \frac{\lambda_{nw}}{D_w} x_1 x_3 - \frac{c}{D_w} x_2 + \frac{\lambda_w}{D_w} x_1 - \frac{\beta}{D_w} \\ x_3' &= x_4 \\ x_4' &= \frac{\lambda_n}{D_n} x_3 - \frac{\chi_n}{D_n} x_2 x_4 - \frac{c}{D_n} x_4 + \frac{\chi_n}{D_n} x_3 \left(\frac{c}{D_w} x_2 - \frac{\lambda_w}{D_w} x_1 - \frac{\lambda_{nw}}{D_w} x_1 x_3 + \frac{\beta}{D_w} \right) \end{aligned}$$

Setting the derivatives on the left hand side equal to zero, and solving for x_1, x_2, x_3, and x_4 gives the steady state $(x_1, x_2, x_3, x_4) = \left(\frac{\beta}{\lambda_w}, 0, 0, 0\right)$. Evaluating the Jacobian of the system at this steady state gives the matrix

$$\mathcal{J}\left(\frac{\beta}{\lambda_w}, 0, 0, 0\right) = \begin{bmatrix} 0 & 1 & 0 & 0 \\ \frac{\lambda_w}{Dw} & \frac{c}{Dw} & \frac{\beta\lambda_{nw}}{Dw\lambda_w} & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 0 & \frac{\lambda_n}{Dn} & \frac{c}{Dn} \end{bmatrix}. \tag{16}$$

To determine the stability of this steady state, we consider the characteristic polynomial of the matrix and check that it satisfies the Routh-Hurwitz criteria. The characteristic polynomial of (16) is

$$\begin{aligned} P(\alpha) &= a_0\alpha^4 + a_1\alpha^3 + a_2\alpha^2 + a_3\alpha + a_4 \\ &= \alpha^4 + \frac{cD_w + cD_n}{D_nD_w}\alpha^3 + \frac{c^2 - \lambda_wD_n - \lambda_nD_w}{D_nD_w}\alpha^2 + \frac{-c(\lambda_w + \lambda_n)}{D_wD_n}\alpha + \frac{\lambda_n\lambda_w}{D_nD_w} \end{aligned}$$

All parameter values are assumed to be positive. Therefore we have that $a_1 > 0$, $a_3 < 0$, and $a_4 > 0$. By the corollary and theorem presented in Appendix B concerning the Routh-Hurwitz conditions, we deduce that there exists an eigenvalue of the above matrix with a non-negative real part. Thus we conclude that the steady state is stable without the process of diffusion, yet unstable when spatial variation is considered. This "diffusion-driven" instability is referred to as a Turing instability, and is quite common in biological reaction-diffusion models. Biologically, this implies that during the inflammatory stage, oxygen levels in the wound will vary spatially, even though these levels may temporally settle. This creates a gradient of oxygen, which is expected biologically.

To have a complete picture of the biological processes that occur during wound healing, the system is first examined during the first 6 hours after the initial injury. This is motivated by [7], which attempts to analyze the amount of oxygen needed during the first day of treatment to promote blood-vessel growth. During the first 6 hours, neutrophils have not entered the wound. Also, because therapy is given

only once every day, if any treatment is sought during the first 6 hours, we assume it is administered at a constant rate α. Without bacteria in the wound, equation (7) becomes

$$\frac{\partial w}{\partial t} = \frac{\partial^2 w}{\partial x^2} + \beta + \alpha - \lambda_w w, \tag{17}$$

with the boundary and initial conditions

$$\begin{aligned} \left.\frac{\partial w}{\partial x}\right|_{x=0} &= 0, \\ w(1,t) &= 1, \\ w(x,0) &= 1. \end{aligned} \tag{18}$$

To find a solution for (18), we transform the boundary conditions into homogeneous conditions by substituting $u(x,t) = w(x,t) - 1$. This transforms the boundary value problem (17)-(18) into

$$\frac{\partial u}{\partial t} - \frac{\partial^2 u}{\partial x^2} + \lambda_w u = \kappa, \tag{19}$$

$$u(1,t) = 0, \tag{20}$$

$$\left.\frac{\partial u}{\partial x}\right|_{x=0} = 0, \tag{21}$$

$$u(x,0) = 0, \tag{22}$$

where $\kappa = \beta + \alpha - \lambda_w$. We find the solution for the boundary value problem (19)-(22) using Green's functions:

$$u(x,t) = \int_0^t \int_0^1 \kappa G(x,\xi,t-s) d\xi ds.$$

where κ is given above, and

$$G(x,\xi,t) = 2\sum_{n=0}^{\infty} \cos\left(\tfrac{2n\pi+\pi}{2}\xi\right) \cos\left(\tfrac{2n\pi+\pi}{2}x\right) \mathrm{e}^{-\left((\frac{2n\pi+\pi}{2})^2+\lambda_w\right)t},$$

which is derived in Appendix A. Evaluating the integral and shifting the data back we have the solution

$$w(x,t) = 1+2\sum_{n=0}^{\infty} \frac{(-1)^n(\beta+\alpha-\lambda_w)}{\lambda_w\left(\frac{2n\pi+\pi}{2}\right)+\left(\frac{2n\pi+\pi}{2}\right)^3}\cos\left(\frac{2n\pi+\pi}{2}x\right)\left(1-\mathrm{e}^{-((\frac{2n\pi+\pi}{2})^2+\lambda_w)t}\right).$$

To simulate the removal of bacteria from the wound, we must have $\frac{\partial b}{\partial t} < 0$. Notice that if $b = 0$ at any time, then b remains zero for all further time. Assuming that the bacteria concentration is not initially zero and that it reaches a steady state fairly soon, to begin bacteria removal from the wound during the first six hours after trauma, we must satisfy the following inequality through the application of oxygen treatment

$$w(0, 0.108)(\delta - (k_b(1-b) - \lambda_b)(\lambda_{rb}+1)) > K_w(k_b(1-b)-\lambda_b)(\lambda_{rb}+1). \quad (23)$$

Time $t = 0.108$ is a nondimensional value representing 6 hours after the initial trauma. From here, we present two cases for the amount of oxygen necessary to stimulate bacteria removal. Recall that δ represents the ROS produced by cells other than the neutrophils. Inequality (23) reduces to the following cases:

$$\text{If } \delta > f(b), \text{ then } w(0, 0.108) > \frac{f(b)K_w}{\delta - f(b)}, \quad (24)$$

and

$$\text{if } \delta < f(b), \text{ then } w(0, 0.108) < \frac{f(b)K_w}{\delta - f(b)}, \quad (25)$$

where $f(b) = (k_b(1-b) - \lambda_b)(\lambda_{rb}+1)$. For (25), when $\delta < f(b)$, we have

$$\frac{f(b)K_w}{\delta - f(b)} < 0, \quad (26)$$

which implies that $w(0, 0.108)$ must be negative. However, the range of w is strictly positive. Thus we conclude that for (25), treatment through oxygen therapy can never begin the removal of bacteria from the wound. That is, if the total amount of ROS created by cells other than the neutrophils is less than $f(b)$, where b is the total concentration of bacteria, the wound will not be able to begin the healing

Bacteria	Oxygen	α
0.639	5.25468	47.7221
0.64	2.83338	21.8377
0.641	1.80359	10.82897
0.642	1.23364	4.73599
0.643	0.871659	0.8663

Table 1: As bacteria concentrations approach their steady state value in the wound from the left, the amount of treatment needed to apply during the first session decreases. The closer the bacteria concentration gets to the steady state, the slower the bacteria concentration grows. That is, when b is much different from the steady state, we have that $\frac{\partial b}{\partial t} >> 0$. Note that if α becomes 0, after the first 6 hours, with the parameters in Table (2), the oxygen levels go to 0.790263 at the center of the wound region.

process without the neutrophils.

Given that $\delta > f(b)$, by (24) we require w at the center of the wound and after the first six hours to be at a certain level. As b approaches the steady state, the necessary amount of oxygen required to stimulate bacteria removal decreases. Table 1 shows necessary levels of oxygen w and necessary treatment levels α for different bacteria concentrations b as b approaches the steady state from the left using nondimensional variables and nondimensional parameter values from Table 2 in Chapter 4.

While $\delta > f(b)$ is a sufficient condition to instigate the removal of the bacteria from the wound, it is not a very efficient condition. There is a small range of bacteria concentration such that oxygen therapy during the first six hours will have a beneficial impact. As time progresses, and neutrophils enter the wound, the range of bacteria that can be eradicated will grow.

CHAPTER 4

NUMERICAL RESULTS

The system of equations (7)-(9) are solved in MATLAB using the built-in PDE solver "pdepe", which utilizes a finite difference scheme to approximate solutions. The dimensionless parameters in (7)-(9) are fixed at the values presented in Figure 2. The choice of parameter values is discussed later in this section.

Parameter	Non-Dimensional	Dimensional	References
w_0	1	$5.4 * 10^{-6}$ g $\cdot$ cm^{-1}	[14]
n_0	1	$1 * 10^{-3}$ g $\cdot$ cm^{-1}	[14]
b_0	1	$3 * 10^{-9}$ g $\cdot$ cm^{-1}	[16]
D_w	1	$5 * 10^{-6}$ cm^2 $\cdot$ s^{-1}	oc
D_n	0.02	$1 * 10^{-7}$ cm^2 $\cdot$ s^{-1}	oc
χ_n	1.08	1 cm^5 $\cdot$ g^{-1} $\cdot$ s^{-1}	oc
β	0.2284	$6.1667 * 10^{-12}$ cm^{-1} $\cdot$ g $\cdot$ s^{-1}	oc
λ_{nw}	37	0.185 cm $\cdot$ g^{-1} $\cdot$ s^{-1}	[14]
λ_w	2.4667	$0.01233 * 10^{-3}$ s^{-1}	oc
λ_n	5	$2.5 * 10^{-5}$ s^{-1}	oc
λ_{bw}	22.7872		[15]
k_b	14.26	$7.13 * 10^{-5}$ s^{-1}	[16]
K_w	0.75	$4.05 * 10^{-6}$ g $\cdot$ cm^{-1}	[15]
δ	0.7992		oc
k_{nr}	2		oc
λ_{rb}	3.73		[15]
λ_b	5	$2.5 * 10^{-6}$ s^{-1}	oc
k_{ni}	14.28		[15]
λ_{ni}	0.1728		[15]
e	100		[15]

Table 2: The order of magnitude of some parameters were collected from other works, including [14]. Other parameter values were determined through experimentation with the knowledge of certain biological assumptions. "oc" stands for "our choice."

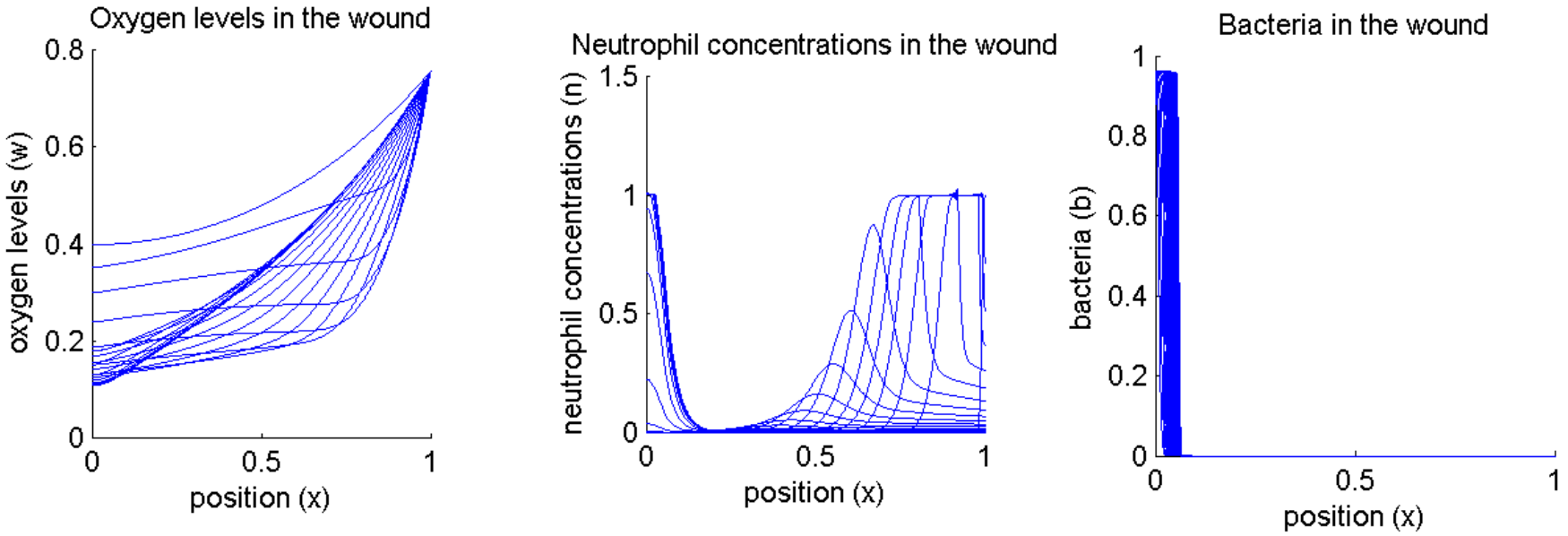

Figure 1: (Left) Oxygen levels remain constant on the wounds edge nearest the healthy skin. Notice that at $x = 1$, oxygen levels are not 1. During the inflammatory stage, blood vessels (which transport oxygen through the blood and into the wound) are not flush with the edge of the wound, but instead are approximately 0.2-0.3cm from the exposed area. Oxygen is lost in the wounded region due to the bacteria located at $x = 0$, the neutrophils that are moving through the wounded area, and natural causes. (Center) Neutrophils rush in to the wound site as a result of the initial trauma. The carrying capacity of the wound limits the total number of neutrophils at any one location in the wound. With the bacteria concentration at the center of the wound is located, the neutrophils are recruited there. (Right) Bacteria is assumed to be located initially in the center of the wound. Bacteria grows as time progresses; it is also killed by the neutrophils once the white blood cells reach the location of the bacteria. This solution represents the first 10 days after the initial trauma.

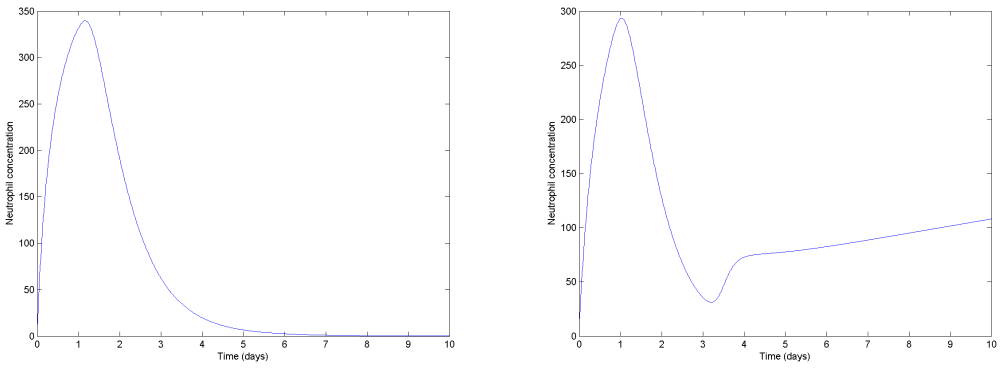

Figure 2: (Left) Without bacteria present in the wound, neutrophils peak around the first day and are gone from the wound after approximately six days. (Right) With bacteria present in the wound, neutrophils still peak after approximately one day, but persist in the wound until the bacteria is removed.

The numerical solutions to the boundary value problem (7)-(12) are produced by the code in Appendix C and are pictured in Figure 1.

Numerical simulations were performed to justify and choose various parameter values. Neutrophils peak in the wound region around the first day, and are gone from the wound sometime between day four and day six, given that there is no bacteria in the wound [11]. Parameter values for the chemotactic rate, χ_n, and decay rate, λ_n, of the neutrophils were chosen so that the model agreed with the literature. As seen in Figure 2, when bacteria is not present in the wound, neutrophils peak in the wound around day one and are effectively gone from the wound around day five. Figure 2 also relates the neutrophil concentration in the wound over time when there is bacteria present in the wound.

To determine an appropriate initial condition, we make the assumption that during the first six hours oxygen levels in the wound stabilize. That is, at the end of six hours we assume in equation (7) that $\frac{\partial w}{\partial t} = 0$. Solving the resulting ordinary differential equation with the boundary conditions $w'(0) = 0$ and $w(1) = 1$ gives

$$w(x) = \text{sech}(\sqrt{\tfrac{\lambda_w}{D_w}})\cosh(\sqrt{\tfrac{\lambda_w}{D_w}}x) + \tfrac{\beta}{\lambda_w}.$$

The boundary condition at $x = 1$ for the ODE assumes that blood vessels are located immediately outside of the wound region and close enough to keep oxygen levels at the skin capacity. However, there is some distance between the wound region edge and the blood vessels. To accommodate for this oxygen depression at the wound edge we rescale the solution to the ODE by choosing $w(0.8x)$ to be our initial condition, as seen in (10).

Figure 3 shows the oxygen concentration, neutrophil amounts, and bacteria concentrations in a wound receiving topical oxygen treatment. Oxygen was applied directly to the wound and to the boundary for 90 minutes a day once a day for 10 days. Simulations were unsuccessful in removing the bacteria from the wound. This could be attributed to the exponential decay of the neutrophils on the boundary of the wound. The total amount of neutrophils on the boundary is approaching zero to rapidly, and thus not enough neutorphils are entering the wound via diffusion and their chemotactic like response. Similar results were obtained when modeling hyperbaric oxygen treatment regimens. To simulate hyperbaric oxygen treatment, we supply oxygen only to the wound edge and at a greater rate than that of the simulated topical therapy.

With the current model, neutrophils are strongly attracted to gradients of oxygen. Without treatment, the bacteria located at the center of the wound consume enough oxygen to create a gradient to which the neutrophils are attracted. However, when oxygen treatment is applied, the gradient of oxygen in the wound varies, causing the neutrophils to spread throughout the wound instead of gathering in the center of the wound where the bacteria are located.

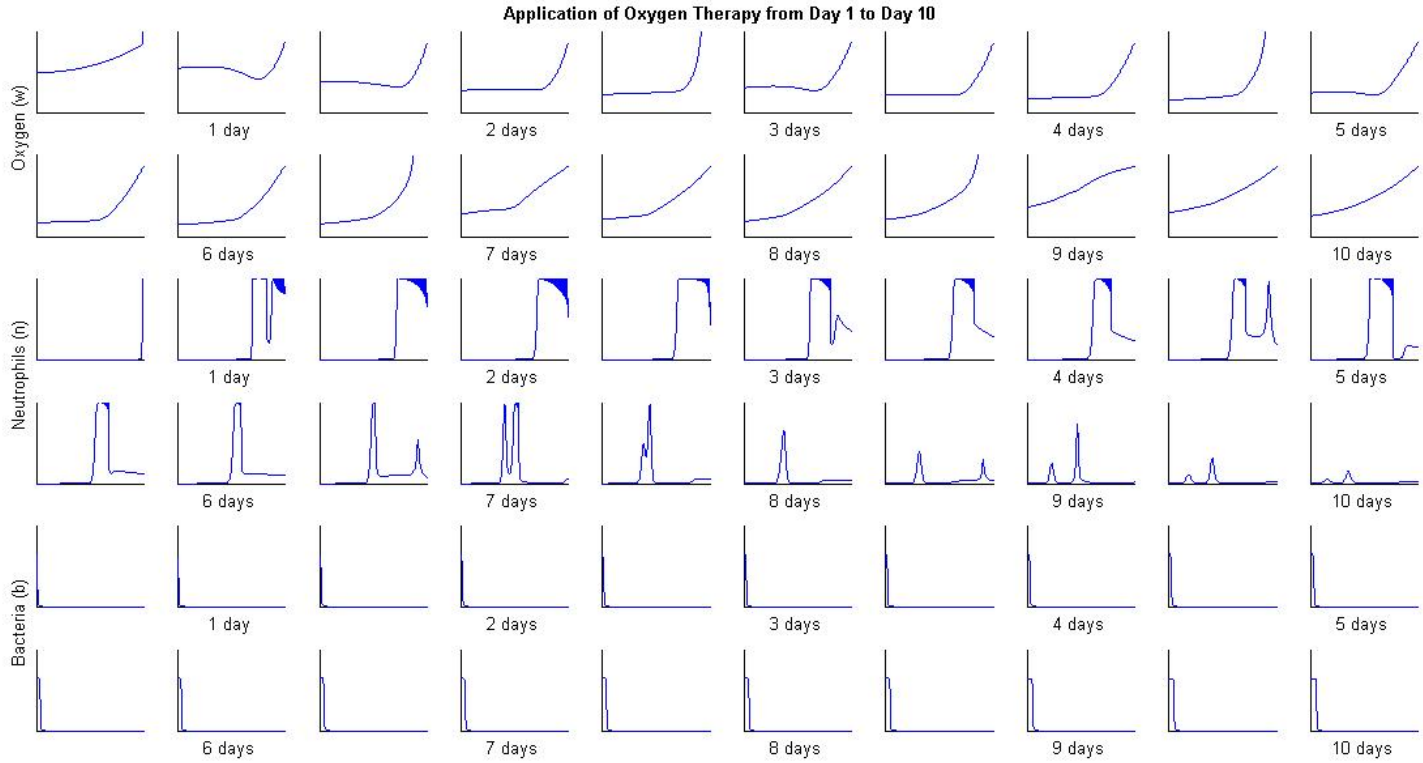

Figure 3: Numerical simulations of the application of oxygen therapy were performed. However, under the current state of the model, treatments were not ultimately effective in removing bacteria from the wound. As seen above, oxygen levels fluctuate from day to day due to the topical oxygen therapy. Oxygen was supplied to both the boundary and the wound itself. Neutrophils rush into the wound after the initial trauma, and continue to enter the wound in waves corresponding with treatment sessions. However, the total amount of neutrophils on the boundary decays exponentially, not allowing more neutrophils to enter the wound. Ideally, the boundary condition would depend on the bacteria concentration. Similar results were obtained simulating hyperbaric oxygen therapy.

CHAPTER 5

CONCLUSIONS AND FUTURE WORK

The mathematical model presented with equations (1)-(6) represents the relation between oxygen concentrations, neutrophil levels, and bacteria concentrations in a wound after injury. Analytical results show that the steady states are biologically accurate. Analyzing the analytical results to the model with certain biological assumptions provided realistic results and potentially useful data for treating patients with certain oxygen therapy techniques. Numerical solutions and simulations provided motivation for parameter values that were not necessarily known from the literature.

For more analytical results the model might be solved with various perturbation methods. Two interesting questions that were raised during this research are (1) can the model be solved for different time scales—one time scale representing the first six hours after trauma and a second representing after six hours—and (2) can the model be treated as a boundary-layer problem with two boundaries—one being the center of the wound near the localized bacteria and the other being the remaining wound region? Perturbation methods allow for different analytical results, like those found in [6].

While analytical methods can provide a variety of results, some conclusions can only be drawn through numerical methods. The implications of this model can be further studied through a variety of numerical simulations. Specifically, (1) how will the wound react differently if bacteria are locally concentrated nearer the

edge of the wound rather than the center, (2) how much bacteria can be eliminated from the wound through the use of oxygen therapy techniques, and (3) what is the optimal treatment strategy for a chronic wound and does it vary with each wound? Performing these simulations on actual chronic wound patients is unethical.

Simulations are also helpful when determining how accurately the model describes the biological situation. To further improve the model's accuracy, the attraction of the neutrophils to the wound region might be considered. When dealing only with temporal changes, as in the ODE model in [15], it is appropriate for neutrophil recruitment to supply the wound with higher concentrations. However, when spatial variations are considered, as in the PDE model in this work, is it possible that the neutrophils detect high concentrations of bacteria? Also, how consistent is the boundary condition concerning neutrophils near the healthy skin? Should the boundary condition depend on the total bacteria concentration in the wound? Analyzing an integral equation boundary condition will certainly require further study.

The ultimate goal for this research is to determine the most favorable oxygen therapy treatment strategies for wound patients using optimal control techniques. Before applying such techniques, it is important that the model accurately represent the biological situation and that parameter values be realistically determined.

APPENDIX A

DERIVING GREEN'S FUNCTION

Given the differential equation with inhomogeneous boundary conditions,

$$\frac{\partial w}{\partial t} = D_w \frac{\partial^2 w}{\partial x^2} + \beta - \lambda_w w, \tag{27}$$

$$w(L,t) = f(t), \tag{28}$$

$$\left.\frac{\partial w}{\partial x}\right|_{x=0} = g(t), \tag{29}$$

$$w(x,0) = h(x), \tag{30}$$

we first look for a separated solution. Before finding said solution, we make homogeneous the boundary conditions by making the substitution $u(x,t) = w(x,t) - f(t) - (x-L)g(t)$. This transforms the boundary value problem (27)-(30) into

$$\frac{\partial u}{\partial t} - D_w \frac{\partial^2 u}{\partial x^2} + \lambda_w u = r(x,t), \tag{31}$$

$$u(L,t) = 0, \tag{32}$$

$$\left.\frac{\partial u}{\partial x}\right|_{x=0} = 0, \tag{33}$$

$$u(x,0) = j(x), \tag{34}$$

where $r(x,t) = \beta - f'(t) - (x-L)g'(t) - \lambda_w f(t) - \lambda_w(x-L)g(t)$ such that $'$ denotes a derivative with respect to t, and $j(x) = h(x) - f(0) - (x-L)g(0)$.

We assume a solution of the form $u(x,t) = \sum_{n=0}^{\infty} A_n(t)\cos(\alpha_n x)$, where $\alpha_n = \frac{2n\pi+\pi}{2L}$ are the eigenvalues for the homogeneous eigenvalue problem associated with (31). Substituting this solution in to (31) gives

$$r(x,t) = \sum_{n=0}^{\infty}[A_n'(t) + (D_w\alpha_n^2 + \lambda_w)A_n(t)]\cos(\alpha_n x). \tag{35}$$

We assume $r(x,t)$ in equation (31) and $j(x)$ in (34) can be expanded as Fourier cosine series. That is,

$$r(x,t) = \sum_{n=0}^{\infty} r_n(t)\cos(\alpha_n x), \tag{36}$$

where

$$r_n(t) = \frac{2}{L}\int_0^L r(x,t)\cos(\alpha_n x)dx, \tag{37}$$

and

$$j(x) = \sum_{n=0}^{\infty} B_n\cos(\alpha_n x), \tag{38}$$

where

$$B_n = \frac{2}{L}\int_0^L j(x)\cos(\alpha_n x)dx. \tag{39}$$

Equating equation (35) with (36) shows that the ordinary differential equation produced by the arbitrary functions of t in (35) is equal to the Fourier integral in (37). Solving the ordinary differential equation according to the initial condition $A_n(0) = B_n$ gives

$$A_n(t) = B_n e^{-(D_w\alpha_n^2+\lambda_w)t} + \int_0^t r_n(s)e^{-(D_w\alpha_n^2+\lambda_w)(t-s)}ds \tag{40}$$

where α_n are the eigenvalues as before. Substituting these functions into the

assumed solution provides the separated solution

$$u(x,t) = \sum_{n=0}^{\infty} B_n \mathrm{e}^{-(D_w\alpha_n^2+\lambda_w)t}\cos(\alpha_n x) + \sum_{n=0}^{\infty}\cos(\alpha_n x)\int_0^t r_n(s)\mathrm{e}^{-(D_w\alpha_n^2+\lambda_w)(t-s)}ds. \tag{41}$$

Substituting B_n and $h_n(s)$ in to (41) and interchanging the integrals with the sums gives

$$G(x,\xi,t) = \frac{2}{L}\sum_{n=0}^{\infty}\cos(\alpha_n\xi)\cos(\alpha_n x)\mathrm{e}^{-(D_w\alpha_n^2+\lambda_w)t}, \tag{42}$$

which is Green's function for (27).

APPENDIX B

LINEAR STABILITY CONDITIONS FOR STEADY STATES OF SYSTEMS OF ORDINARY DIFFERENTIAL EQUATIONS

Given the nonlinear, autonomous system of ordinary differential equations $\frac{d\mathbf{x}}{dt} = \mathbf{F}(\mathbf{x})$, the equilibrium points, or steady states, are the points $\mathbf{x}_0 \in \mathbb{R}^n$ which satisfy the equation $\mathbf{F}(\mathbf{x}_0) = 0$. There are various classifications for the stability of a steady state. A steady state $\mathbf{x}_0$ is asymptotically stable if for any solution $\mathbf{x}(t)$ satisfying the system we have $\lim_{t\to\infty} \mathbf{x}(t) = \mathbf{x}_0$. To effectively determine the stability of a given steady state, we should solve the system. However, with a nonlinear system of equations, this can be difficult, and thus take a different approach. We linearize the nonlinear terms using a Taylor expansion about the steady state $\mathbf{x}_0$. That is, we let

$$\mathbf{F}(\mathbf{x}) = \mathbf{F}(\mathbf{x}_0) + \left.\frac{\partial \mathbf{F}}{\partial \mathbf{x}}\right|_{\mathbf{x}=\mathbf{x}_0} (\mathbf{x} - \mathbf{x}_0) + \left.\frac{\partial^2 \mathbf{F}}{\partial \mathbf{x}^2}\right|_{\mathbf{x}=\mathbf{x}_0} (\mathbf{x} - \mathbf{x}_0)^2 + \cdots.$$

However, by definition $\mathbf{F}(\mathbf{x}_0) = 0$. Thus we are justified in linearly approximating $\mathbf{F}(\mathbf{x})$ in the following manner:

$$\mathbf{F}(\mathbf{x}) \approx \left.\frac{\partial \mathbf{F}}{\partial \mathbf{x}}\right|_{\mathbf{x}=\mathbf{x}_0} (\mathbf{x} - \mathbf{x}_0).$$

This approximation transforms our nonlinear system of ordinary differential equations to a system of the form

$$\frac{d\mathbf{x}}{dt} = A\mathbf{x}, \tag{43}$$

where A is the matrix of the linearized nonlinear terms, or the Jacobian of the system evaluated at the steady state. Solving this system and disregarding the trivial solution $\mathbf{x} = \mathbf{0}$ gives the solution

$$\bar{\mathbf{x}}(t) = \mathbf{u}e^{\lambda t}$$

where $\mathbf{u} \neq \mathbf{0}$ is a constant vector and λ is a constant to be determined. Substituting this solution into (43) shows that the constant vector $\mathbf{u}$ and the constant λ must satisfy the equation

$$|A - \lambda I|\mathbf{u} = \mathbf{0},$$

where $|\cdot|$ refers to the determinant of the matrix. Because $\mathbf{u} \neq \mathbf{0}$ we must have $|A - \lambda I| = 0$. The resulting polynomial $P(\lambda)$ is referred to as the characteristic polynomial of the of the matrix A, and all constants λ satisfying the equation $P(\lambda) = 0$ are referred to as the eigenvalues of the matrix A. For the steady state $\mathbf{x}_0$ to be stable, we must have that $\lim_{t\to\infty} \mathbf{x}(t) = \mathbf{x}_0$ for all solutions $\mathbf{x}$ to the nonlinear system. Because of our choice of approximation for $\mathbf{F}$, this means that we must have $\bar{\mathbf{x}}(t) \to \mathbf{0}$ as $t \to \infty$, which will only occur if $\mathrm{Re}(\lambda) < 0$ for all eigenvalues λ.

The Routh-Hurwitz conditions, presented in the following Theorem, provide a convenient method for determining the sign of the real part of the eigenvalues of a matrix.

Theorem. *Given the characteristic polynomial,*

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n,$$

where the coefficients a_i are real constants, $i = 1, 2, ..., n$, define n matrices using the coefficients a_i of the characteristic polynomial:

$$D_1 = [a_1],\ D_2 = \begin{bmatrix} a_1 & a_3 \\ 1 & a_2 \end{bmatrix},\ D_3 = \begin{bmatrix} a_1 & a_3 & a_5 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{bmatrix},\ ...,$$

and

$$D_n = \begin{bmatrix} a_1 & a_3 & a_5 & a_7 & \cdots & a_{2n-1} \\ 1 & a_2 & a_4 & a_6 & \cdots & a_{2n-2} \\ 0 & 1 & a_1 & a_3 & \cdots & a_{2n-3} \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_n \end{bmatrix},$$

where $a_j = 0$ *if* $j > n$. *All roots of the polynomial* $P(\lambda)$ *are negative or have negative real part iff the determinants of the defined matrices are positive:*

$$|D_j| > 0,\ j = 1, 2, ..., n.$$

For a fourth degree polynomial, $P(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0$ where each of the a_i's are nonzero, the conditions stipulate that we must have

$$|D_1| = |a_1| = a_1 > 0$$

$$|D_2| = \begin{vmatrix} a_1 & a_3 \\ 1 & a_2 \end{vmatrix} = a_1a_2 - a_3 > 0$$

$$|D_3| = \begin{vmatrix} a_1 & a_3 & 0 \\ 1 & a_2 & a_4 \\ 0 & a_1 & a_3 \end{vmatrix} = a_1a_2a_3 - a_3^2 - a_1^2a_4 > 0$$

$$|D_4| = \begin{vmatrix} a_1 & a_3 & 0 & 0 \\ 1 & a_2 & a_4 & 0 \\ 0 & a_1 & a_3 & 0 \\ 0 & 1 & a_2 & a_4 \end{vmatrix} = a_1a_2a_3a_4 - a_3^2a_4 - a_1^2a_4^2 > 0$$

for $\mathrm{Re}(\lambda) < 0$.

Corollary. *Given the polynomial*

$$P(\lambda) = \lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4$$

with real coefficients such that $a_1 > 0$, $a_3 < 0$, *and* $a_4 > 0$, *there exists a* λ^* *such that* $P(\lambda^*) = 0$ *and* $Re(\lambda^*) \geq 0$.

Proof. Suppose to the contrary that each root of the fourth degree polynomial P has a negative real part. Then the polynomial P must satisfy the Routh-Hurwitz conditions. Therefore, referring to the notation in the previous theorem, we must have that

$$|D_3| = (a_1a_2 - a_3)a_3 - a_1^2a_4 = |D_2|a_3 - a_1^2a_4 > 0.$$

That is, under the assumption that each root of the polynomial P has a negative real part, it must be that

$$|D_2|a_3 > a_1^2a_4.$$

Because $a_1^2 > 0$ and $a_4 > 0$, we must have that $|D_2|a_3 > 0$. However, because $a_3 < 0$, we must also have that $|D_2| < 0$. This contradicts the assumption that P satisfies the Routh-Hurwitz conditions. Therefore, at least one of the four roots of the polynomial P must have a non-negative real part. □

APPENDIX C

MATLAB CODE

```
function PDE_Thesis
wo = 5.4*10^(-6);
no = 1*10^(-3);
%bo =
Lo = 1;
Dwo = 5*10^(-6);
Dno = 1*10^(-8);
chino = 1.08;
betao = 6.16667*10^(-12);
lambdanwo = 0.185;
lambdawo = (0.185/15)*10^(-3);
lambdano = 2.5*10^(-5);
%lambdaio =
%lambdabwo =
%kbo =
%Kwo =
%Δo =
%knro =
%lambdarbo =
%lambdabo =
%knio =
%kino =
%epsilono =
m = 0;
x = linspace(0,1,1000);
t = linspace(0,4.32,800);
Dw = 1;
Dn = Dno/Dwo;
chin = chino*wo/Dwo;
%chib = 0.9;
beta = betao*Lo^2/(wo*Dwo);
lambdanw = lambdanwo*no*Lo^2/Dwo;
lambdaw = lambdawo*Lo^2/Dwo;
lambdan = lambdano*Lo^2/Dwo;
lambdabw = 22.7872; %lambdabwo*bo*Lo^2/Dwo;
Db = 1*10^(-5);
kb = 14.26; %kbo*L^2/Dwo;
Kw = 0.75; %Kwo/wo;
Δ = 0.7992; %Δo*lambdaro*Lo^2/Dwo;
```

```
knr = 2; %knro*no*lambdaro*Lo^2/Dwo;
lambdarb = 3.73; %lambdarbo*no/lambdaro;
lambdab = 5; %lambdabo*Lo^2/Dwo;
kni = 14.28; %lambdaio*kino*knio*Lo^2*bo/Dwo;
lambdani = 0.1728; %lambdanio*no/lambdaio;
ee = 100; %bo*(1-epsilono)/(epsilono*bo);
eta = 5;%boundary
params = [Dw,Dn,chin,beta,lambdanw,lambdaw,lambdan,lambdabw,Db,kb,...
    Kw,Δ,knr,lambdarb,lambdab,kni,lambdani,ee,eta];
%display(params)
%error('end code')
sol = pdepe(m,@wound_pde_thesis,@wound_ic_thesis,@wound_bc_thesis,...
    x,t,[],params);
w = sol(:,:,1);
n = sol(:,:,2);
b = sol(:,:,3);
x = 1 - x;
save('chasesdata.mat')    %load('chasedata.mat')
for i=1:20
figure(1)
subplot(1, 3, 1);
hold on
plot(x,w(20*(i-1)+1,:))
axis([0 1 0 1])
xlabel('position (x)')
ylabel('oxygen levels (w)')
title('Oxygen levels in the wound')
%figure(2)
%hold on
subplot(1, 3, 2);
hold on
plot(x,n(20*(i-1)+1,:))
axis([0 1 0 1])
xlabel('position (x)')
ylabel('neutrophil concentrations (n)')
title('Neutrophil concentrations in the wound')
%figure(3)
%hold on
subplot(1, 3, 3);
hold on
plot(x,b(20*(i-1)+1,:))
axis([0 1 0 1])
xlabel('position (x)')
ylabel('bacteria (b)')
title('Bacteria in the wound')
keyboard
end
figure(4)
%subplot(2, 2, 4);
td = t*Lo./(Dwo*24*60*60);
%subplot(2, 2, 4);
plot(td,sum(n'))
xlabel('Time (days)')
ylabel('Neutrophils')
figure(5)
```

```
plot(td,sum(b'))
xlabel('Time (days)')
ylabel('Bacteria')


%save('chase_run1.mat')

function [c,f,s] = wound_pde_thesis(x,t,u,DuDx,params)

Dw = params(1);
Dn = params(2);
chin = params(3);
beta = params(4);
lambdanw = params(5);
lambdaw = params(6);
lambdan = params(7);
lambdabw = params(8);
Db = params(9);
kb = params(10);
Kw = params(11);
Δ = params(12);
knr = params(13);
lambdarb = params(14);
lambdab = params(15);
kni = params(16);
lambdani = params(17);
ee = params(18);
eta = params(19);
%chib = params(19);

c = [1; 1; 1];
f = [Dw; Dn; Db].*DuDx + [0; chin; 0].* u(2).*DuDx(1).*...
    heavi_approx3(1 - u(2));% - [0; chib; 0].*u(2).*DuDx(3).*...
    heavi_approx3(1 - u(2));
s = [beta + eta*hbotherapy(t) - lambdanw*u(1).*u(2) - lambdaw*u(1)...
     - lambdabw*u(3).*u(1); (kni*u(3).*u(2).*(gnwrecruitment(u(1)))...
    )/(lambdani*u(2)+1).*(1-u(2))-(lambdan*u(2))/(ee*u(3)+1); kb*u...
    (3).*(1 - u(3)) - u(3).*(u(1)/(Kw + u(1))).*((Δ + knr*u(2))/(...
    lambdarb*u(3)+1)) - lambdab*u(3)];


function u0 = wound_ic_thesis(x,params)

epsilon = 0.01;
Dw = params(1);
lambdaw = params(6);
beta = params(4);

u0 = [1; 0; 0].*(sech(sqrt(lambdaw/Dw)).*cosh(0.8*sqrt(lambdaw/Dw)...
    .*(1-x)) + beta/lambdaw) + [0; 1; 0].*(1-x).^2.*exp(-((x)/...
    epsilon).^2)+[0; 0; 1].*(x).^2.*exp(-((1-(x))/epsilon).^2);


function [pl,ql,pr,qr] = wound_bc_thesis(x1,ul,xr,ur,t,params)

```

```
Dw = params(1);
beta = params(4);
lambdaw = params(6);
eta = params(19);

pl = [ul(1) - sech(sqrt(lambdaw/Dw)).*cosh(0.8*sqrt(lambdaw/Dw)) -...
     beta/lambdaw - eta*hbotherapy(t); ul(2) - exp(-1.96*t); 0];
ql = [0; 0; 1];
pr = [0; 0; 0];
qr = [1; 1; 1];

function H = heavi_approx3(x)

H = atan(1000*x)./pi+1/2;

function H = heavi_approx2(x)

H = atan(1000*x)./pi+1/2;

function g = hbotherapy(t)
tf = 4.32;
lf = 10;
g1 = heavi_approx2(t) - heavi_approx2(t-1.5*tf/24/lf);
g2 = heavi_approx2(t-tf/lf) - heavi_approx2(t-tf/lf-1.5*tf/24/lf);
g3 = heavi_approx2(t-2*tf/lf) - heavi_approx2(t-2*tf/lf-1.5*tf/24/...
    lf);
g4 = heavi_approx2(t-3*tf/lf) - heavi_approx2(t-3*tf/lf-1.5*tf/24/...
    lf);
g5 = heavi_approx2(t-4*tf/lf) - heavi_approx2(t-4*tf/lf-1.5*tf/24/...
    lf);
g6 = heavi_approx2(t-5*tf/lf) - heavi_approx2(t-5*tf/lf-1.5*tf/24/...
    lf);
g7 = heavi_approx2(t-6*tf/lf) - heavi_approx2(t-6*tf/lf-1.5*tf/24/...
    lf);
g8 = heavi_approx2(t-7*tf/lf) - heavi_approx2(t-7*tf/lf-1.5*tf/24/...
    lf);
g9 = heavi_approx2(t-8*tf/lf) - heavi_approx2(t-8*tf/lf-1.5*tf/24/...
    lf);
g10 = heavi_approx2(t-9*tf/lf) - heavi_approx2(t-9*tf/lf-1.5*tf...
    /24/lf);
%g11 = heavi_approx2(t-10*tf/lf) - heavi_approx2(t-10*tf/lf-1.5*tf...
    /24/lf);
%g12 = heavi_approx2(t-11*tf/lf) - heavi_approx2(t-11*tf/lf-1.5*tf...
    /24/lf);
%g13 = heavi_approx2(t-12*tf/lf) - heavi_approx2(t-12*tf/lf-1.5*tf...
    /24/lf);
%g14 = heavi_approx2(t-13*tf/lf) - heavi_approx2(t-13*tf/lf-1.5*tf...
    /24/lf);
%g15 = heavi_approx2(t-14*tf/lf) - heavi_approx2(t-14*tf/lf-1.5*tf...
    /24/lf);
%g16 = heavi_approx2(t-15*tf/lf) - heavi_approx2(t-15*tf/lf-1.5*tf...
    /24/lf);
%g17 = heavi_approx2(t-16*tf/lf) - heavi_approx2(t-16*tf/lf-1.5*tf...
    /24/lf);
%g18 = heavi_approx2(t-17*tf/lf) - heavi_approx2(t-17*tf/lf-1.5*tf...
```

```
    /24/lf);
%g19 = heavi_approx2(t-18*tf/lf) - heavi_approx2(t-18*tf/lf-1.5*tf...
    /24/lf);
%g20 = heavi_approx2(t-19*tf/lf) - heavi_approx2(t-19*tf/lf-1.5*tf...
    /24/lf);
%g21 = heavi_approx2(t-20*tf/lf) - heavi_approx2(t-20*tf/lf-1.5*tf...
    /24/lf);
g = g1 + g2 + g3 + g4 + g5 + g6 + g7 + g8 + g9 + g10;% + g18 + g19...
     + g20 + g21;% + g15 + g16 + g17 + g18 + g19 + g20 + g21;
%h1 = length(t);
%h = zeros(1,h1);
%for i = 1:h1
%    if  mod(t(i)*10^6/24/3600,1) < (1.5+10^(-10))/24
%        h(i) = 1;
%    else
%        h(i) = 0;
%    end
%end

function g = gnwrecruitment(w)

i = length(w);
g = zeros(1,i);
for j = 1:i
    if w(j) < 1
        g(j) = 2*w(j)^3 - 3*w(j)^2 + 2;
    else
        g(j) = 1;
    end
end
```

BIBLIOGRAPHY

[1] Nakhle H. Asmar. *Partial Differential Equations with Fourier Series and Boundary Value Problems*. Pearson Education, Inc., Upper Saddle River, NJ 07458, 2nd edition, 2005.

[2] S. Barrientos, O. Stojadinovic, M. S. Golinko, H. Brem, and M. Tomic-Canic. Growth factors and cytokines in wound healing. *Wound Repair and Regeneration*, 16:585–601, 2008.

[3] Paul Dale, Sherratt Jonathan A, and Phillip K. Maini. A mathematical model for collagen fibre formation during foetal and adult dermal wound healing. *Proceedings of The Royal Society*, 263(1370):653–660, 1996.

[4] Paul D. Dale, Jonathon A. Sherratt, and Philip K. Maini. Role of fibroblast migration in collagen fiber formation during fetal and adult dermal wound healing. *Bulletin of Mathematical Biology*, 59(6):1077–1100, 1997.

[5] F. H. Epstein, A. J. Singer, and R. A. F. Clark. Cutaneous wound healing. *The New England Journal of Medicine*, 341:738–746, 1999.

[6] Jennifer A. Flegg, Helen M. Byrne, Mark B. Flegg, and D.L. Sean McElwain. Wound healing angiogenesis: The clinical implications of a simple mathematical model. *Journal of Theoretical Biology*, 300:309–316, 2012.

[7] Jennifer A. Flegg, Donald L. S. McElwain, Helen M. Byrne, and Ian W. Turner. A three species model to simulate application of hyperbaric oxygen therapy to chronic wounds. *PLoS Computational Biology*, 5(7), 2009.

[8] B. M. Hantash, L. Zhao, J. A. Knowles, and H. P. Lorenz. Adult and fetal wound healing. *Frontiers in Bioscience*, 13:51–61, 2008.

[9] Mark H. Holmes. *Introduction to Perturbation Methods*. Texts in applied mathematics. Springer-Verlag New York, Inc., 175 Fifth Avenue, New York, NY 10010, USA, 2nd edition, 1995.

[10] B. M. Kuehn. Chronic wound care guidelines issued. *Journal of the American Medical Association*, 297(9):938–939, 2007.

[11] MD Maria B. Witte and MD Adrian Barbul. General principles of wound healing. *Surgical Clinics of North America*, 77(3):509–528, June 1997.

[12] J. D. Murray. *Mathematical Biology I: An introduction*. Springer-Verlag New York Inc., 175 Fifth Avenue, New York, NY 10010, 3rd edition, 2002.

[13] S. Roy, S. Biswas, S. Khanna, G. M. Gordillo, V. Bergdall, J. Green, C. B. Marsh, L. J. Gould, and C. K. Sen. Characterization of a pre-clinical model of chronic ischemic wound. *Physiological Genomics*, 2009.

[14] Richard C. Schugart, Avner Friedman, Rui Zhao, and Chandan K. Sen. Wound angiogenesis as a function of tissue oxygen tension: A mathematical model. *Proceedings of the National Academy of Sciences*, 105(7):2628–2633, February 2008.

[15] Richard C. Schugart, Chuan Xue, Sashwati Roy, and Chandan K. Sen. A mathematical model for chronic wound healing. In preparation.

[16] J. P. Ward, J. R. King, A. J. Koerber, P. Williams, J. M. Croft, and R. E. Sockett. Mathematical modelling of quorum sensing in bacteria. *Institute of Mathematics and its Applications Journal of Mathematics Applied in Medicine and Biology*, 18(3):263–292, September 2001.