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Application of a Numerical Method and Optimal Control Theory to a Partial Differential Equation Model for a Bacterial Infection in a Chronic Wound

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APPLICATION OF A NUMERICAL METHOD AND OPTIMAL CONTROL
THEORY TO A PARTIAL DIFFERENTIAL EQUATION MODEL FOR A
BACTERIAL INFECTION IN A CHRONIC WOUND

A Thesis
Presented to
The Faculty of the Department of Mathematics Masters Program
Western Kentucky University
Bowling Green Kentucky

In Partial Fulfillment
Of the Requirements for the Degree
Master of Mathematics


By
Stephen Guffey

May 2015

APPLICATION OF A NUMERICAL METHOD AND OPTIMAL CONTROL
THEORY TO A PARTIAL DIFFERENTIAL EQUATION MODEL FOR A
BACTERIAL INFECTION IN A CHRONIC WOUND

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I would like to dedicate my thesis my friends, family, and professors.

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APPLICATION OF A NUMERICAL METHOD AND OPTIMAL CONTROL THEORY TO
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In this work, we study the application both of optimal control techniques and a numerical method to a system of partial differential equations arising from a problem in wound healing. Optimal control theory is a generalization of calculus of variations, as well as the method of Lagrange Multipliers. Both of these techniques have seen prevalent use in the modern theories of Physics, Economics, as well as in the study of Partial Differential Equations. The numerical method we consider is the method of lines, a prominent method for solving partial differential equations. This method uses finite difference schemes to discretize the spatial variable over an N -point mesh, thereby converting each partial differential equation into N ordinary differential equations. These equations can then be solved using numerical routines defined for ordinary differential equations.

CHAPTER 1

INTRODUCTION

The primary motivation of this work is to explore the possibility of finding the optimal level of hyperbaric oxygen to administer to patients with chronic wounds. These wounds can develop for a variety of reasons including ischemia, which inhibits the body's ability to supply oxygen and nutrients to the leukocytes in the wound. This results in an inefficiency of the leukocytes oxidatively [13]. These wounds affect an estimated 1.3 – 3 million Americans each year. The annual cost for research and treatment for these wounds is estimated to be \$5-10 billion [8].

In this current work, we formulate a partial-differential-equation model that is to capture the dynamics of the oxygen, neutrophils (a type of leukocyte), invasive bacteria, and chemoattractant (a chemical that attracts the neutrophils to the bacteria). Our model is an expansion on the model used in Brandon Russell's WKU Honors College CE/T Project [14]. Specifically, we have added a governing equation for the chemoattractant released by the bacteria. It is this chemical release that attracts the neutrophils towards high concentrations of bacteria. In chapter 2, we discuss the biological background of the model and how this relates to the system of partial differential equations (PDEs) we will study. We also non-dimensionalize the system in preparation for our analytic and numeric work.

We will apply optimal control theory to our system. Optimal control theory, in a sense, is the study of how to maximize (or minimize) a system through one or more variables we can control. In applying optimal control theory, we wish

to optimize our system, *i.e.*, we wish to minimize the system with respect to a pre-determined objective. In particular, we wish to minimize the total number of bacteria as well as the amount of supplemental oxygen given. In order to do so, we must first find whether our system of equations have a solution. If a solution exists, we also require the solution is unique and bounded. If a unique, bounded solution exists, we wish to find whether an optimal control exists. These inquiries all serve the purpose of validating differentiating our objective functional to find the functional's minimum. When we do this, we are able to find a characterization of the optimal control in terms of the state system and its derivatives.

In chapter 3, we study the application of Optimal Control techniques to the system of partial differential equations. We first search for the existence and uniqueness of solutions to the state system. The state system refers to the system of equations which we are trying to optimize, the unknown function for each equation being referred to as a state. Due to the equations being nonlinear, we will follow the common approach for these systems of formulating the system in terms of an abstract quasilinear operator equation. This will reduce our problem to an ordinary differential Cauchy problem with operator coefficients. We discuss results established by Yagi [22] that are similar to what we wish to prove. We do this to give background on what inspired our given approach.

With the Cauchy problem set up, we will attempt to prove existence and uniqueness of the system. Then we will need to find lower bounds for our state solutions in the appropriate space. Once the existence and uniqueness of the state solutions are verified, we may then consider the existence of an optimal control for

our system. Lower bounds on our state solutions give us a minimizing sequence of controls for our objective functional. From there, we are able to use the weak formulation of the state equations to obtain a bound for the minimizing sequences, thereby obtaining convergent subsequences by employing the properties of reflexive Banach spaces. These sequences will weakly converge to the optimal control and associated states. From there, we employ Sobolev inequalities to prove that the weak convergences are strong convergences in the appropriate spaces. As our functional is written in terms of an L^p norm, we have lower semi-continuity of the functional with respect to weak convergences. We use this lower semi-continuity to show that the limit of the control sequence is the optimal control; *i.e.*, the control which minimizes our functional.

With the existence of the state and optimal control, we then wish to obtain a characterization of the optimal control. This will require differentiation of the objective functional with respect to the control. In this process, we will be required to obtain the directional derivative of the states with respect to the control. These directional derivatives will be referred to as sensitivities. Associated with the sensitivity system is the adjoint system, which is defined in such a way as to form the duality between our state solution space and its dual space. With the sensitivity and adjoint systems calculated, we may then differentiate the objective functional in the appropriate sense, and using standard arguments, find the characterization of the optimal control. This characterization will be an expression of the optimal control in terms of the sensitivities and adjoint variables.

In chapter 4, we turn our attention to the numerical work done on our equations. The goal of our numerical work was to write code which solved the state system, and compare our results to those obtained by the pre-packaged *Matlab* procedure, *pdepe.m*. The reason for writing a code to solve our system with the method of lines is to overcome *pdepe.m*'s inability to solve systems involving hyperbolic equations, since we eventually wish to drop the diffusion term for bacteria. After discussing the method of lines and our spatial discretization, we give our results obtained from both our method-of-lines code as well as the solution obtained from *pdepe.m*. We plot the two corresponding solutions on the same plots over equidistant time steps to qualitatively assess our method. Finally, we run our method-of-lines code for the corresponding parabolic-hyperbolic system, and display the obtained results.

CHAPTER 2

INTRODUCTION TO THE MODEL

Our model describes the interactions between bacteria, neutrophils, oxygen, and a chemoattractant in a radially symmetric wound under hyperbaric oxygen therapy. In our work, let x correspond to the radial distance from the center of the wound, $0 \leq x \leq L$, where L is the maximal radial distance from the center, measured in centimeters. Let t denote the time from the start of treatment, measured in seconds. The variable w will denote the concentration of oxygen in grams per centimeter. The variable n is the concentration of the neutrophils, measured in grams per centimeter. We let b denote the concentration of bacteria in grams per centimeter. Finally, c will represent the concentration of the chemoattractant released by the bacteria, also in grams per centimeter.

2.1. Oxygen Equation

The oxygen in the wound is assumed to have a constant rate of diffusion, D_w , measured in cm^2 per second. We assume that oxygen may enter the wound from below at a constant rate β , measured in grams per centimeter-seconds. Along with this, oxygen increases through the supplemental oxygen given as therapy, denoted by $G(t)$, measured in grams per centimeter seconds. Oxygen will be used by the neutrophils and the bacteria, thus contributing to the loss of oxygen at rates λ_{nw} and λ_{bw} , respectively, and measured in centimeters per gram seconds. Furthermore, we include a constant rate of loss for the oxygen λ_w due do natural decay of oxygen.

Thus, our model for the oxygen in the wound becomes

$$\frac{\partial w}{\partial t} = D_w \frac{\partial^2 w}{\partial x^2} + \beta + \kappa G(t) - \lambda_{nw}nw - \lambda_{bw}bw - \lambda_w w,$$

where

$$G(t) = \begin{cases} 1, & \text{when oxygen is administered,} \\ 0 & \text{otherwise.} \end{cases}$$

Furthermore, we assume that oxygen is initially distributed at the normal level of oxygen; *i.e.*, $w(x, 0) = w_0$. Due to the radial symmetry of the problem, we impose a zero flux condition at the center of the wound. We also impose the condition that the oxygen remains at the normal level of oxygen on the boundary of the wound. We write these conditions as $\frac{\partial w}{\partial x}|_{x=0} = 0$ and $w(L, t) = w_0$, respectively.

2.2. Neutrophil Equation

The neutrophils are assumed to have a constant rate of random motility, D_n , measured in centimeters squared per second. This movement, however, is assumed to be small relative to the chemotactic response, which occurs at a constant rate χ_n , measured in cm^5 per gram seconds. This motion describes the attraction of the neutrophils to the bacteria via means of sensing a gradient of the chemoattractant released by the bacteria. We incorporate a source for the neutrophils in terms of logistic growth term, which becomes multiplied by the concentration of the bacteria as well as a function $g_n(\frac{w}{w_0})$. These imply that the proliferation of the neutrophils is also dependent on the presence of bacteria and oxygen. This dependence on the levels of bacteria and oxygen present at that point in the wound is also observed in the modeling of the decay for the neutrophils. With this model in place, we write the

equation for the neutrophils as

$$\frac{\partial n}{\partial t} = D_n \frac{\partial^2 n}{\partial x^2} - \chi_n \frac{\partial}{\partial x} \left(n \frac{\partial c}{\partial x} \right) + k_{bn} b n g_n \left(\frac{w}{w_0} \right) \left(1 - \frac{n}{n_0} \right) - \frac{\lambda_n \epsilon b_0 n (1 + h_n(\frac{w}{w_0}))}{\epsilon b_0 + b(1 - \epsilon)},$$

where

$$g_n \left(\frac{w}{w_0} \right) = \begin{cases} 2 \left(\frac{w}{w_0} \right)^3 - 3 \left(\frac{w}{w_0} \right)^2 + 2, & \text{for } 0 \leq \frac{w}{w_0} < 1, \\ 1, & \text{for } \frac{w}{w_0} \geq 1, \end{cases}$$

and

$$h_n \left(\frac{w}{w_0} \right) = \begin{cases} 2, & \text{for } \frac{w}{w_0} < 0.15, \\ 4000 \left(\frac{w}{w_0} \right)^3 - 2400 \left(\frac{w}{w_0} \right)^2 + 450 \left(\frac{w}{w_0} \right) - 25, & \text{for } 0.15 \leq \frac{w}{w_0} < 0.25, \\ 0, & \text{for } 0.25 \leq \frac{w}{w_0} < 2.95, \\ -4000 \left(\frac{w}{w_0} \right)^3 + 36000 \left(\frac{w}{w_0} \right)^2 - 107970 \left(\frac{w}{w_0} \right) + 107911, & \text{for } 2.95 \leq \frac{w}{w_0} < 3.05, \\ 2, & \text{for } \frac{w}{w_0} \geq 3.05. \end{cases}$$

Again we will impose the zero flux condition at the center of the wound, so that $\frac{\partial n}{\partial x} \Big|_{x=0} = 0$. We will also assume that the neutrophils are at their carrying capacity at the edge of the wound, so that $n(L, t) = n_0$. The neutrophils are assumed to be originally concentrated heavily near the edge of the wound, with a quick decay in their levels to nonexistence inside the wound. We write this condition as $n(x, 0) = n_0 \left(\frac{x}{L} \right)^2 e^{-\left(\frac{x-L}{\epsilon L} \right)^2}$.

2.3. Bacterial Equation

For simplicity of analysis of the system, we impose an artificial constant random motility for the bacteria ϵ_b , which is assumed to be at least a few orders of magnitude smaller than the other diffusion coefficients, and measured in cm^2 per second. The primary influence for the bacteria is the proliferation of the bacteria, which occurs

from the center of the wound where the bacteria are initially concentrated. As with the neutrophils assume logistic growth. We incorporate two terms for death. The first represents oxidative killing of the bacteria while the second describes natural death at a rate λ_b , measured in concentration per second. Under these conditions we model the concentration of bacteria in the wound as

$$\frac{\partial b}{\partial t} = \epsilon_b \frac{\partial^2 b}{\partial x^2} + k_b b \left(1 - \frac{b}{b_0}\right) - b \frac{w}{K_w + w} \frac{\delta + k_{nr} n}{\lambda_{rb} b + \lambda_r} - \lambda_b b$$

Along with the zero flux condition in the center of the wound, we also impose a zero flux condition on the edge of the wound, namely $\frac{\partial b}{\partial x}|_{x=0} = 0$, and $\frac{\partial b}{\partial x}|_{x=L} = 0$. The bacteria are assumed to be initially concentrated densely in the center of the wound and nonexistent elsewhere. As with the neutrophils, we model this with $b(x, 0) = b_0 \left(\frac{L-x}{L}\right)^2 e^{-\left(\frac{x}{\epsilon L}\right)^2}$.

2.4. Chemoattractant Equation

The chemoattractant is assumed to have a constant rate of diffusion, D_c , to be measured in cm^2 per second. Furthermore, since the chemoattractant is produced by the bacteria, we incorporate this at a constant rate k_c , measured in concentration per second. Finally, the chemoattractant is assumed to decay at a constant rate λ_c , also measured in concentration per second. We thus obtain

$$\frac{\partial c}{\partial t} = D_c \frac{\partial^2 c}{\partial x^2} + k_c b - \lambda_c c$$

as the governing equation for the chemoattractant. We use the same boundary conditions for the chemoattractant as the bacteria. Thus, $\frac{\partial c}{\partial x}|_{x=0} = 0$ and $\frac{\partial c}{\partial x}|_{x=L} = 0$. Furthermore, we assume that the chemoattractant is initially distributed in such a

way that is proportional to the distribution of the bacterial population. As such, the initial condition for the chemoattractant becomes $c(x, 0) = c_0 \left(\frac{x-L}{L}\right)^2 e^{-\left(\frac{x}{\epsilon L}\right)^2}$.

2.5. Non-dimensionalization

In this section we will re-write our system from its current, dimensional form in terms of non-dimensional values. The purpose of this is two-fold. First, we be able simplify our equations in terms of grouped parameters that will make our equations cleaner, and therefore easier to work with. Second, non-dimensionalization of systems is commonly performed in order to ease the computational cost to solve the system.

We begin with the scaled system:

$$\begin{aligned}
\frac{\partial w}{\partial t} &= D_w \frac{\partial^2 w}{\partial x^2} + \beta + \kappa G(t) - \lambda_{nw}nw - \lambda_{bw}bw - \lambda_w w \\
\frac{\partial n}{\partial t} &= D_n \frac{\partial^2 n}{\partial x^2} - \chi_n \frac{\partial}{\partial x} \left(n \frac{\partial c}{\partial x} \right) + k_{bn}bn g_n \left(\frac{w}{w_0} \right) \left(1 - \frac{n}{n_0} \right) - \frac{\lambda_n \epsilon b_0 n (1 + h_n(\frac{w}{w_0}))}{\epsilon b_0 + b(1 - \epsilon)} \\
\frac{\partial b}{\partial t} &= \epsilon_b \frac{\partial^2 b}{\partial x^2} + k_b b \left(1 - \frac{b}{b_0} \right) - b \frac{w}{K_w + w} \frac{\delta + k_{nr}n}{\lambda_{rb}b + \lambda_r} - \lambda_b b \\
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + k_c b - \lambda_c c,
\end{aligned} \tag{2.5.1}$$

where

$$g_n\left(\frac{w}{w_0}\right) = \begin{cases} 2\left(\frac{w}{w_0}\right)^3 - 3\left(\frac{w}{w_0}\right)^2 + 2, & \text{for } 0 \leq \frac{w}{w_0} < 1, \\ 1, & \text{for } \frac{w}{w_0} \geq 1, \end{cases}, \text{ and}$$

$$h_n\left(\frac{w}{w_0}\right) = \begin{cases} 2, & \text{for } \frac{w}{w_0} < 0.15, \\ 4000\left(\frac{w}{w_0}\right)^3 - 2400\left(\frac{w}{w_0}\right)^2 + 450\left(\frac{w}{w_0}\right) - 25, & \text{for } 0.15 \leq \frac{w}{w_0} < 0.25, \\ 0, & \text{for } 0.25 \leq \frac{w}{w_0} < 2.95, \\ -4000\left(\frac{w}{w_0}\right)^3 + 36000\left(\frac{w}{w_0}\right)^2 - 107970\left(\frac{w}{w_0}\right) + 107911, & \text{for } 2.95 \leq \frac{w}{w_0} < 3.05, \\ 2, & \text{for } \frac{w}{w_0} \geq 3.05, \end{cases}$$

$$G(t) = \begin{cases} 1, & \text{when oxygen is administered,} \\ 0, & \text{otherwise} \end{cases}$$

subject to the following initial and boundary conditions :

$$\begin{aligned} \frac{\partial w}{\partial x}\Big|_{x=0} &= 0 & \frac{\partial n}{\partial x}\Big|_{x=0} &= 0 \\ w(L, t) &= w_0 & n(L, t) &= n_0 \\ w(x, 0) &= 1 & n(x, 0) &= n_0 \left(\frac{x}{L}\right)^2 e^{-\left(\frac{x-L}{\epsilon L}\right)^2} \end{aligned} \tag{2.5.2}$$

$$\begin{aligned} \frac{\partial b}{\partial x}\Big|_{x=0} &= 0 & \frac{\partial c}{\partial x}\Big|_{x=0} &= 0 \\ \frac{\partial b}{\partial x}\Big|_{x=L} &= 0 & \frac{\partial c}{\partial x}\Big|_{x=L} &= 0 \\ b(x, 0) &= b_0 \left(\frac{x-L}{L}\right)^2 e^{-\left(\frac{x}{\epsilon L}\right)^2} & c(x, 0) &= c_0 \left(\frac{x-L}{L}\right)^2 e^{-\left(\frac{x}{\epsilon L}\right)^2}. \end{aligned}$$

In order to non-dimensionalize the system, we make the following definitions: $x = \bar{x}x^*, t = \bar{t}t^*, b = \bar{b}b^*, c = \bar{c}c^*, n = \bar{n}n^*, w = \bar{w}w^*$, where $(\bar{\cdot})$ represents the dimensional characteristic unit and $(\cdot)^*$ represents the non-dimensional parameter. With these

definitions, we re-write our system of equations as

$$\begin{aligned}
\frac{\bar{w}}{\bar{t}} \frac{\partial w^*}{\partial t^*} &= D_w \frac{\bar{w}}{\bar{x}^2} \frac{\partial^2 w^*}{\partial x^{*2}} + \beta + \kappa G(\bar{t}t^*) - \bar{n}\bar{w}\lambda_{nw}n^*w^* - \bar{b}\bar{w}\lambda_{bw}b^*w^* - \bar{w}\lambda_w w^* \\
\frac{\bar{n}}{\bar{t}} \frac{\partial n^*}{\partial t^*} &= D_n \frac{\bar{n}}{\bar{x}^2} \frac{\partial^2 n^*}{\partial x^{*2}} - \chi_n \frac{\bar{n}\bar{c}}{\bar{x}^2} \frac{\partial}{\partial x^*} \left(n^* \frac{\partial c^*}{\partial x^*} \right) + \bar{b}\bar{n}k_{bn}b^*n^*g_n \left(\frac{\bar{w}w^*}{w_0} \right) \left(1 - \frac{\bar{n}n^*}{n_0} \right) - \\
&\quad \frac{\lambda_n \epsilon b_0 \bar{n}n^* \left(1 + h_n \left(\frac{w^*\bar{w}}{w_0} \right) \right)}{\epsilon b_0 + \bar{b}b^* (1 - \epsilon)} \\
\frac{\bar{b}}{\bar{t}} \frac{\partial b^*}{\partial t^*} &= \epsilon_b \frac{\bar{b}}{\bar{x}^2} \frac{\partial^2 b^*}{\partial x^{*2}} + k_b \bar{b}b^* \left(1 - \frac{\bar{b}b^*}{b_0} \right) - \bar{b}b^* \frac{\bar{w}w^*}{K_w + \bar{w}w^*} \frac{\delta + k_{nr}\bar{n}n^*}{\bar{b}\lambda_{rb}b^* + \lambda_r} - \bar{b}\lambda_b b^* \\
\frac{\bar{c}}{\bar{t}} \frac{\partial c^*}{\partial t^*} &= D_c \frac{\bar{c}}{\bar{x}^2} \frac{\partial^2 c^*}{\partial x^{*2}} + \bar{b}k_c b^* - \bar{c}\lambda_c c^*.
\end{aligned}$$

Upon rearrangement, we may write the system as

$$\begin{aligned}
\frac{\bar{x}^2}{D_w \bar{t}} \frac{\partial w^*}{\partial t^*} &= \frac{\partial^2 w^*}{\partial x^{*2}} + \frac{\beta \bar{x}^2}{D_w \bar{w}} + \frac{\kappa \bar{x}^2}{D_w \bar{w}} G(\bar{t}t^*) - \frac{\bar{n}\bar{x}^2 \lambda_{nw} n^* w^*}{D_w} - \frac{\bar{b}\bar{x}^2 \lambda_{bw} b^* w^*}{D_w} - \frac{\bar{x}^2 \lambda_w w^*}{D_w} \\
\frac{\bar{x}^2}{D_n \bar{t}} \frac{\partial n^*}{\partial t^*} &= \frac{\partial^2 n^*}{\partial x^{*2}} - \frac{\chi_n \bar{c}}{D_n} \frac{\partial}{\partial x^*} \left(n^* \frac{\partial c^*}{\partial x^*} \right) + \frac{\bar{x}^2 \bar{b}k_{bn} b^* n^* g_n \left(\frac{\bar{w}w^*}{w_0} \right) \left(1 - \frac{\bar{n}}{n_0} n^* \right) -}{D_n} \\
&\quad \frac{\bar{x}^2 \lambda_n n^* \left(1 + h_n \left(\frac{w^*\bar{w}}{w_0} \right) \right)}{D_n \left(1 + b^* \left(\frac{1-\epsilon}{\epsilon} \right) \right)} \\
\frac{\bar{x}^2}{\epsilon_b \bar{t}} \frac{\partial b^*}{\partial t^*} &= \frac{\partial^2 b^*}{\partial x^{*2}} + \frac{k_b b^* \bar{x}^2}{\epsilon_b} \left(1 - \frac{\bar{b}}{b_0} b^* \right) - b^* \frac{w^*}{\frac{K_w}{w} + w} \frac{\frac{\bar{x}\lambda_r}{\epsilon_b} (\delta + k_{nr}\bar{n}n^*)}{\frac{\bar{b}\lambda_{rb}}{\lambda_r} b^* + 1} - \bar{b}\lambda_b b^* \\
\frac{\bar{x}^2}{D_c \bar{t}} \frac{\partial c^*}{\partial t^*} &= \frac{\partial^2 c^*}{\partial x^{*2}} + \frac{\bar{b}k_c \bar{x}^2}{\bar{c}D_c} b^* - \frac{\bar{x}^2 \lambda_c}{D_c} c^*.
\end{aligned}$$

We make the following definitions,

$$\begin{aligned}
\{x^*, t^*, b^*, c^*, n^*, w^*\} &= \left\{ \frac{x}{L}, \frac{D_w t}{L^2}, \frac{b}{b_0}, \frac{c}{c_0}, \frac{n}{n_0}, \frac{w}{w_0} \right\}, \\
\{D_w^*, \beta^*, \kappa^*, \lambda_{nw}^*, \lambda_{bw}^*, \lambda_w^*\} &= \left\{ 1, \frac{\beta L^2}{D_w w_0}, \frac{\kappa L^2}{D_w w_0}, \frac{\lambda_{nw} n_0 L^2}{D_w}, \frac{\lambda_{bw} b_0 L^2}{D_w}, \frac{\lambda_w L^2}{D_w} \right\}, \\
\{D_n^*, \chi_n^*, k_{bn}^*, \lambda_n^*, e^*\} &= \left\{ \frac{D_n}{D_w}, \frac{\chi_n c_0}{D_w}, \frac{L^2 b_0 k_{bn}}{D_w}, \frac{\lambda_n L^2}{D_w}, \frac{(1-\epsilon)}{\epsilon} \right\}, \\
\{\epsilon_b^*, k_b^*, K_w^*, \delta^*, k_{nr}^*, \lambda_{rb}^*, \lambda_b^*\} &= \left\{ \frac{\epsilon_b}{D_w}, \frac{k_b L^2}{D_w}, \frac{K_w}{w_0}, \frac{\delta L^2}{D_w}, \frac{k_{nr} n_0 L^2 \lambda_r}{D_w}, \frac{b_0 \lambda_{rb}}{\lambda_r}, \lambda_b b_0 \right\}, \\
\{D_c^*, k_c^*, \lambda_c^*\} &= \left\{ \frac{D_c}{D_w}, \frac{b_0 k_c L^2}{c_0 D_w}, \frac{L^2 \lambda_c}{D_w} \right\}.
\end{aligned}$$

With these definitions we may write our system dropping the asterisks for notational convenience) as

$$\begin{aligned}
\frac{\partial w}{\partial t} &= \frac{\partial^2 w}{\partial x^2} + \beta + \kappa G(t) - \lambda_{nw} n w - \lambda_{bw} b w - \lambda_w w \\
\frac{\partial n}{\partial t} &= D_n \frac{\partial^2 n}{\partial x^2} - \chi_n \frac{\partial}{\partial x} \left(n \frac{\partial c}{\partial x} \right) + k_{bn} b n g_n(w) (1-n) - \lambda_n \frac{n(1+h_n(w))}{1+eb} \\
\frac{\partial b}{\partial t} &= \epsilon_b \frac{\partial^2 b}{\partial x^2} + k_b b (1-b) - b \frac{w}{K_w + w} \frac{\delta + k_{nr} n}{\lambda_{rb} b + 1} - \lambda_b b \\
\frac{\partial c}{\partial t} &= D_c \frac{\partial^2 c}{\partial x^2} + k_c b - \lambda_c c,
\end{aligned} \tag{2.5.3}$$

where

$$\begin{aligned}
g_n(w) &= \begin{cases} 2(w)^3 - 3(w)^2 + 2, & \text{for } 0 \leq w < 1, \\ 1, & \text{for } w \geq 1, \end{cases} \text{ and} \\
h_n(w) &= \begin{cases} 2, & \text{for } w < 0.15, \\ 4000(w)^3 - 2400(w)^2 + 450(w) - 25, & \text{for } 0.15 \leq w < 0.25, \\ 0, & \text{for } 0.25 \leq w < 2.95, \\ -4000(w)^3 + 36000(w)^2 - 107970(w) + 107911, & \text{for } 2.95 \leq w \leq 3.05, \\ 2, & \text{for } w \geq 3.05, \end{cases}
\end{aligned}$$

subject to the following initial and boundary conditions :

$$\begin{aligned}
 \frac{\partial w}{\partial x} \Big|_{x=0} &= 0 & \frac{\partial n}{\partial x} \Big|_{x=0} &= 0 \\
 w(1, t) &= 1 & n(1, t) &= 1 \\
 w(x, 0) &= 1 & n(x, 0) &= x^2 e^{-\left(\frac{1-x}{\epsilon}\right)^2} \\
 & & & (2.5.4)
 \end{aligned}$$

$$\begin{aligned}
 \frac{\partial b}{\partial x} \Big|_{x=0} &= 0 & \frac{\partial c}{\partial x} \Big|_{x=0} &= 0 \\
 \frac{\partial b}{\partial x} \Big|_{x=0} &= 0 & \frac{\partial c}{\partial x} \Big|_{x=1} &= 0 \\
 b(x, 0) &= (1-x)^2 e^{-\left(\frac{x}{\epsilon}\right)^2} & c(x, 0) &= (1-x)^2 e^{-\left(\frac{x}{\epsilon}\right)^2}.
 \end{aligned}$$

CHAPTER 3

OPTIMAL CONTROL

3.1. Introduction

Optimal control is a branch of mathematics concerned with maximizing or minimizing a system subject to prescribed constraints. It is an outgrowth of a wide range of mathematics. One of the first optimization problems is the well known Problem of Queen Dido [7], also known as the isoperimetric problem, in which one must find the planar curve that maximizes the contained area of a curve of given perimeter. Interest in these problems grew after the invention of calculus, which presented new machinery that allowed mathematicians to effectively analyze minimization principles. Some of the most notable contributions to this area were due to Joseph-Louis Lagrange, who introduced Lagrange multipliers into systems as a way to incorporate constraints into the system to be optimized. These efforts were expanded during the early-to-mid 1900s in the form of linear and dynamic programming. The latter of these would lead to what we today know as optimal control theory. The prominent feature of optimal control theory is Pontryagin's Maximum Principle (sometimes known as Pontryagin's Minimum Principle), which gives the necessary conditions for the existence of an optimal control for a system governed by ordinary differential equations (ODEs). In particular, given an ODE equation (or system of such equations), one can explicitly find characterization of the optimal control in terms of the Hamiltonian of the system. Extensions of Pontryagin's principle exists for stochastic problems [10].

For PDEs, however, there is no full generalization of such a theorem. In particular, we have no such result for system (2.5.3), which shall be referred to as the

state system. As we have no extension of Pontryagin's principle, we give the method by which we shall proceed. We first wish to find a solution to (2.5.3) with boundary and initial conditions (2.5.4). As our system is coupled and nonlinear, we will find this solution by formulating the problem as a quasilinear abstract evolution equation. From this, we shall prove a solution exists in a given Sobolev space. For background in Sobolev spaces, we refer the reader to Appendix A, which attempts to give all necessary background information. In addition to the existence of a solution to the state system, we will also require uniqueness and lower bounds. Due to a theorem of Sobolevskii, we wish to obtain all of these with a single proof.

Once one has the existence, uniqueness, and lower bounds of the state system, one can investigate the existence of an optimal control. By the existence and lower bounds of the state solution, one is able to obtain a minimizing sequence for a given objective functional. This functional will be written as an integral over time and space, which will be a formulation for the constraints we wish to impose on our system. From the uniqueness of the state solution, we will also be able to obtain minimizing sequences for the state functions by identifying the minimizing state sequences with the sequences associated with the minimizing control sequence. We shall show that these minimizing sequences converge weakly in an appropriate Hilbert space. Using Sobolev embedding theorems, we must then prove this limit exists in the strong sense. Finally, this strong limit must be shown to be the optimal control; *i.e.* the control which minimizes the functional.

After obtaining the existence of the optimal control, we then wish to find the characterization of it in terms of the state solutions. In doing so, we must differentiate

the objective functional with respect to the control. As our functional exists as a mapping between Banach spaces, we shall be differentiating in the sense of Gâteaux. This will require us to also differentiate the state system with respect to the control, which will lead to the formulation of the sensitivity system. The sensitivity system will be a linearization of the state system in terms of the Gâteaux derivatives of the states in the direction of the control. With this linearized system, we shall also be able to define an adjoint system, which will form the duality with the sensitivity system between the state solution space and its dual space. This adjoint system will behave in a similar manner to Lagrange multipliers in that they are what allows us to incorporate in the constraints from the objective functional into the system to be minimized.

Together, the state system, sensitivities, and adjoint system will allow us to find a characterization of the optimal control.

3.2. Existence of a Solution to the State System

Our system of equations from (2.5.3) is as follows on $(0, 1) \times (0, T)$:

$$\begin{aligned}
w_t &= w_{xx} + \beta + \kappa G(t) - \lambda_{nw}nw - \lambda_{bw}bw - \lambda_w w \\
n_t &= D_n n_{xx} - \chi_n (nc_x)_x + k_{bn}bn g_n(w)(1-n) - \frac{\lambda_n(1+h_n(w))n}{eb+1} \\
b_t &= \epsilon_b b_{xx} + k_b b(1-b) - b \frac{w}{k_w+w} \frac{\delta + k_{nr}n}{\lambda_{rb}b+1} \\
c_t &= D_c c_{xx} + k_c b - \lambda_c c,
\end{aligned}$$

subject to the following initial and boundary conditions :

$$\begin{aligned}
\frac{\partial w}{\partial x}\Big|_{x=0} &= 0 & \frac{\partial n}{\partial x}\Big|_{x=0} &= 0 \\
w(1, t) &= 1 & n(1, t) &= 1 \\
w(x, 0) &= 1 & n(x, 0) &= x^2 e^{-\left(\frac{1-x}{\epsilon}\right)^2} \\
\\
\frac{\partial b}{\partial x}\Big|_{x=0} &= 0 & \frac{\partial c}{\partial x}\Big|_{x=0} &= 0 \\
\frac{\partial b}{\partial x}\Big|_{x=1} &= 0 & \frac{\partial c}{\partial x}\Big|_{x=1} &= 0 \\
b(x, 0) &= (1-x)^2 e^{-\left(\frac{x}{\epsilon}\right)^2} & c(x, 0) &= (1-x)^2 e^{-\left(\frac{x}{\epsilon}\right)^2}.
\end{aligned}$$

We wish to find a solution using techniques used by Yagi [19, 20]. We first will state the system Yagi considered, then we will argue for the solution of (2.5.3) under altered boundary conditions. We also formulate how to obtain a solution to (2.5.3) under boundary conditions (2.5.4), though the execution of such a proof is beyond the scope of this manuscript.

We note the following definitions from Yagi [19]:

Definition 3.2.1. The initial-boundary-value problem for a quasilinear parabolic evolution equation has the form

$$\begin{cases}
\frac{\partial u}{\partial t} = \sum_{i,j=1}^n D_j [a_{i,j}(x, u) D_i u] + f(x, u, \nabla u) + g(x, t) \text{ in } \Omega \times (0, T), \\
\sum_{i,j=1}^n v_j(x) a_{i,j}(x, u) D_i u = 0 \text{ on } \partial\Omega \times (0, T), \\
u(x, 0) = u_0(x) \text{ in } \bar{\Omega}
\end{cases} \tag{3.2.1}$$

where Ω is a bounded domain in \mathbb{R}^n with C^2 boundary $\partial\Omega$. Furthermore, we have $0 < T < \infty$ is a fixed real number. The coefficients $a_{i,j}(x, u)$ are real-valued functions for $(x, u) \in \overline{\Omega} \times (\mathbb{R} + i\mathbb{R})$, which are C^∞ with respect to the real variables $x \in \overline{\Omega}$, the real part of u , $\Re u$ and the imaginary part of u , $\Im u$. The function $f(x, u, \zeta)$ is a complex-valued function for $(x, u, \zeta) \in \overline{\Omega} \times (\mathbb{R} + i\mathbb{R}) \times (\mathbb{R} + i\mathbb{R})^n$, which is a smooth function with respect to the real variables $x \in \overline{\Omega}$, $\Re u$, $\Im u$, $\Re \zeta$ and $\Im \zeta$. The function $g(x, t)$ is an external forcing function and u_0 is the initial condition.

Definition 3.2.2. By a quasilinear abstract evolution equation we will be referring to the Cauchy problem

$$\begin{cases} \frac{dU}{dt} + A(U)U = F(U), & 0 < t \leq T, \\ U(0) = U_0 \end{cases} \quad (3.2.2)$$

in a Banach space X . Furthermore, let Z refer to another Banach space continuously embedded in X . $A(U)$ will refer to a family of closed linear operators in X defined for $U \in K = \{U \in Z; \|U - U_0\|_Z < R\}$ for positive and finite R . The domains $D(A(U))$ of $A(U)$ are independent of $U \in K$. F is an X -valued function in K . U_0 is an initial condition in K , and $U(t)$ is our unknown function on $(0, T]$.

We note that we will make use of the following standard notations; $H^k(\Omega)$ will represent the Sobolev space $W^{k,2}(\Omega)$, and $H^{k+\theta}(\Omega)$ will represent the intermediate space between $H^k(\Omega)$ and $H^{k+1}(\Omega)$ for any $0 < \theta < 1$. By $W_0^{k,p}(\Omega)$ we shall mean the closure of $C_c^\infty(\Omega)$; *i.e.*, $u \in W_0^{k,p}(\Omega)$ if and only if there is a sequence of functions $\{u_m\}_{m=1}^\infty \in C_c^\infty(\Omega)$ such that $u_m \rightarrow u$ in $W^{k,p}(\Omega)$. Let I be the interval in $[0, \infty)$. The space $L^p(I; X)$ is the L^p space of p -integrable functions on the interval I with values in the Banach space X . The space $C^m(I; X)$ will denote the space of m -times

differentiable functions with continuous derivatives up to order m . We will denote the space of Hölder continuous functions in I with values in X as $C^\theta(I; X)$.

In the following, let the following conditions be satisfied:

Hypothesis 3.2.1. (1) The resolvent sets $\rho(A(U)), U \in K$, contain a sector

$$\Sigma = \{\lambda \in \mathbb{C}; |\arg \lambda| \geq \theta_0\}$$

for some $0 < \theta_0 < \pi$ and the resolvents $(\lambda - A(U))^{-1}$, $U \in K$, satisfy the estimate

$$\|(\lambda - A(U))^{-1}\|_{\mathcal{L}(X)} \leq \frac{M}{|\lambda| + 1}, \lambda \in \Sigma,$$

for some uniform constant M .

(2) $A(\cdot)$ satisfies a Lipschitz condition

$$\|\{A(U) - A(V)\}A(V)^{-1}\|_{\mathcal{L}(X)} \leq N\|U - V\|_Z, \quad U, V \in K.$$

(3) For some $0 < \alpha < 1$, $D(A(U_0)^\alpha) \subset Z$ with continuous embedding $\|\cdot\|_Z \leq D\|A(U_0)^\alpha \cdot\|_X$.

(4) $F(\cdot)$ satisfies the Lipschitz condition

$$\|F(U) - F(V)\|_X \leq L\|U - V\|_Z, \quad U, V \in K.$$

(5) For some $\alpha < \beta < 1$, $U_0 \in D(A(U_0)^\beta) \subset Z$.

With these definitions in place, we note the following theorem, which may be found in Friedman [4]:

Theorem 3.2.1. (Sobolevskii)

Let $0 < \eta < \beta - \alpha$ be an arbitrary exponent. Then, in the function space $C^\eta([0, T]; Z)$, problem (3.2.2) possess a unique local solution $U \in C^1((0, S]; X)$, $A(U)U \in C((0, S]; X)$; in addition, the solution U satisfies the estimate

$$\|A(U(t))U(t)\|_X \leq Ct^{\beta-1}, \quad 0 < t \leq S.$$

The interval $[0, S]$ of existence, $0 < S \leq T$, is estimated by the exponents and constants appearing in Hypotheses (3.2.1 (1)-(5)) and by the norm $\|A(U_0)^\beta U_0\|_X$.

It is with this theorem of Sobolevskii that Yagi produces his results, and from which we expect to extract similar results. Before discussing our system, we note the following system considered by Yagi in [20]:

$$\begin{cases} \frac{\partial u}{\partial t} = \nabla \cdot \{a(u, \rho)\nabla u - ub(\rho)\nabla \rho\} & \text{in } \Omega \times (0, \infty), \\ \frac{\partial \rho}{\partial t} = d\Delta \rho + uf(\rho) - g(\rho)\rho & \text{in } \Omega \times (0, \infty), \\ \frac{\partial u}{\partial n} = \frac{\partial \rho}{\partial n} = 0 & \text{on } \partial\Omega \times (0, \infty), \\ u(x, 0) = u_0(x), \rho(x, 0) = \rho_0(x) & \text{in } \bar{\Omega}. \end{cases} \quad (3.2.3)$$

For this system, Yagi was able to prove the following theorems:

Theorem 3.2.2. (Yagi)

Let u_0, ρ_0 satisfy:

$$\begin{cases} u_0, \rho_0 \in H^{1+\epsilon}(\Omega), \\ u_0(x) \geq 0, \rho_0(x) \geq \delta_0 > 0 \text{ on } \bar{\Omega}. \end{cases} \quad (3.2.4)$$

Assume that a real local solution u, ρ to (3.2.3) exists on the interval $[0, S]$ such that

$$u, \rho \in \mathcal{C}([0, S]; H^{1+\epsilon_1}(\Omega)) \cap \mathcal{C}((0, S]; H^2(\Omega)) \cap \mathcal{C}^1((0, S]; L^2(\Omega)),$$

with some $\epsilon_1 > 0$. In addition, assume that ρ satisfies $\rho(x, t) > 0$ on $\bar{\Omega} \times [0, S]$ and an estimate

$$\|\rho(t)\|_{H^2} \leq At^{(\epsilon_2-1)/2}, \quad 0 < t \leq S,$$

with some $\epsilon_2 > 0$ and constant A . Then $u(x, t) \geq 0$ and $\rho(x, t) \geq \underline{\rho}(t)$ for all $(x, t) \in \bar{\Omega} \times [0, S]$, where $\underline{\rho}$ denotes a positive function defined as the global solution to the ordinary differential equation

$$\begin{cases} \frac{d\rho}{dt} = -g(\underline{\rho})\underline{\rho}, & 0 < t < \infty, \\ \underline{\rho}(0) = \delta_0 > 0. \end{cases} \quad (3.2.5)$$

Theorem 3.2.3. (Yagi)

The system (3.2.3) may be formulated into the abstract equation (3.2.2) in the product L^2 -space. We define two product spaces $X = \mathbb{L}^2(\Omega)$ and $Z = \mathbb{H}^{1+\epsilon_1}(\Omega)$ with some fixed $0 < \epsilon_1 < \min\{\epsilon_0, \frac{1}{2}\}$. From the (3.2.4), the initial function $U_0 = \begin{pmatrix} u_0 \\ \rho_0 \end{pmatrix}$ is in Z . Fix a number $R > 0$ such that

$$a(\mathfrak{R}u, \mathfrak{R}\rho) \geq \frac{a_0}{2} \text{ and } \mathfrak{R}\rho \geq \frac{\delta_0}{2} \text{ on } \bar{\Omega}$$

for u, ρ such that $\sqrt{\|u - u_0\|_{H^{1+\epsilon_1}}^2 + \|\rho - \rho_0\|_{H^{1+\epsilon_1}}^2} \leq R$, we define an open ball

$$K = \left\{ U = \begin{pmatrix} u \\ \rho \end{pmatrix} \in Z; \|U - U_0\|_Z < R \right\}$$

of Z . For $U \in K$, $A(U)$ denotes linear operators in X defined by

$$\begin{cases} D(A(U)) = \left\{ \tilde{U} = \begin{pmatrix} \tilde{u} \\ \tilde{\rho} \end{pmatrix} \in \mathbb{H}^2(\Omega); \frac{\partial \tilde{u}}{\partial n} = \frac{\partial \tilde{\rho}}{\partial n} = 0 \text{ on } \partial\Omega \right\} \\ A(U)\tilde{U} = \begin{pmatrix} -\nabla \cdot \{a(\mathfrak{R}(u), \mathfrak{R}(\rho))\nabla \tilde{u} - ub(\mathfrak{R}(\rho))\nabla \tilde{\rho} + a_0\tilde{u}\} \\ (-\Delta + g_0)\tilde{\rho} \end{pmatrix} \end{cases} . \quad (3.2.6)$$

The function $F(U)$ is defined by

$$F(U) = \begin{pmatrix} a_0u \\ uf(\mathfrak{R}(\rho)) - \{g(\mathfrak{R}(\rho)) - g_0\}\rho \end{pmatrix}, U = \begin{pmatrix} u \\ \rho \end{pmatrix} \in K. \quad (3.2.7)$$

The proof of Theorem (3.2.3) relies heavily on Theorem (3.2.1), which then gives necessary conditions for the lower bounds in Theorem (3.2.2). As our system has similar properties of that considered by Yagi (namely a parabolic system of coupled, nonlinear equations with a chemotactic response) we follow the example set by Fister [3] and use the theorems of Sobolevskii and Yagi to prove the existence of the solution to system (2.5.3) with the Neumann boundary conditions.

The system (2.5.3) may be formulated as the Cauchy problem (3.2.2) in the product space of four L^2 spaces. Let $X = \mathbb{L}^2(\Omega)$ denote the product space of square integrable functions over $(0, 1)$ in space. Let $Z = \mathbb{H}^{1+\epsilon_1}(\Omega)$ with $\epsilon_1 = \min\{\epsilon_0, \frac{1}{2}\}$ for $0 < \epsilon_0 < 1$ denote the product interpolation space over $(0, 1)$. The given initial

conditions are

$$w_0 = w(x, 0) = 1$$

$$n_0 = n(x, 0) = x^2 e^{-\left(\frac{1-x}{\epsilon}\right)^2}$$

$$b_0 = b(x, 0) = (1-x)^2 e^{-\left(\frac{x}{\epsilon}\right)^2}$$

$$c_0 = c(x, 0) = (1-x)^2 e^{-\left(\frac{x}{\epsilon}\right)^2}.$$

As such, $U_0 = (w_0 \ n_0 \ b_0 \ c_0)^\top \in Z$. Furthermore, we impose Neumann conditions on both ends for all functions; *i.e.*,

$$\frac{\partial w}{\partial x} = \frac{\partial n}{\partial x} = \frac{\partial b}{\partial x} = \frac{\partial c}{\partial x} = 0 \text{ on } \partial\Omega.$$

Theorem 3.2.4. Our system 2.5.3 with Neumann conditions has a unique local solution

$$w, n, b, c \in C([0, S]; H^{1+\epsilon_1}(\Omega)) \cap C((0, S]; H^2(\Omega)) \cap C^1((0, S]; L^2(\Omega)).$$

Proof. We fix a real number $R > 0$ such that $\mathfrak{R}(w) \geq \frac{a_0}{2}$ on $[0, 1]$ whenever

$$\sqrt{\|w - w_0\|_{H^{1+\epsilon_1}}^2 + \|n - n_0\|_{H^{1+\epsilon_1}}^2 + \|b - b_0\|_{H^{1+\epsilon_1}}^2 + \|c - c_0\|_{H^{1+\epsilon_1}}^2} < R.$$

Define K to be an open ball of radius R about U_0 in Z . For $U \in K$, let $A(U)$ denote the linear operators in X defined by

$$A(U) = \begin{pmatrix} \frac{\partial^2}{\partial x^2} - \lambda_{nw}n - \lambda_{wb}b - \lambda_w \\ D_n \frac{\partial^2}{\partial x^2} - \chi_n(c_x \frac{\partial}{\partial x} + c_{xx}) + k_{bn} b g_n(\mathfrak{R}(w)) - \frac{\lambda_n(1+h_n(\mathfrak{R}(w)))}{eb+1} \\ \epsilon \frac{\partial^2}{\partial x^2} - \lambda_b + k_b \\ D_c \frac{\partial^2}{\partial x^2} - \lambda_c \end{pmatrix} \quad (3.2.8)$$

so that $A(U)\tilde{U}$ is

$$A(U)\tilde{U} = \begin{pmatrix} \frac{\partial^2 \tilde{w}}{\partial x^2} - \lambda_{nw}\tilde{w}n - \lambda_{wb}\tilde{w}b - \lambda_w\tilde{w} \\ D_n \frac{\partial^2 \tilde{n}}{\partial x^2} - \chi_n(c_x \frac{\partial \tilde{n}}{\partial x} + \tilde{n}c_{xx}) + k_{bn}b\tilde{n}g_n(\mathfrak{R}(w)) - \frac{\lambda_n\tilde{n}(1+h_n(\mathfrak{R}(w)))}{eb+1} \\ \epsilon \frac{\partial^2 \tilde{b}}{\partial x^2} - \lambda_b\tilde{b} + k_b\tilde{b} \\ D_c \frac{\partial^2 \tilde{c}}{\partial x^2} - \lambda_c\tilde{c} \end{pmatrix} \quad (3.2.9)$$

and our inhomogeneous term $F(U)$ becomes

$$F(U) = \begin{pmatrix} \beta + \kappa G(t) \\ -k_{bn}bn^2g_n(w) \\ \frac{w}{k_w+w} \frac{\delta+k_{nr}n}{\lambda_{rb}b+1} + k_b b^2 \\ k_c b \end{pmatrix}. \quad (3.2.10)$$

Our operator has the domain

$$D(A(U)) = \{U \in \mathbb{H}^2(\Omega); w_x = n_x = b_x = c_x = 0 \text{ on } \partial(0, 1)\}.$$

As such, our system has the same properties as Yagi, therefore we conclude by Theorem (3.2.2) to have a unique local solution

$$w, n, b, c \in C([0, S]; H^{1+\epsilon_1}(\Omega)) \cap C((0, S]; H^2(\Omega)) \cap C^1((0, S]; L^2(\Omega)),$$

□

In attempting to find a solution to (2.5.3) with boundary conditions (2.5.4), we initially considered the theorems by Yagi [20], as his system involved the same chemotactic response. Upon further consideration, however, we realized the need for a different domain. Instead, we wish to use the theorem due to Sobolevskii (3.2.1). The clearest path to being able to apply this theorem is to redefine our equations

for $w(x, t)$ and $n(x, t)$ to impose zero Dirichlet conditions. As such, we redefine our equations with substitutions

$$\bar{w}(x, t) = w(x, t) - 1 \text{ and } \bar{n}(x, t) = n(x, t) - 1$$

so that $\bar{w}(1, t) = 0$ and $\bar{n}(1, t) = 0$. With this, our new system becomes

$$\bar{w}_t = \bar{w}_{xx} + \beta + \kappa G(t) - \lambda_{nw} (\bar{n}\bar{w} + \bar{n} + \bar{w}) - \lambda_{bw} b\bar{w} - \lambda_w \bar{w} - \lambda_{nw} - \lambda_{bw} - \lambda_w$$

$$\bar{n}_t = D_n \bar{n}_{xx} - \chi_n (\bar{n}_x c_x + \bar{n} c_{xx} + c_{xx}) + k_{bn} b \bar{n} g_n(\bar{w} + 1)(\bar{n} + 1)$$

$$- \frac{\lambda_n (1 + h_n(\bar{w} + 1))(\bar{n} + 1)}{eb + 1}$$

$$b_t = \epsilon_b b_{xx} + k_b b(1 - b) - b \frac{\bar{w} + 1}{k_w + \bar{w} + 1} \frac{\delta + k_{nr} \bar{n} + k_{nr}}{\lambda_{rb} b + 1}$$

$$c_t = D_c c_{xx} + k_c b - \lambda_c c$$

on $(0, 1) \times (0, T)$, subject to the following initial and boundary conditions :

$$\left. \frac{\partial \bar{w}}{\partial x} \right|_{x=0} = 0$$

$$\left. \frac{\partial \bar{n}}{\partial x} \right|_{x=0} = 0$$

$$\bar{w}(1, t) = 0$$

$$\bar{n}(1, t) = 0$$

$$\bar{w}(x, 0) = 0$$

$$\bar{n}(x, 0) = x^2 e^{-\left(\frac{1-x}{\epsilon}\right)^2} - 1$$

$$\left. \frac{\partial b}{\partial x} \right|_{x=0} = 0$$

$$\left. \frac{\partial c}{\partial x} \right|_{x=0} = 0$$

$$\left. \frac{\partial b}{\partial x} \right|_{x=1} = 0$$

$$\left. \frac{\partial c}{\partial x} \right|_{x=1} = 0$$

$$b(x, 0) = (1 - x)^2 e^{-\left(\frac{x}{\epsilon}\right)^2}$$

$$c(x, 0) = (1 - x)^2 e^{-\left(\frac{x}{\epsilon}\right)^2}$$

and where we simply exchange $\bar{w} + 1$ for w in the definitions of $g_n(w)$ and $h_n(w)$.

Our operator is then defined such that $A(U)\tilde{U}$ is (dropping the bar for notational

simplicity):

$$A(U)\tilde{U} = \begin{pmatrix} \frac{\partial^2 \tilde{w}}{\partial x^2} - \lambda_{nw}\tilde{w}n - \lambda_{nw}\tilde{w} - \lambda_{wb}\tilde{w}b - \lambda_w\tilde{w} \\ D_n \frac{\partial^2 \tilde{n}}{\partial x^2} - \chi_n (c_x \frac{\partial \tilde{n}}{\partial x} + \tilde{n}c_{xx}) + k_{bn}b\tilde{n}g_n(\mathfrak{R}(w+1)) - \frac{\lambda_n \tilde{n}(1+h_n(\mathfrak{R}(w+1)))}{eb+1} \\ \epsilon \frac{\partial^2 \tilde{b}}{\partial x^2} - \lambda_b \tilde{b} + k_b \tilde{b} \\ D_c \frac{\partial^2 \tilde{c}}{\partial x^2} - \lambda_c \tilde{c} \end{pmatrix} \quad (3.2.11)$$

and our inhomogeneous term $F(U)$ becomes

$$F(U) = \begin{pmatrix} \beta + \kappa G(t) - \lambda_{nw}n - \lambda_{nw} - \lambda_{bw} - \lambda_w \\ -k_{bn}bn^2g_n(w+1) - \frac{\lambda_n(1+h_n(w+1))}{eb+1} \\ \frac{w+1}{k_w+w+1} - \frac{\delta+k_{nr}n+k_{nr}}{\lambda_{rb}b+1} + k_b b^2 \\ k_c b \end{pmatrix} \quad (3.2.12)$$

The domain of our operator becomes

$$D(A(U)) = \{U \in H_0^1(\Omega) \cap H^2(\Omega) \times H_0^1(\Omega) \cap H^2(\Omega) \times H^2(\Omega) \times H^2(\Omega)\}.$$

After we are able to verify assumptions (1)-(5) stated at the beginning of the section, we would then be able to prove existence and uniqueness for the modified system using Theorem (3.2.1). For future work, we would like to verify this existence. Lower bounds for the solutions can then be verified using a similar technique as used in [20] that were used to prove Theorem (3.2.1). This will prove the existence of the equivalent system (2.5.3) under boundary-initial conditions (2.5.4).

3.3. Existence of Optimal Control

Once we are able to verify the existence, uniqueness, and lower bounds for the state system, we are then able to inquire about the existence of an optimal control. We consider the variational formulation of the state system (2.5.3). We look for weak solutions $(w, n, b, c) \in W^4$, $W = L^2((0, T); H^1(0, 1))$, where W is a subset of the solution space to be determined in the existence of the state solutions, namely the solution space for

$$\begin{aligned}
& \int_0^T \langle w_t, v \rangle dt + \int_0^T \int_0^1 w_x v_x \, dx dt = \\
& \quad \int_0^T \int_0^1 [\beta + \gamma G(t) - \lambda_{nw} n w - \lambda_{bw} b w - \lambda_w] v \, dx dt \\
& \int_0^T \langle n_t, v \rangle dt + \int_0^T \int_0^1 D_n n_x v_x \, dx dt - \int_0^T \int_0^1 \chi_n n c_x v_x \, dx dt = \\
& \quad \int_0^T \int_0^1 \left[k_{bn} b n g_n(w) (1 - n) - \frac{\lambda_n (1 + h_n(w)) n}{eb + 1} \right] v \, dx dt \\
& \int_0^T \langle b_t, v \rangle dt + \int_0^T \int_0^1 \epsilon b_x v_x \, dx dt = \\
& \quad \int_0^T \int_0^1 \left[k_b (1 - b) - b \frac{w}{k_w + w} \frac{\delta + k_{nr} n}{\lambda_{rb} b + 1} \right] v \, dx dt \\
& \int_0^T \langle c_t, v \rangle dt + \int_0^T \int_0^1 D_c c_x v_x \, dx dt = \\
& \quad \int_0^T \int_0^1 [k_c - \lambda_c c] v \, dx dt
\end{aligned} \tag{3.3.1}$$

for all functions $v \in H_c^1(0, 1)$, the Hilbert space of differentiable functions with compact support in $(0, 1)$, where $\langle \cdot, \cdot \rangle$ is the duality between $H^1(0, 1)$ and its dual, $(H^1(0, 1))^*$. The set of admissible controls will be

$$A = \{G(t) \in L^\infty([0, 1] \times [0, T]) \mid 0 \leq G(t) \leq G_{\max} < \infty \text{ a.e. in } [0, 1] \times [0, T]\}, \tag{3.3.2}$$

with functional

$$J(G) = \int_0^t \int_0^1 b(t) + \frac{1}{2} \kappa G^2 dx dt. \quad (3.3.3)$$

The cost functional is designed to minimize the bacterial infection as well as the level of supplemental oxygen administered via hyperbaric oxygen therapy. In particular, we have incorporated the oxygen into the functional using a quadratic to model a nonlinear benefit to the wound-healing process for a linear increase of supplemental oxygen.

Conjecture 3.3.1. There exists an optimal control in A that minimizes the functional $J(G)$

We will use a minimizing sequence for the control, and then use estimates to give convergence of the sequences. Under the assumption that our state solutions are bounded below, combined with the control being bounded below, we obtain the existence of a minimizing sequence $\{G_m\} \in A$ such that our functional is at a minimum. Furthermore, the uniqueness of the state system allows us to identify unique minimizing sequences $w^m = w(G_m)$, $n^m = n(G_m)$, $b^m = b(G_m)$, and $c^m = c(G_m)$ for each $m \in \mathbb{N}$ and each G_m . We use the weak formulation (3.3.1), then develop estimates and convergence of sequences. We add the formulations together with the appropriate test functions for each equation in observation of the usual product norm. This results in

$$\begin{aligned} & \int_0^T \langle w_t^m, w^m \rangle + \langle n_t^m, n^m \rangle + \langle b_t^m, b^m \rangle + \langle c_t^m, c^m \rangle dt + \int_0^T \int_0^1 w_x^m w_x^m dx dt \\ & + \int_0^T \int_0^1 D_n n_x^m n_x^m dx dt + \int_0^T \int_0^1 \epsilon b_x^m b_x^m dx dt + \int_0^T \int_0^1 D_c c_x^m c_x^m dx dt \\ & - \int_0^T \int_0^1 \chi_n n^m c_x^m n_x^m dx dt \end{aligned}$$

$$\begin{aligned}
&= \int_0^T \int_0^1 [\beta + \gamma G(t) - \lambda_{nw} n^m w^m - \lambda_{bw} b^m w^m - \lambda_w] w^m dx dt \\
&+ \int_0^T \int_0^1 \left[k_{bn} b^m n^m g_n(w^m) (1 - n^m) - \frac{\lambda_n (1 + h_n(w^m)) n^m}{e b^m + 1} \right] n^m dx dt \\
&+ \int_0^T \int_0^1 \left[k_b b^m (1 - b^m) - \frac{w^m}{k_w + w^m} \frac{\delta + k_{nr} n^m}{\lambda_{rb} b^m + 1} \right] b^m dx dt + \int_0^T \int_0^1 [k_c - \lambda_c c^m] c^m dx dt.
\end{aligned}$$

We can use the Fundamental Theorem of Calculus to write this as

$$\begin{aligned}
&\frac{1}{2} \int_0^1 (w^m)^2 + (n^m)^2 + (b^m)^2 + (c^m)^2 dx + \frac{1}{2} \int_0^1 [(w_0^m)^2 + (n_0^m)^2 + (b_0^m)^2 + (c_0^m)^2] dx \\
&+ \int_0^T \int_0^1 (w_x^m)^2 dx dt + \int_0^T \int_0^1 D_n (n_x^m)^2 dx dt \\
&+ \int_0^T \int_0^1 \epsilon (b_x^m)^2 dx dt + \int_0^T \int_0^1 D_c (c_x^m)^2 dx dt - \int_0^T \int_0^1 \chi_n c_x^m n^m n_x^m dx dt \\
&= \int_0^T \int_0^1 [\beta + \gamma G(t) - \lambda_{nw} n^m w^m - \lambda_{bw} b^m w^m - \lambda_w] w^m dx dt \\
&+ \int_0^T \int_0^1 \left[k_{bn} b^m n^m g_n(w^m) (1 - n^m) - \frac{\lambda_n (1 + h_n(w^m)) n^m}{e b^m + 1} \right] n^m dx dt \\
&+ \int_0^T \int_0^1 \left[k_b b^m (1 - b^m) - b^m \frac{w^m}{k_w + w^m} \frac{\delta + k_{nr} n^m}{\lambda_{rb} b^m + 1} \right] b^m dx dt + \int_0^T \int_0^1 [k_c - \lambda_c c^m] c^m dx dt.
\end{aligned}$$

Letting $M = \min\{1, D_n, \epsilon_b, D_c\}$, we obtain

$$\begin{aligned}
&\frac{1}{2} \int_0^1 (w^m)^2 + (n^m)^2 + (b^m)^2 + (c^m)^2 dx \\
&+ M \int_0^T \int_0^1 (w_x^m)^2 + (n_x^m)^2 + (b_x^m)^2 + (c_x^m)^2 dx dt - \int_0^T \int_0^1 \chi_n c_x^m n^m n_x^m dx dt \\
&\leq \int_0^T \int_0^1 [\beta + \gamma G(t) - \lambda_{nw} n^m w^m - \lambda_{bw} b^m w^m - \lambda_w] w^m dx dt \\
&+ \int_0^T \int_0^1 \left[k_{bn} b^m n^m g_n(w^m) (1 - n^m) - \frac{\lambda_n (1 + h_n(w^m)) n^m}{e b^m + 1} \right] n^m dx dt \\
&+ \int_0^T \int_0^1 \left[k_b b^m (1 - b^m) - b^m \frac{w^m}{k_w + w^m} \frac{\delta + k_{nr} n^m}{\lambda_{rb} b^m + 1} \right] b^m dx dt + \int_0^T \int_0^1 [k_c - \lambda_c c^m] c^m dx dt \\
&+ \frac{1}{2} \int_0^1 [(w_0^m)^2 + (n_0^m)^2 + (b_0^m)^2 + (c_0^m)^2] dx.
\end{aligned}$$

Under the assumption of boundedness of the coefficients and $G(t), w, n, b, c, g_n(w)$ and $h_n(w)$, we obtain (by Lebesgue Dominated Convergence Theorem)

$$\frac{1}{2} \int_0^1 (w^m)^2 + (n^m)^2 + (b^m)^2 + (c^m)^2 dx$$

$$\begin{aligned}
& +M \int_0^T \int_0^1 (w_x^m)^2 + (n_x^m)^2 + (b_x^m)^2 + (c_x^m)^2 dxdt - \int_0^T \int_0^1 \chi_n c_x^m n_x^m n^m dxdt \\
& \leq \frac{1}{2} \int_0^1 [(w_0^m)^2 + (n_0^m)^2 + (b_0^m)^2 + (c_0^m)^2] dx + C,
\end{aligned}$$

Moving the chemoattractant integral to the right-hand side and using Cauchy's inequality with epsilon, we obtain

$$\begin{aligned}
& \frac{1}{2} \int_0^1 (w^m)^2 + (n^m)^2 + (b^m)^2 + (c^m)^2 dx \\
& +M \int_0^T \int_0^1 (w_x^m)^2 + (n_x^m)^2 + (b_x^m)^2 + (c_x^m)^2 dxdt \\
& \leq K \int_0^t \int_0^1 (n^m)^2 dxdt + \frac{\epsilon}{2} \int_0^t \int_0^1 (c_x^m)^2 + (n_x^m)^2 dxdt + \\
& \frac{1}{2} \int_0^1 [(w_0^m)^2 + (n_0^m)^2 + (b_0^m)^2 + (c_0^m)^2] dx + C,
\end{aligned}$$

where we observe that K is dependent on the bounds for n^m . Letting $\epsilon < 2M$, we may apply Grönwall's inequality to the above relation and obtain

$$\begin{aligned}
& \sup_t [\int_0^1 (w^m)^2 + (n^m)^2 + (b^m)^2 + (c^m)^2 dx] \\
& +M \int_0^T \int_0^1 (w_x^m)^2 + (n_x^m)^2 + (b_x^m)^2 + (c_x^m)^2 dxdt \\
& \leq e^{KT} \int_0^1 (n_0(x)^m)^2 dx.
\end{aligned}$$

Therefore,

$$\begin{aligned}
& \sup_t [\int_0^1 (w^m)^2 + (n^m)^2 + (b^m)^2 + (c^m)^2 dx] + \int_0^T \int_0^1 (w_x^m)^2 + (n_x^m)^2 + (b_x^m)^2 + (c_x^m)^2 dxdt \\
& \leq e^{KT} \int_0^1 (n_0(x)^m)^2 + (w_0(x)^m)^2 + (b_0(x)^m)^2 + (c_0(x)^m)^2 dx.
\end{aligned}$$

We now proceed with using the above calculations to obtain weakly convergent sequences, and then embed these sequences into spaces with higher regularity when we need a strongly convergent sequence. With $\{G^m\}_{m=1}^\infty$ being L^∞ -bounded in $([0, 1] \times [0, T])$, there exists a weakly convergent subsequence $\{G^{m_j}\}_{m_j=1}^\infty$ such that $\{G^{m_j}\} \rightharpoonup G^*$ in $L^2([0, 1] \times [0, T])$. From the above calculations, we also know that

$\{w^m\}_{m=1}^\infty, \{n^m\}_{m=1}^\infty, \{b^j\}_{m=1}^\infty$ and $\{c^m\}_{m=1}^\infty$ are bounded in $L^2(0, T; H^1(0, 1))$, thus also have weakly convergent subsequences $\{w^{m_j}\}_{m_j=1}^\infty, \{n^{m_j}\}_{m_j=1}^\infty, \{b^{m_j}\}_{m_j=1}^\infty, \{c^{m_j}\}_{m_j=1}^\infty$ such that $w^{m_j} \rightharpoonup w^*, n^{m_j} \rightharpoonup n^*, b^{m_j} \rightharpoonup b^*, c^{m_j} \rightharpoonup c^*$ in $L^2(0, T; H^1(0, 1))$. Considering the weak formulation (3.3.1) and the boundedness of our state functions, we necessarily have that w_t^m, n_t^m, b_t^m and c_t^m lie in bounded subsets of $L^2(0, T; (H^1(0, 1))^*)$. Therefore, we get weakly convergent subsequences such that $w_t^{m_j} \rightharpoonup w_t^*, n_t^{m_j} \rightharpoonup n_t^*, b_t^{m_j} \rightharpoonup b_t^*, c_t^{m_j} \rightharpoonup c_t^*$ in $L^2(0, T; (H^1(0, 1))^*)$. We note the following lemma, found in Simon [16], :

Lemma 3.3.1. Aubin-Lions-Simon Lemma

Let the embedding $X \rightarrow B$ be compact, where $B \subset Y$ and X, B, Y are Banach spaces. Let F be a family of functions bounded in $L^p(0, T; X)$ and let F be relatively compact in $L^p(0, T; Y)$ for $1 \leq p \leq \infty$. Then F is relatively compact in $L^p(0, T; B)$.

Using this lemma with $X = B = L^2(0, T; H^1(0, 1))$ and $Y = L^2([0, 1] \times [0, 1])$, we obtain that $w^m \rightarrow w^*, n^m \rightarrow n^*, b^m \rightarrow b^*, c^m \rightarrow c^*$ in $L^2(0, T; H^1(0, 1))$. If we can verify results similar to (3.2.2) and (3.2.3), in particular that $c \in C^1((0, T]; L^2(0, 1))$, then with our chemoattractant equation

$$c_t = D_c c_{xx} k_c b - \lambda_c c,$$

we know that $c_{xx} \in L^2(0, 1)$. From this, we know $\|c_x\|_{L^\infty([0, 1] \times [0, T])} < \infty$; *i.e.*, c_x is bounded. Thus, there exists a weakly convergent (sub)sequence $c_x^m \rightharpoonup c_x^*$. Since we have the strong convergence $w^m \rightarrow w^*$, we also have $w^m c_x^m \rightarrow w^* c_x^*$ in $L^2(0, T; H^1(0, 1))$. Furthermore, we note that continuous images of convergent sequences are convergent, therefore $g_n(w^m) \rightarrow g_n(w^*)$ and $h_n(w^m) \rightarrow h_n(w^*)$. We employ the convergences of

$h_n(w^m), n^m$ and b^m , as well as the lower bound on b^m for each m (contingent on a result like (3.2.2)) to obtain

$$\frac{\lambda_n n^m (1 + h_n(w^m))}{eb^m + 1} \rightarrow \frac{\lambda_n n^* (h_n(w^*))}{eb^* + 1} \text{ in } L^2(0, T; H^1(0, 1)).$$

A similar argument can be applied to infer that

$$\frac{w^m}{K_w + w^m} \rightarrow \frac{w^*}{K_w + w^*}$$

and

$$\frac{\delta + k_{nr} n^m}{\lambda_{rb} b^m + 1} \rightarrow \frac{\delta + k_{nr} n^*}{\lambda_{rb} b^* + 1}$$

strongly in $L^2(0, T; H^1(0, 1))$. With this, we may now pass to the limit in (3.3.1) and associate (w^*, n^*, b^*, c^*) to the optimal states associated with G^* .

We now verify that G^* is an optimal control that minimizes our functional. By the lower semi-continuity of L^p norms with respect to weak convergences,

$$\begin{aligned} J(G^*) &= \int_0^T \int_0^1 \left(b^* + \frac{1}{2} \kappa G^* \right) dx dt \\ &\leq \lim_{m \rightarrow \infty} \int_0^T \int_0^1 \left(b^m + \frac{1}{2} \kappa G^m \right) dx dt \\ &= \lim_{m \rightarrow \infty} J(G^m) \\ &= \inf_{G \in A} J(G). \end{aligned}$$

Thus, G^* is an optimal control that minimizes our functional.

3.4. Sensitivities

We now discuss the form of the sensitivities. The sensitivities are the Gâteaux derivatives, which are a generalization of directional derivatives for Banach space. Formally,

Definition 3.4.1. The map $u \mapsto w(u)$ is weakly differentiable in the directional derivative sense if as $\epsilon \rightarrow 0^+$, for any variation $k \in L^\infty((0,1) \times (0,T))$ such that $(u + \epsilon k) \in A = \{\text{admissible controls}\}$,

$$\lim_{\epsilon \rightarrow 0^+} \frac{w(u + \epsilon k) - w(u)}{\epsilon} = \psi.$$

When this limit exists the function ψ is referred to as the sensitivity of the state with respect to the control.

To find the equations for the sensitivities: we form the appropriate difference quotients. Let $w^\epsilon = w(G + \epsilon k)$, $n^\epsilon = n(G + \epsilon k)$, $b^\epsilon = b(G + \epsilon k)$ and $c^\epsilon = c(G + \epsilon k)$. Then we begin by noting the difference of the variation minus the function:

$$w_t^\epsilon - w_t = w_{xx}^\epsilon - w_{xx} + \gamma G(t) + \gamma \epsilon k - \gamma G(t) - \lambda_{nw} (n^\epsilon w^\epsilon - nw) - \lambda_{bw} (b^\epsilon w^\epsilon - bw) - \lambda_w (w^\epsilon - w)$$

$$n_t^\epsilon - n_t = D_n (n_{xx}^\epsilon - n_{xx}) - \chi_n (n_x^\epsilon c_x^\epsilon + n_x^\epsilon c_{xx} - n_x c_x - n c_{xx}) + k_{bn} (b^\epsilon n^\epsilon g_n^\epsilon(w^\epsilon) - b^\epsilon n^{\epsilon^2} g_n^\epsilon(w^\epsilon) - b n g_n(w) + b n^2 g_n(w)) - \lambda_n \left(\frac{n^\epsilon (1 + h_n^\epsilon(w^\epsilon))}{e b^\epsilon + 1} - \frac{n (1 + h_n(w))}{e b + 1} \right)$$

$$b_t^\epsilon - b_t = \epsilon_b (b^\epsilon - b)_{xx} + k_b (b^\epsilon - b^{\epsilon^2} - (b - b^2)) - \frac{w^\epsilon}{K_w + w^\epsilon} \frac{b^\epsilon (\delta + k_{nr} n^\epsilon)}{\lambda_{rb} b^\epsilon + 1} + \frac{w}{K_w + w} \frac{b (\delta + k_{nr} n)}{\lambda_{rb} b + 1} - \lambda_b (b^\epsilon - b)$$

$$c_t^\epsilon - c_t = D_c (c^\epsilon - c) + k_c (b^\epsilon - b) - \lambda_c (c^\epsilon - c)$$

Next, we group terms of form $u^\epsilon - u$ in anticipation of forming the difference quotients. For terms of form $u^\epsilon v^\epsilon - uv$, we add and subtract $u^\epsilon v$ similar to the proof of the product rule in elementary calculus. Likewise for the quotients, we create common denominators and combine fractions. Due to the large new numerator in the bacteria equation, we then also separate the fraction over summation or subtraction in the numerator.

$$w_t^\epsilon - w_t = w_{xx}^\epsilon - w_{xx} + \gamma G(t) + \gamma \epsilon k - \gamma G(t) - \lambda_{nw} (n^\epsilon w^\epsilon + n^\epsilon w - n^\epsilon w - nw) \\ - \lambda_{bw} (b^\epsilon w^\epsilon + b^\epsilon w - b^\epsilon w - bw) - \lambda_w (w^\epsilon - w)$$

$$n_t^\epsilon - n_t = D_n (n_{xx}^\epsilon - n_{xx})$$

$$- \chi_n (n_x^\epsilon c_x^\epsilon - n_x^\epsilon c_x + n_x^\epsilon c_x - n_x c_x + n_x^\epsilon c_{xx} - n^\epsilon c_{xx} + n^\epsilon c_{xx} - n c_{xx}) \\ + k_{bn} (b^\epsilon n^\epsilon g_n^\epsilon(w^\epsilon) - b^\epsilon n g_n(w) + b^\epsilon n g_n(w) - b n g_n(w)) \\ - k_{bn} (b^\epsilon n^{\epsilon^2} g_n^\epsilon(w^\epsilon) - b^\epsilon n^2 g_n(w) + b^\epsilon n^2 g_n(w) - b n^2 g_n(w)) \\ - \lambda_n \frac{(n^\epsilon + n^\epsilon h_n^\epsilon(w^\epsilon)) (eb + 1) - (n + n h_n(w)) (eb^\epsilon + 1)}{(eb^\epsilon + 1) (eb + 1)}$$

$$b_t^\epsilon - b_t = \frac{bb^\epsilon n^\epsilon w^\epsilon k_{nr} K_w \lambda_{rb}}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ + \frac{b^\epsilon n^\epsilon w^\epsilon k_{nr} K_w}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ - \frac{bb^\epsilon n w k_{nr} K_w \lambda_{rb}}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ + \frac{bb^\epsilon n^\epsilon w w^\epsilon k_{nr} \lambda_{rb}}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ + \frac{b^\epsilon n^\epsilon w w^\epsilon k_{nr}}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ - \frac{bb^\epsilon n w w^\epsilon k_{nr} \lambda_{rb}}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ + \frac{bb^\epsilon \delta w^\epsilon K_w \lambda_{rb}}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ + \frac{-bb^\epsilon \delta w K_w \lambda_{rb} + b^\epsilon \delta w^\epsilon K_w + b^\epsilon \delta w w^\epsilon}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ + \frac{-bn w k_{nr} K_w - bn w w^\epsilon k_{nr} - b \delta w K_w - b \delta w w^\epsilon}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\ - \lambda_b (b^\epsilon - b) + \epsilon_b (b_{xx}^\epsilon - b_{xx}) + k_b (b^2 - (b^\epsilon)^2 + b^\epsilon - b)$$

$$c_t^\epsilon - c_t = D_c (c^\epsilon - c) + k_c (b^\epsilon - b) - \lambda_c (c^\epsilon - c)$$

Next, we gather like gather like terms together in the neutrophil and bacteria equations, particularly in the quotient terms.

$$w_t^\epsilon - w_t = w_{xx}^\epsilon - w_{xx} + \gamma G(t) + \gamma \epsilon k - \gamma G(t) - \lambda_{nw} (n^\epsilon w^\epsilon + n^\epsilon w - n^\epsilon w - nw) \\ - \lambda_{bw} (b^\epsilon w^\epsilon + b^\epsilon w - b^\epsilon w - bw) - \lambda_w (w^\epsilon - w)$$

$$n_t^\epsilon - n_t = D_n (n_{xx}^\epsilon - n_{xx}) - \chi_n (n_x^\epsilon (c_x^\epsilon - c_x) + c_x (n_x^\epsilon - n_x) + n^\epsilon (c_{xx}^\epsilon - c_{xx}) + c_{xx} (n^\epsilon - n)) \\ + k_{bn} (b^\epsilon (n^\epsilon g_n^\epsilon(w^\epsilon) - n^\epsilon g_n(w) + n^\epsilon g_n(w) - n g_n(w)) + n g_n(w) (b^\epsilon - b)) \\ - k_{bn} (b^\epsilon (n^{\epsilon^2} g_n^\epsilon(w^\epsilon) - n^{\epsilon^2} g_n(w) + n^{\epsilon^2} g_n(w) - n^2 g_n(w)) + n^2 g_n(w) (b^\epsilon - b)) \\ - \lambda_n \frac{e(bn^\epsilon - nb^\epsilon) + (n^\epsilon - n) + e(bn^\epsilon h_n^\epsilon(w^\epsilon) - b^\epsilon n h_n(w))}{(eb^\epsilon + 1)(eb + 1)} \\ - \lambda_n \frac{n^\epsilon h_n^\epsilon(w^\epsilon) - n h_n(w)}{(eb^\epsilon + 1)(eb + 1)}$$

$$b_t^\epsilon - b_t = - \frac{bb^\epsilon k_{nr} K_w (nw - n^\epsilon w^\epsilon) \lambda_{rb}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ - \frac{k_{nr} K_w (bnw - b^\epsilon n^\epsilon w^\epsilon)}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ - \frac{bb^\epsilon (n - n^\epsilon) w w^\epsilon k_{nr} \lambda_{rb}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ - \frac{w w^\epsilon (bn - b^\epsilon n^\epsilon) k_{nr}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ - \frac{\delta (bw - b^\epsilon w^\epsilon) K_w}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ - \frac{bb^\epsilon \delta (w - w^\epsilon) K_w \lambda_{rb}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ - \frac{(b - b^\epsilon) \delta w w^\epsilon}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ - (b^\epsilon - b) \lambda_b + (b^\epsilon + (b - b^\epsilon)(b^\epsilon + b) - b) k_b + (b_{xx}^\epsilon - b_{xx}) \epsilon_b$$

$$c_t^\epsilon - c_t = D_c (c^\epsilon - c) + k_c (b^\epsilon - b) - \lambda_c (c^\epsilon - c)$$

We perform another iteration of adding terms of $u^\epsilon v - u^\epsilon v$ into the newly added terms of form $u^\epsilon v^\epsilon - uv$ in the neutrophil and bacteria equations.

$$w_t^\epsilon - w_t = w_{xx}^\epsilon - w_{xx} + \gamma G(t) + \gamma \epsilon k - \gamma G(t) - \lambda_{nw} (n^\epsilon w^\epsilon + n^\epsilon w - n^\epsilon w - nw)$$

$$- \lambda_{bw} (b^\epsilon w^\epsilon + b^\epsilon w - b^\epsilon w - bw) - \lambda_w (w^\epsilon - w)$$

$$n_t^\epsilon - n_t = D_n (n_{xx}^\epsilon - n_{xx}) - \chi_n (n_x^\epsilon (c_x^\epsilon - c_x) + c_x (n_x^\epsilon - n_x) + n^\epsilon (c_{xx}^\epsilon - c_{xx}) + c_{xx} (n^\epsilon - n))$$

$$+ k_{bn} (b^\epsilon (n^\epsilon (g_n^\epsilon(w^\epsilon) - g_n(w)) + (n^\epsilon - n)g_n(w)) + n g_n(w) (b^\epsilon - b))$$

$$- k_{bn} (b^\epsilon (n^{\epsilon^2} (g_n^\epsilon(w^\epsilon) - g_n(w)) + (n^\epsilon + n)(n^\epsilon - n)g_n(w)) + n^2 g_n(w) (b^\epsilon - b))$$

$$- \lambda_n \frac{e(b(n^\epsilon - n)) - n(b^\epsilon - b) + (n^\epsilon - n)}{(eb^\epsilon + 1)(eb + 1)}$$

$$- \lambda_n \frac{e(b(n^\epsilon (h_n^\epsilon(w^\epsilon) - h_n(w)) + h_n(w)(n^\epsilon - n)) - n h_n(w)(b^\epsilon - b))}{(eb^\epsilon + 1)(eb + 1)}$$

$$- \lambda_n \frac{n^\epsilon (h_n^\epsilon(w^\epsilon) - h_n(w)) + h_n(w)(n^\epsilon - n)}{(eb^\epsilon + 1)(eb + 1)}$$

$$\begin{aligned} b_t^\epsilon - b_t = & \frac{bb^\epsilon (n^\epsilon - n) w k_{nr} K_w \lambda_{rb}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ & + \frac{b^\epsilon (n^\epsilon - n) w k_{nr} K_w}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ & + \frac{bb^\epsilon (n^\epsilon - n) w w^\epsilon k_{nr} \lambda_{rb}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ & + \frac{b^\epsilon (n^\epsilon - n) w w^\epsilon k_{nr}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ & + \frac{bb^\epsilon n^\epsilon (w^\epsilon - w) k_{nr} K_w \lambda_{rb}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ & + \frac{b^\epsilon n^\epsilon (w^\epsilon - w) k_{nr} K_w}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \\ & + \frac{(b^\epsilon - b) n w w^\epsilon k_{nr}}{(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon \lambda_{rb} + 1)} \end{aligned}$$

$$\begin{aligned}
& + \frac{(b^\epsilon - b) n w k_{nr} K_w}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\
& + \frac{(b^\epsilon - b) \delta w w^\epsilon}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\
& + \frac{b b^\epsilon \delta (w^\epsilon - w) K_w \lambda_{rb}}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\
& + \frac{b^\epsilon \delta (w^\epsilon - w) K_w}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} \\
& + \frac{(b^\epsilon - b) \delta w K_w}{(K_w + w) (K_w + w^\epsilon) (b \lambda_{rb} + 1) (b^\epsilon \lambda_{rb} + 1)} + (b_{xx}^\epsilon - b_{xx}) \epsilon_b \\
& - (b^\epsilon - b) \lambda_b + (b^\epsilon + (b - b^\epsilon) (b^\epsilon + b) - b) k_b
\end{aligned}$$

$$c_t^\epsilon - c_t = D_c (c^\epsilon - c) + k_c (b^\epsilon - b) - \lambda_c (c^\epsilon - c)$$

Finally, we divide by ϵ to form the difference quotients.

$$\begin{aligned}
\left(\frac{w^\epsilon - w}{\epsilon} \right)_t &= \left(\frac{w^\epsilon - w}{\epsilon} \right)_{xx} + \gamma k - \lambda_{nw} \left(n^\epsilon \left(\frac{w^\epsilon - w}{\epsilon} \right) + w \left(\frac{n^\epsilon - n}{\epsilon} \right) \right) \\
&\quad - \lambda_{bw} \left(b^\epsilon \left(\frac{w^\epsilon - w}{\epsilon} \right) + w \left(\frac{b^\epsilon - b}{\epsilon} \right) \right) - \lambda_w \left(\frac{w^\epsilon - w}{\epsilon} \right) \\
\left(\frac{n^\epsilon - n}{\epsilon} \right)_t &= D_n \left(\frac{n^\epsilon - n}{\epsilon} \right)_{xx} - \chi_n \left(n_x^\epsilon \left(\frac{c^\epsilon - c}{\epsilon} \right)_x + c_x \left(\frac{n^\epsilon - n}{\epsilon} \right)_x + n^\epsilon \left(\frac{c^\epsilon - c}{\epsilon} \right)_{xx} \right) \\
&\quad - \chi_n c_{xx} \left(\frac{n^\epsilon - n}{\epsilon} \right) \\
&\quad + k_{bn} \left(b^\epsilon \left(n^\epsilon \left(\frac{g_n^\epsilon(w^\epsilon) - g_n(w)}{\epsilon} \right) + \left(\frac{n^\epsilon - n}{\epsilon} \right) g_n(w) \right) + n g_n(w) \left(\frac{b^\epsilon - b}{\epsilon} \right) \right) \\
&\quad - k_{bn} \left(b^\epsilon \left(n^{\epsilon^2} \left(\frac{g_n^\epsilon(w^\epsilon) - g_n(w)}{\epsilon} \right) + (n^\epsilon + n) \left(\frac{n^\epsilon - n}{\epsilon} \right) g_n(w) \right) \right) \\
&\quad - k_{bn} b^\epsilon n^2 g_n(w) \left(\frac{b^\epsilon - b}{\epsilon} \right) \\
&\quad - \lambda_n \frac{e(b(n^\epsilon - n) - n(b^\epsilon - b) + (n^\epsilon - n))}{\epsilon (eb^\epsilon + 1) (eb + 1)}
\end{aligned}$$

$$\begin{aligned}
& -\lambda_n \frac{e(b(n^\epsilon(h_n^\epsilon(w^\epsilon) - h_n(w)) + h_n(w)(n^\epsilon - n)) - nh_n(w)(b^\epsilon - b))}{\epsilon(eb^\epsilon + 1)(eb + 1)} \\
& -\lambda_n \frac{n^\epsilon(h_n^\epsilon(w^\epsilon) - h_n(w)) + h_n(w)(n^\epsilon - n)}{\epsilon(eb^\epsilon + 1)(eb + 1)} \\
\left(\frac{b^\epsilon - b}{\epsilon}\right)_t &= \frac{bb^\epsilon(n^\epsilon - n)wk_{nr}K_w\lambda_{rb}}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{b^\epsilon(n^\epsilon - n)wk_{nr}K_w}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{bb^\epsilon(n^\epsilon - n)ww^\epsilon k_{nr}\lambda_{rb}}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{b^\epsilon(n^\epsilon - n)ww^\epsilon k_{nr}}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{bb^\epsilon n^\epsilon(w^\epsilon - w)k_{nr}K_w\lambda_{rb}}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{b^\epsilon n^\epsilon(w^\epsilon - w)k_{nr}K_w}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{(b^\epsilon - b)nww^\epsilon k_{nr}}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{(b^\epsilon - b)nwk_{nr}K_w}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{(b^\epsilon - b)\delta ww^\epsilon}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{bb^\epsilon\delta(w^\epsilon - w)K_w\lambda_{rb}}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{b^\epsilon\delta(w^\epsilon - w)K_w}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} \\
& + \frac{(b^\epsilon - b)\delta wK_w}{\epsilon(K_w + w)(K_w + w^\epsilon)(b\lambda_{rb} + 1)(b^\epsilon\lambda_{rb} + 1)} + \epsilon_b \left(\frac{b^\epsilon - b}{\epsilon}\right)_{xx} \\
& - \lambda_b \left(\frac{b^\epsilon - b}{\epsilon}\right) + k_b \left(\frac{b^\epsilon + (b - b^\epsilon)(b^\epsilon + b) - b}{\epsilon}\right) \\
\left(\frac{c^\epsilon - c}{\epsilon}\right) &= D_c \left(\frac{c^\epsilon - c}{\epsilon}\right)_{xx} + k_c \left(\frac{b^\epsilon - b}{\epsilon}\right) - \lambda_c \left(\frac{c^\epsilon - c}{\epsilon}\right)
\end{aligned}$$

At this point, one needs to prove the convergence of this system in $L^2((0, T); \mathbb{H}^1(0, 1))$ to obtain the existence of the sensitivities. Since we only require the weak convergence to hold, we would rewrite the above system in terms of the weak formulation of the above equations; *i.e.*, write the equations in terms of weak derivatives in the product space norm. Once we are able to bound the estimates for our weak derivatives, we then extract a weakly convergent subsequences. The limit of these subsequences we define as our sensitivities. By the compact embedding of $L^2((0, T); H^1(0, 1))$ into $L^2((0, 1) \times (0, T))$, we would obtain the strong convergence to our sensitivities in $L^2((0, 1) \times (0, T))$. In this case, we make the following definitions:

$$\begin{aligned} \lim_{\epsilon \rightarrow 0^+} \frac{w^\epsilon - w}{\epsilon} &\rightarrow \psi_4 \\ \lim_{\epsilon \rightarrow 0^+} \frac{n^\epsilon - n}{\epsilon} &\rightarrow \psi_3 \\ \lim_{\epsilon \rightarrow 0^+} \frac{b^\epsilon - b}{\epsilon} &\rightarrow \psi_1 \\ \lim_{\epsilon \rightarrow 0^+} \frac{c^\epsilon - c}{\epsilon} &\rightarrow \psi_2 \\ \lim_{\epsilon \rightarrow 0^+} \frac{g_n(w^\epsilon) - g_n(w)}{\epsilon} &\rightarrow \phi_1 \\ \lim_{\epsilon \rightarrow 0^+} \frac{g_n(w^\epsilon) - h_n(w)}{\epsilon} &\rightarrow \phi_2 \end{aligned}$$

provided the convergences hold. We note we have numbered the sensitivities based on alphabetical order of the unknown functions. With these definitions in place, we

may write the sensitivity equations as:

$$\begin{aligned}
\psi_{4_t} &= \psi_{4_{xx}} + \gamma k - w\lambda_{bw}\psi_1 - w\lambda_{nw}\psi_3 - (b\lambda_{bw} - n\lambda_{nw} - \lambda_w)\psi_4 \\
\psi_{3_t} &= \psi_3 \left(bwk_{bn}g_n - 2bnwk_{bn}g_n - \frac{bewh_n\lambda_n}{(eb+1)^2} - \frac{be\lambda_n}{(eb+1)^2} - c_{xx}\chi_n - \frac{e\lambda_n}{(eb+1)^2} \right) \\
&\quad + \phi_1 (bnk_{bn} - bn^2k_{bn}) - \frac{ben\phi_2\lambda_n}{(eb+1)^2} \\
&\quad + \psi_1 \left(n^2(-w)k_{bn}g_n + nwk_{bn}g_n + \frac{enwh_n\lambda_n}{(eb+1)^2} + \frac{en\lambda_n}{(eb+1)^2} \right) \\
&\quad - c_x\chi_n\psi_{3_x} + D_n\psi_{3_{xx}} - \chi_n\psi_{2_x}n_x - n\chi_n\psi_{2_{xx}} \\
\psi_{1_t} &= \frac{b^2n\psi_4k_{nr}K_w\lambda_{rb}}{(K_w+w)^2(b\lambda_{rb}+1)^2} + \frac{b^2w^2\psi_3k_{nr}\lambda_{rb}}{(K_w+w)^2(b\lambda_{rb}+1)^2} + \frac{b^2w\psi_3k_{nr}K_w\lambda_{rb}}{(K_w+w)^2(b\lambda_{rb}+1)^2} \\
&\quad + \frac{b^2\delta\psi_4K_w\lambda_{rb}}{(K_w+w)^2(b\lambda_{rb}+1)^2} + \frac{nw^2\psi_1k_{nr}}{(K_w+w)^2(b\lambda_{rb}+1)^2} + \frac{bn\psi_4k_{nr}K_w}{(K_w+w)^2(b\lambda_{rb}+1)^2} \\
&\quad + \frac{nw\psi_1k_{nr}K_w}{(K_w+w)^2(b\lambda_{rb}+1)^2} + \frac{bw^2\psi_3k_{nr}}{(K_w+w)^2(b\lambda_{rb}+1)^2} + \frac{bw\psi_3k_{nr}K_w}{(K_w+w)^2(b\lambda_{rb}+1)^2} \\
&\quad + \frac{\delta w^2\psi_1}{(K_w+w)^2(b\lambda_{rb}+1)^2} + \frac{b\delta\psi_4K_w}{(K_w+w)^2(b\lambda_{rb}+1)^2} + \frac{\delta w\psi_1K_w}{(K_w+w)^2(b\lambda_{rb}+1)^2} \\
&\quad + \epsilon_b\psi_{1_{xx}} - \psi_1\lambda_b + k_b(\psi_1 - 2b\psi_1) \\
\psi_{2_t} &= D_c\psi_{2_{xx}} + k_c\psi_1 - \lambda_c\psi_2.
\end{aligned}$$

After some simplification, our system becomes:

$$\begin{aligned}
\psi_{4t} &= \psi_{4_{xx}} + \gamma k - \lambda_{bw} w \psi_1 - \lambda_{nw} w \psi_3 - (\lambda_{nw} n + \lambda_{bw} b + \lambda_w) \psi_4 \\
\psi_{3t} &= D_n \psi_{3_{xx}} + \psi_3 \left(b w k_{bn} g_n - 2 b n w k_{bn} g_n - \frac{b e w h_n \lambda_n}{(e b + 1)^2} - \frac{b e \lambda_n}{(e b + 1)^2} - c_{xx} \chi_n - \frac{e \lambda_n}{(e b + 1)^2} \right) \\
&\quad + \phi_1 (b n k_{bn} - b n^2 k_{bn}) - \frac{b e n \phi_2 \lambda_n}{(e b + 1)^2} \\
&\quad + \psi_1 \left(n^2 (-w) k_{bn} g_n + n w k_{bn} g_n + \frac{e n w h_n \lambda_n}{(e b + 1)^2} + \frac{e n \lambda_n}{(e b + 1)^2} \right) \\
&\quad - c_x \chi_n \psi_{3_x} - \chi_n \psi_{2_x} n_x - n \chi_n \psi_{2_{xx}} \\
\psi_{1t} &= \epsilon_b \psi_{1_{xx}} + \psi_1 \left(\frac{n w k_{nr} + \delta w}{(K_w + w) (b \lambda_{rb} + 1)^2} - 2 b k_b + k_b - \lambda_b \right) + \frac{b w k_{nr}}{(K_w + w) (b \lambda_{rb} + 1)} \psi_3 \\
&\quad + \frac{(b n k_{nr} K_w + b \delta K_w)}{(K_w + w)^2 (b \lambda_{rb} + 1)} \psi_4 \\
\psi_{2t} &= D_c \psi_{2_{xx}} + k_c \psi_1 + \lambda_c \psi_2.
\end{aligned}$$

We may write this system as the operator equation

$$\mathcal{L}[\vec{\Psi}] = \begin{pmatrix} \gamma k \\ -\phi_1 (b n k_{bn} - b n^2 k_{bn}) + \frac{b e n \lambda_n^2}{(e b + 1)} \phi_2 \\ 0 \\ 0 \end{pmatrix},$$

where

$$\mathcal{L}[\vec{\Psi}] = \begin{pmatrix} \mathcal{L}_4\psi_4 \\ \mathcal{L}_3\psi_3 \\ \mathcal{L}_1\psi_1 \\ \mathcal{L}_2\psi_2 \end{pmatrix} - M \begin{pmatrix} \psi_4 \\ \psi_3 \\ \psi_1 \\ \psi_2 \end{pmatrix},$$

$$\begin{pmatrix} \mathcal{L}_4\psi_4 \\ \mathcal{L}_3\psi_3 \\ \mathcal{L}_1\psi_1 \\ \mathcal{L}_2\psi_2 \end{pmatrix} = \begin{pmatrix} \psi_{4t} - \psi_{4xx} \\ \psi_{3t} - D_n\psi_{3xx} - \chi_n c_x \psi_{3x} - c_{xx} \chi_n - \chi_n (n_x \psi_{2x} + n \psi_{2xx}) \\ \psi_{1t} - \epsilon_b \psi_{1xx} \\ \psi_{2t} - D_c \psi_{2xx} \end{pmatrix},$$

and

$$M = \begin{pmatrix} -(\lambda_{nw}n + \lambda_{bw}b + \lambda_w) & -\lambda_{nw} & -\lambda_{bw}w & 0 \\ 0 & m_{22} & m_{23} & 0 \\ m_{31} & m_{32} & m_{33} & 0 \\ 0 & 0 & k_c & \lambda_c \end{pmatrix},$$

with

$$m_{22} = bwk_{bn}g_n - 2bnwk_{bn}g_n - \frac{bewh_n\lambda_n}{(eb+1)^2} - \frac{be\lambda_n}{(eb+1)^2} - \frac{e\lambda_n}{(eb+1)^2}$$

$$m_{23} = n^2(-w)k_{bn}g_n + nwk_{bn}g_n + \frac{enwh_n\lambda_n}{(eb+1)^2} + \frac{en\lambda_n}{(eb+1)^2}$$

$$m_{31} = \frac{(bnk_{nr}K_w + b\delta K_w)}{(K_w + w)^2 (b\lambda_{rb} + 1)}$$

$$m_{32} = \frac{bwk_{nr}}{(K_w + w) (b\lambda_{rb} + 1)}$$

$$m_{33} = \frac{nwk_{nr} + \delta w}{(K_w + w) (b\lambda_{rb} + 1)^2} - 2bk_b + k_b - \lambda_b,$$

subject to the following initial and boundary conditions :

$$\frac{\partial \psi_4}{\partial x} \Big|_{x=0} = 0 \qquad \frac{\partial \psi_3}{\partial x} \Big|_{x=0} = 0$$

$$\psi_4(1, t) = 0 \qquad \psi_3(1, t) = 0$$

$$\psi_4(x, 0) = 0 \qquad \psi_3(x, 0) = 0$$

$$\frac{\partial \psi_1}{\partial x} \Big|_{x=0} = 0 \qquad \frac{\partial \psi_2}{\partial x} \Big|_{x=0} = 0$$

$$\frac{\partial \psi_1}{\partial x} \Big|_{x=1} = 0 \qquad \frac{\partial \psi_2}{\partial x} \Big|_{x=1} = 0$$

$$\psi_1(x, 0) = 0 \qquad \psi_2(x, 0) = 0$$

We note that the sensitivity system has zero conditions because the state system was independent of the control along the boundary.

3.5. Adjoint System

We now turn our attention to the adjoint system. After one finds the sensitivity system, which is a linearization of the states with respect to the control, we then find the dual pairing with the sensitivity system. Formally, let X be a Hilbert space, and let X^* be its dual space. Then if $\psi \in X$ and $\lambda \in X^*$ have operators $L : X \rightarrow X^*$ and $L^* : X^* \rightarrow X$, respectively, such that

$$\langle L\psi, \lambda \rangle = \langle \psi, L^* \lambda \rangle,$$

then L^* is referred to as the adjoint operator to L . The notation $\langle \cdot, \cdot \rangle$ refers to the pairing in the context of the duality product, also called the duality. In our case, we will be referring to the L^2 inner product when we refer to the duality. As such, to find

the form the adjoint variables must take, we form the inner product $\langle L\psi, L^*\lambda \rangle$ and integrate by parts once in time and twice in space. As we require $\langle L\psi, \lambda \rangle = \langle \psi, L^*\lambda \rangle$, we will need to give the adjoint equations the appropriate boundary-initial conditions in a manner to define an appropriate duality product.

Let λ_1 be the adjoint associated with concentration of bacteria. Let λ_2 refer to the adjoint associated with the concentration of the chemoattractant. The adjoint for the concentration of the neutrophils will be denoted λ_3 and the λ_4 will refer to the adjoint for the level of oxygen. We form the appropriate L^2 product and integrate as a system rather than summing the equations as dictated by the product space norm. First, we multiply our sensitivities with the appropriate adjoint variables and

integrate over space and time.

$$\begin{aligned}
\int_0^T \int_0^1 \psi_{4t} \lambda_4 dx dt &= \int_0^T \int_0^1 \psi_{4_{xx}} \lambda_4 dx dt \\
&\quad + \int_0^T \int_0^1 (-\lambda_{bw} w \psi_1 - \lambda_{nw} w \psi_3 - (\lambda_{nw} n + \lambda_{bw} b + \lambda_w) \psi_4) \lambda_4 dx dt \\
\int_0^T \int_0^1 \psi_{3t} \lambda_3 dx dt &= \int_0^T \int_0^1 D_n \psi_{3_{xx}} \lambda_3 dx dt \\
&\quad + \int_0^T \int_0^1 (b w k_{bn} g_n - 2 b n w k_{bn} g_n) \psi_3 \lambda_3 dx dt \\
&\quad - \int_0^T \int_0^1 \left(\frac{b e w h_n \lambda_n}{(e b + 1)^2} + \frac{b e \lambda_n}{(e b + 1)^2} + \frac{e \lambda_n}{(e b + 1)^2} \right) \psi_3 \lambda_3 dx dt \\
&\quad + \int_0^T \int_0^1 (n^2 (-w) k_{bn} g_n + n w k_{bn} g_n) \psi_1 \lambda_3 dx dt \\
&\quad + \int_0^T \int_0^1 \left(\frac{e n w h_n \lambda_n}{(e b + 1)^2} + \frac{e n \lambda_n}{(e b + 1)^2} \right) \psi_1 \lambda_3 dx dt \\
&\quad + \int_0^T \int_0^1 (-c_x \chi_n \psi_{3_x} - \chi_n \psi_{2_x} n_x - n \chi_n \psi_{2_{xx}} - c_{xx} \chi_n \psi_3) \lambda_3 dx dt \\
\int_0^T \int_0^1 \psi_{1t} \lambda_1 dx dt &= \int_0^T \int_0^1 \epsilon_b \psi_{1_{xx}} \lambda_1 dx dt \\
&\quad + \int_0^T \int_0^1 \psi_1 \lambda_1 \left(\frac{n w k_{nr} + \delta w}{(K_w + w) (b \lambda_{rb} + 1)^2} - 2 b k_b + k_b - \lambda_b \right) dx dt \\
&\quad + \int_0^T \int_0^1 \frac{b w k_{nr}}{(K_w + w) (b \lambda_{rb} + 1)} \psi_3 \lambda_1 dx dt \\
&\quad + \int_0^T \int_0^1 \frac{(b n k_{nr} K_w + b \delta K_w)}{(K_w + w)^2 (b \lambda_{rb} + 1)} \psi_4 \lambda_1 dx dt \\
\int_0^T \int_0^1 \psi_{2t} \lambda_2 dx dt &= \int_0^T \int_0^1 D_c \psi_{2_{xx}} \lambda_2 dx dt + \int_0^T \int_0^1 (k_c \psi_1 + \lambda_c \psi_2) \lambda_2 dx dt
\end{aligned}$$

After integrating once in space and once in time, our equations become:

$$\begin{aligned}
& \int_0^1 \lambda_4 \psi_4 \Big|_0^T dx - \int_0^T \int_0^1 \psi_4 \lambda_{4_t} dx dt = \int_0^T \psi_{4_x} \lambda_4 \Big|_0^1 dt - \int_0^T \int_0^1 \psi_{4_x} \lambda_{4_x} dx dt \\
& \quad + \int_0^T \int_0^1 (-\lambda_{bw} w \psi_1 - \lambda_{nw} w \psi_3 - (\lambda_{nw} n + \lambda_{bw} b + \lambda_w) \psi_4) \lambda_4 dx dt \\
& \int_0^1 \lambda_3 \psi_3 \Big|_0^T dx - \int_0^T \int_0^1 \psi_3 \lambda_{3_t} dx dt = \int_0^T D_n \psi_{3_x} \lambda_3 \Big|_0^1 dt - \int_0^T \int_0^1 D_n \psi_{3_x} \lambda_{3_x} dx dt \\
& \quad + \int_0^T \int_0^1 (b w k_{bn} g_n - 2 b n w k_{bn} g_n) \psi_3 \lambda_3 dx dt \\
& \quad - \int_0^T \int_0^1 \left(\frac{b e w h_n \lambda_n}{(e b + 1)^2} + \frac{b e \lambda_n}{(e b + 1)^2} + \frac{e \lambda_n}{(e b + 1)^2} \right) \psi_3 \lambda_3 dx dt \\
& \quad + \int_0^T \int_0^1 (n^2 (-w) k_{bn} g_n + n w k_{bn} g_n) \psi_1 \lambda_3 dx dt \\
& \quad + \int_0^T \int_0^1 \left(\frac{e n w h_n \lambda_n}{(e b + 1)^2} + \frac{e n \lambda_n}{(e b + 1)^2} \right) \psi_1 \lambda_3 dx dt \\
& \quad - \chi_n \int_0^T c_x \psi_3 \lambda_3 \Big|_0^1 dt + \chi_n \int_0^T \int_0^1 \psi_3 c_{xx} \lambda_3 dx dt \\
& \quad + \chi_n \int_0^T \int_0^1 \psi_3 c_x \lambda_{3_x} dx dt + \chi_n + \chi_n \int_0^T \int_0^1 n_{xx} \lambda_3 \psi_2 dx dt \\
& \quad + \int_0^T \int_0^1 n_x \lambda_{3_x} \psi_2 dx dt - \chi_n \int_0^T \psi_2 n_x \lambda_3 \Big|_0^1 dt \\
& \quad - \chi_n \int_0^T n \lambda_3 \psi_{2_x} \Big|_0^1 dt + \chi_n \int_0^T \int_0^1 n_x \lambda_3 \psi_{2_x} dx dt \\
& \quad - \chi_n \int_0^T \int_0^1 c_{xx} \lambda_3 \psi_3 dx dt + \chi_n \int_0^T \int_0^1 n \lambda_{3_x} \psi_{2_x} dx dt \\
& \int_0^1 \lambda_1 \psi_1 \Big|_0^T dx - \int_0^T \int_0^1 \psi_1 \lambda_{1_t} dx dt = \int_0^T \epsilon_b \psi_{1_x} \lambda_1 \Big|_0^1 dt - \int_0^T \int_0^1 \epsilon_b \psi_{1_x} \lambda_{1_x} dx dt \\
& \quad + \int_0^T \int_0^1 \psi_1 \lambda_1 \left(\frac{n w k_{nr} + \delta w}{(K_w + w) (b \lambda_{rb} + 1)^2} - 2 b k_b + k_b - \lambda_b \right) dx dt \\
& \quad + \int_0^T \int_0^1 \frac{b w k_{nr}}{(K_w + w) (b \lambda_{rb} + 1)} \psi_3 \lambda_1 dx dt \\
& \quad + \int_0^T \int_0^1 \frac{(b n k_{nr} K_w + b \delta K_w)}{(K_w + w)^2 (b \lambda_{rb} + 1)} \psi_4 \lambda_1 dx dt
\end{aligned}$$

$$\begin{aligned} \int_0^1 \lambda_2 \psi_2 \Big|_0^T dx - \int_0^T \int_0^1 \psi_2 \lambda_{2t} dx dt &= \int_0^T D_c \psi_{2x} \lambda_2 \Big|_0^1 dt \\ &- \int_0^T \int_0^1 D_c \psi_{2x} \lambda_{2x} dx dt + \int_0^T \int_0^1 (k_c \psi_1 + \lambda_c \psi_2) \lambda_2 dx dt. \end{aligned}$$

After the second integration in space, our system becomes

$$\begin{aligned} \int_0^1 \lambda_4 \psi_4 \Big|_0^T dx - \int_0^T \int_0^1 \psi_4 \lambda_{4t} dx dt &= \int_0^T \psi_{4x} \lambda_4 \Big|_0^1 dt - \int_0^T \lambda_{4x} \psi_4 \Big|_0^1 dt \\ &+ \int_0^T \int_0^1 \lambda_{4xx} \psi_4 dx dt \\ &+ \int_0^T \int_0^1 (-\lambda_{bw} w \psi_1 - \lambda_{nw} w \psi_3 - (\lambda_{nw} n + \lambda_{bw} b + \lambda_w) \psi_4) \lambda_4 dx dt \\ \int_0^1 \lambda_3 \psi_3 \Big|_0^T dx - \int_0^T \int_0^1 \psi_3 \lambda_{3t} dx dt &= \int_0^T D_n \psi_{3x} \lambda_3 \Big|_0^1 dt - \int_0^T D_n \lambda_{3x} \psi_3 \Big|_0^1 dt \\ &+ \int_0^T \int_0^1 D_n \lambda_{3xx} \psi_3 dx dt \\ &+ \int_0^T \int_0^1 \left(b w k_{bn} g_n - 2 b n w k_{bn} g_n - \frac{b e w h_n \lambda_n}{(e b + 1)^2} \right) \psi_3 \lambda_3 dx dt \\ &- \int_0^T \int_0^1 \left(\frac{b e \lambda_n}{(e b + 1)^2} + \frac{e \lambda_n}{(e b + 1)^2} \right) \psi_3 \lambda_3 dx dt \\ &+ \int_0^T \int_0^1 \left(n^2 (-w) k_{bn} g_n + n w k_{bn} g_n + \frac{e n w h_n \lambda_n}{(e b + 1)^2} + \frac{e n \lambda_n}{(e b + 1)^2} \right) \psi_1 \lambda_3 dx dt \\ &- \chi_n \int_0^T c_x \psi_3 \lambda_3 \Big|_0^1 dt + \chi_n \int_0^T \int_0^1 \psi_3 c_x \lambda_{3x} dx dt - \chi_n \int_0^T \psi_2 n_x \lambda_3 \Big|_0^1 dt \\ &- \chi_n \int_0^T n \lambda_3 \psi_{2x} \Big|_0^1 dt + \chi_n \int_0^T n_x \lambda_3 \psi_2 \Big|_0^1 dt - \chi_n \int_0^T \int_0^1 \psi_2 n_x \lambda_{3x} dx dt \\ &+ \chi_n \int_0^T n \lambda_{3x} \psi_2 \Big|_0^1 dt dx dt - \chi_n \int_0^T \int_0^1 \psi_2 n \lambda_{3xx} dx dt \end{aligned}$$

$$\begin{aligned}
& \int_0^1 \lambda_1 \psi_1 \Big|_0^T dx - \int_0^T \int_0^1 \psi_1 \lambda_{1t} dx dt = \int_0^T \epsilon_b \psi_{1x} \lambda_1 \Big|_0^1 dt - \int_0^T \epsilon_b \lambda_{1x} \psi_1 \Big|_0^1 dt \\
& \quad + \int_0^T \int_0^1 \epsilon_b \lambda_{1xx} \psi_1 dx dt \\
& \quad + \int_0^T \int_0^1 \psi_1 \lambda_1 \left(\frac{nw k_{nr} + \delta w}{(K_w + w)(b\lambda_{rb} + 1)^2} - 2bk_b + k_b - \lambda_b \right) dx dt \\
& \quad + \int_0^T \int_0^1 \frac{bw k_{nr}}{(K_w + w)(b\lambda_{rb} + 1)} \psi_3 \lambda_1 dx dt \\
& \quad + \int_0^T \int_0^1 \frac{(bn k_{nr} K_w + b\delta K_w)}{(K_w + w)^2 (b\lambda_{rb} + 1)} \psi_4 \lambda_1 dx dt \\
& \int_0^1 \lambda_2 \psi_2 \Big|_0^T dx - \int_0^T \int_0^1 \psi_2 \lambda_{2t} dx dt = \int_0^T D_c \psi_{2x} \lambda_2 \Big|_0^1 dt - \int_0^T D_c \lambda_{2x} \psi_2 \Big|_0^1 dt \\
& \quad + \int_0^T \int_0^1 D_c \lambda_{2xx} \psi_2 dx dt + \int_0^T \int_0^1 (k_c \psi_1 + \lambda_c \psi_2) \lambda_2 dx dt.
\end{aligned}$$

This implies that our adjoint equations are

$$\lambda_{4t} = -\lambda_{4xx} + \lambda_{bw} w \lambda_4 + \lambda_{nw} w \lambda_4 + (\lambda_{nw} n + \lambda_{bw} b + \lambda_w) \lambda_4 + 1$$

$$\begin{aligned}
\lambda_{3t} &= -D_n \lambda_{3xx} - \chi_n \lambda_{3x} c_x + \chi_n (n_x \lambda_{3x} + n \lambda_{3xx}) \\
& - \left(k_{bn} n g_n(w) - k_{bn} n^2 g_n(w) - \frac{\lambda_n (en - en h_n(w))}{(eb + 1)^2} \right) \lambda_1 \\
& - \left(k_{bn} b g_n(w) - 2k_{bn} b n g_n(w) - \frac{\lambda_n (eb + e + eb h_n(w) + h_n(w))}{(eb + 1)^2} \right) \lambda_3 \\
& - \left(k_{bn} b n \phi_1 - k_{bn} b n^2 \phi_1 - \frac{\lambda_n (eb n \phi_2 - n \phi_2)}{(eb + 1)^2} \right) \lambda_4 \tag{3.5.1}
\end{aligned}$$

$$\begin{aligned}
\lambda_{1t} &= -\epsilon_b \lambda_{1xx} - \left(2k_b b + \frac{(\delta w + k_{nr} w n)}{(K_w + 1)(\lambda_{rb} b + 1)^2} + \lambda_b \right) \lambda_1 - k_b \lambda_2 - \frac{(k_{nr} \lambda_{rb} b^2 w + k_{nr} b w)}{(K_w + 1)(\lambda_{rb} b + 1)^2} \lambda_3 \\
& - \frac{(\delta \lambda_{rb} b^2 + \delta b + k_{nr} \lambda_{rb} b^2 n + k_{nr} b n)}{(K_w + 1)(\lambda_{rb} b + 1)^2} \lambda_4
\end{aligned}$$

$$\lambda_{2t} = -D_c \lambda_{2xx} - k_c \lambda_1 - \lambda_c \lambda_2$$

subject to the following terminal, initial and boundary conditions:

$$\begin{aligned} \frac{\partial \lambda_4}{\partial x} \Big|_{x=0} &= 0 & \frac{\partial \lambda_3}{\partial x} \Big|_{x=0} &= 0 \\ \lambda_4(1, t) &= 0 & \lambda_3(1, t) &= 0 \\ \lambda_4(x, T) &= 0 & \lambda_3(x, T) &= 0 \end{aligned}$$

$$\begin{aligned} \frac{\partial \lambda_1}{\partial x} \Big|_{x=0} &= 0 & \frac{\partial \lambda_2}{\partial x} \Big|_{x=0} &= 0 \\ \frac{\partial \lambda_1}{\partial x} \Big|_{x=1} &= 0 & \frac{\partial \lambda_2}{\partial x} \Big|_{x=1} &= 0 \\ \lambda_1(x, T) &= 0 & \lambda_2(x, T) &= 0. \end{aligned}$$

We note we have chosen these boundary conditions to define the duality product between $L^2(0, T; H^1(0, 1))$ and $L^2(0, T; (H^1(0, 1))^*)$. We may write our adjoint operator L^* as:

$$\begin{aligned} \mathcal{L}^*[\vec{\lambda}] &= \begin{pmatrix} \mathcal{L}^*_4 \lambda_4 \\ \mathcal{L}^*_3 \lambda_3 \\ \mathcal{L}^*_1 \lambda_1 \\ \mathcal{L}^*_2 \lambda_2 \end{pmatrix} - M^T \begin{pmatrix} \lambda_4 \\ \lambda_3 \\ \lambda_1 \\ \lambda_2 \end{pmatrix}, \\ &= \begin{pmatrix} \mathcal{L}^*_4 \lambda_4 \\ \mathcal{L}^*_3 \lambda_3 \\ \mathcal{L}^*_1 \lambda_1 \\ \mathcal{L}^*_2 \lambda_2 \end{pmatrix} - \begin{pmatrix} -\lambda_{4t} - \lambda_{4xx} \\ -\lambda_{3t} - D_n \lambda_{3xx} + \chi_n c_x \lambda_{3x} \chi_n n_x \lambda_{3x} + \chi_n n \lambda_{3xx} \\ -\lambda_{1t} - \epsilon_b \lambda_{1xx} \\ -\lambda_{2t} - D_c \lambda_{2xx} \end{pmatrix}, \end{aligned}$$

where M^T is the transpose of our coefficient matrix from the sensitivity equations.

3.6. Classification of the Optimality System

3.6.1. Classification of the Optimality System. Given our system (2.5.3)

with boundary conditions (2.5.4), we may derive our optimality system as follows.

Let $G(t) \in A = \{\text{admissible controls}\}$. Assume the mappings $G \rightarrow w, n, b, c$ are differentiable in the Gâteaux sense, and let k be a variation. Suppose

$$\begin{aligned} \frac{w(G(t) + \epsilon k) - w(G(t))}{\epsilon} &\rightarrow \psi_4, \\ \frac{n(G(t) + \epsilon k) - n(G(t))}{\epsilon} &\rightarrow \psi_3, \\ \frac{b(G(t) + \epsilon k) - b(G(t))}{\epsilon} &\rightarrow \psi_1, \\ \frac{c(G(t) + \epsilon k) - c(G(t))}{\epsilon} &\rightarrow \psi_2 \text{ in } L^2((0, 1) \times (0, T)). \end{aligned}$$

We further need to assume the convergence of the maps $g_n(w), h_n(w)$ such that

$$\frac{g_n(w(G(t)+\epsilon k)) - g_n(w(G(t)))}{\epsilon} \rightarrow \phi_1 \psi_4 \text{ and } \frac{h_n(w(G(t)=\epsilon k)) - h_n(w(G(t)))}{\epsilon} \rightarrow \phi_2 \psi_4 \text{ as } \epsilon \rightarrow 0^+ \text{ for any}$$

$G \in A$ and $k \in L^\infty([0, 1])$. As these are continuous mappings from cubic spines, this assumption will hold given the differentiability of the $w(x, t)$ mapping.

Theorem 3.6.1. Given an optimal control $G^*(t)$, and corresponding solutions w, n, b and c of (2.5.3), there exist weak solutions

$$(\lambda_4, \lambda_3, \lambda_1, \lambda_2)^\top \in \mathbb{L}^2((0, T); (H^1(0, 1))^*)$$

satisfying the adjoint system

$$\lambda_{4t} = -\lambda_{4xx} + \lambda_{bw}w\lambda_4 + \lambda_{nw}w\lambda_4 + (\lambda_{nw}n + \lambda_{bw}b + \lambda_w)\lambda_4 + 1$$

$$\lambda_{3t} = -D_n\lambda_{3xx} - \chi_n\lambda_{3x}c_x + \chi_n(n_x\lambda_{3x} + n\lambda_{3xx})$$

$$- \left(k_{bn}ng_n(w) - k_{bn}n^2g_n(w) - \frac{\lambda_n(en - enh_n(w))}{(eb+1)^2} \right) \lambda_1$$

$$- \left(k_{bn}bg_n(w) - 2k_{bn}bng_n(w) - \frac{\lambda_n(eb + e + ebh_n(w) + h_n(w))}{(eb+1)^2} \right) \lambda_3$$

$$- \left(k_{bn}bn\phi_1 - k_{bn}bn^2\phi_1 - \frac{\lambda_n(ebn\phi_2 - n\phi_2)}{(eb+1)^2} \right) \lambda_4$$

$$\lambda_{1t} = -\epsilon_b\lambda_{1xx} - \left(2k_b b + \frac{(\delta w + k_{nr}wn)}{(K_w + 1)(\lambda_{rb}b + 1)^2} + \lambda_b \right) \lambda_1 - k_b\lambda_2 - \frac{(k_{nr}\lambda_{rb}b^2w + k_{nr}bw)}{(K_w + 1)(\lambda_{rb}b + 1)^2} \lambda_3$$

$$- \frac{(\delta\lambda_{rb}b^2 + \delta b + k_{nr}\lambda_{rb}b^2n + k_{nr}bn)}{(K_w + 1)(\lambda_{rb}b + 1)^2} \lambda_4$$

$$\lambda_{2t} = -D_c\lambda_{2xx} - k_c\lambda_1 - \lambda_c\lambda_2$$

subject to the following initial and boundary conditions:

$$\frac{\partial \lambda_4}{\partial x} \Big|_{x=0} = 0$$

$$\frac{\partial \lambda_3}{\partial x} \Big|_{x=0} = 0$$

$$\lambda_4(1, t) = 0$$

$$\lambda_3(1, t) = 0$$

$$\lambda_4(x, T) = 0$$

$$\lambda_3(x, T) = 0$$

$$\frac{\partial \lambda_1}{\partial x} \Big|_{x=0} = 0$$

$$\frac{\partial \lambda_2}{\partial x} \Big|_{x=0} = 0$$

$$\frac{\partial \lambda_1}{\partial x} \Big|_{x=1} = 0$$

$$\frac{\partial \lambda_2}{\partial x} \Big|_{x=1} = 0$$

$$\lambda_1(x, T) = 0$$

$$\lambda_2(x, T) = 0.$$

Proof. Let $G(t)$ be an optimal control and (w, n, b, c) be the corresponding solution. Let $G(t) + \epsilon k \in A$ for $\epsilon > 0$ and let $w^\epsilon, n^\epsilon, b^\epsilon, c^\epsilon$ be the corresponding weak state solutions to (2.5.3). We compute the directional derivative of the functional J in the direction of our variation k . We use the sensitivity and adjoint systems to compute the minimum value:

$$\begin{aligned}
0 &\geq \frac{J(G + \epsilon k) - J(G)}{\epsilon} \\
&= \lim_{\epsilon \rightarrow 0^+} \frac{1}{\epsilon} \int_0^T \int_0^1 b^\epsilon + \frac{1}{2} \kappa (G(t) + \epsilon k)^2 - b - \frac{1}{2} \kappa G^2(t) dx dt \\
&= \lim_{\epsilon \rightarrow 0^+} \frac{1}{\epsilon} \int_0^T \int_0^1 b^\epsilon + \frac{1}{2} \kappa G^2(t) + \kappa G(t) \epsilon k + \frac{1}{2} \kappa \epsilon^2 k^2 - b - \frac{1}{2} \kappa G^2(t) dx dt \\
&= \lim_{\epsilon \rightarrow 0^+} \frac{1}{\epsilon} \int_0^T \int_0^1 b^\epsilon - b + \kappa G(t) \epsilon k + \frac{1}{2} \kappa \epsilon^2 k^2 dx dt \\
&= \int_0^T \int_0^1 \psi_1 + \kappa k G(t) dx dt \\
&= \int_0^T \int_0^1 \begin{pmatrix} \psi_1 & \psi_2 & \psi_3 & \psi_4 \end{pmatrix} \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix} dx dt + \int_0^T \int_0^1 \kappa k G(t) dx dt \\
&= \int_0^T \int_0^1 \begin{pmatrix} \psi_1 & \psi_2 & \psi_3 & \psi_4 \end{pmatrix} \left(\begin{pmatrix} -\lambda_{1t} \\ -D_c \lambda_{2t} \\ -D_n \lambda_{3t} \\ -\lambda_{4t} \end{pmatrix} - \begin{pmatrix} \epsilon_b \lambda_{1xx} \\ D_c \lambda_{2xx} \\ D_n \lambda_{3xx} \\ \lambda_{4xx} \end{pmatrix} + M^T \begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \\ \lambda_4 \end{pmatrix} \right) dx dt \\
&\quad + \int_0^T \int_0^1 \kappa k G(t) dx dt
\end{aligned}$$

$$\begin{aligned}
&= \int_0^T \int_0^1 \begin{pmatrix} \psi_1 & \psi_2 & \psi_3 & \psi_4 \end{pmatrix} \begin{pmatrix} -\lambda_{1t} \\ -D_c \lambda_{2t} \\ -D_n \lambda_{3t} \\ -\lambda_{4t} \end{pmatrix} - \begin{pmatrix} \psi_1 & \psi_2 & \psi_3 & \psi_4 \end{pmatrix} \begin{pmatrix} \epsilon_b \lambda_{1_{xx}} \\ D_c \lambda_{2_{xx}} \\ D_n \lambda_{3_{xx}} \\ \lambda_{4_{xx}} \end{pmatrix} \\
&\quad + \begin{pmatrix} \psi_1 & \psi_2 & \psi_3 & \psi_4 \end{pmatrix} M^T \begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \\ \lambda_4 \end{pmatrix} dxdt + \int_0^t \int_0^1 \kappa k G(t) dxdt \\
&= \int_0^T \int_0^1 -\lambda_{1t} \psi_1 - D_c \psi_2 \lambda_{2t} - D_n \psi_3 \lambda_{3t} + \psi_4 \lambda_{4t} dxdt \\
&\quad - \int_0^T \int_0^1 \psi_1 \epsilon_b \lambda_{1_{xx}} + \psi_2 \lambda_{2_{xx}} + D_n \psi_3 \lambda_{3_{xx}} + \psi_4 \lambda_{4_{xx}} dxdt \\
&\quad + \int_0^T \int_0^1 \begin{pmatrix} \psi_1 & \psi_2 & \psi_3 & \psi_4 \end{pmatrix} M^T \begin{pmatrix} \lambda_1 \\ \lambda_2 \\ \lambda_3 \\ \lambda_4 \end{pmatrix} dxdt + \int_0^t \int_0^1 \kappa k G(t) dxdt \\
&= \int_0^1 [-\lambda_1 \psi_1 - D_c \psi_2 \lambda_2 - D_n \psi_3 \lambda_3 + \psi_4 \lambda_4] \Big|_0^T dx \\
&\quad + \int_0^T \int_0^1 -\lambda_1 \psi_{1t} - D_c \psi_{2t} \lambda_2 - D_n \psi_{3t} \lambda_3 + \psi_{4t} \lambda_4 dxdt \\
&\quad - \int_0^T [\psi_{1_x} \epsilon_b \lambda_{1_x} + \psi_{2_x} \lambda_{2_x} + D_n \psi_{3_x} \lambda_{3_x} + \psi_{4_x} \lambda_{4_x}] \Big|_0^1 dt \\
&\quad + \int_0^T \int_0^1 \psi_{1_{xx}} \epsilon_b \lambda_1 + \psi_{2_{xx}} \lambda_2 + D_n \psi_{3_{xx}} \lambda_3 + \psi_{4_{xx}} \lambda_4 dxdt \\
&\quad + \int_0^T \int_0^1 \begin{pmatrix} \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 \end{pmatrix} M \begin{pmatrix} \psi_1 \\ \psi_2 \\ \psi_3 \\ \psi_4 \end{pmatrix} dxdt + \int_0^T \int_0^1 \kappa k G(t) dxdt
\end{aligned}$$

$$\begin{aligned}
&= \int_0^T \int_0^1 \begin{pmatrix} \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 \end{pmatrix} \left(\begin{pmatrix} \psi_{1t} \\ D_c \psi_{2t} \\ D_n \psi_{3t} \\ \psi_{4t} \end{pmatrix} - \begin{pmatrix} \epsilon \psi_{1xx} \\ D_c \psi_{2xx} \\ D_n \psi_{3xx} \\ \psi_{4xx} \end{pmatrix} + M \begin{pmatrix} \psi_1 \\ \psi_2 \\ \psi_3 \\ \psi_4 \end{pmatrix} \right) dxdt \\
&\quad + \int_0^T \int_0^1 \kappa k G(t) dxdt \\
&= \int_0^T \int_0^1 \begin{pmatrix} \lambda_1 & \lambda_2 & \lambda_3 & \lambda_4 \end{pmatrix} \begin{pmatrix} 0 \\ 0 \\ \phi_1 (bnk_{bn} - bn^2 k_{bn}) - \frac{ben\lambda_n^2}{(eb+1)} \phi_2 \\ \kappa \gamma k \end{pmatrix} dxdt \\
&\quad + \int_0^T \int_0^1 2k G(t) dxdt \\
&= \int_0^T \int_0^1 \lambda_4 \kappa k + \lambda_3 \left(\phi_1 (bnk_{bn} - bn^2 k_{bn}) - \frac{ben\lambda_n^2}{(eb+1)} \phi_2 \right) \\
&\quad + 2\kappa k G(t) dxdt.
\end{aligned}$$

By standard optimality techniques, this implies that the characterization of our optimal control is

$$G(t) = \min \left\{ \sup \{G\}, \max \left\{ \frac{-\lambda_4}{2} - \frac{-\lambda_3}{2\kappa k} \left(\phi_1 (bnk_{bn} - bn^2 k_{bn}) - \frac{ben\lambda_n^2}{(eb+1)} \phi_2 \right), 0 \right\} \right\}.$$

□

We note that optimality system comprises of the state system (2.5.3), the adjoint system (3.5.1), as well as the boundary conditions, initial conditions and the adjoint final-time conditions. The uniqueness of this system implies the uniqueness of the optimal control [10]. Typically we can only do for small time. Future work can assess the uniqueness of our solution. If that is established, then the optimality system itself can be solved using forward-backward sweep numerical methods ([10]).

CHAPTER 4

NUMERICAL METHODS AND RESULTS

4.1. Introduction

To solve the state system (2.5.3) with boundary conditions (2.5.4), we shall be using the method of lines (MOL) in *Matlab*. The idea of the method of lines is to replace the spatial derivatives in a PDE with a finite difference approximation to the derivative along an N -point spatial grid. For example, given the non-dimensional heat equation

$$\frac{\partial u}{\partial t} = \frac{\partial^2 u}{\partial x^2},$$

we could replace the spatial derivative with the second order centered difference approximation

$$\frac{\partial^2 u}{\partial x^2} \approx \frac{u_{i+1} - 2u_i + u_{i-1}}{\Delta x^2}$$

to obtain

$$\frac{\partial u_i}{\partial t} = \frac{u_{i+1} - 2u_i + u_{i-1}}{\Delta x^2}, \quad 1 \leq i \leq N,$$

where i is a spatial indexing along an N -point mesh of spacing Δx . By incorporating this approximation, we effectively turn our PDE into a system of N ODEs which can be solved using methods for systems of ODEs [15]. For our applications in *Matlab*, we will be using *ode15s.m*, a solver for stiff ODE problems. We will then compare the results we obtain from the MOL to *Matlab*'s pre-packaged PDE solver, *pdepe.m*. This solver is designed to solve parabolic-elliptic systems, with the constraint that there must be at least one parabolic equation given. The motivation for attempting a method of lines solution for this particular problem stems from the inability of

pdepe.m to solve systems involving hyperbolic equations. Since the bacterial diffusion in system (2.5.3) was introduced artificially, we wish to develop a more general routine that is able to solve parabolic-hyperbolic systems.

4.2. The Discretized System

Given the system (2.5.3), we rewrite the spatial derivatives using the second order central-difference approximation as stated above. Though central difference methods are known to be only conditionally stable, *Matlab's pdepe.m* also discretizes using a central difference method. Further work may be done to incorporate unconditionally stable discretizations and comparing with our current results.

Let $w(x_i, t) = W_i(t)$, $n(x_i, t) = N_i(t)$, $b(x_i, t) = B_i(t)$, and $c(x_i, t) = C_i(t)$. Substituting into (2.5.3), our new system of equations becomes

$$\begin{aligned}
\frac{\partial W_i}{\partial t}(t) &= \frac{W_{i+1}(t) - 2W_i(t) + W_{i-1}(t)}{\Delta x^2} + \beta + \kappa G(t) - \lambda_{nw} N_i(t) W_i(t) \\
&\quad - \lambda_{bw} B_i(t) W_i(t) - \lambda_w W_i(t) \\
\frac{\partial N_i}{\partial t}(t) &= D_n \frac{N_{i+1}(t) - 2N_i(t) + N_{i-1}(t)}{\Delta x^2} \\
&\quad - \chi_n \frac{N_{i+1}(t) - N_{i-1}(t)}{2\Delta x} \frac{C_{i+1}(t) - C_{i-1}(t)}{2\Delta x} \\
&\quad - \chi_n N_i(t) \frac{C_{i+1}(t) - 2C_i(t) + C_{i-1}(t)}{\Delta x^2} \\
&\quad + k_{bn} B_i(t) N_i(t) g_n(W_i(t)) (1 - N_i(t)) \\
&\quad - \lambda_n \frac{N_i(t) (1 + h_n(W_i(t)))}{1 + eB_i(t)} \\
\frac{\partial B_i}{\partial t}(t) &= \epsilon_b \frac{B_{i+1}(t) - 2B_i(t) + B_{i-1}(t)}{\Delta x^2} + k_b B_i(t) (1 - B_i(t)) \\
&\quad - B_i(t) \frac{W_i(t)}{K_w + W_i(t)} \frac{\delta + k_{nr} N_i(t)}{\lambda_{rb} B_i(t) + 1} \\
&\quad - \lambda_b B_i(t) \\
\frac{\partial C_i}{\partial t}(t) &= D_c \frac{C_{i+1}(t) - 2C_i(t) + C_{i-1}(t)}{\Delta x^2} + k_c B_i(t) - \lambda_c C_i(t), \quad 2 \leq i \leq N-1,
\end{aligned} \tag{4.2.1}$$

where i is an index, $1 \leq i \leq N$. At $i = 1$ and $i = N$, we must incorporate the boundary conditions into the numerical approximation. First, consider the boundary condition at $x = 0$. In general, if

$$\frac{\partial u}{\partial x}(0, t) = 0,$$

then we may approximate this as

$$\frac{\partial u}{\partial x}(0, t) \approx \frac{U_{i+1}(t) - U_{i-1}(t)}{2\Delta x} = 0.$$

This however, implies that

$$U_{i-1}(t) = U_{i+1}.$$

For our indexing, this will imply

$$W_0(t) = W_2(t), \quad N_0(t) = N_2(t), \quad B_0(t) = B_2(t),$$

$$C_0(t) = C_2(t), \quad B_{N+1}(t) = B_{N-1}(t), \quad C_{N+1}(t) = C_{N-1}(t).$$

As for the Dirichlet conditions, if $u(0, t) = \alpha$, $\alpha \in \mathbb{R}$, where u is a differentiable function of t , then this implies $u_t(0, t) = 0$. Thus, on the right boundary we will impose

$$\frac{\partial W_N(t)}{\partial t} = 0, \quad \frac{\partial N_N(t)}{\partial t} = 0.$$

Thus, at the boundaries, our equations become

$$\begin{aligned} \frac{\partial W_1}{\partial t}(t) &= \frac{2(W_2(t) - W_1(t))}{\Delta x^2} + \beta + \kappa G(t) - \lambda_{nw} N_1(t) W_1(t) \\ &\quad - \lambda_{bw} B_1(t) W_1(t) - \lambda_w W_1(t) \end{aligned}$$

$$\begin{aligned} \frac{\partial N_1}{\partial t}(t) &= D_n \frac{2(N_2(t) - N_1(t))}{\Delta x^2} \\ &\quad - \chi_n N_1(t) \frac{2(C_2(t) - C_1(t))}{\Delta x^2} \\ &\quad + k_{bn} B_1(t) N_1(t) g_n(W_1(t)) (1 - N_1(t)) \\ &\quad - \lambda_n \frac{N_1(t) (1 + h_n(W_1(t)))}{1 + e B_1(t)} \end{aligned}$$

$$\begin{aligned} \frac{\partial B_1}{\partial t}(t) &= \epsilon_b \frac{2(B_2(t) - B_1(t))}{\Delta x^2} + k_b B_1(t) (1 - B_1(t)) \\ &\quad - B_1(t) \frac{W_1(t)}{K_w + W_1(t)} \frac{\delta + k_{nr} N_1(t)}{\lambda_{rb} B_1(t) + 1} \\ &\quad - \lambda_b B_1(t) \end{aligned}$$

$$\frac{\partial C_1}{\partial t}(t) = D_c \frac{2(C_2(t) - C_1(t))}{\Delta x^2} + k_c B_1(t) - \lambda_c C_1(t), \quad \text{for } i = 1,$$

and

$$\frac{\partial W_N}{\partial t}(t) = 0$$

$$\frac{\partial N_N}{\partial t}(t) = 0$$

$$\begin{aligned} \frac{\partial B_N}{\partial t}(t) &= \epsilon_b \frac{2(B_{N-1}(t) - B_N(t))}{\Delta x^2} + k_b B_N(t) (1 - B_N(t)) \\ &\quad - B_N(t) \frac{W_N(t)}{K_w + W_N(t)} \frac{\delta + k_{nr} N_N(t)}{\lambda_{rb} B_N(t) + 1} \\ &\quad - \lambda_b B_N(t) \end{aligned}$$

$$\frac{\partial C_N}{\partial t}(t) = D_c \frac{2(C_{N-1}(t) - C_N(t))}{\Delta x^2} + k_c B_N(t) - \lambda_c C_N(t), \quad \text{for } i = N.$$

Parameter	Non-Dimensional	Dimensional	Reference
L	1	1cm	OC
w_0	1	$5.4 * 10^{-6} g * cm^{-1}$	[14]
n_0	1	$1 * 10^{-3} g * cm^{-1}$	[14]
b_0	1	$3 * 10^{-6} g * cm^{-1}$	[14]
c_0	1		OC
D_w	1	$5 * 10^{-6} cm^2 * s^{-1}$	OC
D_n	0.02	$1 * 10^{-7} cm^2 * s^{-1}$	OC
ϵ_b	.0001		OC
D_c	1.5		OC
β	.2284	$6.1667 * 10^{-12} cm^{-1} * g * s^{-1}$	OC
γ	5.4		OC
G	0	0	OC
λ_{nw}	37	$0.185 cm * g^{-1} * s^{-1}$	[14]
λ_{bw}	22.7872		[14]
λ_w	2.4667	$0.01233 * 10^{-3} s^{-1}$	OC
χ_n	10	$1 cm^5 * g^{-1} * s^{-1}$	OC
k_{bn}	14.28		[14]
λ_n	5	$2.5 * 10^{-5} s^{-1}$	[14]
k_b	1.26	$7.13 * 10^{-5} s^{-1}$	[14]
k_w	.75		OC
$k_n r$	2		OC
λ_{rb}	3.73		[14]
λ_b	5	$2.5 * 10^{-6} s^{-1}$	[14]
k_c	10		OC
λ_c	.9		OC
δ	.7992		OC
e	30		OC
ϵ	.01		OC

TABLE 4.1. Parameter values used in numerical methods

4.3. Numerical Results

We will be making a qualitative comparison of our results with the pre-packaged routine *pdepe.m*. For both methods, we use the following values for our parameters.

The parameter values chosen were originally the ones chosen by Russell [14] for his CE/T project, gathered from the literature. In attempting to find a more biologically feasible solution, however, we altered the parameters until settling on

those chosen. To reflect these manipulations, we have labeled these parameters with “OC”, meaning “our choice.”

We will first discuss the solution obtained from *pdepe.m*. For *pdepe.m*, we must write the system as

$$c\left(x, t, u, \frac{\partial u}{\partial x}\right) \frac{\partial u}{\partial t} = x^{-m} \frac{\partial u}{\partial x} \left(x^m f\left(x, t, u, \frac{\partial u}{\partial x}\right) \right) + s\left(x, t, u, \frac{\partial u}{\partial x}\right),$$

where m incorporates slab, cylindrical, or spherical symmetry, depending on whether $m = 0, 1$ or 2 . f is the matrix of flux terms, and s is the source function for the PDEs. Our specific encoding can be found in Appendix B. We were able to solve the system up to 4.5×10^{-3} non-dimensional time units. This corresponds to 15 minutes. Efforts to increase the final time caused failure of the *pdepe.m* code. Further efforts are needed to increase the final time to a significant time scale for the problem. Below we display the solutions generated by *Matlab*, and discuss the results.

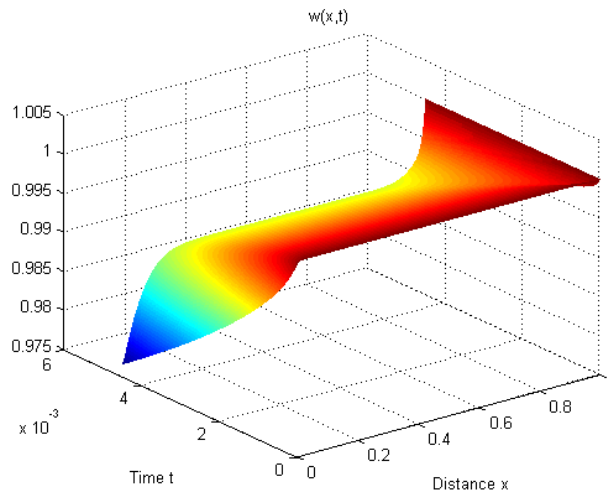


FIGURE 4.1. Oxygen Solution from *pdepe.m*

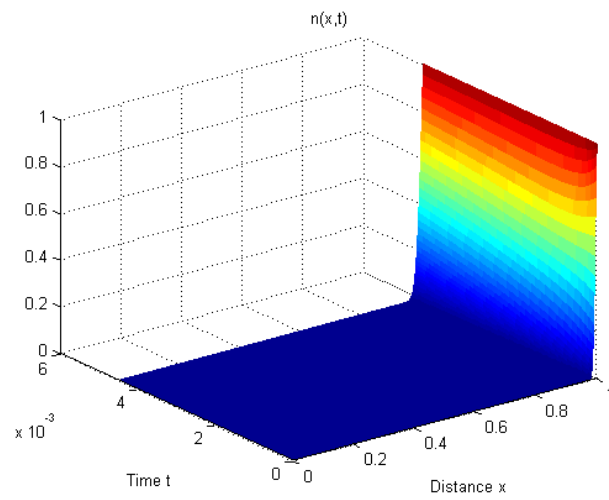


FIGURE 4.2. Neutrophil Solution from *pdepe.m*

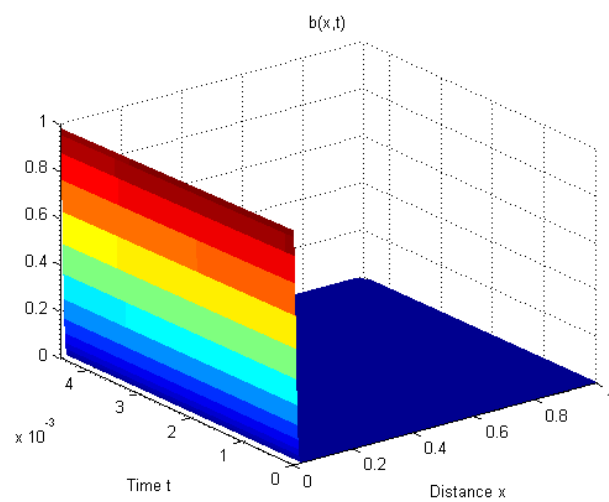


FIGURE 4.3. Bacteria Solution from *pdepe.m*

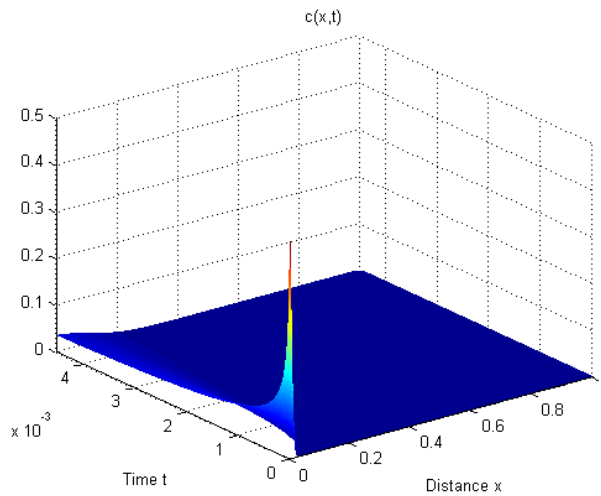


FIGURE 4.4. Chemoattractant Solution from *pdepe.m*

Figures 4.1-4.4 provide numerical solutions to the state equations. Specifically, the oxygen behaves as expected (Figure 4.1), meaning the bacteria in the center of the wound causes a decrease in the level of oxygen locally. Over a larger time scale, we would expect the bacteria to absorb more oxygen as they proliferate, creating a larger gradient. The neutrophils are densely distributed at the edge of the wound (Figure 4.2). We note that as time increases, we expect to see the neutrophils to be chemically attracted towards the center of the wound. We see the chemoattractant is not reaching the edge of the wound, contributing to the lack of movement in the neutrophils (Figure 4.4). However, the chemoattractant is shown to begin to diffuse throughout the wound as we expect. We would expect more of the chemoattractant to be produced as the bacteria proliferate. The bacteria (Figure 4.3) stay heavily concentrated in the center of the wound. Over longer times, we would expect to see more proliferation of the bacteria. We would also be able to search for signs of the bacteria diffusing. This would give us more insight to role being played by the

small ϵ_b -diffusion coefficient, and whether our chosen parameter value is small enough to give us a reasonable approximation to the case when bacteria is not assumed to diffuse.

Next we display results using the method-of-lines code, as discuss the results below.

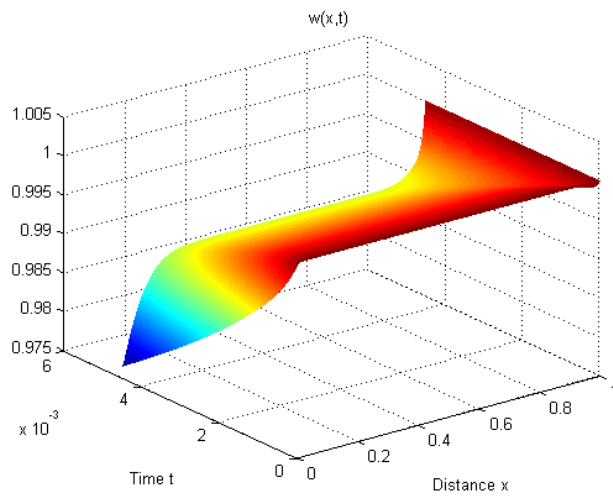


FIGURE 4.5. Oxygen Solution from method of lines

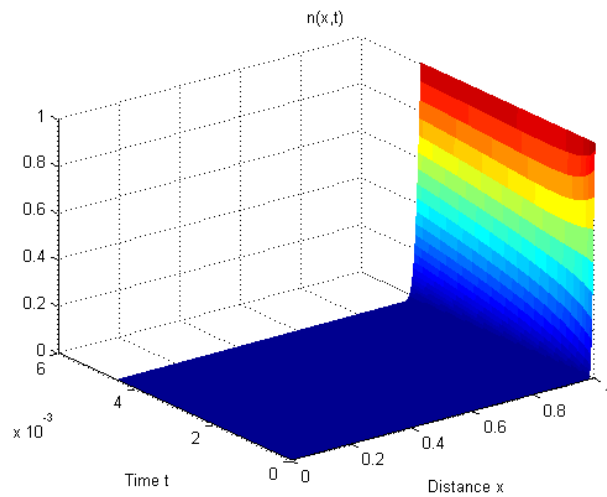


FIGURE 4.6. Neutrophil Solution from method of lines

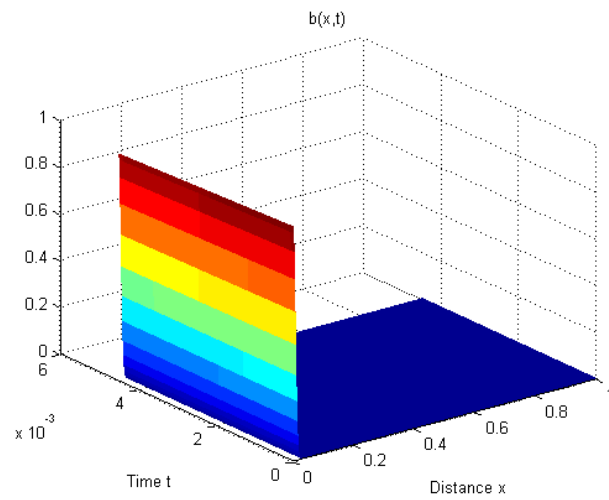


FIGURE 4.7. Bacteria Solution from method of lines

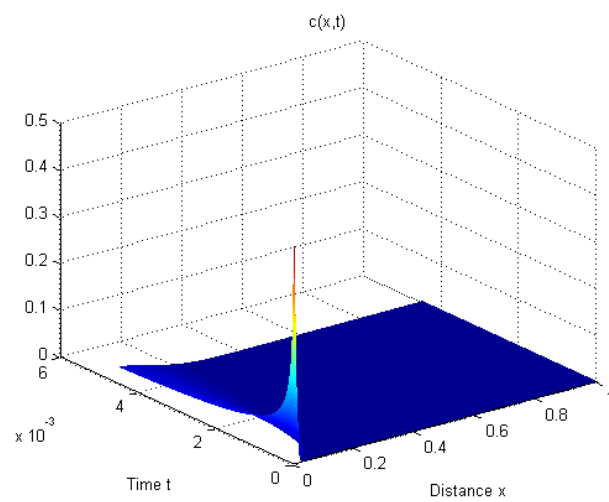


FIGURE 4.8. Chemoattractant Solution from method of lines

We note that the method of lines solutions (Figures 4.5-4.8) generated are qualitatively similar to those produced using *pdepe.m*. The oxygen (Figure 4.5) is being absorbed by the bacteria in the center of the wound. We again note that over larger time intervals, we would expect this interaction to increase, creating a larger gradient in the oxygen distribution in the wound. We observe the neutrophils distributed densely near the edge of the wound as before (Figure 4.6). The bacteria are again highly concentrated near the center of the wound, quickly vanishing in the interior (Figure 4.7). With the solutions being produced over a small time interval, the bacteria have not begun to significantly proliferate. This lack of proliferation has again caused a small amount of the chemoattractant to be produced (Figure 4.8). As in the *pdepe.m* solution, this lack of chemoattractant can be one factor attributing to the lack of movement from the neutrophils. As before, further work must be done to increase the final time for the solutions before we can make accurate assessments of the validity of this model as an explanation of the interactions occurring in chronic wounds.

To test the similarities of the solutions, we plot each solution from the method of lines with its counterpart using *pdepe.m* at four equidistant points in time. Below the plots we discuss the results.

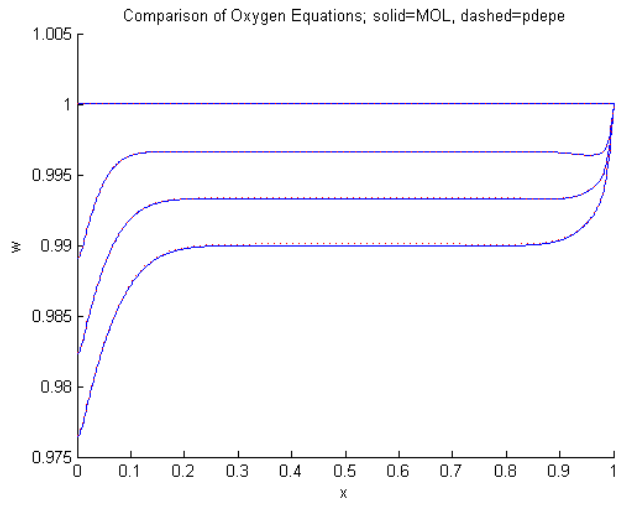


FIGURE 4.9. Comparison of Oxygen Solutions

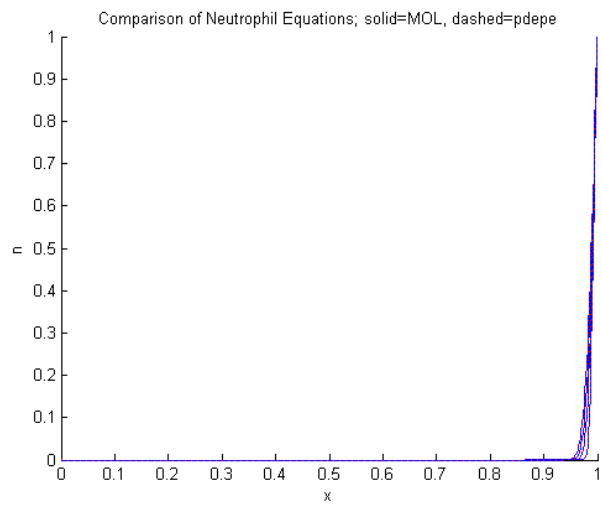


FIGURE 4.10. Comparison of Neutrophil Solutions

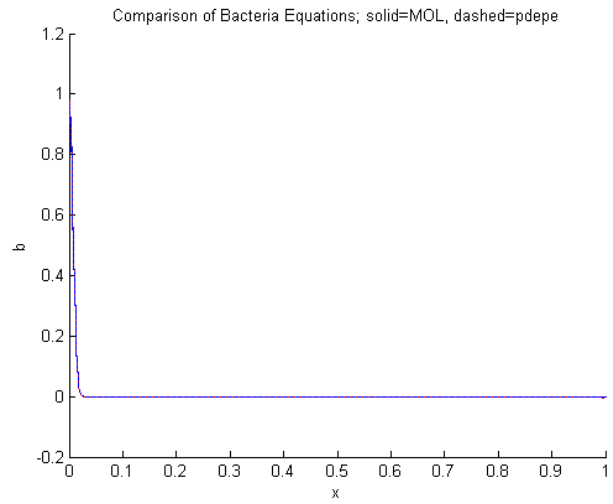


FIGURE 4.11. Comparison of Bacteria Solutions

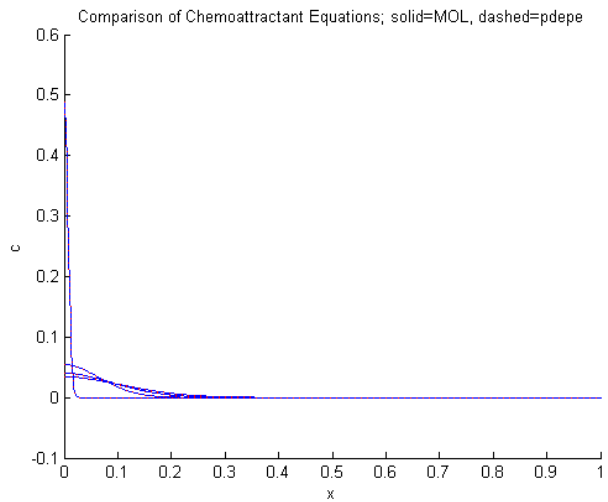


FIGURE 4.12. Comparison of Chemoattractant Solutions

In Figures 4.9-4.12, we observe similarities in the two solutions for the state variables. We observe that the two solutions for the oxygen equation generally agree (Figure 4.9). However, we also note that as time increases, we observe the method of lines solution moving away from the *pdepe.m* solution. As we have only found numerical solutions over a small time scale, we will need to continue assessing this disparity of the two solutions as we work to increase the final time for us to obtain a solution. We note that the neutrophil solutions appear to be identical over the given time interval (Figure 4.10). This similarity, however, could arise out of a lack of movement in the neutrophils which caused the plotted time slices to overlap with each other. Similar difficulties in assessing the model occur in the solution to the bacteria equation (Figure 4.11). Though the bacterial equations do not show a dynamic quality, we do note that the solutions from the two methods appear to coincide over the given time interval. The chemoattractant solutions (Figure 4.12) show highly similar results. Even with the relatively dynamic nature of the solution for the chemoattractant, we see the two solutions coincide, as the dotted *pdepe.m* solution overlaps the solid blue solution produced using the method of lines.

Finally, we wish to test the method-of-lines code in the case when $\epsilon_b = 0$, *i.e.*, when the bacteria are not assumed to have a random motility. We will not be able to directly test this case with *pdepe.m*, as this built-in function file returns an error because it reads the bacteria equation as a hyperbolic equation, which *pdepe.m* can not solve. However, due to the high similarity of the solutions produced by our two methods in the case when ϵ_b is a positive constant, we argue this as evidence that our method-of-lines code is producing accurate results for the given time interval. As

such, we remove the bacterial diffusion term and solve the system over the same time interval. We display the results and discuss the results below.

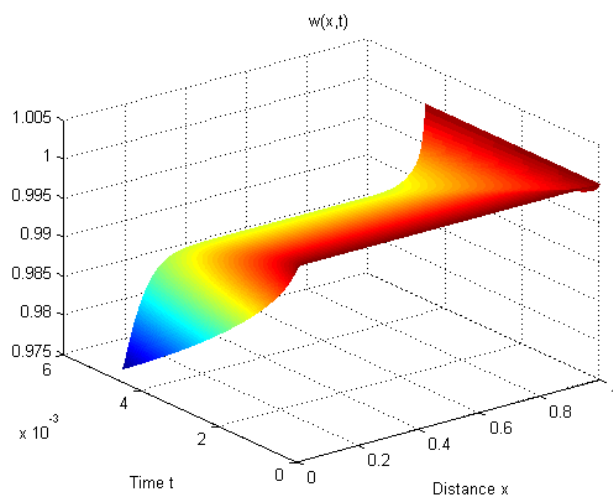


FIGURE 4.13. Oxygen Solution when $\epsilon_b = 0$

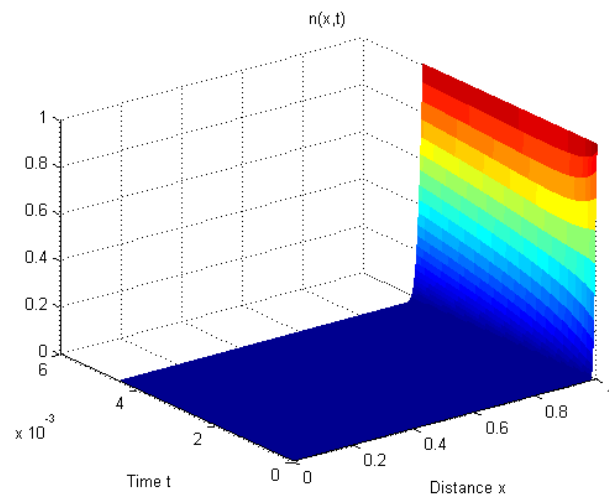


FIGURE 4.14. Neutrophil Solution when $\epsilon_b = 0$

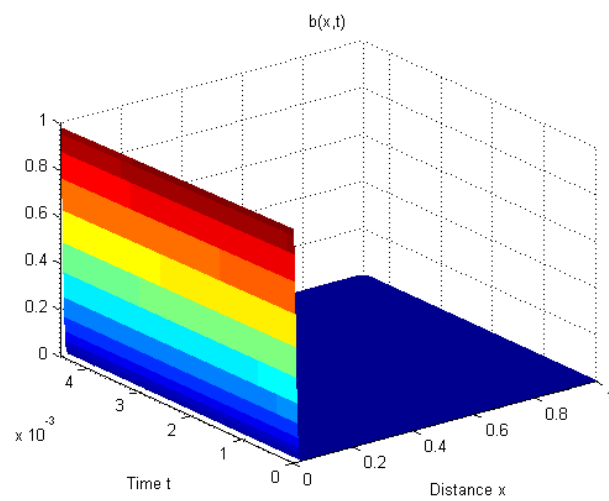


FIGURE 4.15. Bacteria Solution when $\epsilon_b = 0$

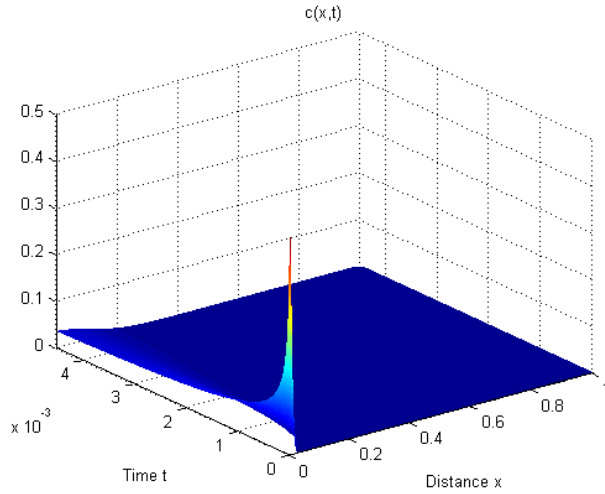


FIGURE 4.16. Chemoattractant Solution when $\epsilon_b = 0$

We note the method of lines produced a similar result to when we assumed a small bacterial diffusion (Figures 4.13-4.16). We again see that the oxygen is being absorbed by the bacteria in the center of the wound, though to a smaller degree than what we would expect when the bacteria proliferate (Figure 4.9). The neutrophil solution (Figure 4.14) remains densely populated near the edge of the wound. As before we note that this may be attributed to the lack of chemoattractant present in the wound (Figure 4.16). As the chemoattractant only diffuses to the $1/5^{th}$ the total distance of the wound before vanishing, the neutrophils can not sense the gradient of the chemoattractant. As such, the neutrophils have no incentive to travel towards the center of the wound. We see that the bacteria are densely distributed in the center of the wound (Figure 4.15) as before, and have shown no significant proliferation over the given time interval. Comparing to the solutions produced before in the method of lines and *pdepe.m*, we note that the bacterial solutions are qualitatively similar

in each case, suggesting that the small diffusion coefficient produces an adequate approximation to reality over small time.

Along with plotting the solution to the state system (Equations 2.5.3) for the same time interval for which we could compare to a solution generated by *pdepe.m*, we also increase the final time to 10.8 non-dimensional time units. This corresponds to 25 days.

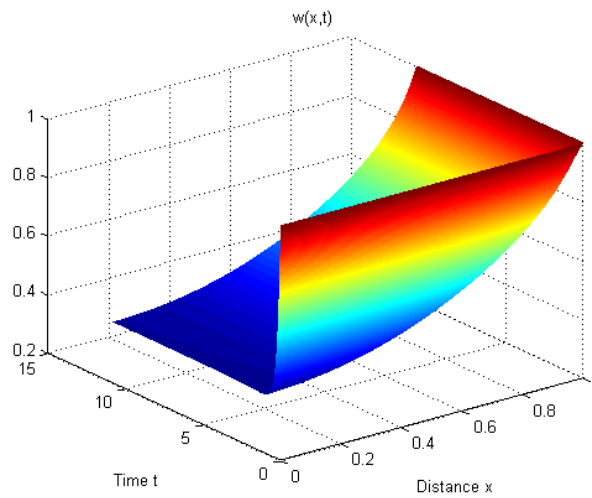


FIGURE 4.17. Oxygen Solution over 25 days

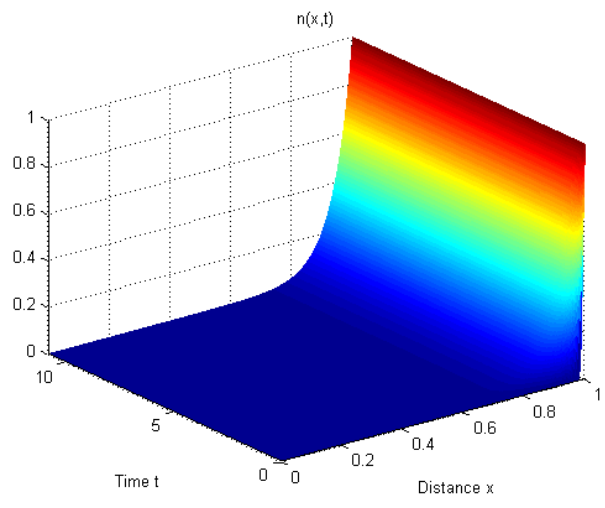


FIGURE 4.18. Neutrophil Solution over 25 days

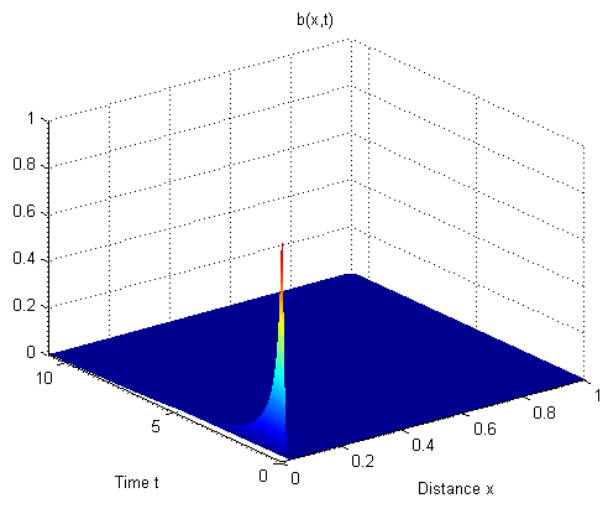


FIGURE 4.19. Bacteria Solution over 25 days

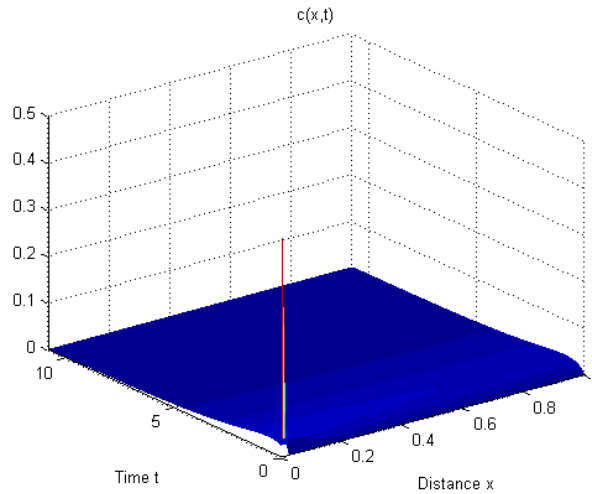


FIGURE 4.20. Chemoattractant Solution over 25 days

The solutions generated over 25 days (Figures 4.17 - 4.20) give us more information of our parameter estimates. We see the oxygen is being absorbed significantly by the bacteria (Figure 4.17). The solution of the oxygen equation is shown to decrease from a constant level on the outside boundary of the wound to a significantly lower level near the center of the wound where the bacteria are densely populated. The neutrophils diffuse into the wound as expected (Figure 4.18). The neutrophils are seen to die before the chemoattractant attracts them into the wound toward the bacteria. This may be due to the low levels of the chemoattractant after the starting time, which creates a gradient in the chemoattractant which is too small to attract the neutrophils into the wound (Figure 4.20). One possible explanation for this lack of chemoattractant is the quick loss of the bacteria under our given parameter values (Figure 4.19). This quick decay limits the amount of chemoattractant produced.

The given solutions over 25 days suggests that future work must be done in estimating our parameter values. The bacteria should persist in the wound, producing a chemoattractant that attracts the neutrophils to the center of the wound.

Through further work to increase the solution time interval for our *pdepe.m* solution, we may continue to assess the effect of the small random motility of the bacteria. In addition, further work must be done to improve our estimates for the parameter values. With these changes we will gain a better assessment to the validity of our code.

CHAPTER 5

CONCLUSION AND FUTURE WORK

In this work, we have applied optimal control theory to a system of parabolic PDEs in order to obtain the characterization of the optimal control. We have also obtained numerical solutions for the state systems. First, we have demonstrated the existence of the state solutions for our system with modified boundary conditions. We have then proven that under reasonable assumptions on the states, we obtain the existence of an optimal control. Furthermore, we have demonstrated the form of the sensitivity and adjoint equations for our particular system, as well as their boundary-initial-terminal values. Finally, we have then found the characterization of the optimal control. We have solved the state system using the method of lines in *Matlab*, as well as compared our solution to the solution generated by implementing *pdepe.m*, a well-accepted PDE solver in *Matlab*.

For our future work, we wish to verify the existence of a state solution to our system under the biologically feasible boundary conditions. With this, we would also like to bound the solutions in the appropriate space and prove uniqueness. We will also prove the existence and uniqueness of the adjoint equations. The uniqueness of the adjoint equations will be needed before we attempt to numerically solve for the optimal control, as we will need to simultaneously solve the state system forward in time and the adjoint system backward in time until we get convergence.

Numerically, we first need to improve our estimates for the parameter values. We would also like to expand the method-of-lines code to be able to accept arbitrary functions and boundary conditions, so that it can be programmed in a manner similarly

to *pdepe.m*, while being able to accept hyperbolic equations. Finally, we would like to develop the forward-backward sweep method [10] in order to obtain a numerical solution to the optimal control system comprising of the state system (2.5.3), the adjoint system (3.5.1) and the objective functional (3.3.3), with appropriate boundary, initial and terminal conditions.

APPENDIX A

PRELIMINARIES

In this appendix we give background theorems and definitions being used explicitly or implicitly in this work. Many definitions and theorems come from either Hudson, Pym and Cloud [6], Brezis [1], or Evans [2].

Definition A.0.1. Vector Space

Let V be a non-empty set, and suppose $f, g \in V \implies f + g \in V$, and let a, b be scalars.

Then V is called a vector, or linear space if the following hold:

- (1) $f + g = g + f$;
- (2) $f + (g + h) = (f + g) + h$;
- (3) $\exists 0 \in V \forall f \in V f + 0 = 0 + f = f$;
- (4) $\forall f \in V \exists (-f) \in V$ such that $f + (-f) = 0 = (-f) + f$;
- (5) $\forall f \in V, a(f + g) = a \cdot f + a \cdot g$
- (6) $(a + b)f = a \cdot f + b \cdot g$.
- (7) $(ab)f = a(bf)$
- (8) $1 \cdot f = f$

The elements f, g, h, \dots of V are known as points, elements, or vectors (depending on the context).

Definition A.0.2. Linear Independence

A finite set $S = \{f_j\}_{j=1}^n$ of elements of V is called linearly dependent if and only if

there exists scalars $\{a_i\}_{i=1}^n$, not all zero, such that $\sum_{i=1}^n a_i f_i = 0$. If S is not such a set, then S is called linearly independent.

Definition A.0.3. Basis for a Vector Space

A set S of elements from a vector space V is called a basis if and only if every vector in V can be written as a linear combination of elements from S ; *i.e.*, if $f = \sum_{i=1}^n a_i g_i, \forall f \in V$.

A point must be emphasized: in first introductions to vector spaces, we typically think of vectors as arrows in the Euclidean \mathbb{R}^n n -dimensional space. In our contexts, we will typically be working in function spaces, where each functions are analogous to a point. Though the geometric interpretation of \mathbb{R}^n will mostly be lost in our spaces, many of the definitions from Euclidean geometry will be generalized to suit our purposes.

Definition A.0.4. Linear Subspace

A space M is a linear subspace of a vector space V if M is a subset of V which is closed in the same sense as V . If M is the trivial subspace containing only the zero element, then we will write $M = 0$.

Definition A.0.5. Linear Span

The linear span of a non-empty set S is the set of all finite linear combinations of points in S , and we will denote this by $Span(S)$. $Span(S)$ is always a linear space.

Definition A.0.6. Convex Sets, Convex Hull

A subset S of a vector space V is said to be convex if and only if for every $f, g \in S$, $\alpha f + (1 - \alpha)g$ is in S for any $\alpha \in [0, 1]$. The convex hull, $co(S)$ of S in V is the smallest convex subset of V containing S .

Definition A.0.7. Metric, Metric Space

Let X be a set. A metric $d(\cdot, \cdot)$ on X is non-negative function such that for all $f, g, h \in V$,

- (1) $d(f, g) = 0$ if and only if $f = g$,
- (2) $d(f, g) = d(g, f)$,
- (3) $d(f, g) \leq d(f, h) + d(h, g)$.

If X has an associated metric, X is called a metric space.

Definition A.0.8. Norm, Normed Linear Space

Let V be a vector space. Let $\|f\|$ be a non-negative number associated with each $f \in V$ such that if $f, g \in V$, then

- (1) $\|f\| = 0 \iff f = 0$,
- (2) $\|af\| = |a|\|f\|$,
- (3) $\|f + g\| \leq \|f\| + \|g\|$.

Then $\|\cdot\|$ is referred to as a norm. If V is a vector space with an associated norm, then V is called a normed vector (or linear) space.

Definition A.0.9. Open, Closed Balls about f

Let $f \in V$ and a real number $0 < r < \infty$ be given. Then the set of points

$$S(f, r) := \{g : \|f - g\| < r\}$$

$$\bar{S}(f, r) := \{g : \|f - g\| \leq r\},$$

are called the open and closed balls about f , respectively.

Definition A.0.10. Bounded Subsets

A subset S of a vector space V is said to be bounded if and only if it is contained in some ball of finite radius. If S is bounded, then the diameter of the smallest closed ball containing S is called the diameter of S . The distance of a set S to a point f , denoted $dist(f, S)$, is the number $\inf_{g \in S} \|f - g\|$.

Definition A.0.11. Closure of a Set, Closed Sets

Let S be a subset of V . Define a new set $\bar{S} \subset V$, called the closure of S , by $\bar{S} = \{f : \exists \{f_n\} \in S \mid f_n \rightarrow f\}$. If $S = \bar{S}$, then S is said to be closed.

Definition A.0.12. A set S is said to be open if either its complement is closed, or if for each point f inside S , there is an open ball about f completely contained in S .

Definition A.0.13. Two numbers p, q with $1 \leq p, q \leq \infty$ are called conjugate indices if $\frac{1}{p} + \frac{1}{q} = 1$.

Definition A.0.14. Let Ω be a subset of \mathbb{R}^n , and suppose that f is a complex valued function defined on Ω . Then f is said to be continuous at the point $x_0 \in \mathbb{R}^n$ if and only if one of the following hold:

- (i). For every $\epsilon > 0$, there is a $\delta > 0$ such that if $x \in \Omega$, $|x - x_0| < \delta \implies |f(x) - f(x_0)| < \epsilon$.
- (ii). For each sequence $\{x_n\}$ in Ω with limit x_0 , $\lim_{n \rightarrow \infty} f(x_n) = f(x_0)$.

A function is said to be continuous on Ω if and only if it is continuous at every point in Ω .

Definition A.0.15. A function is said to be uniformly continuous on Ω if and only if for every $\epsilon > 0$, there is a $\delta > 0$ such that if $x, x_0 \in \Omega$ and $|x - x_0| < \delta$, then

$|f(x) - f(x_0)| < \epsilon$. Note this is a stronger concept than continuity, since the δ must work for every x_0 under consideration.

Definition A.0.16. Suppose $S_1 \subset S_2 \subset \mathcal{B}$. Then S_1 is said to be dense in S_2 if and only if the closure of S_1 in S_2 is S_2 itself.

Theorem A.0.1. Suppose that Ω is a closed, bounded set in \mathbb{R}^n . The set of polynomials in n variables is dense in $\mathcal{C}(\Omega)$ is the sup norm.

Lemma A.0.1. Let $[a, b]$ be a finite interval. The set of continuous piecewise linear functions is dense in $\mathcal{C}([a, b])$ is the sup norm.

Definition A.0.17. The two norms $\|\cdot\|_a$ and $\|\cdot\|_b$ on a vector space \mathcal{V} are equivalent if and only if there exist strictly positive real numbers c_1, c_2 such that

$$c_1 \|f\|_a \leq \|f\|_b \leq c_2 \|f\|_a$$

for all $f \in \mathcal{V}$.

Lemma A.0.2. If a sequence in a normed vector space is convergent, then it is convergent in any equivalent norm. If \mathcal{B} is a Banach space, it is a Banach space in any equivalent norm.

Definition A.0.18. A Banach space is said to be separable if and only if it contains a countable dense set, that is if and only if there is a set $S = \{f_n\}_{n=1}^{\infty}$ in \mathcal{B} such that for every $\epsilon > 0$ and $f \in \mathcal{B}$ there is an $f_n \in S$ with $\|f - f_n\| < \epsilon$.

Lemma A.0.3. If Ω is a closed, bounded subset of \mathbb{R}^n , $\mathcal{C}(\Omega)$ with the sup norm is separable. Furthermore, ℓ_p is separable unless $p = \infty$.

Definition A.0.19. Let \mathcal{V} be a vector space. An inner product is a complex valued function (\cdot, \cdot) on $\mathcal{V} \times \mathcal{V}$ such that for all $f, g, h \in \mathcal{V}$ and $\alpha \in \mathbb{C}$, the following hold:

- (i). $(f, f) \geq 0$, and $(f, f) = 0$ if and only if $f = 0$;
- (ii). $(f, g + h) = (f, g) + (f, h)$;
- (iii). $(f, g) = \overline{(g, f)}$, where $\overline{(\cdot, \cdot)}$ denotes the complex conjugate;
- (iv). $(\alpha f, g) = \alpha(f, g)$.

A vector space with an inner product is called an inner-product space or pre-Hilbert space.

Theorem A.0.2. For any elements f, g of a pre-Hilbert space, we have that

$$|(f, g)| \leq \|f\| \|g\|.$$

Definition A.0.20. A pre-Hilbert space which is complete with respect to its norm $\|f\| = (f, f)^{\frac{1}{2}}$ is called a Hilbert space.

Theorem A.0.3. Let \mathcal{M} be a closed subspace of the Hilbert space \mathcal{H} , then for any $f \in \mathcal{H}$ there is a unique element of \mathcal{M} closest to f .

Theorem A.0.4. A separable Hilbert space has an orthonormal basis.

Definition A.0.21. Let \mathcal{V} and \mathcal{W} be vector spaces. Then A will be an operator from V into W , denoted $A : \mathcal{V} \rightarrow \mathcal{W}$ when it takes objects in \mathcal{V} to objects in \mathcal{W} . The common objects of study will be functions. Definitions of domain, range, pre-image, injective, surjection, and bijection are identical to the definition for functions.

Definition A.0.22. Let \mathcal{V} be a complex (or real) vector space, and suppose that $\mathcal{W} \subseteq \mathbb{C}$. Then an operator from \mathcal{V} into \mathcal{W} is called a functional.

Definition A.0.23. Let \mathcal{V} and \mathcal{W} be normed vector spaces, and suppose that A is an operator from \mathcal{V} into \mathcal{W} . A is said to be continuous at a point $f_0 \in \text{Domain}(A) = D(A)$ if and only if one of the following equivalent conditions hold:

(i). For every $\epsilon > 0$ there is a $\delta > 0$ such that $\|Af - Af_0\| < \epsilon$ if $f \in D(A)$ and

$$\|f - f_0\| < \delta.$$

(ii). For every sequence $\{f_n\}$ in $D(A)$ with limit f_0 , the $\lim Af_n = Af_0$.

The operator A is said to be continuous if and only if it is continuous at every point in $D(A)$.

Lemma A.0.4. The operator A is continuous if and only if the pre-image of every open set in \mathcal{W} is open in $D(A)$.

Definition A.0.24. Let \mathcal{V} and \mathcal{W} be vector spaces, and let $D(A)$ be a linear subspace of \mathcal{V} . An operator L from \mathcal{V} into \mathcal{W} is said to be linear if and only if $L(\alpha f + \beta g) = \alpha Lf + \beta Lg$ for all $\alpha, \beta \in \mathbb{C}$ and all $f, g \in D(L)$.

Given an operator equation $Lf = g$, it seems as if using matrix methods to solve the equation might help, particularly finding an inverse operator L^{-1} such that $f = L^{-1}g$. In the special case when $R(L)$, the range of L , is equal to \mathcal{W} , then we may have solution for all $g \in \mathcal{W}$. Much in the cases of functions or matrices, the following options are possible:

(i). L is not injective. In this case there is no unique way to represent L^{-1} , and $Lf = g$ has more than one solution when $g \in R(L)$.

(ii). L is injective but not surjective. In this case L^{-1} is a linear operator with domain $R(L)$. The equation $Lf = g$ has one solution for $g \in R(L)$, and no solution otherwise.

(iii). L is bijective. Then L^{-1} is a linear operator on \mathcal{W} and $Lf = g$ has a unique solution for each $g \in \mathcal{W}$.

Lemma A.0.5. Let \mathcal{B} and \mathcal{C} denote Banach spaces. Suppose L is a linear operator from \mathcal{B} to \mathcal{C} . Then if L is continuous at some point $f \in D(L)$, it is continuous on $D(L)$.

Definition A.0.25. Suppose L is a linear operator from \mathcal{B} to \mathcal{C} . L is said to be bounded on $D(L)$ if and only if there is a finite number M such that $\|Lf\| \leq M\|f\|$ for all $f \in D(L)$. If $D(L) = \mathcal{B}$, then we simply say L is bounded. If L is not bounded, it is unbounded.

Theorem A.0.5. Suppose L is a linear operator from \mathcal{B} to \mathcal{C} . Then L is bounded on $D(L)$ if and only if L is continuous.

Theorem A.0.6. Let \mathcal{B} and \mathcal{C} be Banach spaces, and suppose that L is a linear operator from \mathcal{B} into \mathcal{C} with a domain dense in \mathcal{B} . Then if L is continuous on $D(L)$, it has a unique continuous extension \tilde{L} to \mathcal{B} itself and this extension has the same norm as L .

Definition A.0.26. Let \mathcal{B} and \mathcal{C} be Banach spaces, perhaps with different norms. Then a linear operator $L : \mathcal{B} \rightarrow \mathcal{C}$ is referred to as an embedding of \mathcal{B} into \mathcal{C} if and only if $Lf = f$ for all $f \in \mathcal{B}$.

Definition A.0.27. Suppose $L : \mathcal{B} \rightarrow \mathcal{C}$ is an operator such that $\|Lf\| = \|f\|$ for all $f \in \mathcal{B}$. Then L is said to be an isometry between the two spaces.

Definition A.0.28. Suppose \mathcal{V} and \mathcal{W} are two vector spaces. An operator $L : \mathcal{V} \rightarrow \mathcal{W}$ is called an isomorphism if and only if L is a linear bijection.

Definition A.0.29. Let \mathcal{V} and \mathcal{W} be vector spaces, and let L be both an isometry and an isomorphism. Then L is called an isometric isomorphism and the spaces \mathcal{V} and \mathcal{W} are called isometrically isomorphic if and only if there exists an isometric

isomorphism between them. Note that this implies that two Banach spaces that are isometrically isomorphic have the same algebraic and analytic properties. As far as Banach spaces are concerned, they are almost the same object.

Theorem A.0.7. Assume that \mathcal{B} and \mathcal{C} are Banach spaces, and that $L : \mathcal{B} \rightarrow \mathcal{C}$ is a bounded linear operator which is surjective. Then L maps open sets to open sets.

Theorem A.0.8. Let \mathcal{B} and \mathcal{C} be Banach spaces, and suppose that $L : \mathcal{B} \rightarrow \mathcal{C}$ is a bounded linear operator. If L is bijective, then it has a bounded inverse.

For solving the equation $Lf = g$, we may attempt to solve a sequence of equations, $L_n f_n = g$, where L_n are operators that approximate L somehow, and f_n are "close" to the solution f . We hope that L_n^{-1} is a reasonable approximation on L^{-1} . However, for this to happen we need a certain framework under which the operators converge. To do this, we create a Banach by choosing our vectors to be bounded linear operators. Specifically, we choose \mathcal{W}, \mathcal{V} to be vector spaces, with linear operators $L_1, L_2 : \mathcal{W} \rightarrow \mathcal{V}$. Then if α is a scalar, we make the following definitions:

$$(L_1 + L_2)f = L_1f + L_2f,$$

$$(\alpha L_1)f = \alpha L_1f.$$

By doing so, the set of linear operators from \mathcal{W} to \mathcal{V} form a vector space, denoted $\mathcal{L}(\mathcal{V}, \mathcal{W})$.

Definition A.0.30. Let L be a bounded linear operator from \mathcal{B} to \mathcal{C} . Then the infimum of all constants m such that $\|Lf\| \leq m\|f\|$ is called the operator norm of L . Equivalently, we could define the operator norm as

$$\|L\| = \sup_{f \in D(L), f \neq 0} \frac{\|Lf\|}{\|f\|}.$$

If $\phi : \mathbb{R} \rightarrow \mathbb{R}$ is a linear operator, then from the above we get that $|\phi(x)| = |\lambda x| = |\lambda||x|$, where $\phi(x) = \lambda x$ can then be studied. In this context, $|\lambda|$ is thought of the measure of the gradient of ϕ , and the norm of the operator L is thought of as the maximum gradient of the operator.

Definition A.0.31. Let \mathcal{B} and \mathcal{C} be Banach spaces. The normed vector space of bounded linear operators from \mathcal{B} to \mathcal{C} with the operator norm is denoted by $\mathcal{L}(\mathcal{B}, \mathcal{C})$, or $\mathcal{L}(\mathcal{B})$ when $\mathcal{B} = \mathcal{C}$.

The notation $L^{-1} \in \mathcal{L}(\mathcal{B}, \mathcal{C})$ will mean that L has a bounded inverse.

Theorem A.0.9. Let \mathcal{B} and \mathcal{C} be Banach spaces. Then $\mathcal{L}(\mathcal{B}, \mathcal{C})$ will be a Banach space.

Proof. Since $\mathcal{L}(\mathcal{B}, \mathcal{C})$ is obviously a normed space, we only prove completeness. Let $\{L_n\}$ be a Cauchy sequence of operators from $\mathcal{L}(\mathcal{B}, \mathcal{C})$. We prove that $\{L_n\}$ has a limit which is also a bounded linear operator.

We construct the limit operator L . For all $f \in \mathcal{B}$, $\|L_n f - L_m f\| \leq \|L_n - L_m\| \|f\|$, thus $\{L_n f\}$ is Cauchy in \mathcal{C} . Set $Lf = g = \lim L_n f$, which exists since \mathcal{C} is complete. By linearity of limiting processes, we see that L is a linear operator.

To see that L is bounded, note that $\|\|L_n\| - \|L_m\|\| \leq \|L_n - L_m\|$. Thus, the sequence $\{\|L_n\|\}$ is a Cauchy sequence of real numbers. Thus, the limit of this sequence exists as a real number. Call it m . Thus, we have that

$$\|Lf\| = \lim \|L_n f\| \leq \lim \|L_n\| \|f\| = m \|f\|.$$

Finally, we check that $\lim \|L_n - L\| = 0$. Since $\{L_n\}$ is Cauchy, for any $\epsilon > 0$ there exists an $n_0 \in \mathbb{N}$ such that for all $n, m \geq n_0$, we have that $\|L_n f - L_m f\| \leq \epsilon$. Thus, for any $f \in \mathcal{B}$ and any $m, n \geq n_0$, we have that $\|L_n f - L_m f\| \leq \epsilon \|f\|$, whence

$$\|L_n f - L\| = \lim_{m \rightarrow \infty} \|L_n f - L_m f\| \leq \epsilon \|f\|.$$

Therefore, $\lim \|L_n - L\| = 0$. □

Theorem A.0.10. The Principle of Uniform Boundedness

Assume \mathcal{B} and \mathcal{C} are Banach spaces. For some α in a set S , let $\{L_\alpha\}$ be a family of operators in $\mathcal{L}(\mathcal{B}, \mathcal{C})$, and suppose that given any $f \in \mathcal{B}$, the set $\{L_\alpha f\}$ of vectors is bounded. Then the family $\{L_\alpha\}$ of vectors is also bounded in $\mathcal{L}(\mathcal{B}, \mathcal{C})$; that is there is an $m < \infty$ such that $\|L_\alpha\| \leq m$ for all $\alpha \in S$.

Definition A.0.32. Let $\{L_n\}$ be a sequence of bounded linear operators mapping \mathcal{B} to \mathcal{C} . We write $L_n \rightarrow L$ or $\lim L_n = L$ if and only if the sequence converges in the operator norm (converges in $\mathcal{L}(\mathcal{B}, \mathcal{C})$). In this case, the sequence is said to converge uniformly. Equivalently, we could define the uniform convergence to the existence of a sequence $\{\epsilon_n\}$ of real numbers converging to zero such that $\|(L_n - L)f\| \leq \epsilon_n \|f\|$ for all $f \in \mathcal{B}$. In this regard, the definition of uniform convergence mimics that of the uniform convergence of real function on \mathbb{R} , since the ϵ_n is independent of the functions f .

Example A.0.1. Consider the initial value problem for a system of n simultaneous linear differential equations:

$$u'_i(t) = \sum_{j=1}^n a_{ij} u_j(t) \quad (t > 0),$$

$$u_i(0) = u_{0i}$$

If u is a function $\mathbb{R} \rightarrow \mathbb{C}^n$, this system may be written as

$$u'(t) = Lu(t) \quad t > 0,$$

$$u(0) = u_0,$$

where $u_0 \in \mathbb{C}^n$ and $L : \mathbb{R} \rightarrow \mathbb{C}^n$ is a linear operator. If L is bounded, then we may obtain a solution in a similar manner to the one used in one dimension by using the uniform convergence of the operator.

Definition A.0.33. Let \mathcal{B} be a Banach space and take $\Omega = [0, \infty)$. The Banach space valued function $u : \Omega \rightarrow \mathcal{B}$ is said to be differentiable at $t \in \Omega$ if and only if there is a vector $u'(t)$ in \mathcal{B} such that

$$\lim_{\substack{h \rightarrow 0 \\ t+h \in \Omega}} \left\| \frac{u(t+h) - u(t)}{h} - u'(t) \right\| = 0.$$

If such a vector exists, it is called the derivative of u at t . The function u is said to be differentiable on Ω if and only if it is differentiable at every $t \in \Omega$.

Now, suppose $L \in \mathcal{L}(\mathcal{B})$, and for $t \geq 0$ consider the series

$$\sum_{j=0}^{\infty} (tL)^j / j!.$$

Since

$$\sum_{j=0}^{\infty} \| (tL)^j \| / j! \leq \sum_{j=0}^{\infty} t^j \| L \|^j / j! < \infty,$$

the series is absolutely convergent in $\mathcal{L}(\mathcal{B})$, and therefore the sum is an operator in $\mathcal{L}(\mathcal{B})$. We denote the operator by e^{tL} . We can prove, using an argument similar to the case when L is a complex number, that this operator is differentiable and that $e^{(t_1+t_2)L} = e^{t_1L}e^{t_2L}$. The latter property is called the semigroup property.

Lemma A.0.6. Let \mathcal{B} and \mathcal{C} be Banach spaces, and assume that $\{L_n\}$ is a bounded sequence in $\mathcal{L}(\mathcal{B}, \mathcal{C})$. Suppose that $\{L_n f\}$ converges for all f in a dense subset S of \mathcal{B} . Then there is a unique $L \in \mathcal{L}(\mathcal{B}, \mathcal{C})$ such that $\lim L_n f = Lf$ for all $f \in \mathcal{B}$.

Corollary A.0.1. Assume that $\{L_n\}$ is a sequence in $\mathcal{L}(\mathcal{B}, \mathcal{C})$ such that $\{L_n f\}$ is convergent for all $f \in \mathcal{B}$. Then there is a unique $L \in \mathcal{L}(\mathcal{B}, \mathcal{C})$ such that $\lim L_n f = Lf$ for all $f \in \mathcal{B}$.

Definition A.0.34. A sequence $\{L_n\}$ of operators in $\mathcal{L}(\mathcal{B}, \mathcal{C})$ is said to converge strongly if and only if the sequence $\{L_n f\}$ converges for each $f \in \mathcal{B}$. The operator L (which exists by the previous corollary) such that $\lim L_n f = Lf$ is called the strong limit of $\{L_n\}$, and we write $L_n \xrightarrow{s} L$. If $L_n \xrightarrow{s} L$, for every f there is a sequence $\{\epsilon_n\}$ of real numbers tending to zero such that

$$\|(L_n - L)f\| \leq \epsilon_n \|f\|.$$

Here, the epsilon sequence may now depend on f , so this concept is a generalization of the usual convergence on the real line. It follows from this, of course, that uniform convergence implies strong convergence.

Let X be a set (not necessarily with an algebraic structure), and let $(Y_i)_{i \in I}$ be a collection of topological spaces on X . Let $(\phi_i)_{i \in I}$ be a set of maps $\phi_i : X \rightarrow Y_i$. We would like to make ϕ_i continuous for each i . One way to do this would be to endow X with the discrete topology, then the pre-image of anything in Y_i would be open since it would be the union of open sets. However, this would give a rather strong restriction on the topology of X , so instead we wish to find the “weakest” topology on X for which ϕ_i is always continuous.

Since $\forall \omega_i \subset Y_i$ open, $\phi_i^{-1}(\omega_i)$ would necessarily be open (by restricting ϕ_i to be continuous.) We may then run through all of the sets open in Y_i and obtain a family of sets open in X . This would not necessarily be a topology. We use this in the construction of a topology \mathcal{F} on X that would satisfy our needs.

To do so, let X be a set, and let $(U_\lambda)_{\lambda \in \Lambda}$ be a collection of subsets in X . From $(U_\lambda)_{\lambda \in \Lambda}$, let $V \in \mathcal{F}$ if $V = \cap_{\lambda \in \Gamma} U_\lambda, \Gamma \subseteq \Lambda$ finite. Let $(V) \equiv \Phi$. Then, take all the sets $W = \cup V$ for $V \in \Phi$ and let them be in \mathcal{F} . As such, \mathcal{F} is a collection of subsets of X such that \mathcal{F} is the “most economic” topology with respect to (ϕ_i) , *i.e.*, \mathcal{F} is closed with respect to arbitrary unions, finite intersections, complementation and contains X .

Fact For every $x \in X$, we obtain a basis of neighborhoods of x for the topology \mathcal{F} which is the weakest topology with respect to (ϕ_i) be the above construction.

Proposition A.0.1. Let (x_n) be a sequence in X . Then $x_n \rightarrow x \in X \iff \phi_i(x_n) \rightarrow \phi_i(x), \forall i \in I$.

Proposition A.0.2. Let Z be a topological space and $\psi : Z \rightarrow X$. Then ψ is continuous $\iff \phi_i \circ \psi$ is a continuous mapping $Z \rightarrow Y_i, \forall i$.

Now, let E be a Banach space and let $f \in E^*$ =space of all continuous linear functionals on E with norm

$$\|f\|_{E^*} = \sup_{\substack{\|x\| < 1 \\ x \in E}} |f(x)|.$$

Denote $\psi_f : E \rightarrow \mathbb{R}$ as the linear functional $\phi_f = \langle f, x \rangle$. As f runs through E^* we obtain a collection $(\phi_f)_{f \in E^*}$ of maps from E to \mathbb{R} . We ignore the usual topology on E (associated with $\|\cdot\|_E$) and define the new topology:

Definition A.0.35. The weak topology $\sigma(E, E^*)$

The weak topology, denoted $\sigma(E, E^*)$ is the coarsest topology associated with $(\phi_f)_{f \in E^*}$ in the same sense as above with $X = E, Y_i = \mathbb{R} \forall i, I = E^*$.

We note that every map ϕ_f is continuous in the usual topology. Thus, the weak topology is weaker than the usual topology generated by the norm of the space.

Definition A.0.36. Bidual space E^{**}

Let E be a normed vector space, and let E^* be the dual space with the norm

$$\|f\|_{E^*} = \sup_{\substack{x \in E \\ \|x\| \leq 1}} |\langle f, x \rangle|.$$

Then the bidual space E^{**} is the dual of E^* with the norm

$$\|\xi\|_{E^{**}} = \sup_{\substack{f \in E^* \\ \|f\| \leq 1}} |\langle \xi, f \rangle|, \quad \xi \in E^{**}.$$

Proposition A.0.3. The weak topology is Hausdorff.

Proposition A.0.4. Let $x_0 \in E$. Given $\varepsilon > 0$ and $\{f_1, \dots, f_k\} \in E^*$, consider

$$V = V(f_1, \dots, f_k; \varepsilon) = \{x \in E \mid \langle f_i, x - x_0 \rangle < \varepsilon\}.$$

Then V is a neighborhood of x_0 for $\sigma(E, E^*)$, and we obtain a basis of neighborhoods of x_0 for $\sigma(E, E^*)$ by varying ε, k , and the f_i 's in E^* .

Proposition A.0.5. Let $(x_n) \in E$ Then

Remark. When E is infinite dimensional, there exist open (closed) sets in the strong topology that are not open (closed) in the weak topology.

Example A.0.2. (1) The unit sphere $S = \{x \in E : \|x\| = 1\}$ is never closed in $\sigma(E, E^*)$.

(2) The unit ball $U = \{x \in E : \|x\| < 1\}$ is never open in the weak topology on E .

Remark. In infinite dimensional spaces, the weak topology is never metrizable, i.e., no metric on E induces $\sigma(E, E^*)$. However, if E^* is separable, one can define a norm on E that induces the weak topology on the bounded sets of E . Furthermore, if E^* is separable or if E is reflexive (as is the case with L^p spaces for $1 < p < \infty$), there exist sequences that converge weakly but not strongly.

Corollary A.0.2. If $x_n \rightharpoonup x, \exists (y_n)$ made of convex combinations of x_n 's such that $y_n \rightarrow x$.

Definition A.0.37. Lower semi-continuity

A function $\varphi : E \rightarrow (-\infty, \infty]$ is said to be lower semi-continuous (l.s.c.) if $\forall \lambda \in \mathbb{R}, \{x \in E : \varphi(x) \leq \lambda\}$ is closed.

Corollary A.0.3. Let $\varphi : E \rightarrow (-\infty, \infty]$ be convex and l.s.c. in the strong topology. Then φ is l.s.c. in the weak topology.

Remark. In general, nonlinear mappings that are continuous from E strong to F strong are not continuous E weak to F weak.

Definition A.0.38. The weak* topology $\sigma(E^*, E)$ is the weakest topology on E^* associated to $(\phi_x)_{x \in E}$, in the same sense as before with $X = E^*, Y_i = \mathbb{R} \quad \forall i, I = E$.

Note: Since $E \subseteq E^{**}$, it is clear that $\sigma(E^*, E)$ is coarser than $\sigma(E^*, E^{**})$.

Now, with all these definitions laid out, why would we possibly care about all of these weak topologies? Well, for one thing a coarser topology has more compact sets than a finer topology. Since compact sets have desirable properties (such as the existence of minimizers), the study of the weak* topology is justified.

Theorem A.0.11. The weak* topology is Hausdorff.

Proposition A.0.6. Let $f_0 \in E^*$. Given $\varepsilon > 0$ and $\{x_1, \dots, x_n\} \subset E$, consider

$$V = V(x_1, \dots, x_n; \varepsilon) = \{f \in E^*; |f - f_0, x_i| < \varepsilon \quad \forall i = 1, \dots, n\}.$$

Then V is a neighborhood of f_0 for the weak topology $\sigma(E, E^*)$. Moreover, we obtain a basis of neighborhoods of f_0 by varying ε, n , and the x_i 's in E .

If $(f_n) \in E^*$ converges to f in $\sigma(E^*, E)$, we write $f_n \xrightarrow{*} f$.

Proposition A.0.7. Let (f_n) be a sequence in E^* . Then

- (1) $f_n \xrightarrow{*} f$ in $\sigma(E^*, E)$ if and only if $\langle f_n, x \rangle \rightarrow \langle f, x \rangle, \quad \forall x \in E$.
- (2) $f_n \rightarrow f$ strongly $\implies f_n \rightarrow f$ in $\sigma(E^*, E^{**})$ implies $f_n \rightarrow f$ in $\sigma(E^*, E)$.
- (3) $f_n \xrightarrow{*} f$ in $\sigma(E^*, E)$ implies $(\|f_n\|)$ is bounded and $\|f\| \leq \liminf (\|f_n\|)$.
- (4) If $f_n \xrightarrow{*} f$ in $\sigma(E^*, E), x_n \rightarrow x$ in E implies $\langle f_n, x_n \rangle \rightarrow \langle f, x \rangle$.

Remark. Assuming $f_n \xrightarrow{*} f$ in $\sigma(E^*, E)$ or $f_n \rightharpoonup f$ in $\sigma(E^*, E^{**})$ and $x_n \rightharpoonup x$ in $\sigma(E, E^*)$ does NOT give us that $\langle f_n, x_n \rangle \rightarrow \langle f, x \rangle$. In other words, we need the strong convergence.

Theorem A.0.12. The closed unit ball

$$B_{E^*} = \{f \in E^* : \|f\| \leq 1\}$$

is compact in the weak* topology.

Definition A.0.39. The canonical injection $J : E \rightarrow E^{**}$ is defined as follows:

Given $x \in E$, the map $f \mapsto \langle f, x \rangle$ is a continuous linear functional on E^* , thus is an element of E^{**} , denoted J_x . Furthermore, we have that $\langle J_x, f \rangle_{E^{**}, E^*} = \langle f, x \rangle_{E^*, E} \forall f \in E^*, \forall x \in E$. From this it is clear that J_x is a linear isometry between E and the bidual space. As the spaces are therefore isometric, we commonly identify E with the bidual space, *i.e.*, $E = E^{**}$.

Note: L^p spaces with $1 < p < \infty$ and all Hilbert spaces are all reflexive. We note further that L^1, L^∞ , and $\mathcal{C}(K)$ (K compact), are not reflexive.

Definition A.0.40. Let E be a Banach space and

$$J : E \rightarrow E^{**}$$

be the canonical injection from E into E^{**} . The space E is reflexive if J is surjective, that is, if $E = E^{**}$.

Theorem A.0.13. Let E be a Banach space. Then E is reflexive if and only if

$$B_E = \{x \in E : \|x\| \leq 1\}$$

is compact in $\sigma(E, E^*)$.

Theorem A.0.14. Assume E is a reflexive Banach space and let (x_n) be a bounded sequence in E . Then there is a subsequence $(x_{n_k}) \ni (x_{n_k}) \rightharpoonup x \in \sigma(E, E^*)$.

Theorem A.0.15. Assume E is reflexive and $M \subset E$ is a closed, linear subspace. Then M is reflexive.

Corollary A.0.4. A Banach space is reflexive if and only if its dual space is.

Corollary A.0.5. Let E be a reflexive Banach space. Let $K \subseteq E$ be a bounded, closed, convex subset of E . Then K is compact in $\sigma(E, E^*)$.

Corollary A.0.6. Let E be a reflexive Banach space and let $A \subseteq E$ be a nonempty, closed, convex subset of E . Let $\varphi : A \rightarrow (-\infty, \infty]$ be a convex l.s.c. function such that $\varphi \not\equiv \infty$ and $\lim_{\substack{x \in A \\ \|x\| \rightarrow \infty}} \varphi(x) = \infty$. Then φ achieves its minimum on A , i.e., $\exists x_0 \in A \ni \varphi(x_0) = \min_x \varphi$.

Theorem A.0.16. Let E, F be reflexive Banach spaces. Let $A : D(A) \subseteq E \rightarrow F$ be an unbounded linear operator that is densely defined and closed. Then $D(A^*)$ is dense in F^* . Thus, A^{**} is well defined ($A^{**} : D(A^{**}) \subseteq E^{**} \rightarrow F^{**}$) and it may also be viewed as an unbounded operator from E to F . Then we have $A^{**} = A$.

Definition A.0.41. A metric space E is called separable if there exists $D \subset E$ that is countable and dense.

Corollary A.0.7. Let E be a Banach space. Then E is reflexive and separable $\iff E^*$ is reflexive and separable.

Definition A.0.42. A Banach space is uniformly convex if $\forall \varepsilon > 0 \exists \delta > 0$

$$[x, y \in E, \|x\|, \|y\| < 1 \text{ and } \|x - y\| > \varepsilon] \text{ implies } \left[\left\| \frac{x + y}{2} \right\| < 1 - \delta \right].$$

We note the following facts: L^p spaces are uniformly convex for $1 < p < \infty$, Hilbert spaces are always uniformly convex.

Theorem A.0.17. The Riesz Representation Theorem

Let $1 < p < \infty$ and $\phi \in (L^p)^*$. Then $\exists! u \in L^{p'}$ such that

$$\langle \phi, f \rangle = \int u f \quad \forall f \in L^p, \|u\|_{L^{p'}} = \|\phi\|_{(L^p)^*}.$$

In other words, every continuous linear functional on L^p can be represented as a “concrete” integral from the space itself. Thus, we may identify $(L^p)^* = L^{p'}$.

Theorem A.0.18. $C_c(\mathbb{R}^n)$ is dense in $L^p(\mathbb{R}^n) \forall 1 \leq p < \infty$.

Definition A.0.43. A measure space Ω is separable if there exists a countable family (E_n) in $\mathcal{M} = \{\text{measurable sets}\}$ such that the σ -algebra generated by $(E_n) = \mathcal{M}$.

Example A.0.3. \mathbb{R}^n is separable and $L^p(\Omega)$ is separable when Ω is for $1 \leq p < \infty$.

Theorem A.0.19. $\Omega \subseteq \mathbb{R}^n$ implies $C_0(\Omega)$ is dense in $L^p(\Omega)$ for $1 \leq p < \infty$.

Theorem A.0.20. Ascoli-Arzelà

Let K be a compact metric space and let \mathcal{H} be a bounded subset of $\mathcal{C}(K)$. If \mathcal{H} is uniformly continuous, *i.e.*,

$$\forall \varepsilon > 0 \exists \delta > 0 \forall f \in \mathcal{H} \ni d(x, y) < \delta \implies |f(x_1) - f(x_2)| < \varepsilon$$

then $\overline{\mathcal{H}} \subseteq \mathcal{C}(K)$ is compact.

Remark. We note that the translation of a function $f(x+h)$ will be denoted $\tau_h f(x)$.

Theorem A.0.21. Let \mathcal{F} be a bounded set in $L^p(\mathbb{R}^n)$ with $1 \leq p < \infty$. Assume that

$$\lim_{|h| \rightarrow 0} \|\tau_h f - f\|_{L^p} = 0$$

uniformly in $f \in \mathcal{F}$. Then $\overline{\mathcal{F}}|_{\Omega} \subset L^p(\Omega)$ is compact for all measurable $\Omega \subset \mathbb{R}^n$ with $\mu(\Omega) < \infty$.

Definition A.0.44. Let Ω be a measure space and E be a Banach space. The space $L^p(\Omega; E)$ consists of all functions F defined on Ω with values in E that are measurable in some appropriate sense and that

$$\int_{\Omega} \|f(x)\|^p d\mu < \infty.$$

Then most properties hold on $L^p(\Omega; E)$ with some restrictions on E .

Example A.0.4. If E is reflexive and $1 < p < \infty$, then $L^p(\Omega; E)$ is reflexive and its dual space is $L^{p'}(\Omega; E^*)$.

Theorem A.0.22. Every Hilbert space is uniformly convex, therefore it is reflexive.

Theorem A.0.23. Let $K \subseteq \mathcal{H}$ be a nonempty, closed convex set. Then for all $f \in \mathcal{H} \exists! u \in K \ni$

$$\|f - u\| = \min_{v \in K} \|f - v\| = \text{dist}(f, K).$$

Given a Hilbert space \mathcal{H} , it is easy to write down a continuous linear functional on \mathcal{H} , since $\forall f \in \mathcal{H}, u \mapsto (f, u)$ is a continuous linear functional on \mathcal{H} . The odd thing is that *all* continuous linear functionals are obtained that way. This result is known as the Riesz-Fréchet Representation Theorem, stated below.

Theorem A.0.24. Riesz-Fréchet Representation Theorem

$\forall \phi \in \mathcal{H}^*; \exists! f \in \mathcal{H} \ni \langle \phi, u \rangle = (f, u) \forall u \in \mathcal{H}$ and $\|\phi\| = \|f\|_{\mathcal{H}^*}$.

Definition A.0.45. A bilinear form $a : \mathcal{H} \times \mathcal{H} \rightarrow \mathbb{R}$ is said to be

- (1) continuous if $\exists C \in \mathbb{R}$ s.t. $|a(u, v)| \leq C\|u\|\|v\| \quad \forall u, v \in \mathcal{H}$;

(2) coercive if $a(v, v) \geq \alpha|v|^2 \quad \forall v \in \mathcal{H}$,

where $|u| \equiv (u, u)^{\frac{1}{2}}$.

Theorem A.0.25. Stampacchia's Theorem

Assume that $a(u, v)$ is a continuous and coercive bilinear form on \mathcal{H} . Let $K \subseteq \mathcal{H}$ be a nonempty and closed convex subset. Then, given $\varphi \in \mathcal{H}^*$, there is a unique $u \in K$ such that

$$a(u, v - u) \geq \langle \varphi, v - u \rangle \quad \forall v \in K.$$

Moreover, if a is symmetric, then $u \in K$ and

$$\frac{1}{2}a(u, u) - \langle \varphi, u \rangle = \min_{v \in K} \left\{ \frac{1}{2}a(u, v) - \langle \varphi, v \rangle \right\}.$$

Definition A.0.46. Let f be an extended real-valued or complex-valued function. Then f is said to be integrable on X with respect to the measure μ if and only if f is measurable and $\int |f|d\mu < \infty$. When X is a subset of \mathbb{R}^n , f is called locally integrable (or locally summable) if and only if it is integrable on each $S \subset X$, S compact in \mathbb{R}^n .

Definition A.0.47. Let f be measurable, and suppose that $p \geq 1$. Set

$$\|f\|_{L^p} = \left\{ \int |f|^p d\mu \right\}^{\frac{1}{p}}$$

$$\|f\|_{L^\infty} = \text{ess sup } |f| = \inf \{k : f(x) \leq k \text{ a.e.}\}.$$

Then the space L^p is the set of measurable functions with the finite norm. Furthermore, the space L^p_{loc} is the set of functions belonging to $L^p(S)$ for each compact set in \mathbb{R}^n .

Theorem A.0.26. (Cauchy's Inequality with ϵ)

For $a, b, \epsilon > 0$,

$$ab \leq \epsilon a^2 + \frac{b^2}{(2\epsilon)^{1/2}}.$$

Theorem A.0.27. (Hölder's Inequality)

Assume $1 \leq p, q \leq \infty$ with $1/p + 1/q = 1$ (so that p, q are conjugate indices.) Then if $u \in L^p, v \in L^q$, we have

$$\int_U |uv| dx \leq \|u\|_{L^p(U)} \|v\|_{L^q(U)}$$

for $U \subset \mathbb{R}^n$.

Theorem A.0.28. (Minkowski's Inequality)

Assume $1 \leq p \leq \infty$ and let $u, v \in L^p(U)$ for $U \subset \mathbb{R}^n$. Then

$$\|u + v\|_{L^p(U)} \leq \|u\|_{L^p(U)} + \|v\|_{L^p(U)}.$$

Theorem A.0.29. If $p \geq 1$, under the norm $\|\cdot\|_p$, L^p is a Banach space. The space L^p is separable for all p finite. The space L^2 is a Hilbert space under the inner product $(f, g) = \int_U f \bar{g} d\mu$.

Theorem A.0.30. Let U be an open subset of \mathbb{R}^n , and let μ by the Lebesgue measure. Then if $1 \leq p < \infty$, the following are dense in $L^p(U)$:

(i). the set of integrable simple functions;

(ii). the set $C_0^\infty(U)$ of $C^\infty(U)$ functions with bounded support contained in the interior of U .

Theorem A.0.31. (Grönwall's Inequality, differential form)

Let $\eta(\cdot)$ be a nonnegative, absolutely continuous function on $[0, T]$, which satisfies

the almost everywhere (a.e.) inequality

$$\eta'(t) \leq \phi(t)\eta(t) + \psi(t),$$

where ϕ, ψ are nonnegative, summable functions on $[0, T]$. Then

$$\eta(t) \leq e^{\int_0^t \phi(s) ds} \left[\eta(0) + \int_0^t \psi(s) ds \right]$$

for all $0 \leq t \leq T$.

Definition A.0.48. A sequence $\{u_k\}_{k=1}^{\infty}$ in a vector space X is said to converge (strongly) to some $u \in X$, written

$$u_k \rightarrow u,$$

if

$$\lim_{k \rightarrow \infty} \|u_k - u\| = 0.$$

Definition A.0.49. We say a sequence $\{u_k\}$ in a Banach space X converges weakly to $u \in X$, written

$$u_k \rightharpoonup u$$

if

$$\langle u_k, u^* \rangle \rightarrow \langle u, u^* \rangle$$

for every bounded linear functional $u^* \in X^*$, where X^* the dual space of X .

Theorem A.0.32. Let X be a reflexive Banach space; *i.e.* $(X^*)^* = X$. Suppose the sequence $\{u_k\}_{k=1}^{\infty}$ in X is bounded. Then there exists a subsequence $\{u_{k_j}\}_{j=1}^{\infty}$ such that $u_{k_j} \rightharpoonup u$ for some $u \in X$. In other words, every bounded sequence in a reflexive Banach space contains a weakly convergent subsequence.

Remark. U, V , and W usually denote open subsets of \mathbb{R}^n . We write $V \subset\subset U$ if $V \subset \bar{V} \subset U$, \bar{V} compact, and say that V is compactly contained in U .

Definition A.0.50. If $u : U \rightarrow \mathbb{R}$ is bounded and continuous, we write

$$\|u\|_{C(\bar{U})} := \sup_{x \in U} |u(x)|.$$

The γ^{th} -Hölder seminorm of $u : U \rightarrow \mathbb{R}$ is

$$[u]_{C^{0,\gamma}(\bar{U})} := \sup_{\substack{x,y \in U \\ x \neq y}} \left\{ \frac{|u(x) - u(y)|}{|x - y|^\gamma} \right\},$$

and the γ^{th} -Hölder norm is

$$\|u\|_{C^{0,\gamma}(\bar{U})} := \|u\|_{C(\bar{U})} + [u]_{C^{0,\gamma}(\bar{U})}$$

Definition A.0.51. The Hölder space $C^{k,\gamma}(\bar{U})$ consists of all functions $u \in C^k(\bar{U})$ for which the norm

$$\|u\|_{C^{k,\gamma}(\bar{U})} := \sum_{|\alpha| \leq k} \|D^\alpha u\|_{C(\bar{U})} + \sum_{|\alpha|=k} [D^\alpha u]_{C^{0,\gamma}(\bar{U})}$$

is finite.

Theorem A.0.33. The space of functions $C^{k,\gamma}(\bar{U})$ is a Banach space.

We note that $C_0^\infty(U)$ denotes the space of infinitely differentiable functions $\phi : U \rightarrow \mathbb{R}$, with compact support in U . These can also be referred to as test functions.

Definition A.0.52. Suppose $u, v \in L^1_{\text{loc}}(U)$ (L^1 -locally summable functions) and α is a multi-index. We say that v is the α^{th} weak partial derivative of u , written

$$D^\alpha u = v,$$

provided

$$\int_U u D^\alpha \phi dx = (-1)^{|\alpha|} \int_U v \phi dx$$

for all test functions $\phi \in C_c^\infty(U)$.

Definition A.0.53. The Sobolev space

$$W^{k,p}(U)$$

consists of all locally summable functions $u : U \rightarrow \mathbb{R}$ such that for each multi-index α with $|\alpha| \leq k$, $D^\alpha u$ exists in the weak sense and belongs to $L^p(U)$. If $p = 2$, we will write $H^k(U)$. We also note the $H^0(U) = L^2(U)$.

Definition A.0.54. If $u \in W^{k,p}(U)$, we define its norm to be

$$\|u\|_{W^{k,p}(U)} := \begin{cases} \left(\sum_{|\alpha| \leq k} \int_U |D^\alpha u|^p dx \right)^{\frac{1}{p}} & (1 \leq p < \infty) \\ \sum_{|\alpha| \leq k} \text{ess sup}_U |D^\alpha u| & (p = \infty) \end{cases}$$

Definition A.0.55. Let X and Y be Banach space, $X \subset Y$. We say that X is compactly embedded in Y , written $X \subset\subset Y$ provided

- (1) $\|u\|_Y \leq C\|u\|_X$ for some constant C , and
- (2) each bounded sequence in X is compact in Y ; *i.e.*, if $\{u_k\}_{k=1}^\infty$ is a sequence in X with $\sup_k \|u_k\|_X < \infty$, then there is a subsequence $\{u_{k_j}\}_{j=1}^\infty$ that converges in Y to some limit u ($\lim_{j \rightarrow \infty} \|u_{k_j} - u\|_Y = 0$).

Definition A.0.56. (1) Let $\{u_m\}_{m=1}^\infty, u \in W^{k,p}(U)$. We say that u_m converges to u in $W^{k,p}(U)$, written

$$u_m \rightarrow u \quad \text{in } W^{k,p}(U),$$

provided

$$\lim_{m \rightarrow \infty} \|u_m - u\|_{W^{k,p}(U)} = 0.$$

(2) We write

$$u_m \rightarrow u \quad \text{in } W_{\text{loc}}^{k,p}(U)$$

to mean

$$u_m \rightarrow u \quad \text{in } W^{k,p}(V)$$

for each $U \subset\subset V$.

Definition A.0.57. We denote by $W_0^{k,p}(U)$ the closure of $C_0^\infty(U)$ in $W^{k,p}(U)$.

Theorem A.0.34. For each $k = 1, 2, \dots$ and $1 \leq p \leq \infty$, the Sobolev space $W^{k,p}(U)$ is a Banach space.

Theorem A.0.35. Assume U is bounded, and suppose that $u \in W^{k,p}(U)$ for some $1 \leq p < \infty$. Then there exist functions $u_m \in C^\infty(U) \cap W^{k,p}(U)$ such that $u_m \rightarrow u$ in $W^{k,p}(U)$.

Theorem A.0.36. Let U be a bounded, open subset of \mathbb{R}^n , and suppose that ∂U is C^1 . Assume $n < p \leq \infty$ and $u \in W^{1,p}(U)$. Then there is a $u^* = u$ a.e. such that $u^* \in C^{0,\gamma}(\bar{U})$, for $\gamma = 1 - n/p$ with estimate

$$\|u^*\|_{C^{0,\gamma}(\bar{U})} \leq C \|u\|_{W^{1,p}(U)}$$

where the constant C depends only on p, n and U .

Remark. We note that this theorem states conditions in which $u \in W^{k,p}(U)$ is continuous a.e. When applicable, we will always identify u with its continuous version.

Theorem A.0.37. Assume U is a bounded, open subset of \mathbb{R}^n and ∂U is C^1 . Suppose $1 \leq r < n$. Then $W^{1,p}(U) \subset\subset L^q(U)$ for each $1 \leq r < q$.

Remark. Since $q > p$ and $q \rightarrow \infty$ as $p \rightarrow n$, we have

$$W^{1,p}(U) \subset\subset L^p(U)$$

for all $1 \leq p \leq \infty$. We also note that $W_0^{1,p}(U) \subset\subset L^p(U)$, even if ∂U is C^1 .

Remark. Let the notation $\mathbf{f} : [0, T] \rightarrow X$ denote a mapping from $[0, T], T > 0$, to X a real Banach space.

Definition A.0.58. (1) A function $\mathbf{s} : [0, T] \rightarrow X$ is called simple if it has the form

$$\mathbf{s}(t) = \sum_{i=1}^m \chi_{E_i}(t) u_i \quad (0 \leq t \leq T),$$

where each E_i is a Lebesgue measurable subset of $[0, T]$ and $u_i \in X (i = 1, \dots, m)$.

(2) A function $\mathbf{f} : [0, T] \rightarrow X$ is strongly measurable if there exists simple functions $\mathbf{s}_k : [0, T] \rightarrow X$ such that

$$\mathbf{s}_k(t) \rightarrow \mathbf{f}(t) \quad \text{for a.e } 0 \leq t \leq T.$$

(3) A function $\mathbf{f} : [0, T] \rightarrow X$ is weakly measurable if for each $u^* \in X^*$, the mapping $t \mapsto \langle u^*, \mathbf{f}(t) \rangle$ is Lebesgue measurable.

(4) We say $\mathbf{f} : [0, T] \rightarrow X$ is almost separably valued if there exists a subset $N \subset [0, T]$, with $|N| = 0$, such that the set $\{\mathbf{f}(t) | t \in [0, T] - N\}$ is separable.

Theorem A.0.38. The mapping $\mathbf{f} : [0, T] \rightarrow X$ is strongly measurable if and only if \mathbf{f} is weakly measurable and separably valued.

Definition A.0.59. (1) If $\mathbf{s}(t) = \sum_{i=1}^m \chi_{E_i}(t)u_i$ is simple, we define

$$\int_0^T \mathbf{s}(t)dt := \sum_{i=1}^m |E_i|u_i.$$

(2) We say the strongly measurable function $\mathbf{f} : [0, T] \rightarrow X$ is summable if there exists a sequence $\{\mathbf{s}_k\}_{k=1}^\infty$ of simple functions such that

$$\int_0^T \|\mathbf{s}_k(t) - \mathbf{f}(t)\|dt \rightarrow 0 \text{ as } k \rightarrow \infty.$$

(3) If f is summable, we define

$$\int_0^T \mathbf{f}(t)dt = \lim_{k \rightarrow \infty} \int_0^T \mathbf{s}_k(t)dt.$$

Theorem A.0.39. A strongly measurable function $\mathbf{f} : [0, T] \rightarrow X$ is summable if and only if $t \mapsto \|\mathbf{f}(t)\|$ is summable. In this case,

$$\left\| \int_0^T \mathbf{f}(t)dt \right\| \leq \int_0^T \|\mathbf{f}(t)\|dt,$$

and

$$\langle u^*, \int_0^T \mathbf{f}(t)dt \rangle = \int_0^T \langle u^*, \mathbf{f}(t) \rangle dt$$

for each $u^* \in X^*$.

Definition A.0.60. The space $L^p(0, T; X)$ consists of all strongly measurable function $\mathbf{u} : [0, T] \rightarrow X$ with

$$(1) \|\mathbf{u}\|_{L^p(0,T;X)} := \left(\int_0^T \|\mathbf{u}(t)\|^p dt \right)^{1/p} \text{ for } 1 \leq p < \infty \text{ and}$$

$$(2) \|\mathbf{u}\|_{L^\infty(0,T;X)} := \operatorname{ess\,sup}_{0 \leq t \leq T} \|\mathbf{u}(t)\| < \infty.$$

Definition A.0.61. The space $C([0, T]; X)$ consists of all continuous functions $\mathbf{u} : [0, T] \rightarrow X$ with

$$\|\mathbf{u}\|_{C([0,T];X)} := \max_{0 \leq t \leq T} \|\mathbf{u}(t)\| < \infty.$$

Definition A.0.62. Let $\mathbf{u} \in L^1(0, T; X)$. We say that $\mathbf{v} \in L^1(0, T; X)$ is the weak derivative of \mathbf{u} , written $\mathbf{u}' = \mathbf{v}$, provided

$$\int_0^T \phi'(t) \mathbf{u}(t) dt = \int_0^T \phi(t) \mathbf{v}(t) dt$$

for all scalar test functions $\phi \in C_c^\infty(0, T)$.

Definition A.0.63. (1) The Sobolev space

$$W^{1,p}(0, T; X)$$

consists of all functions $\mathbf{u} \in L^p(0, T; X)$ such that \mathbf{u}' exists in the weak sense and each belongs to $L^p(0, T; X)$. Furthermore,

$$\|\mathbf{u}\|_{W^{1,p}(0,T;X)} := \begin{cases} \left(\int_0^T \|\mathbf{u}(t)\|^p + \|\mathbf{u}'(t)\|^p dt \right)^{1/p} & (1 \leq p < \infty) \\ \operatorname{ess\,sup}_{0 \leq t \leq T} (\|\mathbf{u}(t)\| + \|\mathbf{u}'(t)\|) & (p = \infty). \end{cases}$$

(2) We write $H^1(0, T; X) = W^{1,2}(0, T; X)$.

Definition A.0.64. Let $\mathbf{u} \in W^{1,p}(0, T; X)$ for some $1 \leq p \leq \infty$. Then

(1) $\mathbf{u} \in C([0, T]; X)$ (after possibly being redefined on a set of measure zero.)

(2) $\mathbf{u}(t) = \mathbf{u}(s) = \int_0^t \mathbf{u}'(\tau) d\tau$ for all $0 \leq s \leq t \leq T$.

(3) Furthermore, we have the estimate

$$\max_{0 \leq t \leq T} \|\mathbf{u}(t)\| \leq C \|\mathbf{u}\|_{W^{1,p}(0,T;X)},$$

where the constant C depends only on T .

Theorem A.0.40. Suppose $\mathbf{u} \in L^2(0, T; H_0^1(U))$, with $\mathbf{u}' \in L^2(0, T; H^{-1}(U))$.

(1) Then

$$\mathbf{u} \in C([0, T]; L^2(U))$$

(after possibly being redefined on a set of measure zero).

(2) The mapping

$$t \mapsto \|\mathbf{u}(t)\|_{L^2(U)}^2$$

is absolutely continuous, with

$$\frac{d}{dt} \|\mathbf{u}(t)\|_{L^2(U)}^2 = 2\langle \mathbf{u}'(t), \mathbf{u}(t) \rangle$$

for all $0 \leq t \leq T$.

(3) Furthermore, we have the estimate

$$\max_{0 \leq t \leq T} \|\mathbf{u}(t)\|_{L^2(U)} \leq C \left(\|\mathbf{u}\|_{L^2(0,T;H_0^1(U))} + \|\mathbf{u}'\|_{L^2(0,T;H^{-1}(U))} \right),$$

where the constant depends only on T .

Theorem A.0.41. Assume that U is open, bounded and ∂U is smooth. Take m to be a nonnegative integer. Then if $\mathbf{u} \in L^2(0, T; H^{m+2}(U))$, with $\mathbf{u}' \in L^2(0, T; H^m(U))$,

(1) Then $\mathbf{u} \in C([0, T]; H^{m+1}(U))$ after possibly being redefined on a set of measure zero.

(2) Further, we have the estimate

$$\max_{0 \leq t \leq T} \|\mathbf{u}(t)\|_{H^{m+1}(U)} \leq C \left(\|\mathbf{u}\|_{L^2(0, T; H^{m+2}(U))} + \|\mathbf{u}'\|_{L^2(0, T; H^m(U))} \right),$$

the constant C depending only on T, U and m .

Theorem A.0.42. Assume U is bounded and ∂U is C^1 . Then there exists a bounded linear operator

$$T : W^{1,p}(U) \rightarrow L^p(\partial U)$$

such that

$$Tu = u|_{\partial U} \text{ if } u \in W^{k,p}(U) \cap C(\bar{U})$$

and

$$\|Tu\|_{L^p(\partial U)} \leq C \|u\|_{W^{1,p}(U)},$$

for each $u \in W^{1,p}(U)$, with constant C depending on p and U . The operator T the trace of u on ∂U .

Theorem A.0.43. Assume U is bounded and ∂U is C^1 . Suppose further that $u \in W^{1,p}(U)$. Then $u \in W^{1,p}(U)$ if and only if $Tu = 0$ on ∂U .

Theorem A.0.44. Assume $1 \leq p < n$. There exists a constant C , depending on p and n , such that

$$\|u\|_{L^q(\mathbb{R}^n)} \leq C \|Du\|_{L^p(\mathbb{R}^n)}$$

for all $u \in C_c^\infty(\mathbb{R}^n)$.

Theorem A.0.45. Let U be a bounded, open subset of \mathbb{R}^n , and suppose that ∂U is C^1 . Assume $1 \leq p < n$ and that $u \in W^{1,p}(U)$. Then $u \in L^q(U)$ with the estimate

$$\|u\|_{L^q(U)} \leq C \|u\|_{W^{1,p}(U)},$$

the constant C depending only on p, n , and U .

Theorem A.0.46. Assume U is a bounded, open subset of \mathbb{R}^n . Suppose $u \in W_0^{1,p}(U)$ for some $1 \leq p < n$. Then we have

$$\|u\|_{L^r(U)} \leq C \|Du\|_{L^p(U)}$$

for each $1 \leq r \leq q$, the constant C depending on p, r, n and U .

Theorem A.0.47. Assume $n < p \leq \infty$. Then there exists a constant C , depending on p and n such that

$$\|u\|_{C^{0,\gamma}(\mathbb{R}^n)} \leq C \|u\|_{W^{1,p}(\mathbb{R}^n)}$$

for all $u \in C^1(\mathbb{R}^n)$, where $\gamma := 1 - n/p$.

APPENDIX B

pdepe.m CODE

Here we give the *Matlab* code used for solving our state system using *pdepe.m*.

```
function thesissystem

tic

m = 0;

tf = 900*5*10(-6);

x = linspace(0,1,1001);

t = linspace(0,tf,3001);

sol = pdepe(m,@pdefun,@icfun,@bcfun,x,t);

b = sol(:,:,1);

c = sol(:,:,2);

n = sol(:,:,3);

w = sol(:,:,4);

figure

surf(x,t,b,'edgecolor','none')

title('b(x,t)')

xlabel('Distance x')

ylabel('Time t')

figure
```

```

surf(x,t,c, 'edgecolor','none')

title('c(x,t)')

xlabel('Distance x')

ylabel('Time t')

figure

surf(x,t,n, 'edgecolor','none')

title('n(x,t)')

xlabel('Distance x')

ylabel('Time t')

figure

surf(x,t,w, 'edgecolor','none')

title('w(x,t)')

xlabel('Distance x')

ylabel('Time t')

toc

save('pdepethesis_run3_3.mat')

%-----

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

%We note that b=u(1),c=u(2),n=u(3),w=u(4).

```

```
Dw = 1;
Dn = 0.02;
epsilonb = .0001;
Dc = 1.5;
beta = .2284;
gamma = 5.4;
G = 0;
lambdanw = 37;
lambdabw = 22.7872;
lambdaw = 2.4667;
chin = 10;
kbn = 14.28;
lambdan = 5;
kb = 1.26;
kw = .75;
knr = 2;
lambdarb = 3.73;
lambdab = 5;
kc = 10;% 0C
lambdac = .9; %0C
delta = .7992;
Da = [Dw;Dn;epsilonb;Dc];
e = 30;
```

```

%bcnw

c = [1;1;1;1];

f = [Da(3);Da(4);Da(2);Da(1)].*DuDx; -[0;0;chin*u(3);0]...

    *DuDx(2).*heavi_approx3(1-u(3));

s = [kb*u(1).*(1-u(1))-u(4)./(kw+u(4))...

    .*(delta+knr*u(3))./(lambdarb*u(1)+1)-lambdab*u(1);...

kc*u(1)-lambdac*u(2);...

kbn*u(1).*u(3).*gfunc5002(u(4)).*(1-u(3))-u(3).*...

    (lambdan*(1))./(e*u(1)+1);...

beta+gamma.*G-lambdanw.*u(3).*u(4)-lambdabw.*u(1).*u(4)...

-lambdaw*u(4)];

%-----

function u0 = icfun(x)

epsilon1 = .01; %0C

epsilon2 = .01; %0C

u0 = [(1-x).^2.*exp(-(x/epsilon1).^2);.5*(1-x)...

.^2.*exp(-(x/epsilon1).^2)...

;x.^2.*exp(-((1-x)/epsilon2).^2);1];

%-----

```



```

function [pl,ql,pr,qr] = bcfun(xl,ul,xr,ur,t)

gamma1 = 1;

gamma2 = 1;

pl = [0;0;0;0];
ql = [1;1;1;1];
pr = [0;0;ur(3)-1;ur(4)-1];
qr = [1;1;0;0];

%-----

function g=gfunc5002(w)

i = length(w);
g = zeros(1,i);
for j = 1:i
    if 0 < w(j) < 1
        g(j) = 2*w(j).^3-3*w(j).^2+2;
    else
        g(j)=1;
    end
end
end

```

```

%-----
function h = hfunc(w)

h1 = length(w);
h = zeros(1,h1);
for j = 1:h1
    if w(j) < .15
        h(j) = 2;
    elseif .15<w(j)<.25
        h(j)=4000*w(j).^3-2400*w(j).^2+450*w(j)-25;
    elseif .25< w(j) <2.95
        h(j)=0;
    elseif 2.95< w(j)< 3.05
        h(j) = -4000*w(j).^3+3600*w(j).^2-107970*w(j)+107911;
    else
        h(j) = 2;
    end
end

end

%Try arctangent approx.
%-----

```

```
function H=heavi_approx3(x)
```

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

```
%-----
```

APPENDIX C

METHOD-OF-LINES CODE

Below is the code used in *Matlab* to produce the solution to the state system.

```
%clear previous files

tic

%clear all

%clc

global ncall N n w b c x

%Set up spatial grid, define initial time

N=601;

t0=0.0;

%Spatial increment

dx=0.1/(N-1);

%Initializing Spatial Grid

x= linspace(0,1,N);

%Initial Conditions

epsilon = .01;

for i=1:N
```

```

w(i) = 1;
n(i) = ( x(i).^2 ).*exp( -( ( 1-x(i) )/epsilon ).^2 );
b(i) = ( 1-x(i) )^2 .* exp( -(x(i)/epsilon )^2 );
c(i) = 0.5*( 1-x(i) )^2 .* exp( -(x(i)/(epsilon) )^2 );

y0(i) = w(i);
y0(i+N)= n(i);
y0(i+2*N) = b(i);
y0(i+3*N) = c(i);

end

ncall=0;

%Call to initial conditions routine

tf=900*5*10^(-6);
nout=3001;
tout=linspace(t0,tf,nout);
ncall = 0;

%Integration
reltol=1.0e-08; abstol=1.0e-08;

```

```

options=odeset('RelTol', reltol, 'AbsTol', abstol);

[t,y] = ode15s(@thesis_pde_MOL_1, tout, y0, options);

%Separate the solution vector into separate vectors for plotting
for it=1:nout
    for i=1:N
        w(it,i) = y(it,i);
        n(it,i) = y(it,i+N);
        b(it,i) = y(it,i+2*N);
        c(it,i) = y(it, i+3*N);
    end
end

size(x)
size(w)

%Parametric plots
figure(1);
subplot(1,4,1)
plot(x,w,'-k'); axis tight
title('w(x,t) vs x');
    xlabel('x'); ylabel('w(x,t)')
subplot(1,4,2)

```

```

plot(x, n, '-k'); axis tight
title('n(x,t) vs x');
    xlabel('x'); ylabel('n(x,t)')
subplot(1,4,3)
plot(x, b, '-k'); axis tight
title('b(x,t) vs x');
    xlabel('x'); ylabel('b(x,t)')
subplot(1,4,4)
plot(x, c, '-k'); axis tight
title('c(x,t) vs x');
    xlabel('x'); ylabel('c(x,t)')

```

```
%Surface plots
```

```

figure
surf(x,t,b,'edgecolor','none')
title('b(x,t)')
xlabel('Distance x')
ylabel('Time t')

```

```

figure
surf(x,t,c, 'edgecolor','none')
title('c(x,t)')
xlabel('Distance x')

```

```

ylabel('Time t')

figure
surf(x,t,n, 'edgecolor','none')
title('n(x,t)')
xlabel('Distance x')
ylabel('Time t')

figure
surf(x,t,w, 'edgecolor','none')
title('w(x,t)')
xlabel('Distance x')
ylabel('Time t')

save( 'thesis_run3_3.mat')

toc
%-----
function yt=pde_MOL_1(t,y)

global ncall...

    N    w    n    b    c ...
        wt  nt  bt  ct ...

```


x

```
Dw = 1;
Dn = 0.02;
epsilonb = .0001;
Dc = 1.5;
beta = .2284;
gamma = 5.4;
G = 0;
lambdanw = 37;
lambdabw = 22.7872;
lambdaw = 2.4667;
chi = 10;
kbn = 14.28;
lambdan = 5;
kb = 1.26;
kw = .75;
knr = 2;
lambdarb = 3.73;
lambdab = 5;
kc = 10;% 0C
lambdac = .9; %0C
delta = .7992;
Da = [Dw;Dn;epsilonb;Dc];
```

```

e = 30;

dx=1/(N-1);

%Creating separate functions from y solution vector

for i=1:N

    w(i)=y(i);

    n(i)=y(i+N);

    b(i)=y(i+2*N);

    c(i)=y(i+3*N);

end

wt = zeros(N);

nt = zeros(N);

bt = zeros(N);

ct = zeros(N);

wt(1) = (2*Dw)/(dx^2)*(w(2)-w(1))+ beta+gamma*G ...
        - lambdan*w*n(1).*w(1)-lambdabw*b(1).*w(1)-lambdaw*w(1);

nt(1) = (2*Dn)/(dx^2)*(n(2)-n(1))-chi*( n(1).*(...
        (c(2)-2*c(1)+c(2))/(dx^2))).*heavi_approx3(1-n(1))
        ...+ kbn*b(1).*n(1).*gfunc5002(w(1)).*( 1-n(1))...
        - (lambdan*n(1).*(1+hfunc(w(1))/(e*b(1)+1)));

bt(1) = (2*epsilonb)/(dx^2)*(b(2)-b(1))+kb*b(1).*(1-b(1))...
        - b(1).*( w(1)/ ( kw+w(1))).*(...

```

```

        (delta+knr*n(1))/(lambdarb*b(1)+1))-lambdab*b(1);
ct(1) = (2*Dc)/(dx^2)*(c(2)-c(1))+kc*b(1)-lambdac*c(1);

for i = 2:(N-1);

    wt(i) = Dw/(dx^2) * ( w(i+1)-2*w(i)+w(i-1) )+ beta+gamma*G ...
        - lambdanw*n(i).*w(i)-lambdabw*b(i).*w(i)-lambdaw*w(i);

    nt(i) = Dn/(dx^2) * ( n(i+1)-2*n(i)+n(i-1) ) -chi*( (...
        (n(i+1)-n(i-1))/(2*dx) ).*( (c(i+1)-c(i-1))/(2*dx) )+...
        n(i).*( (c(i+1)-2*c(i)+c(i-1))/(dx^2))).*heavi_approx3(1-n(i))
        +kbn*b(i).*n(i).*gfunc5002(w(i)).*( 1-n(i))...
        - (lambdan*n(i).*(1+hfunc(w(i)))/(e*b(i)+1))) ) ;

    bt(i) = epsilonb/(dx^2) * ( b(i+1)-2*b(i)+b(i-1) )...
        +kb*b(i).*(1-b(i))...
        - b(i).*( w(i)/ ( kw+w(i)) ).*( (...
        (delta+knr*n(i))/(lambdarb*b(i)+1))-lambdab*b(i);

    ct(i) = Dc/(dx^2) * ( c(i+1)-2*c(i)+c(i-1) )+kc*b(i)-lambdac*c(i);

end

wt(N) = 0;

```

```

nt(N) = 0 ;

bt(N) = (2*epsilonb)/(dx^2)* (b(N-1) - b(N) )+kb*b(N).*(1-b(N))...
        - b(N).*( ( w(N)/ ( kw+w(N)))).*(...
        (delta+knr*n(N))/(lambdarb*b(N)+1))-lambdab*b(N);

ct(N) = (2*Dc)/(dx^2)* (c(N-1) - c(N) )+kc*b(N)-lambdac*c(N);

%Four vectors to one vectors

for i=1:N

    yt(i) =    wt(i);

    yt(i+N) =  nt(i);

    yt(i+2*N) = bt(i);

    yt(i+3*N) = ct(i);

end

yt=yt';

ncall=ncall+1;

%-----

function g=gfunc5002(w)

i = length(w);

g = zeros(1,i);

for j = 1:i

    if 0 < w(j) < 1

        g(j) = 2*w(j).^3-3*w(j).^2+2;

```

```

        else
            g(j)=1;
        end
    end

end

%-----

function h = hfunc(w)

h1 = length(w);
h = zeros(1,h1);
for j = 1:h1
    if w(j) < .15
        h(j) = 2;
    elseif .15<w(j)<.25
        h(j)=4000*w(j).^3-2400*w(j).^2+450*w(j)-25;
    elseif .25< w(j) <2.95
        h(j)=0;
    elseif 2.95< w(j)< 3.05
        h(j) = -4000*w(j).^3+3600*w(j).^2-107970*w(j)+107911;
    else
        h(j) = 2;
    end
end

end

%Try arctangent approx.

%-----

```

```
function H=heavi_approx3(x)
```

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

```
%-----
```

APPENDIX D

NON-CONVERGENT CODES

The code in this chapter we list attempted test problems for the methods used in chapter 3.

D.1. Schugart *et al.* Article Using *pdepe.m*

We begin with the code testing a simplified version of the wound-healing model given in Schugart et al. [17] in order to test the code against given numerical methods to a similar system found in Thackham [19]. The *chasescode* function file defines the solution given using *pdepe.m*.

```
function chasescode

global params

tic

mm = 0;

%tf = 38.4;

tf = 6;

Da = [1*10(-8), 7*10(-9), 5*10(-6), 5*10(-7), ...
      1*10(-6), 1.7*10(-10), 1*10(-11), 1*10(-9)];

D = 1*10(-6);

Da = Da./D;

chi = [10, 1, 1];

lambda = [2.16*10(-1), 2.16*10(-2), 2.25*10(-2), 2.25*10(-1), ...
```

```

        2.25*10(-1), 0.1388, 0.277, 4.16, 0.045, 100, ...
        .0009, .0090, .00009, 0.25, 5.2*10(-3), 0.25];

gamma = [2.22, 2.96];

params = [Da, chi, lambda, gamma, 1, 1];

x = linspace(0,1,1001);

t = linspace(0,tf,401);

sol = pdepe(mm,@wound_pde_australia2,@wound_ic_australia2,...
    @wound_bc_australia2,x,t,[],params);

n = sol(:,:,1);

b = sol(:,:,2);

%w = sol(:,:,3);

m = sol(:,:,4);

a = sol(:,:,3);

%f = sol(:,:,6);

%rho = sol(:,:,7);

x = 1 - x; %I can write a statement

kk = length(x);

figure

surf(x,t,n, 'edgecolor','none')

title('n(x,t)')

xlabel('Distance x')

ylabel('Time t')

```



```

rotate3d on

figure

surf(x,t,b, 'edgecolor','none')

title('b(x,t)')

xlabel('Distance x')

ylabel('Time t')

rotate3d on

figure

surf(x,t,a, 'edgecolor','none')

title('a(x,t)')

xlabel('Distance x')

ylabel('Time t')

rotate3d on

figure

surf(x,t,m, 'edgecolor','none')

title('m(x,t)')

xlabel('Distance x')

ylabel('Time t')

rotate3d on

    save('stephen_run1.mat')

toc

%-----

function [c,f,s] = wound_pde_australia2(x,t,u,DuDx,params)

```

```

Da = params(1:8);

chi = params(8:10);

lambda = params(11:26);

gamma = params(27:28);

kk = 1;

delta = params(29);

eta = params(30);

lambdam = .001;

%nbam-order of functions

c = [1; 1; 1;1];

f = [Da(1); Da(2); Da(5); 10].*DuDx + ...
    [0; kk*Da(1); 0;0].*u(2).*DuDx(1)...
    +[-chi(1);0;0;0].*u(1).*heavi_approx2(1-u(1)).*DuDx(3)...
    -[0;kk*Da(8);0;0].*u(2).*DuDx(1)...
    -[0;kk*chi(1);0;0].*u(2).*u(1).*heavi_approx2(1-u(1)).*DuDx(3)...
    +[0;0;0;chi(2)].*u(4).*heavi_approx2(1-u(4));

s = [(lambda(1)*u(3).*u(2) + lambda(2)*u(3).*u(1)).*heavi_approx2(1 - u(1))...
    - (lambda(3)*u(2) + lambda(4)*u(1)).*u(1);
    lambda(5)*u(2).*(1 - u(2));...
    +lambda(10)*u(4)-(lambda(11)*u(1) + lambda(12)*u(2)+ lambda(13)).*u(3);...
    -lambdam*u(4)];

```

```

%-----
function u0 = wound_ic_australia2(x,params)

xbar = .05;

epsilon=0.1;

u0 = [1;1.5;0;0].*test_ic_func(x,xbar)+[0;0;0;1].*...
(1-x).^2.*exp(-(x./epsilon).^2);

%u0 = [1; 1; 0;1].*(1 - x).^2.*exp(-(x./epsilon).^2);
%-----
function [pl,q1,pr,qr] = wound_bc_australia2(xl,ul,xr,ur,t,params)

gamma = params(27:28);

delta = params(29);

eta = params(30);

alpha = .5;

pl = [ul(1) - exp(-gamma(1)*t); ul(2) - 1; 0; ul(4) - exp(-alpha*t)];

q1 = [0; 0; 1;0];

pr = [0; 0; 0;0];

qr = [1; 1; 1;1];

%-----
function g=gfunc4002(w)

```

```

i = length(w);
g = zeros(1,i);
for j = 1:i
    if w(j) < 1/2
        g(j) = 0;
    else
        g(j) = 2*w(j) - 1;
    end
end

%-----
function g=gfunc5002(w)

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

```

```

%-----
function H=heavi_approx2(x)

H = atan(10*x)./pi+1/2;

%-----

function H=heavi_approx3(x)

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

%-----

function H=tanhapprox(x)

H = 1/2*tanh( (1-x)/.01);

%-----

function g=test_ic_func(x,xbar)

if x<xbar

    g=(x-xbar)*(2*x^2-xbar*x-xbar^2)/xbar^3;

else

    g=0;

end

```

D.2. Schugart *et al.* Article Using method of lines

```

%clear previous files

tic

clear all

clc

global ncall N n a b m x params

```

```

Da = [1*10(-8), 7*10(-9), 5*10(-6), 5*10(-7),...
      1*10(-6), 1.7*10(-10), 1*10(-11), 1*10(-9)];

D = 1*10(-6);

Da = Da./D;

chi = [10, 1, 1];

lambda = [2.16*10(-1), 2.16*10(-2), 2.25*10(-2), 2.25*10(-1),...
         2.25*10(-1), 0.1388, 0.277, 4.16, 0.045, 100, ...
         .0009, .0090, .00009, 0.25, 5.2*10(-3), 0.25];

gamma = [2.22, 2.96];

params = [Da, chi, lambda, gamma, 1, 1];

%Set up spatial grid, define initial time

N=1001;

t0=0.0;

%-----

%Spatial increment

dx=0.1/(N-1);

%Initializing Spatial Grid

x= linspace(0,1,N);

%Initial Conditions nbam

```

```

for i=1:N
    xbar = .05;
epsilon=0.1;
    if x(i) < xbar
        n(i)=(x(i)-xbar)*(2*x(i)^2-xbar*x(i)-xbar^2)/xbar^3;
    else
        n(i)=0;
    end
    a(i) = 0;
    if x(i) < xbar
        b(i)=1.5*(x(i)-xbar)*(2*x(i)^2-xbar*x(i)-xbar^2)/xbar^3;
    else
        b(i)=0;
    end
    if x(i)< xbar
        m(i) = (1-x(i)).^2.*exp(-(x(i)./epsilon).^2);
    else
        m(i) = 0;
    end
    end
    % b(i) = ((bhat-bbar)./xbar^3)*(x(i)-xbar)*(2*x(i)^2-xbar.*x(i)
    -xbar.^2).*(atan(80000*(.05-x(i)))./pi+1/2);
    y0(i) = n(i);
    y0(i+N)= a(i);

```

```

        y0(i+2*N) = b(i);
        y0(i+3*N) = m(i);
    end

    %Call to initial conditions routine

    tf=6;

    nout=401;

    tout=linspace(t0,tf,nout);

    %Integration

    reltol=1.0e-08; abstol=1.0e-08;

    options=odeset('RelTol', reltol, 'AbsTol', abstol);

    [t,y] = ode15s(@pde_MOL_2, tout, y0, options);

    %Separate the solution vector into separate vectors for plotting

    for it=1:nout
        for i=1:N
            n(it,i)=y(it,i);
            a(it,i)=y(it,i+N);
            b(it,i)=y(it,i+2*N);
            m(it,i)=y(it, i+3*N);
        end
    end

end

```



```

y
%
%size(x)
%size(mn)
%size(aa)
%size(b)

%Parametric plots
figure(1);
subplot(1,3,1)
plot(x,n,'-k'); axis tight
title('n(x,t) vs x');
    xlabel('x'); ylabel('n(x,t)')
subplot(1,3,2)
plot(x, a, '-k'); axis tight
title('a(x,t) vs x');
    xlabel('x'); ylabel('a(x,t)')
subplot(1,3,4)
plot(x, b, '-k'); axis tight
title('b(x,t) vs x');
    xlabel('x'); ylabel('b(x,t)')
subplot(1,4,4)
plot(x, m, '-k'); axis tight

```

```

title('b(x,t) vs x');

    xlabel('x'); ylabel('m(x,t)')

%Surface plots

figure(2);

surf(nn, 'edgecolor', 'none'); axis tight

xlabel('x grid number');

ylabel('t grid number');

zlabel('n(x,t)');

title('Thackem System');

view([-115 36])

colormap jet;

rotate3d on;

figure(3);

surf(aa, 'edgecolor', 'none'); axis tight

xlabel('x grid number');

ylabel('t grid number');

zlabel('a(x,t)');

title('Thackem System');

view([170 24]);

colormap jet

rotate3d on;

figure(4);

```

```

surf(b, 'edgecolor', 'none' ); axis tight
xlabel('x grid number');
ylabel('t grid number');
zlabel('b(x,t)');
title('Thackem System');
view([170 24]);

colormap hot
rotate3d on;

save('Thackem_MOL_run_1.m')

toc

% -----
function yt=pde_MOL_1(t,y)

global ncall params ...

    n    a    b m...

    nt   at   bt mt...

    N x

Da = [1*10(-8), 7*10(-9), 5*10(-6), 5*10(-7),...
      1*10(-6), 1.7*10(-10), 1*10(-11), 1*10(-9)];

D = 1*10(-6);

Da = Da./D;

chi = [10, 1, 1];

lambda = [2.16*10(-1), 2.16*10(-2), ...

```

```

2.25*10(-2), 2.25*10(-1),...
    2.25*10(-1), 0.1388, 0.277, 4.16, 0.045, 100,
    .0009, .0090, .00009, 0.25, 5.2*10(-3), 0.25];
gamma = [2.22, 2.96];
kk=length(x);
dx = 1/(N-1);
%Creating separate functions from y solution vector
for i=1:N
    n(i)=y(i);
    a(i)=y(i+N);
    b(i)=y(i+2*N);
    m(i)=y(i+3*N);
end
%nt = zeros(n);
%at = zeros(n);
%bt = zeros(n);

nt(1) = Da(1).*( (n(2)-2*n(1)+n(2))/(dx^2) )- chi(1).*...
    ( n(1).*heavi_approx3(1-n(1)).*...
    ( (a(2)-2*a(1)+a(2))/(dx^2) ) ) ...
    + (lambda(1).*a(1).*b(2)+lambda(2)...
    .*a(2).*n(2)).*heavi_approx3(1-n(2));

```

```

at(1) = Da(5).*( (a(2)-2*a(1)+a(2))/(dx^2) )...
+ lambda(10).*m(1)...
      -( lambda(11).*n(1)+lambda(12)...
        .*b(1)+lambda(13) ).*a(1);
bt(1) = Da(2).*( (b(2)-2*b(1)+b(2))/(dx^2) )+kk*Da(1).*...
      b(1).*( (n(2)-2*n(1)+n(2) )/(dx^2) ) ...
      -kk*chi(2).*( b(1).*n(1).*...
      heavi_approx3( 1-n(1) ).*( (n(2)-2*n(1)+n(2))/(2*dx) ) )...
      +lambda(5).*b(1).*b(2);

mt(1) = Da(4).*( (m(2)-2*m(1)+m(2))/(dx^2) )-lambda(9).*m(i);

for i = 2:(N-1);
    nt(i) = Da(1).*( (n(i+1)-2*n(i)+n(i-1) )/(dx^2) )- chi(1).*...
      ( ( (n(i+1)-n(i-1))/(2*dx) ).*heavi_approx3(1-n(i)).*...
      ( (a(i+1)-a(i-1))/(2*dx) )+n(i).*( -1000/( 1+1000^2*...
      (1-n(i))^2 ) ).*( (n(i+1)-n(i-1))/(2*dx) ).*...
      ( (a(i+1)-a(i-1))/(2*dx) ) + n(i).*...
      heavi_approx3(1-n(i)).*( (a(i+1)-2*a(i)+a(i-1))/...
      (dx^2) ) )+ (lambda(1).*a(i).*b(i)...
      +lambda(2).*a(i).*n(i)).*heavi_approx3(1-n(i));

at(i) = Da(5).*( (a(i+1)-2*a(i)+a(i-1))/(dx^2) ) + ...

```

```

lambda(10).*m(i)-( lambda(11).*n(i)+lambda(12)...
.*b(i)+lambda(13) ).*a(i);

bt(i) = Da(2).*( (b(i+1)-2*b(i)+b(i-1))/(dx^2) )+kk*Da(1).*...
( (b(i+1)-b(i-1))/(2*dx).*( ( n(i+1)-n(i-1) )./(2*dx) )...
+b(i).*( (n(i+1)-2*n(i)+n(i-1) )/(dx^2) ) )...
-kk*chi(2).*( ( (b(i+1)-b(i-1))/(2*dx) ).*n(i).*...
heavi_approx3( 1-n(i) ).*( (a(i+1)-a(i-1) )/(2*dx) )...
+b(i).*((n(i+1)-n(i-1))/(2*dx)).*heavi_approx3(1-n(i))...
.*( (a(i+1)-a(i-1))/(2*dx) )...
+b(i).*n(i).*( -1000/( 1+( 1000*(1-n(i)) )^2 ) )...
.*((n(i+1)-n(i-1))/(2*dx)).*((a(i+1)-a(i-1))/(2*dx))...
+b(i).*n(i).*heavi_approx3( 1-n(i) ).*(...
(n(i+1)-2*n(i)+n(i-1))/(2*dx) ) )...
+lambda(5).*b(i).*b(i-1);

mt(i) = Da(4).*( (m(i+1)-2*m(i)+m(i-1))/(dx^2) ) ...
+chi(3).*( ( (m(i+1)-m(i-1))/(2*dx) )...
.*heavi_approx3(1-(m(i)))+m(i).*(-1000/(...
1+ (1000*(1-m(i))).^2))...
.*( (m(i+1)-m(i-1))/(2*dx) ) )
-lambda(9).*m(i);

```

end

```

nt(N)= -gamma(1).*exp(-gamma(1)*t ) ;
at(N)= Da(5).*( (a(N-1)-2*a(N)+a(N-1))/(dx^2) ) + lambda(10).*m(N)...
        -( lambda(11).*n(N)+lambda(12).*b(N)+lambda(13) ).*a(N);
bt(N)=0 ;
mt(N)=-gamma(2).*exp(-gamma(2)*t );
%Three vectors to two vectors
for i=1:N
    yt(i)=nt(i);
    yt(i+N)=at(i);
    yt(i+2*N)=bt(i);
    yt(i+3*N)=mt(i);
end
yt
yt=yt';
ncall=ncall+1;
%-----
function g=gfunc4002(w)

i = length(w);
g = zeros(1,i);
for j = 1:i
    if w(j) < 1/2

```

```

        g(j) = 0;
    else
        g(j) = 2*w(j) - 1;
    end
end

end

%-----

function g=gfunc5002(w)

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

end

%-----

function H=heavi_approx3(x)

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

%-----

```



```
function H=tanhapprox(x)
```

```
H = 1/2*tanh( (1-x)/.01);
```

```
%-----
```

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