Using Optimal Control Theory to Optimize the Use of Oxygen Therapy in Chronic Wound Healing

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USING OPTIMAL CONTROL THEORY TO OPTIMIZE THE USE OF
OXYGEN THERAPY IN CHRONIC WOUND HEALING

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Master of Science

By
Donna Lynn Daulton

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USING OPTIMAL CONTROL THEORY TO OPTIMIZE THE USE OF OXYGEN THERAPY IN CHRONIC WOUND HEALING

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Approximately 2 to 3 million people in the United States suffer from chronic wounds, which are defined as wounds that do not heal in 30 days time; an estimated $25 billion per year is spent on their treatment in the United States. In our work, we focused on treating chronic wounds with bacterial infections using hyperbaric and topical oxygen therapies.

We used a mathematical model describing the interaction between bacteria, neutrophils and oxygen. Optimal control theory was then employed to study oxygen treatment strategies with the mathematical model. Existence of a solution was shown for both therapies. Uniqueness was also shown for hyperbaric therapy. We then used a forward-backward sweep method to find numerical solutions for the therapies. We concluded by putting forth ideas for how this problem could progress toward finding applicable treatment strategies.
I. INTRODUCTION

Introduction: Biology

The skin is the largest organ in the body; it has six primary functions (protection, sensation, thermoregulation, excretion, metabolism, and body image). When skin is damaged and a wound is formed, it undergoes three main phases of healing: inflammation, proliferation, and remodeling (Diegelmann & Evans, 2004; Thackham et al., 2008). These phases overlap providing a cascade of wound-healing events. The main functions of the inflammatory phase is to control bleeding, remove debris, and prepare for new tissue by killing bacteria and redirecting blood flow (Brown et al., 2001). There are two parts of this phase, hemostasis and inflammation. Hemostasis only lasts a few hours and its purpose is to control bleeding through vasoconstriction, thromboplastin production and clot formation (Broderick, 2009). After bleeding is controlled, the inflammation part of this phase begins. The inflammatory phase is characterized by pain, redness, swelling and heat, normally lasting 1-to-4 days post injury. Neutrophils are the first of the inflammatory cells to arrive at the wound and begin removing debris and killing bacteria. Following neutrophils, monocytes are introduced into the wound and become activated macrophages. They convert macromolecules into amino acids and sugars necessary for wound healing. Macrophages also produce chemoattractants (enzymes that stimulate angiogenesis, fibroblasts, and growth factors), which attract cells needed for new tissue growth. The main function of the proliferation phase is to deposit connective tissue and crosslink collagen (Brown et al., 2001). There are two parts to this phase, granulation and epithelialization. Granulation refers to the dermal layer of skin and epithelialization the epidermal layer of skin. After debris is removed from the wound, granulation tissue, which is comprised of
macrophages, fibroblasts, extracellular matrix (including immature collagen), blood vessels, and ground substance (water, electrolytes, and plasma proteins), fill the wound. Angiogenesis, the creation of new blood vessels by endothelial cells from existing ones, is stimulated by the need to create a blood supply (Broderick, 2009). Epithelialization begins after the wound is filled with granulation tissue as epithelial cells, through a process called “contact guidance”, begin to seal the wound (Hess, 2002). This is similar to a pond freezing from the outside into the center (Broderick, 2009). A scar forms when this phase is complete, usually within 4 to 20 days post injury. The remodeling phase occurs as collagen fibers are strengthened and reorganized. It increases the tensile strength of the granulation tissue and the wound continues to contract. The scar continues to shrink and becomes paler and thinner. The new skin only has about 80% of the tensile strength of normal skin (Brown et al., 2001).

Two ways to categorize wounds are acute and chronic. Acute wounds follow the wound-healing stages described above. They heal at a predictable rate and manner. Chronic wounds begin as acute wounds but do not progress through the normal stages of healing. They do not heal within a reasonable amount of time, defined to be more than 30 days. The most common chronic wounds are lower extremity ulcers. Chronic venous insufficiency (CVI) accounts for 80% to 90% of lower extremity ulcers and affects 2% to 5% of the population. The cost of treating CVI ulcers alone is estimated at $1 billion/year in the United States (Broderick, 2009). An estimated $25 billion/year is spent in the United States for the treatment of chronic wounds (Sen et al., 2009) and approximately 2 to 3 million people suffer from them in the United States. Improving the healing response of chronic wounds could significantly reduce the cost of treatment (Kuehn, 2007; Broderick, 2009).

Chronic wounds often remain in a prolonged inflammatory state (Broderick, 2009). There are many reasons for a wound not to heal properly. Factors impacting
healing include: underlying conditions such as diabetes mellitus, immunodeficiencies or infection, aging (the elderly have a higher percentage of chronic illnesses), oxygen availability to the wound, nutrition, age of the wound, bioburden (number of bacteria in the wound), and stressors (Broderick, 2009). When a chronic wound is unable to heal in a reasonable time frame, additional treatment strategies are necessary to produce a successful healing response. These therapies can include hyperbaric and topical oxygen, electrical stimulation, hydrotherapy, ultrasound, nutritional support, compression (elastic stockings or bandaging for lower extremities), support surfaces (cushions, mattresses, etc.) and topical growth factors (Hess, 2002).

One reason chronic wounds do not progress to the proliferation phase is that inflammatory cells, like neutrophils, struggle to remove bacteria from the wound. This is due, in part, to a lack of oxygen in the wound. Inflammatory cells and macrophages require adequate tissue oxygenation to kill bacteria in the wound as they convert oxygen to reactive oxygen species, which is toxic to bacteria (Roy et al., 2009). Decreased oxygen availability also impacts collagen formation, angiogenesis, and epithelialization (Broderick, 2009), as well as the control of infection (Morison et al., 1997).

In our work, we will focus on treating chronic wounds with bacterial infections using various oxygen therapies. Two methods of delivering supplemental oxygen to a wound are hyperbaric and topical oxygen therapies (Thackham et al., 2008; Gordillo & Sen, 2009). During hyperbaric oxygen therapy, patients are placed in pressurized chambers where they breathe 100% oxygen at 2-3 atmospheres of pressure for 1-2 hours per session (Thackham et al., 2008; Gordillo & Sen, 2009). Treatment is usually administered once or twice per day for five days per week for 2-6 weeks, depending on the severity of the wound. Hyperbaric therapies can be administered in two ways - a monoplace chamber or a multiplace chamber.
monoplace chamber administers oxygen systemically through the vascularized system and topically by placing the person in a full body chamber where their whole body is surrounded by pure oxygen. The multiplace chamber administers oxygen systemically by only breathing the pure oxygen (Geris et al., 2010). Hyperbaric oxygen has been shown to significantly reduce the number of amputations (Faglia et al., 1996).

Topical oxygen therapy is typically administered by attaching an inflatable device around the wound region that delivers 100% oxygen to the wound at or slightly above 1 ATM of pressure for about 90 minutes each session once per day for about four days followed by three days of rest with no treatment. This process is continued until the wound has ideally healed (Gordillo et al., 2003; Rodriguez et al., 2008; Gordillo & Sen, 2009). The greatest benefit of topical oxygen therapy is seen in tissues with compromised blood flow (Hess, 2002).

Introduction: Mathematical Modeling

Over the past 20 years, mathematical modeling of the wound-healing process has been an active area of research (Schugart et al., 2008; Thackham et al., 2008). Recent mathematical models have focused on analyzing treatment strategies (Geris et al., 2010). One area of mathematics that analyzes the decision-making process is optimal control theory. To date, optimal control theory has not been used to analyze treatment strategies in wound healing. However, optimal control theory has been used to study problems in biology, including cancer and HIV modeling (Fister, et al., 1998; Fister & Panetta, 2003; Lenhart & Workman, 2007). The purpose of this work is to use optimal control theory in order to analyze oxygen therapy on the treatment of a bacterial infection in a wound.

We will use a model originally developed by Schugart and Joyce to model the
interaction between bacteria, neutrophils, and oxygen. Their model in non-dimensionalized form is:

\[
\frac{db}{dt} = k_b b (1 - b) - b \frac{k_{mr} n + \delta}{\lambda_{rb} b + 1} \ast \frac{w}{w + k_w} - \lambda_b b
\]  

where \( b \) denotes the density of bacteria, \( n \) denotes the level of neutrophils, and \( w \) denotes the oxygen concentration in the wound.

In the \( \frac{db}{dt} \) equation, the first term \( k_b b (1 - b) \) represents the bacterial proliferation using a logistic growth term. The second term \( -b \frac{k_{mr} n + \delta}{\lambda_{rb} b + 1} \ast \frac{w}{w + k_w} \) models oxidative killing of bacteria. The last term \( -\lambda_b b \) represents the loss of bacteria due to natural death. The first term of the \( \frac{dn}{dt} \) equation \( k_p e^{-\lambda_p t} (1 - n) \) models the activation of the neutrophils. The second term \( \frac{k_{ni} b n (1 - n) g_{nw}(w)}{\lambda_{ni} n + 1} \) describes the recruitment of the neutrophils while the third term \( -\lambda_n n \frac{1 + e b}{1 + eb} \) represents the death of neutrophils. The third differential equation models the change in oxygen. \( \beta \) represents the amount of oxygen that diffuses into the system from the surrounding blood vessels and \( \gamma \ast u(t) \) represents the external input of oxygen scaled by gamma. The terms \( -\lambda_{bw} b w - \lambda_{nw} n w \), describe the uptake of oxygen by bacteria and inflammatory cells, respectively, and \( -\lambda_w w \) represents the decay of oxygen. The \( u \) is our control variable and it represents the input of oxygen.
Introduction: Optimal Control Theory

Optimal control theory allows us to make decisions about complex biological situations when we adjust a control variable. State variable(s) describe the behavior of the underlying dynamical system. We can change the behavior of the state variable(s) by adjusting the control function(s). The goal is to maximize or minimize a prescribed objective functional.

As in Lenhart and Workman (2007), to define the control set for given $a, b, t_1 > 0$, let

$$\mathbf{U} \equiv \{u(t) : a \leq u(t) \leq b, t_0 \leq t \leq t_1, u(t) \text{ is Lebesgue measurable.}\}$$

(4)

The changes in the state $\vec{x}(t) \in \mathbb{R}^n$, under a given control $u \in \mathbf{U}$, are determined by a system of ordinary differential equations:

$$\frac{d\vec{x}}{dt}(t) = \vec{g}(t, x, u),$$
$$\vec{x}(0) = \vec{x}_0, \text{ and } \vec{x}(t_1) \text{ free;}$$

(5)

where the basic optimal control problem consists of finding a piecewise continuous control $u(t)$ and the associated state variable $\vec{x}(t)$ to minimize (or maximize) the given objective functional:

$$J[u] = \min_{a \leq u \leq b} \int_{t_0}^{t_1} f(t, x(t), u(t)) \, dt$$

which may also be written as:

$$J[u^*] = \min_{u \in \mathbf{U}} J[u]$$

subject to the above state system (5) where $u^*$ represents the optimal state of $U$. 
The $\vec{x}(t_1)$ free term means that the value $\vec{x}(t_1)$ is unrestricted, where $f$ and $g$ are continuously differentiable functions in all three arguments. Thus, the control(s) will be piecewise continuous and the state variables will be piecewise differentiable.

Necessary conditions are derived using Pontryagin’s Maximum Principle which is given in Theorem I.1 from Lenhart and Workman (2007). See Appendix A for more details.

**Theorem I.1.** For the control $\vec{u} = (u_1, \ldots, u_m)^\top$ belonging to the admissible control set $U$ and related trajectory $\vec{x} = (x_1, \ldots, x_n)^\top$ that satisfies

$$\frac{d\vec{x}}{dt} = g_i(\vec{x}, \vec{u}, t) \quad \text{(state equations)},$$

$$\vec{x}_i(a) = c_i \quad \text{(initial conditions)}$$

but with free end conditions, to minimize the performance criterion

$$J = \phi(\vec{x}, t)|^b_a + \int_a^b f(\vec{x}, \vec{u}, t)dt$$

it is necessary that a vector $\vec{\lambda} = \vec{\lambda}(t)$ exists such that

$$\frac{d\vec{\lambda}}{dt} = -\frac{\partial H}{\partial \vec{x}_i} \quad \text{(adjoint equations)},$$

$$\vec{\lambda}_i(b) = \phi_{x_i}(\vec{x}(b), b) \quad \text{(adjoint final conditions)},$$

where the Hamiltonian

$$H(t, \vec{x}, u) = f(t, \vec{x}, u) + \lambda^\top \ast \vec{g}(t, \vec{x}, u),$$

$$= \text{integrand} + \text{adjoint} \ast \text{RHS of DE}$$

for all $t$, $a \leq t \leq b$, and all $\vec{u} \in U$, satisfies

$$H[\vec{\lambda}(t), \vec{x}^*(t), \vec{u}] \geq H[\vec{\lambda}(t), \vec{x}^*(t), \vec{u}^*].$$
Adjoint functions are similar to Lagrange multipliers because they add constraints to variables being maximized or minimized.
II. NON-LINEAR CONTROL

Forming the Hamiltonian for Non-linear Control

The objective functional $J[u(t)]$ for the nonlinear control is

$$J[u(t)] = \int_0^{T_1} \left[ b(t) + \frac{c}{2} u^2(t) \right] dt$$

where $0 \leq u \leq M^2$.  

This models supplemental oxygen administered in the wound through hyperbaric oxygen therapy. A nonlinear function is reasonable because it is unlikely the body is systematically processing the oxygen in a linear way. We use the differential equations (1-3) from Schugart and Joyce. The Hamiltonian for the non-linear control without bounds is:

$$H = b + \frac{c}{2} u^2 + \lambda_1 \left( k_b b(1 - b) - b \frac{k_{nr} n + \delta}{\lambda_{rb} b + 1} \frac{w}{w + k_w} - \lambda b \right) + \lambda_2 \left( k_p e^{-\lambda_p t} (1 - n) + \frac{k_{ni} bn(1 - n)(g_{nw}(w))}{\lambda_{ni} n + 1} - \frac{\lambda_n n}{1 + eb} \right) + \lambda_3 (\beta + \gamma u(t) - \lambda w - \lambda_{bw} bw - \lambda_{nw} nw)$$

Thus the adjoint equations (by Theorem I.1) are as follows:

$$\lambda'_1 = -\frac{\partial H}{\partial b}$$

$$= -\left[ 1 + \lambda_1 \left( k_b - 2 k_b b - \lambda b + \frac{(k_{nr} n + \delta)b \lambda_{rb} - (\lambda_{rb} b + 1)(k_{nr} n + \delta)}{(\lambda_{rb} b + 1)^2} \frac{w}{w + k_w} \right) + \lambda_2 \left( \frac{k_{ni} n(1 - n)(g_{nw}(w))}{\lambda_{ni} n + 1} + \frac{\lambda_n ne}{(1 + eb)^2} \right) + \lambda_3 (-\lambda_{bw} w) \right]$$
\[ \lambda_2' = -\frac{\partial H}{\partial n} = \lambda_1 \frac{-bk_n r}{\lambda_rb+1} \frac{w}{w+k_w} \]

\[ + \lambda_2 \left( \frac{g_{nw}(w)[(\lambda_n n + 1)(k_n b - 2 k_n b n) - k_n b n (1 - n) \lambda_n]}{(\lambda_n n + 1)^2} - \frac{\lambda}{1 + eb - k_p e^{-\lambda t}} \right) \]

\[ + \lambda_3 \left( -\lambda_{nw} w \right) \]

\[ \lambda_3' = -\frac{\partial H}{\partial w} = \lambda_1 \left( \frac{-b (k_n n + \delta)}{\lambda_rb+1} \frac{k_w}{(w+k_w)^2} \right) + \lambda_2 \left( k_n b_n (1 - n) \left( g_{nw}(w) \right) \right) \]

\[ + \lambda_3 \left( -\lambda_w - \lambda_{bw} \lambda_{nw} n \right) \]

where \( g_{nw}(w) = \begin{cases} 6w^2 - 6w & \text{for } 0 \leq w < 1, \\ 0 & \text{for } w \geq 1, \end{cases} \)

with the final time values:

\[ \lambda_1(T) = 0, \lambda_2(T) = 0, \lambda_3(T) = 0. \]

Since \( \frac{\partial H}{\partial u} = cu + \gamma \lambda_3 \), the optimality conditions are given below:

\[ u^*(t) = \begin{cases} 0 & \text{implies } cu + \gamma \lambda_3 \geq 0 \text{ at } t, \\ 0 < -\frac{\gamma \lambda_3}{c} < M2 & \text{implies } cu + \gamma \lambda_3 = 0 \text{ at } t, \\ M2 & \text{implies } cu + \gamma \lambda_3 \leq 0 \text{ at } t. \end{cases} \]

Thus the optimality system that characterizes our optimum control
is a Lebesgue-integrable function on the interval $U$ right-hand side of the differential equations,\n\[ D \]

Let $L$ be the integrand of the objective functional, $\bar{g}$ be the right-hand side of the differential equations, $U$ be a closed subset of $E^n$, the space of $n$ tuples $x = (x_1, ..., x_n)$ of real numbers. Let $\mathcal{F}^t$ be the class of all $(x_0, u)$ such that $u$ is a Lebesgue-integrable function on the interval $[t_0, t_1]$ with values in $U$ and the

\[ J[u(t)] = \int_{t_0}^{t_1} \left[ b(t) + \frac{c}{2} u^2(t) \right] \, dt \] is given by:

\[
\begin{align*}
\frac{db}{dt} &= k_b(b(1 - b) - b \frac{\kappa}{\lambda} n + \delta) \frac{w}{\lambda + k_b + 1} w + k_w - \lambda_b b \\
\frac{dn}{dt} &= k_p c - \lambda_p (1 - n) + \frac{\kappa}{\lambda} n (1 - n) \frac{w}{\lambda + k_b + 1} w + k_w - \lambda_n n \\
\frac{dw}{dt} &= \beta + \gamma n(t) - \lambda_w w - \lambda_b w - \lambda_n w w \\
\end{align*}
\]

The Cauchy problem $x(t)$, $x(t)$, $t = \tau$ is $\xi$ where $(\tau, \xi) \in D$, with $D$ a nonempty open subset of $\mathbb{R} \times \mathbb{R}^n$ and $f : D \to \mathbb{R}^n$ has a solution if for some $R_{a,b} = \{(t, x) : |t - \tau| \leq a, |x - \xi| \leq b, a, b > 0\} \subset D$ centered about $(\tau, \xi)$ the restriction of $g$ to $R_{a,b}$ is continuous in $x$ for fixed $t$, measurable in $t$ for fixed $x$, and satisfies $|g(t, x)| \leq m(t)$, $(t, x) \in R_{a,b}$ for some $m$ integrable over the interval $[\tau - a, \tau + a]$. Existence of an optimal control is shown in Theorem II.3.

Theorem II.2. The Cauchy problem $\frac{dx}{dt} = g(t, x(t))$, $x(t) = \xi$ where $(\tau, \xi) \in D$, with $D$ a nonempty open subset of $\mathbb{R} \times \mathbb{R}^n$ and $f : D \to \mathbb{R}^n$ has a solution if for some $R_{a,b} = \{(t, x) : |t - \tau| \leq a, |x - \xi| \leq b, a, b > 0\} \subset D$ centered about $(\tau, \xi)$ the restriction of $g$ to $R_{a,b}$ is continuous in $x$ for fixed $t$, measurable in $t$ for fixed $x$, and satisfies $|g(t, x)| \leq m(t)$, $(t, x) \in R_{a,b}$ for some $m$ integrable over the interval $[\tau - a, \tau + a]$. Existence of an optimal control is shown in Theorem II.3.

Theorem II.3. Let $L$ be the integrand of the objective functional, $\bar{g}$ be the right-hand side of the differential equations, $U$ be a closed subset of $E^n$, the space of $n$ tuples $x = (x_1, ..., x_n)$ of real numbers. Let $\mathcal{F}^t$ be the class of all $(x_0, u)$ such that $u$ is a Lebesgue-integrable function on the interval $[t_0, t_1]$ with values in $U$ and the

\[ J[u(t)] = \int_{t_0}^{t_1} \left[ b(t) + \frac{c}{2} u^2(t) \right] \, dt \] is given by:

\[
\begin{align*}
\frac{db}{dt} &= k_b(b(1 - b) - b \frac{\kappa}{\lambda} n + \delta) \frac{w}{\lambda + k_b + 1} w + k_w - \lambda_b b \\
\frac{dn}{dt} &= k_p c - \lambda_p (1 - n) + \frac{\kappa}{\lambda} n (1 - n) \frac{w}{\lambda + k_b + 1} w + k_w - \lambda_n n \\
\frac{dw}{dt} &= \beta + \gamma n(t) - \lambda_w w - \lambda_b w - \lambda_n w w \\
\end{align*}
\]

\[ J[u(t)] = \int_{t_0}^{t_1} \left[ b(t) + \frac{c}{2} u^2(t) \right] \, dt \] is given by:

\[
\begin{align*}
\frac{db}{dt} &= k_b(b(1 - b) - b \frac{\kappa}{\lambda} n + \delta) \frac{w}{\lambda + k_b + 1} w + k_w - \lambda_b b \\
\frac{dn}{dt} &= k_p c - \lambda_p (1 - n) + \frac{\kappa}{\lambda} n (1 - n) \frac{w}{\lambda + k_b + 1} w + k_w - \lambda_n n \\
\frac{dw}{dt} &= \beta + \gamma n(t) - \lambda_w w - \lambda_b w - \lambda_n w w \\
\end{align*}
\]
solution of the differential equations satisfying the end conditions \( e \in S \). Let \( S \) be a given subset of \( E^{2n+2} \) and \( J(x_0, u) = \phi_j(t_0, t_1, x(t_0), x(t_1)) = \phi(e) \) for \( j = 2, \ldots, k \) and \( e \) denotes a \((2n+2)\)-tuple of end points. For each \((t, x) \in E^{n+1}\), let

\[
\tilde{F}(t, x) = \{ \tilde{z} : z = g(t, x, u), z_{n+1} \geq L(t, x, u), u \in U \}.
\]

Suppose that \( \tilde{g} \) is continuous; there exist positive constants \( C_1, C_2 \) such that

(a) \( |\tilde{g}(t, x, u)| \leq C_1(1 + |x| + |u|) \),

(b) \( |\tilde{g}(t, x', u) - g(t, x, u)| \leq C_2|x' - x|(1 + |u|) \) for all \( t \in E^1, x, x' \in E^n \), and

\( u \in U, L \) is continuous,

and that:

1. \( \mathcal{F}' \) is not empty;
2. \( U \) is closed;
3. \( S \) is compact and \( \phi \) is continuous on \( S \);
4. \( \tilde{F}(t, x) \) is convex for each \( (t, x) \in E^{n+1} \);
5. \( L(t, x, u) \geq h(u) \), where \( h \) is continuous and \( |u|^{-1}h(u) \to +\infty \) as \( |u| \to \infty, u \in U \). Then there exist \((x_0^*, u^*)\) minimizing \( J(x_0, u) \) on \( \mathcal{F}' \).

In order to show the above we must check the following properties which are equivalent to the general conditions stated above (Joshi, 2002):

1. The set of controls and corresponding state variables is non-empty.
2. The control \( U \) set is convex and closed.
3. The RHS of the state system is bounded by a linear function in the state and control variables.
4. The integrand of the objective functional is convex on \( U \).
5. There exist constants \( c_1, c_2 > 0 \), and \( \beta > 1 \) such that the integrand \( L(t, x, u) \) satisfies

\[
L(t, x, u) \geq c_1|u|^\beta - c_2.
\]

We apply the above result to minimize equation (6) with respect to the state system described by equations 1-3 with the appropriate initial conditions.
Proof. In order to show:

1. We use a result by Lukes (Theorem 9.2.1 pg 182 (see Theorem II.2); Differential Equations: Classical to Controlled) which gives the existence of solutions of ODEs with bounded coefficients.

2. $U$, as defined in (4), is closed and convex because our differential equation is linear in $u$ so it is convex. $U$ is closed because $0 \leq u \leq M2$.

3. The RHS of the state system is bounded by a linear function in the state and control because we know that bacteria and neutrophils are bounded by the carrying capacities $b_0$ and $n_0$, respectively. Note that the non-dimensional values for $b_0$ and $n_0$ are one. The amount of oxygen is bounded by
$$\max \left\{ w_{init}, \frac{\beta + \gamma \ast M2}{\lambda_w} \right\},$$
where $M2$ is the maximum amount of oxygen input allowed.

To show this, we know that $0 \leq u \leq M2$ and allowing $\alpha = \beta + \gamma \ast M2$ we have that $\frac{dw}{dt} = \alpha - \lambda_w \ast w$ is maximized because we are inputting the maximum amount of oxygen ($u = M2$) and we are not accounting for any oxygen used by bacteria or neutrophils by letting $n = b = 0$. Solving the differential equation, by separation of variables,

$$\frac{dw}{dt} = \alpha - \lambda_w \ast w$$

$$\int \frac{dw}{\alpha - \lambda_w \ast w} = \int dt \text{ letting } u = \alpha - \lambda_w \ast w, du = -\lambda_w dw$$

$$\ln |\alpha - \lambda_w \ast w| = -\lambda_w t + c$$

$$\alpha - \lambda_w \ast w = e^{-\lambda_w t + c}$$

$$w = \frac{\alpha - C \ast e^{-\lambda_w t}}{\lambda_w}$$

$$w(0) = \frac{\alpha - C}{\lambda_w} = w_{init}$$

$$C = \alpha - \lambda_w \ast w_{init}.$$
Thus we claim that

\[ \bar{w}(t) = \frac{\alpha(1 - e^{-\lambda w t}) + \lambda w \cdot w_{\text{init}}e^{-\lambda w t}}{\lambda w} \]

bounds our oxygen function, \( w \), above. We need to show that \( \bar{w}(t) \) is decreasing when \( w_{\text{init}} > \frac{\alpha}{\lambda w} \) and increasing when \( w_{\text{init}} < \frac{\alpha}{\lambda w} \). If \( \bar{w}(t) \) is decreasing, then the maximum value is \( \bar{w}(0) = w_{\text{init}} \). If \( \bar{w}(t) \) is increasing then the maximum value is \( \lim_{t \to \infty} \bar{w}(t) = \frac{\alpha}{\lambda w} = \beta + \gamma \cdot M^2 \lambda w \). Where,

\[ \bar{w}'(t) = \frac{d\bar{w}(t)}{dt} = (\alpha - \lambda w \cdot w_{\text{init}})e^{-\lambda w t}. \]

Thus \( w \) is bounded above by \( \bar{w} \) and the maximum value for the oxygen is given by \( \max \left\{ w_{\text{init}}, \frac{\beta + \gamma \cdot M^2}{\lambda w} \right\} \). Thus,

\[ M = \max \left\{ b_0, n_0, w_{\text{init}}, \frac{\beta + \gamma \cdot M^2}{\lambda w} \right\} \]

bounds the states and control variables and provides a constant function that bounds the RHS of the state system.

4. The integrand of the objective function is convex on \( U \) because \( b + \frac{c}{2} u^2 \) is a convex function as defined in Bartle and Sherbert, Theorem 5.4.6: “Let \( I \) be an open interval and suppose that \( f : I \to \mathbb{R} \) has a second derivative on \( I \). Then \( f \) is a convex function on \( I \) iff \( f''(x) \geq 0 \) for all \( x \in I \).” The second derivative of \( b + \frac{c}{2} u^2 = c > 0 \).

5. Let \( c_1 = c > 0, c_2 > 0 \) and \( \beta = 2 \). Thus \( b + cu^2 \geq c_1|u|^2 - c_2 \).

\[ \square \]

**Nonlinear Uniqueness**

To show uniqueness of the optimal control solutions for the optimality system, we use a theorem given in Joshi et al. 2006. The optimality system consists of the state
system, adjoint system, initial conditions, transversality conditions and the
characterization of the optimal control.

Consider the boundary value problem

\[
\begin{align*}
\vec{x}'(t) &= \vec{p}(t, x, \lambda) = (b(t)', n'(t), w'(t))', \\
\vec{\lambda}'(t) &= \vec{q}(t, x, \lambda) = (\lambda_1'(t), \lambda_2'(t), \lambda_3'(t))', \\
\vec{x}(0) &= \vec{x}_0, \quad \vec{\lambda}(T) = \vec{\lambda}_T,
\end{align*}
\]

where \( \vec{x} \in \mathbb{R}^m, \vec{\lambda} \in \mathbb{R}^n, \) and \( \vec{p}: \mathbb{R} \times \mathbb{R}^m \times \mathbb{R}^n \to \mathbb{R}^m \) and \( \vec{q}: \mathbb{R} \times \mathbb{R}^m \times \mathbb{R}^n \to \mathbb{R}^n \) are continuous.

**Theorem II.4.** Assume that \( \vec{p} \) and \( \vec{q} \) are bounded and satisfy a Lipschitz condition relative to \( \vec{x} \) and \( \vec{\lambda} \) with constant \( C > 0 \). Then solutions of system above are unique if \( T \) is sufficiently small.

**Proof.** Suppose our two-point boundary problem has two solutions \((\vec{x}_1(t), \vec{\lambda}_1(t))\) and \((\vec{x}_2(t), \vec{\lambda}_2(t))\). The Lipschitz condition on \( \vec{p} \) and \( \vec{q} \) imply

\[
\|\vec{x}_1(t) - \vec{x}_2(t)\| \leq \int_0^t C(\|\vec{x}_1(s) - \vec{x}_2(s)\| + \|\vec{\lambda}_1(s) - \vec{\lambda}_2(s)\|)ds. \tag{8}
\]

\[
\|\vec{\lambda}_1(t) - \vec{\lambda}_2(t)\| \leq \int_0^t C(\|\vec{x}_1(s) - \vec{x}_2(s)\| + \|\vec{\lambda}_1(s) - \vec{\lambda}_2(s)\|)ds. \tag{9}
\]

Adding (8) and (9) together yields

\[
\|\vec{x}_1(t) - \vec{x}_2(t)\| + \|\vec{\lambda}_1(t) - \vec{\lambda}_2(t)\| \leq \int_0^t C(\|\vec{x}_1(s) - \vec{x}_2(s)\| + \|\vec{\lambda}_1(s) - \vec{\lambda}_2(s)\|)ds. \tag{10}
\]

The Mean Value Theorem for Integrals can be applied to conclude that there exists a \( \zeta, 0 \leq \zeta \leq T \), such that

\[
\|\vec{x}_1(t) - \vec{x}_2(t)\| + \|\vec{\lambda}_1(t) - \vec{\lambda}_2(t)\| \leq \int_0^t TC(\|\vec{x}_1(s) - \vec{x}_2(s)\| + \|\vec{\lambda}_1(s) - \vec{\lambda}_2(s)\|)ds.
\]
for all $t \in [0, T]$. If $T$ is so small that $TC < 1$, we arrive at a contradiction, completing the proof. □

**Introduction: Numerical Analysis**

We will use a forward-backward sweep method in order to solve the optimal control problem numerically. In our problem, we are given initial conditions for the state equations $\vec{x}$, but final conditions for the adjoint equations $\vec{\lambda}$. We divide our time interval $[t_0, t_1]$ into $N$ equally spaced points. There are 5 basic steps in the forward-backward sweep method, as outlined in Lenhart and Workman.

1. Make an initial guess about $\vec{u}$ over the interval.

2. Using the initial condition $x_1 = x(t_0) = a$ and the values for $\vec{u}$, solve $\vec{x}$ forward in time according to its differential equation in the optimality system.

3. Using the transversality condition $\lambda_{N+1} = \lambda(t_1) = 0$ and the values for $\vec{u}$ and $\vec{x}$, solve $\vec{\lambda}$ backward in time according to its differential equation in the optimality system.

4. Update $\vec{u}$ by entering the new $\vec{x}$ and $\vec{\lambda}$ values into the characterization of the optimal control.

5. Check convergence. If values of the variables in this iteration and the last iteration are close (based on our convergence criteria), output the current values as solutions. If values are not close, return to step 2.

In order to complete the steps given above, we use a Runge-Kutta 4 routine. Given a step size $h$ and an ODE $x'(t) = f(t, x(t))$ the approximation of $x(t + h)$ given $x(t)$ is

$$x(t + h) \approx x(t) + \frac{h}{6}(k_1 + 2k_2 + 2k_3 + k_4)$$
where

\[ k_1 = f(t, x(t)) \]
\[ k_2 = f(t + \frac{h}{2}, x(t) + \frac{h}{2}k_1) \]
\[ k_3 = f(t + \frac{h}{2}, x(t) + \frac{h}{2}k_2) \]
\[ k_4 = f(t + \frac{h}{2}, x(t) + hk_3). \]

We also use the Runge-Kutta 4 routine to go backwards by replacing \( \frac{h}{2} \) by \(-\frac{h}{2}\).

**Non-linear Bounded Test Problem**

In order to solve our non-linear control numerically, we formulated a test problem that could be solved analytically to test our coding and to help us learn about any potential pitfalls. We wanted this problem to be like our problem

\[ J[u(t)] = \int_0^1 \left[ b(t) + \frac{c}{2}u^2(t) \right] dt. \]

So we chose to solve a similar problem (adapted from Lenhart and Workman Example 3.5):

\[
\min_{-0.5 \leq u \leq 0.5} \int_0^1 [x_2 + u^2]du
\]

subject to:

\[
\begin{align*}
x'_1 &= x_2 \\
x'_2 &= x_1 + u \\
\lambda'_1 &= -\lambda_2 \\
\lambda'_2 &= -\lambda_1 - 1 \\
x_1(0) &= 0, x_2(0) = 0, \lambda_1(1) = 0, \lambda_2(1) = 0.
\end{align*}
\]

Our Hamiltonian for this problem is

\[ H = x_2 + u^2 + \lambda_1 x_2 + \lambda_2 (x_1 + u). \]
partial derivative of $H$ with respect to $u$ is $\frac{\partial H}{\partial u} = 2u + \lambda_2$. Thus we have,

\[
\begin{align*}
\frac{\partial H}{\partial u} > 0 & \Rightarrow u > -\frac{\lambda_2}{2} \quad \text{implies } u^* = -0.5 \Rightarrow \lambda_2 > 1 \\
\frac{\partial H}{\partial u} = 0 & \Rightarrow u = -\frac{\lambda_2}{2} \quad \text{implies } -0.5 \leq u^* \leq 0.5 \Rightarrow -1 \leq \lambda_2 \leq 1 \\
\frac{\partial H}{\partial u} < 0 & \Rightarrow u < -\frac{\lambda_2}{2} \quad \text{implies } u^* = 0.5 \Rightarrow \lambda_2 < -1.
\end{align*}
\]

(11)

Notice that $\lambda_1'' = -\lambda_2'$ so $\lambda_1' = \lambda_1 + 1$ and $\lambda_1(1) = 0$, $\lambda_1'(1) = 0$. Let $y = \lambda_1 + 1$ then $y'' = y$ with $y(1) = 1, y'(1) = 0$. So we have

\[
\begin{align*}
y(t) &= c_1 \cdot e^t + c_2 \cdot e^{-t} \\
y'(1) &= c_1 \cdot e - c_2 \cdot e^{-1} = 0 \\
&\Rightarrow c_2 = c_1 \cdot e. \\
\end{align*}
\]

Then,

\[
\begin{align*}
y(t) &= c_1(e^t + e^{2-t}) \\
y(1) &= c_1(e + e) = 1 \Rightarrow c_1 = .5e^{-1} \\
y(t) &= \frac{1}{2}(e^{t-1} + e^{1-t}) \\
\lambda_1(t) &= \frac{1}{2}(e^{t-1} + e^{1-t}) - 1 \\
-\lambda_2(t) &= \lambda_1'(t) = \frac{1}{2}(e^{t-1} - e^{1-t}) \\
\lambda_2(t) &= -\frac{1}{2}(e^{t-1} + e^{1-t}) = -\sinh(t - 1).
\end{align*}
\]

We want to see what time makes $\lambda_2 > 1$ in (11), so we have $u^*$ in terms of $t$ because when $u^* = -0.5$ then $\lambda_2 > 1$:

\[
\begin{align*}
\lambda_2(t) &= -\sinh(t - 1) > 1 \\
\sinh(t - 1) &< -1 \\
t &< 1 + \sinh^{-1}(-1) = 1 + \ln(-1 + \sqrt{2}) \approx 0.1186.
\end{align*}
\]
Likewise, want to see at what time $\lambda_2 < -1$:

$$\lambda_2(t) = -\sinh (t - 1) < -1$$

$$\lambda_2(t) = \sinh (t - 1) > 1$$

$$t - 1 > \sinh^{-1} (1)$$

$$t > 1 + \sinh^{-1} (1) = 1 + \ln(1 + \sqrt{2}) \approx 1.8814.$$  

The optimal control is:

$$u^* = \begin{cases}  
-0.5 & \text{when } t < 0.1186 \\
\frac{1}{2} \sinh (t - 1) & \text{when } 0.1186 \leq t \leq 1.8814 \\
0.5 & \text{when } t > 1.8814.
\end{cases}$$

This solution is continuous. In order to find $x_1^*(t)$ and $x_2^*(t)$, we will substitute in our values for the optimal control, $u^*$ and solve. We will only be considering two cases because our optimal state is continuous and $0 \leq t \leq 1$, specifically $t < 0.1186$ and $t \geq 0.1186$. We can apply the boundary conditions $x_1(0) = 0, x_2(0) = 0$. As shown previously, $u^*$ during this time frame is -0.5. We must then solve:

$$\begin{cases}  
x_1' = x_2 \\
x_2' = x_1 - 0.5 \\
x_1(0) = 0, x_2(0) = 0.
\end{cases}$$

Similar to what we did with $\lambda_1$ above, we have $x_1'' = x_1 - 0.5$ and $x_1'(0) = 0$. Let $y = x_1 - 0.5$. Then $y'' = y, y(0) = -0.5, y'(0) = 0$. Solving yields

$$y(t) = d_1 * e^t + d_2 * e^{-t}$$

$$y'(0) = d_1 - d_2 = 0 \rightarrow d_1 = d_2$$

$$y(0) = d_1 + d_2 = 2d_1 = -0.5$$

$$y(t) = -0.5 * \frac{e^t + e^{-t}}{2} = -0.5 * \cosh(t).$$
Thus, \( x_1(t) = -0.5 \cosh(t) + 0.5 \) and \( x_2(t) = -0.5 \sinh(t) \). For \( 0.1186 \leq t \leq 1 \) we can no longer use our initial conditions because \( t \neq 0 \). Since our state equations must be continuous, we can solve for our coefficients by setting our solution for case two equal to that of case one at \( t = \sinh^{-1}(-1) + 1 \). In case two our goal is to solve:

\[
\begin{align*}
x_1' &= x_2 \\
x_2' &= x_1 + 0.5 \sinh(t).
\end{align*}
\]

We solved case two using \textit{Mathematica} and concluded:

\[
\begin{align*}
x_1 &= \frac{1}{8} + \frac{\sqrt{2} t}{16} + \frac{1}{8} \cdot (-4 + e(-\frac{3}{2} + \sqrt{2} + \sinh^{-1}(1)) + \frac{-1 + \sqrt{2} + \sinh^{-1}(1)}{e} \cdot \cosh(t)}{16 + e} \\
x_2 &= \frac{\sqrt{2}}{8} - \frac{t}{4} \cdot (-4 + e(-\frac{3}{2} + \sqrt{2} + \sinh^{-1}(1)) + \frac{-1 + \sqrt{2} + \sinh^{-1}(1)}{e} \cdot \cosh(t)}{16 + e} \\
\end{align*}
\]

Putting case one and two together gives us our optimal state equations.

\[
\begin{align*}
x_1^* &\quad \text{for } 0 \leq t < \sinh^{-1}(-1) + 1 \\
&\quad \text{or } \sinh^{-1}(-1) + 1 \leq t \leq 1 \\
&\quad 0.5 - 0.5 \cosh(t) \\
&\quad \frac{1}{8} + \frac{\sqrt{2} t}{16} + \frac{1}{8} \cdot (-4 + e(-\frac{3}{2} + \sqrt{2} + \sinh^{-1}(1)) + \frac{-1 + \sqrt{2} + \sinh^{-1}(1)}{e} \cdot \cosh(t)}{16 + e} \\
\end{align*}
\]

\[
\begin{align*}
x_2^* &\quad \text{for } 0 \leq t < \sinh^{-1}(-1) + 1 \\
&\quad 0.5 + 0.5 \sinh(t) \\
&\quad \frac{\sqrt{2}}{8} - \frac{t}{16} \cdot (-4 + e(-\frac{3}{2} + \sqrt{2} + \sinh^{-1}(1)) + \frac{-1 + \sqrt{2} + \sinh^{-1}(1)}{e} \cdot \cosh(t)}{16 + e} \\
\end{align*}
\]

We let our convergence tolerance be selected as \( \zeta = 0.001 \). We require the relative error to be small and \( \zeta \) chosen to satisfy \( \frac{|u - oldu|}{|u|} \leq \zeta \). In order to allow for zero controls, we cannot divide by zero. This is equivalent to \( \zeta |u| - |u - oldu| \geq 0 \), or \( \zeta \Sigma_{i=1}^{N+1} |u_i| - \Sigma_{i=1}^{N+1} |u_i - oldu_i| \geq 0 \).

After we performed the forward-backward sweep method, we needed to solve
for $u$ using our updated value. Let $u1 = \max(0, \min(u \text{ value when } \frac{\partial H}{\partial u} = 0, M2))$, where $0$ is the lower bound of $u$ and $M2$ is the upper bound of $u$. We average this value with our previous value to determine the updated value of $u$. We then test for convergence of our $u$, $x_1, x_2, \lambda_1$, and $\lambda_2$ to determine if the program needs to run again (there is still a negative term) or has finished (each term is non-negative) and the program can exit the while loop. Figures (1) and (2) show that our numerical and analytical solutions match for the state, adjoint, and control variables.

Figure 1: This figure shows that our values for $\vec{x}$ and $\vec{\lambda}$ from our analytical and numerical solutions match, because the two solutions overlap.
Figure 2: The figure above shows that our values for $u$, our control from our analytical and numerical solutions match, because the two solutions overlap.

**Non-linear Solution**

Using the Hamiltonian given by (7) and the numerical method given in the introduction to numerical analysis, along with testing our numerical methods by comparing different initial conditions and parameters in order to meet our convergence criteria, we have been able to find several biologically reasonable solutions to this problem.

First we tried to follow the numerical method used in our test problems. Using this method our value for $u$, input of oxygen, is updated by a simple average $u = 0.5 \times (u_1 + oldu)$ where $u_1$ is the current iterative value of $u$ and $oldu$ is the previous iteration’s value for $u$. We modified the parameter values of $k_{nr}$, $\delta$, $\lambda_{bw}$ and
\( \lambda_{nw} \), because they work to kill the bacteria faster, in order to increase the likelihood of convergence. The parameter values used are shown in Figure 3. The \( A, B, C, D \) indicate what number was multiplied or divided from \( k_{nr} \), \( \delta \), \( \lambda_{bw} \) and \( \lambda_{nw} \), respectively. We chose \( A \gg B \) since the bulk of the oxidative killing is due to the presence of the neutrophils. To keep the same ratio for \( \frac{\lambda_{bw}}{\lambda_{nw}} \), we chose \( C = D \). Unless otherwise given \( A, B, C, D = 80, 8, 3, 3 \) respectively. These parameters are from the work of Schugart and Joyce. Figure 4 illustrates the numerical solution for the parameter values given in Figure 3. Note that for these parameter values, bacteria persist in the wound.

<table>
<thead>
<tr>
<th>Parameter Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>( c )</td>
</tr>
<tr>
<td>( kb )</td>
</tr>
<tr>
<td>( knr )</td>
</tr>
<tr>
<td>( \delta )</td>
</tr>
<tr>
<td>( \lambda_{bw} )</td>
</tr>
<tr>
<td>( kw )</td>
</tr>
<tr>
<td>( \lambda_{2} )</td>
</tr>
<tr>
<td>( kp )</td>
</tr>
<tr>
<td>( \lambda_{r} )</td>
</tr>
</tbody>
</table>

Figure 3: These are the parameter values used in our codes. Unless otherwise specified, \( A, B, C, D = 80, 8, 3, 3 \), respectively.
Figure 4: These are the results when no oxygen is given. Note that the bacteria persist in the wound.

However, we were unable to find cases that numerically converged and the bacteria persisted with no input of oxygen, but died with oxygen input. We varied initial guesses for bacteria, neutrophils, and oxygen. We also considered different initial conditions for our control, specifically: 0.5, 0, and -M2*t/tf+M2 (see Figure 5). The last is the line from maximum allowed oxygen input (M2=16.37) to minimum oxygen input, 0. Yet, even with these changes, the code failed to converge (see Table 1, where DNC means Does Not Converge) as we let the code run for 25,000 iterations.
Figure 5: These are the initial guess values for $u$. They are entered as a vector and then adjusted with as each iteration of the code runs.

Table 1: These are the results for when $u$ is updated by averaging the previous iteration value of $u$ with its current iteration value.

Since the code failed to converge, we tried changing how we updated $u$ in our code. We used a convex combination of the old $u$ and new $u$ (Figure 6), as suggested in Lenhart and Workman (2007).
for i=1:N-1
    if(u(i) > oldu(i))
        u(i) = M1*(1-.5^k)+oldu(i)*.5^k;
    else
        u(i) = M2*(1-.5^k)+oldu(i)*.5^k;
    end
end

Figure 6: This code compares our old and new $u$ and then creates a weighted average based on the number of iterations run.

While our numerical simulations met convergence criteria, our results with this method varied greatly with different initial guesses for $u$. This potentially suggests that there may be some numerical instability in the code. When we started with a zero value for $u$, the bacteria in the wound persisted, which is indicated by $P$, in Table 2 on page 30. When we started with $u = 0.5$ we had mixed results of bacteria sometimes persisting and sometimes being removed from the wound. The bacteria persisted whenever the parameters were $A, B, C, D = 100, 5, 2, 2$, respectively. However, our $J$ values (the sum over all our time steps of the objective functional) were relatively large suggesting a better numerical method can improve our results. Observe these $J$ values in Table 2. The lowest $J$ value is 624.2647 and 15/27 of the results are greater than 10,000. When we used $u = -M2 * t/tf + M2$ we obtained convergence in all the cases tested, but again our $J$ values were very large, around $1.34 * 10^4$. Figures (7 - 9) and Table (2) illustrate varying these three inputs of $u$ for this case.
Figure 7: Results for $u$ initially 0 and $(b, n, w) = (0.9, 0.2, 0.5)$. The bacteria and neutrophils persist in the wound for the 14 day period. Oxygen is not administered until right before the end of the 14 days.
Figure 8: Results for \( u \) initially 0.5 and \((b, n, w) = (0.9, 0.2, 0.5)\). Here the bacteria is removed quickly from the wound in approximately \( 1/4 \) of a day. The oxygen input remains at the dimensionless maximum of 16.37 for the whole time. Neutrophils leave the wound and the oxygen in the wound \((w)\) rises again because it is not being used by the bacteria or neutrophils. This is not a biologically reasonable solution though because this much oxygen for this length of time would cause oxygen toxicity.
Figure 9: Results for \( u \) initially \(-M^2 \times t/t_f + M^2\) and \((b, n, w) = (0.9, 0.2, 0.5)\). Here the bacteria is removed quickly from the wound in approx 1/4 day. The oxygen input remains at the dimensionless maximum of 16.37 for the whole time. Neutrophils leave the wound and the oxygen in the wound \((w)\) rises again because it is not being used by the bacteria or neutrophils. This is not a biologically applicable solution though because this much oxygen for this length of time would cause oxygen toxicity.
Figure 10: Results for $u$ initially 0.5 and $(b, n, w) = (0.9, 0.2, 0.5)$ changing parameters slightly yields a different shape of $u$ results. Here $A, B, C, D = 80, 8, 4, 4$ respectively. The bacteria is removed from the wound in approximately 1.75 days. Oxygen input is withheld until slightly before 1.75 days and then is given at the dimensionless maximum amount 16.37. Again, this is not a biologically applicable solution though because this much oxygen for this length of time would cause oxygen toxicity.

Table 2: These are the results for when $u$ is updated by weighting the average of the previous iteration value of $u$ with its current iteration value.

Notice that when a initial value of zero is given for our input of oxygen the
bacteria persists but in our other two cases the bacteria levels go to zero and the oxygen input levels remain at the maximum the whole time. These results show dependence on the initial guess of \( u \), which implies instability of the method so we wanted to try to find a numerical scheme that is less likely to be dependent on an initial guess of \( u \).

We decided to try the steepest descent algorithm because the initial guess we use is not crucial for convergence (Kirk, 2004). The steepest descent algorithm works to minimize \( \frac{\partial H}{\partial u} \) (where a minus indicates going in the direction of a minimum). The change in position (\( \frac{\Delta u}{\Delta t} \)) is proportional to the vector in the gradient direction toward minimum point (\( -\frac{\partial H}{\partial u} \)) so,

\[
\frac{\Delta u}{\Delta t} = -\frac{\partial H}{\partial u},
\]

We want to minimize \( \frac{\partial H}{\partial u} \).

\[
u_{i+1} - u_i = \Delta u = -\Delta t \frac{\partial H}{\partial u} \]

Solving for \( u_{i+1} \) yields

\[
u_{i+1} = u_i - \Delta t \frac{\partial H}{\partial u}.
\]

Therefore the code updates \( u \) by making our new \( u \) equal to our old \( u \) minus our step size times the partial of the Hamiltonian with respect to \( u \), where \( \Delta t \) is the step size. How we apply this to our \( u \) is shown in Figure 11. Note that we still ensure that our values for \( u \) are between 0 and M2.

\[
temp = \text{sum(abs(c*u+lambda3*gamma))};
\]

\[
u = \text{max}(M1, \min(u - h*(c*u+lambda3*gamma), M2));
\]

\[
test = \zeta - temp;
\]

Figure 11: Updating \( u \) using steepest descent algorithm.

Our convergence criteria also changes with this algorithm. Now we are testing to see that \( \left\| \frac{\partial H}{\partial u} \right\| \leq \zeta \). We decided to let \( \zeta = 1 \). Solutions did not differ greatly for smaller values of \( \zeta \), such as 0.1, which is why we chose \( \zeta = 1 \). Figures (12-14) show the similarities between our three initial guesses for \( u = 0, 0.5, \) and
Figure 12: Here we see that our bacteria dies in a little under a day. Our oxygen input also goes back to zero shortly after this occurs. This is more biologically applicable solution than our previous results but we cannot administer hyperbaric oxygen for a day because of the risk of oxygen toxicity.
Figure 13: Here we see that our bacteria dies in a little under a day. Our oxygen input also goes back to zero shortly after this occurs. This is more biologically applicable solution than our previous results but we cannot administer hyperbaric oxygen for a day because of the risk of oxygen toxicity.
Figure 14: Here we see that our bacteria dies in a little under a day. Our oxygen input also goes back to zero shortly after this occurs. This is more biologically applicable solution than our previous results but we cannot administer hyperbaric oxygen for a day because of the risk of oxygen toxicity.

Figures 12-14 all show the bacteria being removed from the wound in under a day as well as the input of oxygen being reduced to zero in under a day. The similarity within these results given different initial guesses for $u$, shows the stability of the steepest descent algorithm as compared to the weighted average method. We also see a more biologically applicable solution as the bacteria leave the wound within a day. Table 3 summarizes our results after using the steepest descent algorithm. Notice that the $J$ values are consistent as different initial conditions for $u$ and parameter values are given, especially when the parameter values are 70,6,5,5. The smallest $J$ value is approximately 25 and the largest is approximately 75, which has a difference of 50. Compare this to Table 2 where the smallest was approximately 800 and the largest 13,400, which has a difference of 12,600. This
also indicates that the steepest descent code is stable.

<table>
<thead>
<tr>
<th>Initial Conditions</th>
<th>Parameters</th>
<th>$U=0.5$, non-$1(N+1)$</th>
<th>$U=\text{cos}(1, N+1)$</th>
<th>$U=M^2/N^2$</th>
<th>Healing Time</th>
<th>K# of iterations</th>
<th>Healing Time</th>
<th>K# of iterations</th>
<th>Healing Time</th>
<th>K# of iterations</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9, 0.2, 0.5</td>
<td>100, 5, 2, 1</td>
<td>1558 24.4579 1 3004 40.0739 1</td>
<td>3693 40.0837</td>
<td>70, 6, 3, 5</td>
<td>2520 29.1239 1</td>
<td>2380 29.1292 1</td>
<td>4704 29.1053</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.7, 0.1, 0.4</td>
<td>100, 5, 2, 1</td>
<td>1558 24.4579 1 3004 40.0739 1</td>
<td>4136 74.0336</td>
<td>70, 6, 3, 5</td>
<td>2520 29.1239 1</td>
<td>3096 29.1292 1</td>
<td>4802 74.0381</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5, 0.1, 0.5</td>
<td>100, 5, 2, 1</td>
<td>1558 24.4579 1 3004 40.0739 1</td>
<td>3847 40.0196</td>
<td>70, 6, 3, 5</td>
<td>2520 29.1239 1</td>
<td>3174 40.0131 1</td>
<td>3847 40.0196</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: These are the results for when $u$ is updated by the steepest descent algorithm.

Our oxygen input increased in the beginning until our bacteria died. Then our input of oxygen went back to zero. This follows the behavior we would expect to see biologically.

There are also a couple different functionals that we might want to consider. We have already looked at what happens if we let $c$, our weighting coefficient of $u$ in the objective functional, be negative. This models minimizing bacteria while maximizing oxygen over small time. Since the control is bounded, it is not unreasonable to consider what happens when we maximize the oxygen therapy. The goal is to find an optimal solution that removes the bacteria from the wound.

Letting $c = -0.1$ instead of $c = 0.1$ yields results that do not converge within 25,000 iterations. We also considered what would happen if we minimized $\int_0^{t_1} \left[ b^2 + \frac{cu^2}{2} \right] dt$ as well as $\int_0^{t_1} \left[ b^3 + \frac{cu^2}{2} \right] dt$ and concluded that for $b$ close to one this case is not much different than the case already considered. We then considered what would happen if $\frac{dw}{dt}$ was changed to be $\frac{dw}{dt} = \beta + \gamma * u^\alpha(t) - \lambda_w w - \lambda_{bw} bw - \lambda_{nw} nw$, where our oxygen input is raised to $\alpha$, a power greater than 2. This was determined to have a $u \equiv 0$ as the minimal solution because when we take $\frac{\partial H}{\partial u}$ we can always factor out $u$. 

35
III. LINEAR CONTROL

Forming the Hamiltonian for Linear Control

In this section, we form the Hamiltonian for our linear control

\[
J(u(t)) = \int_0^T [b(t) + cu(t)] \, dt,
\]

where \(0 \leq u \leq M2\).

This will model supplemental oxygen administered in the wound through topical oxygen therapy. A linear function is reasonable because the oxygen is being delivered to the wound directly. We will continue to use the differential equations provided above from Schugart and Joyce.

Linear Existence

We will prove existence using a theorem from the work of Filippov-Cesari from ‘Optimal Control Theory With Economic Applications’ by Seierstad and Sydsaeter (1987, p. 285 Theorem 2). Consider the following problem,

\[
\max \int_{t_0}^{t_1} f_0(x(t), u(t)) \, dt, \quad (t_0, t_1 \text{ fixed})
\]

subject to the vector differential equation and the initial condition

\[
\frac{d\bar{x}}{dt} = f(\bar{x}(t), u(t), t), \quad x(t_0) = x^0 (x^0 \text{ fixed}),
\]
the terminal conditions

\[ x_i(t_1) = x_i^1 \quad i = 1, \ldots, l \quad (x_i^1 \text{ all fixed}) \]
\[ x_i(t_1) \geq x_i^1 \quad i = l + 1, \ldots, m \quad (x_i^1 \text{ all fixed}) \]
\[ x_i(t_1) \text{ free} \quad i = m + 1, \ldots, n, \]

and for all \( t \in [t_0, t_1] \), the constraints

\[ h_k(x(t), u(t), t) \geq 0, \quad k = 1, 2, \ldots, s. \]

If:

1. There exists an admissible pair \((x(t), u(t))\).
2. The set \( N(x, t) = \{ f_0(x, u, t) + \rho, f(x, u, t)) : \rho \leq 0, h(x, u, t) \geq 0 \} \) is convex for all \( x \) and all \( t \in [t_0, t_1] \).
3. There exists a number \( b \) such that \( ||x(t)|| \leq b \) for all admissible pairs \((x(t), u(t))\), and all \( t \in [t_0, t_1] \).
4. There exists a ball \( B(0, b_1) \) in \( \mathbb{R}^r \) which, for all \( x \) with \( U(x, t) = \{ u : h(x, u, t) \geq 0 \} \).

Then there exists an optimal (measurable) control.

**Proof.**

1. \((x(t), u(t))\) is an admissible pair because \( u(t) \) is piecewise continuous, \( x(t) \) is continuous and piecewise continuously differentiable, and it satisfies the vector differential equation, initial conditions, constraints, with free terminal conditions.
2. The set \( N(x, t) = \{ f_0(x, u, t) + \rho, f(x, u, t)) : \rho \leq 0, h(x, u, t) \geq 0 \} \) is convex for all \( \bar{x} \) and all \( t \in [t_0, t_1] \) by the definition given in Lenhart and Workman of convex, “A function \( k(t) \) is said to be convex on \([a, b]\) if \( \alpha k(t_1) + (1 - \alpha)k(t_2) \leq k(\alpha t_1 + (1 - \alpha)t_2) \) for all \( 0 \leq \alpha \leq 1 \) and for any
For our problem, we have:

\[ f_0 = b + cu \]

\[ f_0(\vec{x}, u_1) + \rho = b + cu_1 + \rho \]

\[ f_0(\vec{x}, u_2) + \rho = b + cu_2 + \rho \]

\[ f_0(\vec{x}, u_2) - f_0(\vec{x}, u_1) = c(u_2 - u_1) \]

\[ \frac{\partial f_0(\vec{x}, u)}{\partial u} = c \]

\[ (u_2 - u_1) \frac{\partial f_0(\vec{x}, u_2)}{\partial u} = c(u_2 - u_1), \]

and

\[ f = \beta + \gamma u - \lambda_w w - \lambda_{bw} bw - \lambda_{nw} nw \]

\[ f(\vec{x}, u_1) = \beta + \gamma u_1 - \lambda_w w - \lambda_{bw} bw - \lambda_{nw} nw \]

\[ f(\vec{x}, u_2) = \beta + \gamma u_2 - \lambda_w w - \lambda_{bw} bw - \lambda_{nw} nw \]

\[ f(\vec{x}, u_2) - f(\vec{x}, u_1) = \gamma(u_2 - u_1) \frac{\partial f(\vec{x}, u_2)}{\partial u} = \gamma \]

\[ (u_2 - u_1) \frac{\partial f(\vec{x}, u_2)}{\partial u} = \gamma(u_2 - u_1). \]

Furthermore, if \( k \) is differentiable, then \( k \) is convex if and only if

\[ k(t_2) - k(t_1) \leq (t_2 - t_1)k'(t_2). \]

This property holds trivially in our case because \( ct_2 - ct_1 \leq (t_2 - t_1)c \).

3. There exists a number \( b \) such that \( ||x(t)|| \leq b \) for all admissible pairs \((x(t), u(t))\), and all \( t \in [t_0, t_1] \). \( b = \max \{ b_0, n_0, w_{init}, \frac{\beta + \gamma \cdot M^2}{\lambda_w} \} \) as shown in the section on nonlinear existence.

4. There exists a ball \( B(0, b_1) \) in \( R^r \) which, for all \( x \) with

\[ U(x, t) = \{ u : h(x, u, t) \geq 0 \} \]

which is a convex subset of \( R^r \), where \( r \) is the number of control variables. This is true because \( u \) is always between \([0, M]\), \( ||x(t)|| \leq b \), and \( t \in [0, t_1] \), \( t_1 \) is final time, so \( U(x, t) = \{ u : h(x, u, t) \geq 0 \} \).

Royden 1988 defines convexity by saying, A subset \( k \) of a vector space \( X \) is convex if whenever it contains \( x, y \) it also contains \( \lambda x + (1 - \lambda)y \) for \( 0 \leq \lambda \leq 1 \).

Let \( x, y \in U \). Assume without loss of generality \( 0 \leq x \leq y \leq M \). Let
\( h_1(u) = u \geq 0, \ h_2 = M - u \geq 0. \) Then

\[
\begin{align*}
    h_1(x) &\geq 0 \Rightarrow x \geq 0, \\
    h_1(y) &\geq 0 \Rightarrow y \geq 0, \\
    h_2(x) &\geq 0 \Rightarrow M - x \geq 0, \\
    h_2(y) &\geq 0 \Rightarrow M - y \geq 0.
\end{align*}
\]

Let \( w = \lambda x + (1 - \lambda)y \in U \) for \( 0 \leq \lambda \leq 1 \). We need to show that \( h_1(w) \geq 0 \) and \( h_2(w) \geq 0 \).

\[
\begin{align*}
    h_1(w) & = \lambda x + (1 - \lambda)y \geq 0 \\
    h_2(w) & = M - \lambda x - (1 - \lambda)y \\
    & = M - y + \lambda y - \lambda x \\
    & = M - y + \lambda(y - x) \geq 0 \text{ for } x \leq y.
\end{align*}
\]

Thus, \( U \) is convex.

Thus, there exists an optimal (measurable) control for our linear case. \( \square \)

The Hamiltonian for the linear control without bounds is:

\[
H = b + cu \\
+ \lambda_1 \left( k_b b(1 - b) - b \frac{k_{n'} n + \delta}{\lambda_{b} b + 1} \frac{w}{w + k_w} - \lambda_b * b \right) \\
+ \lambda_2 \left( k_p e^{-\lambda_p t} (1 - n) + \frac{k_{m'} b n (1 - n) (g_{n'}(w))}{\lambda_{m} n + 1} - \frac{\lambda_m n}{1 + e b} \right) \\
+ \lambda_3 (\beta + \gamma * u(t) - \lambda_{w'} w - \lambda_{b w} b w - \lambda_{n w} n w).
\]

(13)
Thus the adjoint equations (from Theorem I.1) are as follows:

\[
\lambda'_1 = -\frac{\partial H}{\partial b} = - \left[ 1 + \lambda_1 \left( k_b - 2k_b b - \lambda_b + \frac{(k_{nr} n + \delta) b \lambda_{rb} - (\lambda_{rb} b + 1)(k_{nr} n + \delta)}{(\lambda_{rb} b + 1)^2} \right) * \frac{w}{w + k_w} \right. \\
+ \lambda_2 \left( \frac{k_{ni} n (1 - n)(g_{nw}(w))}{\lambda_{ni} n + 1} + \frac{\lambda_{n} n e}{(1 + eb)^2} \right) \\
+ \lambda_3(-\lambda_{bw} w) \right],
\]

\[
\lambda'_2 = -\frac{\partial H}{\partial n} = - \left[ \lambda_1 \left( -bk_{nr} \frac{w}{\lambda_{rb} b + 1 w + k_w} \right) \\
+ \lambda_2 \left( g_{nw}(w)((\lambda_{ni} n + 1)(k_{ni} b - 2k_{ni} b n) - k_{ni} b n (1 - n) \lambda_{ni}) - \frac{\lambda_{n} n e}{1 + eb} - k_p e^{-\lambda_p t} \right) \\
+ \lambda_3(-\lambda_{nw} w) \right],
\]

\[
\lambda'_3 = -\frac{\partial H}{\partial w} = - \left[ \lambda_1 \left( \frac{-b(k_{nr} n + \delta)}{\lambda_{rb} b + 1} * \frac{k_w}{(w + k_w)^2} \right) + \lambda_2 \left( \frac{k_{ni} b n (1 - n)(g_{nw}'(w))}{\lambda_{ni} n + 1} \right) \\
+ \lambda_3(-\lambda_w - \lambda_{bw} b - \lambda_{nw} n) \right],
\]

where \( g_{nw}'(w) = \begin{cases} 
6w^2 - 6w & \text{for } 0 \leq w < 1, \\
0 & \text{for } w \geq 1. 
\end{cases} \)

With the final time values:

\[ \lambda_1(T) = 0, \lambda_2(T) = 0, \lambda_3(T) = 0. \]
Thus the optimality system that characterizes our optimum control (12) is given by:

\[
\begin{align*}
\frac{db}{dt} &= k_pb(1-b) - bk_wn + \delta * \frac{w}{w + k_w} - \lambda_b b \\
\frac{dn}{dt} &= k_pe^{-\lambda_p t}(1 - n) + \frac{k_w b n (1 - n) g_{nw}(w)}{\lambda_n n + 1} - \lambda_n n \\
\frac{dw}{dt} &= \beta + \gamma * u(t) - \lambda_w w - \lambda_b w b - \lambda_n w n w \\
n(0) &= 0, b(0) = b_{init}, w(0) = w_{init}.
\end{align*}
\]

\[
\begin{align*}
\lambda_1 &= -\frac{\partial H}{\partial b} = \frac{[k_b b - 2k_pb - \lambda_b + (k_{ar} n + \delta) b \lambda_{vb} - (\lambda_{vb} b + 1) (k_{ar} n + \delta)]}{w + k_w} + \lambda_2 \gamma
\end{align*}
\]

\[
\begin{align*}
\frac{\partial H}{\partial n} &= -[\lambda_1 + (\lambda_{vb} b + 1) \frac{w + k_w}{w + k_w}] + \lambda_2 \frac{k_w b n (1 - n) g_{nw}(w)}{\lambda_n n + 1} - \lambda_n n
\end{align*}
\]

\[
\begin{align*}
\lambda_3 &= \lambda_1 + \lambda_2 \gamma (1 - \lambda_{vb} b - \lambda_n w n)
\end{align*}
\]

Numerical Analysis

Solving a linear control is more difficult than solving for a non-linear control because the optimal solution may be piecewise continuous in \( u^* \), as opposed to continuous.

Following the work of Lenhart and Workman, consider the optimal control problem

\[
\min_u \int_0^{14} b + cu(t) dt
\]

subject to

\[
\begin{align*}
\frac{db}{dt} &= k_pb(1-b) - b k_w n + \delta * \frac{w}{w + k_w} - \lambda_b b \\
\frac{dn}{dt} &= k_pe^{-\lambda_p t}(1 - n) + \frac{k_w b n (1 - n) g_{nw}(w)}{\lambda_n n + 1} - \lambda_n n \\
\frac{dw}{dt} &= \beta + \gamma * u(t) - \lambda_w w - \lambda_b w b - \lambda_n w n w, \\
n(0) &= 0, b(0) = b_{init}, w(0) = w_{init}, \\
0 \leq u(t) \leq 5,
\end{align*}
\]

where \( g_{nw}(w) = \begin{cases} 
2w^3 - 3w^2 + 2 & \text{for } 0 \leq w < 1, \\
1 & \text{for } w \geq 1.
\end{cases} \)
Notice the integrand function $b + cu(t)$ and the right-hand side of the
differential equations $\frac{db}{dt}, \frac{dn}{dt}, \frac{dw}{dt}$ are both linear functions of the variable $u$. Thus,
the Hamiltonian is also a linear function of $u$, and can be written

$$H = b + cu$$

$$+ \lambda_1 \left( k_b b(1 - b) - b \frac{k_{nr} n + \delta}{\lambda_{rbb} + 1} \frac{w}{w + k_w} - \lambda_b b \right)$$

$$+ \lambda_2 \left( k_p e^{-\lambda_p t} (1 - n) + \frac{k_{nw} b n (1 - n)(g_n w)}{\lambda_{mn} n + 1} - \frac{\lambda_n n}{1 + eb} \right)$$

$$+ \lambda_3 \left( \beta + \gamma \ast u(t) - \lambda_{w} w - \lambda_{bw} b w - \lambda_{nw} n w \right)$$

The necessary condition $\lambda' = -\frac{\partial H}{\partial \bar{E}}$ (see the linear Hamiltonian section for these
conditions) is as normal. However, the optimality condition

$$\frac{\partial H}{\partial u} = c + \gamma \lambda_3,$$

contains no information on the control. We must try to minimize the Hamiltonian
$H$ with respect to $u$ using the sign of $\frac{\partial H}{\partial u}$, but when $c + \gamma \lambda_3 = 0$, we cannot
immediately find a characterization of $u^\ast$.

Define $\psi(t) = c + \gamma \lambda_3$, usually called the switching function. If $\psi = 0$ cannot
be sustained over an interval of time, but occurs only at finitely many points, then
the control $u^\ast$ is referred to as bang-bang because it can jump from its maximum to
minimum value or vice-versa. In this case, it is a piecewise constant function,
switching between only the upper and lower bounds.

$u^\ast$ is called singular if $\psi \equiv 0$ over some interval of time. In order to
determine a characterization of $u^\ast$ over the interval where $\psi \equiv 0$, we set $\psi \equiv 0$ and
see if we can solve for any other variable (usually $\lambda$) and then use substitution to
determine the value of $u^\ast(t)$. Care must be taken at this point because if the value
of $u^\ast(t)$ is outside of our boundary conditions for $u$, then the singular control is not
achievable which forces our problem to be bang-bang.

For the linear control in our problem our characterization is given by:

\[
  u^*(t) = \begin{cases} 
  0 & \text{if } \psi(t) > 0 \\
  \frac{\lambda_w w + \lambda bw + \lambda nw - \beta + \frac{dw}{dt}}{\gamma} & \text{if } \psi(t) = 0 \\
  M2 & \text{if } \psi(t) < 0.
  \end{cases}
\] (14)

We determined \(u^*\) by solving for \(u\) in our \(\frac{dw}{dt}\) equation (3) in the introduction to the mathematical model. Our lower bound of oxygen input is 0 and M2 is chosen to be 5 because Schugart and Joyce use 5 as a maximum input of oxygen for topical therapies. The maximum amount of oxygen is lower using topical oxygen therapy than hyperbaric oxygen therapy.

If the problem is bang-bang, we use the same forward-backward sweep that we used for the non-linear case until we determine the control. Now instead of the control being determined by \(\max(0, \min(u \text{ solved for when } \frac{\partial H}{\partial u} = 0, M2))\); we must consider \(\psi\). Now \(u\) is determined by \(\psi\) as given in (14). For the singular case, we could put \(u^*\) as our solution when \(\psi(t) = 0\) but because our method is an approximation it is unlikely that \(\psi\) will ever be exactly zero. We could try to fix this by using the singular value for \(u^*\) when \(\psi\) is around zero (-0.00001,0.00001) but singular problems are often unstable for general control methods because the switching function is identically zero on some interval.

Researchers have determined additional necessary conditions, beyond Pontryagin’s Maximum Principle, which singular optimal controls must satisfy (Lenhart and Workman 2007). These include a generalized Legendre-Clebsch condition (also called a second order condition), which use higher derivatives with respect to the states and time, not just the controls. Also numerical solvers have been developed for problems which are linear in the control including gradient
methods, continuation methods, iterative dynamic programming, modified quasi-linearization methods, function space quasi-Newton methods, and adaptive shooting methods.

**Bang-Bang Test Problem**

In order to solve our linear control numerically, we formulated a simpler problem that could be solved analytically to test our coding. We wanted this problem to be similar to $J[u(t)] = \int_0^{t_1} [b(t) + cu(t)] \, dt$, so we chose to solve a similar problem (from Lenhart and Workman Problem 17.7)

$$\min_{a \leq u \leq b} \int_0^5 [4u(t) + x_1(t)] \, dt, \quad a < b$$

subject to:

$$\begin{cases} 
  x_1' = u(t) - x_2(t) \\
  x_2' = u(t) \\
  x_1(0) = x_{10}, x_2(0) = x_{20}.
\end{cases}$$

Our Hamiltonian for this problem is $H = 4u + x_1 + \lambda_1(u - x_2) + \lambda_2u$. Our partial derivative of $H$ with respect to $u$ is $\frac{\partial H}{\partial u} = 4 + \lambda_1 + \lambda_2$ so we define our switching function $\psi$ to be $\psi = 4 + \lambda_1 + \lambda_2$.

Thus we can solve for $\lambda_1'$ and $\lambda_2'$ using the definitions that $\lambda_1 = -\frac{\partial H}{\partial x_1} = 1$ and $\lambda_2 = -\frac{\partial H}{\partial x_2} = -\lambda_1$. Using $\lambda_1(5) = \lambda_2(5) = 0$ we see that $\lambda_1(t) = t - 5$ and

$$\lambda_2(t) = -\frac{t^2}{2} + 5t - \frac{25}{2}.$$  

If $\psi = 0$ on some interval then $\psi = 4 + \lambda_1 + \lambda_2 = 0$ which occurs when $t = 3$ and 9, but 9 is outside of our $0 \leq t \leq 5$ time frame. So $u^*$ is bang-bang. Assuming $u$
is a constant, $k$ then:

\[
\begin{cases}
  x_1' = k - x_2 = k - kt - x_{20} \rightarrow x_1 = \frac{-kt^2}{2} + kt - x_{20}t + c_1 = \frac{-kt^2}{2} + (k - x_{20})t + x_{10} \\
  x_2' = k \rightarrow x_2 = kt + c_2 = kt + x_{20}
\end{cases}
\]

\[
\psi = 0 \text{ implies that either } k = a \rightarrow x_2 = at + x_{20} \text{ and } k = b \rightarrow x_2 = bt + x_{20}
\]
at $t = 3$ this implies $a = b$ which gives a contradiction to the assumption that $a < b$ therefore $\psi \neq 0$ and $u$ cannot be singular. So we have the following:

\[
x_1(t) = \frac{1}{2} + c_1 \ast \cosh(t) + c_2 \ast \sinh(t)
\]

\[
x_1(0) = \frac{1}{2} + c_1 = 0 \rightarrow c_1 = \frac{-1}{2}
\]

\[
x_1(t) = \frac{1}{2} + \frac{-1}{2} \ast \cosh(t) + c_2 \ast \sinh(t)
\]

\[
x_2(t) = -\frac{1}{2} \ast \sinh(t) + c_2 \ast \cosh(t)
\]

\[
x_2(0) = c_2 = 0.
\]

Using the above and the fact that $x_1$ is continuous at $t = 3$ we solve and find that after assigning values to the variables $a = 0, b = 1, x_1(0) = x_2(0) = 0$ we have:

\[
x_1(t) = \begin{cases} 
  -\frac{t^2}{2} + t & \text{when } t \leq 3 \\
  -3t + \frac{15}{2} & \text{when } t \geq 3,
\end{cases}
\]

\[
x_2(t) = \begin{cases} 
  t & \text{when } t \leq 3 \\
  3 & \text{when } t \geq 3.
\end{cases}
\]

Figures 15 and 16 show that our analytical and numerical solutions match. Another linear test problem is given in Appendix B, which gave a bang-bang solution that is constant, not piecewise constant.
Figure 15: This figure shows that our values for $\vec{x}$ and $\vec{\lambda}$ from our analytical and numerical solutions match, because the two solutions overlap.

Figure 16: This figure shows that our values for $u$ from our analytical and numerical solutions match, because the two solutions overlap. You can also see the bang-bang of this case at $t=3$. 
Linear Solution

Using the Hamiltonian given in the first section and numerical analysis methods given in the section on linear numerical analysis, we have worked to find a linear solution.

We first tried to follow the method used in our test problem. Using this method our value for $u$ is updated by an average as in our non-linear solution. We were unable to meet our convergence criteria for our linear case even after we adjusted parameter values and tried using three different initial guesses for $u$ (0, 0.5, -M2*t/tf+M2), where M2=5 as we had in our non-linear case.

In Figure (17) the code has been adjusted using the convex combination or weighted average update of $u$. Figure (18) shows that the bacteria persists when our initial guess for oxygen is zero. Oxygen is administered at the dimensionless maximum value (5) only right before the end of our 14 day time period. When we start with oxygen being 0.5 (dimensionless value), our oxygen is administered at the dimensionless maximum value (5) on day one, the bacteria is removed in approximately a day but the oxygen input remains at a maximum. When the initial input of oxygen is $u = -M2*t/tf + M2$, oxygen is input at a maximum value for our 14 day time period even though the bacteria is removed in under a day. These results indicate instability with our code because the initial value for $u$ varies our results greatly. These results also are not useful biologically because topical oxygen cannot be given at the maximum value for such an extended period of time.
for $i = 1:N+1$
    $temp = c + gamma*\lambda(i)$;  % psi for our problem=dH/dS
    if abs(temp)<eps
        temp=0;
    end
    if temp < 0
        $u(i) = \text{MIN} \text{ with } x\text{ max oxygen}$
    else
        disp(temp)
        if $i == 1$
            $u(i) = (\text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda})/2/\gamma$;
        elseif $i == N+1$
            $u(i) = (\text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda})/2/\gamma$;
        else
            $u(i) = (\text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda} + \text{lambda})/2/\gamma$;
        end
    end
end

Figure 17: Code for linear weighted average update of $u$.

Figure 18: Results for $u$ initially 0 and $(b, n, w) = (0.9, 0.2, 0.5)$. The bacteria persist in the wound. Oxygen is administered at the dimensionless maximum value, 5, only right before the end of our 14 day time period.
Figure 19: Results for $u$ initially 0.5 and $(b, n, w) = (0.9, 0.2, 0.5)$. Oxygen is administered at the dimensionless maximum value, 5, at approximately a day into the model. The bacteria is removed at that point but the oxygen remains at the maximum value. This is not a biologically applicable solution because we want to minimize the amount of oxygen given.
Figure 20: Results for \( u \) initially \(-M_2t/t_f+M_2\) and \((b, n, w) = (0.9, 0.2, 0.5)\). Oxygen is administered at the dimensionless maximum value (5) at approximately a day into the model. The bacteria is removed at that point but the oxygen remains at the maximum value. This is not a biologically applicable solution because we want to minimize the amount of oxygen given and we cannot give topical oxygen therapy for 14 days continuously.

Table 4: Results for weighted average of \( u \) in linear case.
We are still seeking a better way to update $u$ in order to have convergence and less dependence on the initial guess of $u$. Table 4 shows the instability of this code. All $J$ values for $u$ initially $-M2^t/t_f+M2$ are over 1,000 but they are as low as 625 for $u$ initially zero. Within each set of $J$ values for given initial and parameter values there are no cases where all three $J$ values agree.

Using an interval for when $\psi$ is close to zero (-0.00001,0.00001), as mentioned in the linear numerical analysis section, does not change our results. We cannot use the method of steepest descent because our $\frac{\partial H}{\partial u}$ is not dependent on $u$ in the linear case. Thus we cannot directly control $u$ in order to minimize $\frac{\partial H}{\partial u}$ so this method is not applicable to our linear problem.
IV. CONCLUSIONS AND FUTURE WORK

We have developed a non-linear and linear model using optimal control theory to represent hyperbaric and topical oxygen therapies. We provided existence and uniqueness proofs for our non-linear case and existence for our linear case. We then formulated test problems to compare our numerical methods to analytical solutions before applying it to our model. Our numerical method was modified by testing parameters, adjusting initial guesses for $u$, adjusting how $u$ was updated with each iteration of the code and modifying our convergence criteria. We also considered various objective functionals to solve our problem.

Our results for hyperbaric oxygen treatment suggest that it is best to start administering a large amount of oxygen and then progressively decrease to zero. For most cases, our current results yield a person receiving oxygen for approximately a day. However, that is above the amount of oxygen permitted to be administered because of the risk of oxygen toxicity. We obtain similar results for different initial conditions and parameter values.

For topical treatment, our current results are to wait a period of time and then administer oxygen at the highest amount possible for the duration of the time allotted in the 14 day window given. This is not an ideal result as we want to minimize oxygen intake and this keeps oxygen at the maximum even after the wound is healed. However, oxygen toxicity is not a problem with topical oxygen therapy. While our convergence criteria has been met for our numerical methods, our results indicate numerical instability and further numerical studies are warranted.

There are several areas of future work for this project. First, a more stable method should be found for our linear case. The steepest descent algorithm does not apply to bang-bang cases. The problem with our numerics is that we are trying to use a gradient-based method where $u$ is neither continuous or differentiable.
Thus, more work should be done to approximate our function with a continuous smooth function that can be solved numerically. From that hopefully a more biologically applicable solution will be found.

We have not yet considered looking at minimizing $J[u] = \int (b - cub + \frac{du^2}{2})dt$, where $c$ and $d$ are constants. This would minimize bacteria, while maximizing the input of oxygen’s effect on the bacteria and minimizing the non-linear uptake of oxygen. Another set of functionals to consider are time-dependent functionals. In these, we want to not only minimize the amount of oxygen input into the wound but also the duration, in weeks, of treatments. One could begin looking at minimizing $J[u, T] = \int_0^T \left(1 + b + \frac{c}{2}u^2\right) dt$ because the basic problem to minimize time is to minimize $J[u, T] = \int_0^T 1 dt = T$. Existence and uniqueness would hold by the work shown in the sections on non-linear existence and uniqueness. Note when minimizing final time we have new additional necessary conditions. The Hamiltonian must be zero at the final time if there is no payoff or salvage term. See Lenhart and Workman (Chapters 3, 20, 21) for further details. The numerics for this kind of time dependent problem would be more difficult because we would need to iterate the code for the final time. Newton’s method may also be able to be applied in this situation as well.

After minimizing the duration of treatments over weeks, one could consider minimizing the amount of treatment per day. This would help us get to a case that is optimal and applicable to patients. Our current results are not able to be directly applied because as they are they would cause oxygen toxicity. Another approach to consider is trying to minimize bacteria at the final time. This would change our terminal condition that $\lambda(T) = 0$. Finally, we would want to consider larger-scale models (including more equations and parameters) and partial-differential-equation (PDE) models. However, Pontryagin’s minimum principle cannot be applied to some PDE models (Lenhart and Workman, 2007).
APPENDIX A

The following gives additional explanation to the work given in Lenhart and Workman Chapter 1 pages 8-12.

Our optimal control problem is given with bounded state and control variables to be mapped into \( \mathbb{R} \),

\[
\begin{align*}
  x &: [a, b] \rightarrow \mathbb{R} \quad \text{state variables} \\
  u &: [a, b] \rightarrow \mathbb{R} \quad \text{control variable}.
\end{align*}
\]

Our goal is to maximize or minimize our functional \( J[u] \) with respect to \( u \),

\[
J[u] = \int_{t_0}^{t_1} f(t, x(t), u(t)) dt.
\]

We want to choose \( u \) to maximize or minimize \( J[u] \) such that

\[
\begin{align*}
  x'(t) &= g(t, x(t), u(t)) \\
  x(t_0) &= x_0 \\
  x(t_1) &= x_0 \quad \text{(free)}.
\end{align*}
\]

Our technique to solve the problem is to use our necessary condition: if \( u^*(t), x^*(t) \) optimal values exist then the following conditions hold:

\[
\begin{align*}
  H(t, x, u, \lambda) &= f(t, x, u) + \lambda \ast g(t, x, u) \\
  &= \text{integrand + adjoint} \ast \text{RHS of DE} \\
  \frac{\partial H}{\partial u} &= 0 \text{ at } u^* \Rightarrow f_u + \lambda g_u = 0 \quad \text{(optimality condition)}, \\
  \lambda' &= -\frac{\partial H}{\partial x} \Rightarrow \lambda' = -(f_x + \lambda g_x) \quad \text{(adjoint equation)}, \\
  \lambda(t_1) &= 0 \quad \text{(transversality condition)}.
\end{align*}
\]
We are given the dynamics of the state equation:

\[ x' = g(t, x, u) = \frac{\partial H}{\partial \lambda}, \quad x(t_0) = x_0. \]

Assuming the optimal control exists then \( J[u] \leq J[u^*] < \infty \) (for a maximization problem). Let \( h(t) \) be a piecewise continuous variation function and \( \epsilon \in \mathbb{R} \) a constant. Then,

\[ u^\epsilon(t) = u^*(t) + \epsilon h(t) \]

is another piecewise continuous control. Let \( x^\epsilon \) be the state corresponding to the control \( u^\epsilon \), namely, \( x^\epsilon \) satisfies

\[ \frac{d}{dt}x^\epsilon(t) = g(t, x^\epsilon(t), u^\epsilon(t)) \]

wherever \( u^\epsilon \) is continuous. We have the following four properties:

1. \( \lim_{\epsilon \to 0} u^\epsilon(t) = u^*(t) \forall t \) because \( u^\epsilon(t) = u^*(t) + \epsilon h(t) \) and \( \epsilon h(t) \) goes to 0.
2. \( \left. \frac{\partial u^\epsilon(t)}{\partial \epsilon} \right|_{\epsilon=0} = h(t) \).
3. \( \lim_{\epsilon \to 0} x^\epsilon(t) = x^*(t) \forall t \) because of our assumptions on \( g \).
4. \( \left. \frac{\partial x^\epsilon(t)}{\partial \epsilon} \right|_{\epsilon=0} \) exists for each value of \( t \).

The objective functional at \( u^\epsilon \) is

\[ J[u^\epsilon] = \int_{t_0}^{t_1} f(t, x^\epsilon(t), u^\epsilon(t))dt. \]

The adjoint function \( (\lambda) \) appends the differential equation to the integrand of the objective functional. (This is like adding zero to an equation to make the equation work). Let \( \lambda(t) \) be a piecewise differentiable function on \([t_0, t_1]\). By the
We want to choose our adjoint function to simplify the above equation by making

\[ \int_{t_0}^{t_1} \frac{d}{dt} [\lambda(t)x^\epsilon(t)]dt = \lambda(t_1)x^\epsilon(t_1) - \lambda(t_0)x^\epsilon(t_0), \]

which implies

\[ \int_{t_0}^{t_1} \frac{d}{dt} [\lambda(t)x^\epsilon(t)]dt - \lambda(t_1)x^\epsilon(t_1) + \lambda(t_0)x_0 = 0 \]

because \( x_0 = x^\epsilon(t_0) \). Adding this 0 expression to our \( J[u^\epsilon] \) gives

\[
J[u^\epsilon] = \int_{t_0}^{t_1} \left[ f(t, x^\epsilon(t), u^\epsilon(t)) + \frac{d}{dt} (\lambda(t)x^\epsilon(t)) \right]dt + \lambda(t_0)x_0 - \lambda(t_1)x^\epsilon(t_1)
\]

\[
= \int_{t_0}^{t_1} \left[ f(t, x^\epsilon(t), u^\epsilon(t)) + \lambda(t) \frac{d}{dt} x^\epsilon(t) + x^\epsilon \lambda(t) \right]dt + \lambda(t_0)x_0 - \lambda(t_1)x^\epsilon(t_1)
\]

\[
= \int_{t_0}^{t_1} \left[ f(t, x^\epsilon(t), u^\epsilon(t)) + \lambda(t)g(t, x^\epsilon(t), u^\epsilon(t)) + x^\epsilon \lambda(t) \right]dt + \lambda(t_0)x_0 - \lambda(t_1)x^\epsilon(t_1).
\]

Also, suppose \( \epsilon = f(u^\epsilon) \) then

\[
0 = \frac{d}{du^\epsilon} J[u^\epsilon] = \frac{d}{du^\epsilon} \epsilon \frac{dJ}{d\epsilon}.
\]

Then \( \frac{d}{du^\epsilon} J[u^\epsilon] \) is maximized when \( \frac{dJ}{d\epsilon} \bigg|_{\epsilon=0} \) and when \( \epsilon = 0, \ u^\epsilon(t) = u^* (t) \). So we have

\[
0 = \frac{\partial}{\partial \epsilon} J[u^\epsilon] \bigg|_{\epsilon=0} = \int_{t_0}^{t_1} \left[ f_x \frac{\partial}{\partial \epsilon} x^\epsilon + f_u \frac{\partial}{\partial \epsilon} u^\epsilon + \lambda(t) \left( g_x \frac{\partial}{\partial \epsilon} x^\epsilon + g_u \frac{\partial}{\partial \epsilon} u^\epsilon \right) + \lambda'(t) \frac{\partial}{\partial \epsilon} x^\epsilon \right] dt \bigg|_{\epsilon=0} - \lambda(t_1) \frac{\partial}{\partial \epsilon} x^\epsilon(t_1) \bigg|_{\epsilon=0}.
\]

Note: If \( \epsilon = 0 \), then \( \frac{d}{dx} f(t, x^\epsilon, u^\epsilon) = \frac{d}{d\epsilon} (f, x^\epsilon, u^*) \). Then rearranging the terms gives,

\[
0 = \int_{t_0}^{t_1} \left[ (f_x + \lambda(t)g_x + \lambda'(t)) \frac{\partial}{\partial \epsilon} x^\epsilon(t) \bigg|_{\epsilon=0} + (f_u + \lambda(t)g_u) h(t) \right] dt - \lambda(t_1) \frac{\partial}{\partial \epsilon} x^\epsilon(t_1) \bigg|_{\epsilon=0}.
\]

We want to choose our adjoint function to simplify the above equation by making
the coefficients of $\frac{\partial}{\partial \epsilon} x^\epsilon(t) \bigg|_{\epsilon=0}$ vanish. Thus, we choose the adjoint function $\lambda(t)$ to satisfy

$$\lambda'(t) = -[f_x(t, x^*(t), u^*(t)) + \lambda(t)g_x(t, x^*(t), u^*(t))] \quad \text{(adjoint equation),}$$

and the boundary condition

$$\lambda(t_1) = 0 \quad \text{(transversality condition).}$$

So our equation reduces to

$$0 = \int_{t_0}^{t_1} (f_u(t, x^*(t), u^*(t)) + \lambda(t)g_u(t, x^*(t), u^*(t))) h(t)dt.$$

This holds for any piecewise continuous variation function $h(t)$, so it holds for

$$h(t) = f_u(t, x^*(t), u^*(t)) + \lambda(t)g_u(t, x^*(t), u^*(t)).$$

In this case we have

$$0 = \int_{t_0}^{t_1} (f_u(t, x^*(t), u^*(t)) + \lambda(t)g_u(t, x^*(t), u^*(t)))^2 dt,$$

which implies our optimality condition

$$f_u(t, x^*(t), u^*(t)) + \lambda(t)g_u(t, x^*(t), u^*(t)) = 0 \quad \text{for all} \quad t_0 \leq t \leq t_1.$$
APPENDIX B

Extra Linear Test Problem

In order to solve our linear control numerically, we created a simpler test problem that could be solved analytically to test our coding and to help us learn about any potential pitfalls. We wanted this problem to be similar to the index one

\[ J[u(t)] = \int_{0}^{t_1} [b(t) + cu(t)] \, dt \]

so we formulated a linear problem similar to our non-linear test problem:

\[
\min_{-0.5 \leq u \leq 0.5} \int_{0}^{1} [x_2 + u] \, du
\]

subject to:

\[
\begin{aligned}
  x_1' &= x_2 \\
  x_2' &= x_1 + u \\
  \lambda_1' &= -\lambda_2 \\
  \lambda_2' &= -\lambda_1 - 1.
\end{aligned}
\]

Our Hamiltonian for this problem is \( H = x_2 + u + \lambda_1 x_2 + \lambda_2 (x_1 + u) \). Our partial derivative of \( H \) with respect to \( u \) is \( \frac{\partial H}{\partial u} = 1 + \lambda_2 \) so we define our switching function \( \psi \) to be \( \psi = 1 + \lambda_2 \).

If \( \psi = 0 \) on some interval then \( \psi = 1 + \lambda_2 = 0 \) which means that \( \lambda_2 = -1 \rightarrow \lambda_1' = 1 \) and \( \lambda_2' = 0 = -\lambda_1 - 1 \rightarrow \lambda_1 = 1. \) This causes a contradiction as \( \lambda_1 = 1 \) and \( \lambda_1' = 1 \) cannot both simultaneously be true. Thus \( \psi \neq 0 \) for any time interval. So \( u^* \) only admits a bang-bang solution.

Thus, we have

\[
\begin{cases}
  u^* = -0.5 \iff \psi > 0 \iff 1 + \lambda_2 > 0 \iff \lambda_2 > -1 \\
  u^* = 0.5 \iff \psi < 0 \iff 1 + \lambda_2 < 0 \iff \lambda_2 < -1.
\end{cases}
\]  

(15)

Notice that \( \lambda_1'' = -\lambda_2' \) so \( \lambda_1'' = \lambda_1 + 1 \) and \( \lambda_1(1) = 0, \lambda_1'(1) = 0. \) Let \( y = \lambda_1 + 1. \) Then
\( y'' = y \) with \( y(1) = 1, y'(1) = 0 \). So we have

\[
y(t) = c_1 e^t + c_2 e^{-t}
\]
\[
y'(1) = c_1 e - c_2 e^{-1} = 0
\]
\[
y'(1) = c_1 e^2 - c_2 = 0
\]
\[
\Rightarrow c_2 = c_1 e^2
\]
\[
y(t) = c_1(e^t + e^{-2t})
\]
\[
y(1) = c_1(e + e) = 1 \Rightarrow c_1 = 0.5 e^{-1}
\]
\[
y(t) = \frac{1}{2}(e^{t-1} + e^{1-t})
\]
\[
\lambda_1(t) = \frac{1}{2}(e^{t-1} + e^{1-t}) - 1
\]
\[
-\lambda_2(t) = \lambda_1'(t) = \frac{1}{2} (e^{t-1} - e^{1-t})
\]
\[
\lambda_2(t) = -\frac{1}{2} (e^{t-1} + e^{1-t}).
\]

Then we solved for when \( \lambda_2(t) < -1 \) (15):

\[
\lambda_2(t) = -\sinh(t - 1) < -1
\]
\[
\lambda_2(t) = \sinh(t - 1) > 1
\]
\[
t - 1 > \sinh^{-1}(1)
\]
\[
t > 1 + \sinh^{-1}(1) = 1 + \ln(1 + \sqrt{2}) \approx 1.8814.
\]

Similarly we solved for when \( \lambda_2 > 1 \):

\[
\lambda_2(t) = -\sinh(t - 1) > -1
\]
\[
\sinh(t - 1) < 1
\]
\[
t < 1 + \sinh^{-1}(1) = 1 + \ln(1 + \sqrt{2}) \approx 1.8814.
\]

Thus \( u^* = -0.5 \) for \( 0 \leq t \leq 1.8814 \). In order to find \( x_1^*(t) \) and \( x_2^*(t) \) we will
substitute in our value for the optimal control, \( u^* \) and solve.

\[
\begin{align*}
x'_1 &= x_2 \\
x'_2 &= x_1 - 0.5 \\
x_1(0) &= 0, x_2(0) = 0
\end{align*}
\]  

(19)

Similar to what we did with \( \lambda_1 \) above, we have \( x''_1 = x_1 - 0.5 \) and \( x'_1(0) = 0 \). Let \( y = x_1 - 0.5 \). Then \( y'' = y, y(0) = -0.5, y'(0) = 0 \). Solving yields

\[
y(t) = d_1 * e^t + d_2 * e^{-t} \\
y'(0) = d_1 - d_2 = 0 \rightarrow d_1 = d_2 \\
y(0) = d_1 + d_2 = 2d_1 = -0.5 \\
y(t) = -0.5 * \frac{e^t + e^{-t}}{2} = -0.5 * \cosh(t).
\]

Thus, we have

\[
\begin{align*}
x_1(t) &= 0.5 - 0.5 * \cosh(t) \\
x_2(t) &= -0.5 * \sinh(t).
\end{align*}
\]

Figures (21) and (22) show that our analytical and numerical solutions match, because the two solutions overlap.
Figure 21: This figure shows that our values for $x$ and $\lambda$ from our analytical and numerical solutions match, because the two solutions overlap.

Figure 22: This figure shows that our values for $u$ from our analytical and numerical solutions match, because the two solutions overlap.
APPENDIX C

Figures 23-27 give the basic code that we used for the non-linear case, where 
\( u \) is updated using the average of the old and new \( u \) values. This has been adjusted
to form our other cases (different updates of \( u \) and our linear case). Some of these
adjustments have been given previously, (see Figures (6), (11), and (17)).
function y = problemoneadaptionwithnewaddition(s(b0,n0,w0,A,B,C,D)) % assigns variable b0, n0 and w0 as inputs, y as output

test = -1; % convergence test variable- begins the while loop with a neg % number
zeta = 0.001; % space between nodes
N = 1000; % number of nodes
t = linspace(0,t,N+1); % creates N+1=1001 equally spaced nodes
h = t/N; % spacing is assigned as h
h2 = h/2; % short-hand for Runge-Kutta subroutine (h2 short for h/2)
M1 = 0;
M2 = 16.37;
% u = zeros(1,N+1);
u = zeros(1,N+1);
u = -M2*(t/2 + M2); % initial guess for u where u(1) = 0
n = zeros(1,N+1); % vector n and size
n(1) = n0; % initial condition for n because matlab recognizes 1 as the % first element
% n(N+1) = n;
b = zeros(1,N+1); % vector b and size
b(1) = b0; % initial condition for b
w = zeros(1,N+1); % vector w and size
w(1) = w0; % initial condition for w
lambda1 = zeros(1,N+1); % lambda1 and size
lambda2 = zeros(1,N+1);
lambda3 = zeros(1,N+1);
%exact = zeros(1,N+1);
%exact = zeros(1,N+1);
k = 0;
while(test < 0.5 & k<25000) % when convergence occurs test will become non-negative
  k = k+1;
  c = 1;
  oldu = u; % previous value of u
  oldn = n; % previous value of n
  oldb = b; % previous value of b
  oldw = w; % previous value of w
  oldlambda1 = lambda1; % previous value of lambda1
  oldlambda2 = lambda2; % previous value of lambda2
  oldlambda3 = lambda3; % previous value of lambda3
  kb = 14.256;
  kew = 2*kb;
  delta = 3.84*b;
  lambdabar = 3.73;
  kw = .75;
  lambdab = 0.14256;
  kp = 0.052;
  lambdap = 3.04;
  kri = 10.28;
  lambdani = 8;
  lambdan = .1728;
  gamma = 1;
  lambdaw = 1.0656;
  beta = 0.7992;
  lambdabw = 12.6593/C;
  lambdanw = 25.5744/D;

Figure 23: Basic Code Part 1

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\[ e = 100; \]

% DE solving:
\[
\% b=b(kb*exp[(kni*n+delta)/(lambda*b)]+(kb*exp[(kni*n+delta)/(lambda*b)]+w(1111+kd)-lambda*b)); \]
% n-kn*exp[(lambda*n+delta)/(lambda*b)](n11111+kn1+n)*n(1-n)*gw(w(1111)+lambda*b))
% -lambda*n(1+exp[1])b
% w=w+beta*lambda*b*w-lambda*kn1*b*w-lambda*kn2*b*w
% n(0)=0, b(0)=binit, w(0)=winit

for i = 1:N % begins for loop - i from 1 to N
  k1 = kb*exp[(kni*n+delta)/(lambda*b)]+(kb*exp[(kni*n+delta)/(lambda*b)]+w(1111+kd)-lambda*b)); % Range-Kutta 4 method
  k2 = kb*exp[(kni*n+delta)/(lambda*b)]+(kb*exp[(kni*n+delta)/(lambda*b)]+w(1111+kd)-lambda*b));
  k3 = kb*exp[(kni*n+delta)/(lambda*b)]+(kb*exp[(kni*n+delta)/(lambda*b)]+w(1111+kd)-lambda*b));
  k4 = kb*exp[(kni*n+delta)/(lambda*b)]+(kb*exp[(kni*n+delta)/(lambda*b)]+w(1111+kd)-lambda*b));
  n(i+1) = n(i)+h/2*(k1+2*k2+2*k3+k4); % next step
  b(i+1) = b(i)+h/6*(k1+2*k2+2*k3+4*k4); % next step
  w(i+1) = w(i)+h/6*(k1+2*k2+2*k3+4*k4); % next step
end

% DE solving lambda1 = [1-lambda1*(kb*b*exp[(kni*n+delta)/(lambda*b)] end

% lambda2 = [lambda2*exp[(kni*n+delta)/(lambda*b)](n11111+kn1+n)*n(1-n)*gw(w(1111)+lambda*b))
% -lambda2*n(1+exp[1])b
% w=w+beta*lambda2*b*w-lambda2*kn1*b*w-lambda2*kn2*b*w
% n(0)=0, b(0)=binit, w(0)=winit

\[ \text{Figure 24: Basic Code Part 2} \]
Figure 25: Basic Code Part 3

```plaintext
%lambda3*=[lambda11*(kzn*n+delta))/((lambda*b+1)^(kw))/((w+kw)^(2))+lambda2*[65
%lambda3*=(lambda*b+1)^(kw));

for i = 1:N % begins for loop -- 1:N means i from 1 to N
i = N + 2 - b % j counts backward from N+1 to 2
k11 = (lambda11*(b+2)*kzn*n*delta);

k12 = lambda11*(b+1)*w/(w+kw);

k13 = lambda11*(w+kw)/(w+kw);

k14 = lambda11*(b+1)*w/(w+kw);

k15 = lambda11*(w+kw)/(w+kw);

k16 = lambda11*(b+1)*w/(w+kw);

k21 = lambda11*(b+2)*kzn*n*delta;

k22 = lambda11*(b+1)*w/(w+kw);

k23 = lambda11*(b+1)*w/(w+kw);

k24 = lambda11*(w+kw)/(w+kw);

k25 = lambda11*(b+1)*w/(w+kw);

k26 = lambda11*(w+kw)/(w+kw);

k31 = lambda11*(b+2)*kzn*n*delta;

k32 = lambda11*(b+1)*w/(w+kw);

k33 = lambda11*(b+1)*w/(w+kw);

k34 = lambda11*(w+kw)/(w+kw);

k35 = lambda11*(b+1)*w/(w+kw);

k36 = lambda11*(w+kw)/(w+kw);

k41 = lambda11*(b+2)*kzn*n*delta;

k42 = lambda11*(b+1)*w/(w+kw);

k43 = lambda11*(b+1)*w/(w+kw);

k44 = lambda11*(w+kw)/(w+kw);

k45 = lambda11*(b+1)*w/(w+kw);

k46 = lambda11*(w+kw)/(w+kw);

```

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Figure 26: Basic Code Part 4
```matlab
subplot(4,1,1)
plot(t,b,'r')
ylabel('b')
title('Optimal control results for b, n, w, u(t)')
subplot(4,1,2)
plot(t,n,'r')
ylabel('n')
subplot(4,1,3)
plot(t,w,'r')
ylabel('w')
subplot(4,1,4)
plot(t,u,'r')
ylabel('u(t)')
xlabel('t (in days)')

figure(2)
hold on;

subplot(3,1,1)
plot(t,lambda1,'r')
ylabel('\lambda_1')
title('Optimal control results for \lambda_1, \lambda_2, \lambda_3')
subplot(3,1,2)
plot(t,lambda2,'r')
ylabel('\lambda_2')
subplot(3,1,3)
plot(t,lambda3,'r')
ylabel('\lambda_3')
xlabel('t (in days)')

%display(k =)
display(k)
%-------------------------------------------------------------------------
function gnwvalue=gnw(w)
if w<1
  % if w<0
  %   error('w is negative')
  %end
gnwvalue=2*w^3-3*w^2+2;
else
gnwvalue=1;
end
%--------------------------------------------------------------------------
function gnwprimevalue=gnwprime(w)
if w<1
  if w<0
    error('w is negative')
  end
gnwprimevalue=6*w^2-6*w;
else
gnwprimevalue=0;
end
```

Figure 27: Basic Code Part 5
REFERENCES


factor expression and improves closure of clinically presented chronic wounds.

Clinical and Experimental Pharmacology and Physiology 35(8): 957 - 964.


