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Numerical Simulations for Optimal Control of a Cancer Cell Model With Delay

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Abstract

Mathematical models are often created to analyze the complicated behavior of many physical systems. One such system is that of the interaction between cancer cells, the immune system, and various treatments such as chemotherapy, radiation, and immunotherapy. Using models that depict these relationships gives researchers insight on the dynamics of this complicated system and possibly ideas for improved treatment schedules.

The model presented here gives the relationship of cancer cells in different phases of development, along with immune cells and cycle-specific chemotherapy treatment. This model includes a constant delay term in the mitotic phase, where cells divide, which leads to more complicated analyses. Optimal control theory is used to minimize the cost of the chemotherapy and the number of cancer cells. Numerical methods, such as a forward-backward sweep method and adjusted methods to evaluate delays, are used to show qualitative treatment options.

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Chapter 1

Introduction

Cancer is a term used to describe over 100 diseases in which cells are changed in negative ways. These cells typically develop in three major phases: the mitotic (dividing) phase, the quiescent (resting) phase, and the interphase (cell growth). The body's natural defense against these cells are the white blood cells, or lymphocytes. However, when the cancer cells overpower the lymphocytes, it is common for the cells to be treated with chemotherapy. Liu et al. [19] consider this system of interactions between the cancer cells, lymphocytes, and chemotherapy extensively.

Using chemotherapy as a treatment option presents a serious drawback. While this treatment will kill the cancer cells, it will also kill the lymphocytes and presents a toxicity concern to the patient. This complexity brings about varying strategies of treatment. Immunotherapy is one such treatment, which could increase the patient's success with combating cancer by boosting the immune system while other treatments are applied. Research from Barsoumian et al. [1] investigate stimulating immune system cells at checkpoints before cancer cells are detected to combat cancer before it becomes malignant. Kirschner and Panetta [17] investigated a treatment combining chemo- and immunotherapies, but found that their specific treatment is better suited as a monotherapy or with other immune components.

Mathematical approaches are often sought out to preface clinical trials, as different scenarios can be considered without consequence. This allows for a more accurate approach to treatments and a better quality of life for patients [21]. Several mathematical researchers have taken on this project in different ways. Optimal control theory is often applied to cancer treament by creating a means of quantifying the most desired, or "best," behavior of the tumor and immune system dynamics. In the case of cancer treatment, "best" usually means minimizing the number of cancer cells while minimizing the toxicity and damage done to the body caused by chemotherapy. Fister and Donnelly [10] extended the Kirschner and Panetta work using optimal control theory to define and analyze a "best" solution concept. de Pillis et al. [7] analyzed optimal control strategies with traditional nonlinear controls in the objective functionals for the case of chemo-immunotherapeutic treatments. Works by Kim et al. [16], Swan and Vincent [24], and Murray [22] are examples of successfully applying this concept as well. In this thesis, we analyze two situations of "best," which are given by the objective functionals. The first minimizes cancer cell count and the cost associated with chemotherapy throughout the entire process, while the second seeks to minimize the cost of the chemotherapy throughout, as well as the cancer cell count at the final time.

Other researchers utilize delays to model the interaction between the tumor cells and the immune system. The recent work by Cui and Xu [5] studies delay terms in the phase shift from the mitotic phase to the production of the daughter cells in models that investigate nonnecrotic and necrotic tumors. The aforementioned study by Liu et al. [19] delves deeply into a cycle-specific model, and considers the presence of a delay between the interphase and mitotic phase. Their work shows that the delay greatly influences the cancer as a whole when considering treatment. Delays in differential equations present a unique challenge to analysis, as shown in [2]. Challenges become more difficult to accommodate when the delay is time– or state–dependent. The case for Liu et al. [19] considers a constant delay. Here, we investigate the nondimensionalized model from [19], attempting to find an optimal treatment

schedule while incorporating the importance of the delay.

Collins et al. [3] provides the existence and uniqueness of a solution for the delay differential equation system and the existence of an optimal control. From there, this paper seeks to approximate solutions for a treatment schedule, differing from [19] in that we seek to incorporate both the delay and the optimal control.

The arrangement of this thesis begins with a description of the model being used in Chapter 2, with Chapter 3 giving context to the objective functionals and the characterization of an optimal control. Numerical methods, such as Runge-Kutta and forward-backward sweep methods, are located in Chapter 4. A discussion of results is provided in Chapter 5, which presents different cases of a "best" situation and a scheduled treatment approach to better model real life. We conclude with Chapter 6, summarizing results and exploring possibilities for future work.

Chapter 2

The Model

Several models in the literature analyze the effects of chemotherapy on patients. Most focus on minimizing both the amount of chemotherapy administrated and the final size of the tumor. Some researchers model different aspects of the immune system, while others investigate an immunotherapeutic approach [17]. Newer models propose a combined immuno–chemotherapy treatment, or focus on the different cell phases, as in [25] and [19].

Optimal control theory is often applied to cancer therapy models. The works of Swan and Vincent [24] and Murray [22] use optimal control theory to minimize the toxicty of chemotherapy. Other research by de Pillis et al. [7] and Fister and Donnelly [10] utilize optimal control theory to find an effective treatment schedule.

2.1 The Model

This model considers the effect of including different phase shifts of the tumor cells. There are three phases of the cell cycle: the mitotic phase where cells divide, the quiescent phase where cells rest, and the interphase when cells prepare for mitosis. Liu et al. [19] developed the relationships between the cells in the three phases, the immune system, and the cycle-specific

drug. Table 2.1 gives a description of each variable.

Variable	*Variable Description*
x	number of cancer cells in interphase phase
y	number of cancer cells in the mitotic phase
z	number of cancer cells in the quiescent phase
I	number of lymphocytes
u	biomass of chemotherapy drug in mg

Table 2.1: Description of Variables

2.1.1 Existence and Uniqueness

Existence and uniqueness of a solution for this delay differential equation system was established using results from Driver [9] and can be found in Collins et al. [3]. The control term, $v(t)$, represents the inclusion of chemotherapy as a drug administration, placing it appropriately in the differential equation that quantifies the amount of drug in the system.

2.1.2 The Equations

The system of differential equations is given by:

$$\frac{dx}{dt} = s\alpha_3 z(t) - \alpha 1 x(t) - (\sigma_1 + k_1 I(t))x(t) \tag{2.1.1}$$

$$\frac{dy}{dt} = \alpha_1 x(t-\tau) - (\alpha_2 + \sigma_2 + k_2 I(t)y(t) - k_4(1 - e^{-k_5 u(t)})y(t) \tag{2.1.2}$$

$$\frac{dz}{dt} = 2s^{-1}\alpha_2 y(t) - (\alpha_3 + \sigma_3 + k_3 I(t))z(t) \tag{2.1.3}$$

$$\begin{aligned}\frac{dI}{dt} = k + \left(\frac{\rho I(t)(x+y+sz)^n}{a + (x+y+sz)^n}\right) - (\sigma_4 + c_1 x(t) + c_2 y(t) + c_3 z(t))I(t) \\ - k_6(1 - e^{-k_7 u(t)})I(t)\end{aligned} \tag{2.1.4}$$

$$\frac{du}{dt} = -\gamma u(t) + v(t) \tag{2.1.5}$$

where the initial conditions are

$$x(t) = \phi(t),\ t \in [-\tau, 0],\ y(0) = y_0,\ z(0) = z_0,\ I(0) = I_0,\ u(0) = u_0.$$

Here, all constants are positive and the interphase is the only phase with a delay present. We note that Liu et al. [19] present two versions of this model, one of which is nondimensionalized. For this thesis, we analyze the nondimensionalized model. Note that the nondimensionalization process introduces a parameter s, which represents the number of inital cancer cells in the resting phase per number of initial cells in the interphase, as shown above. Table 2.2 provides a brief description of the parameters, while Table 2.3 gives the allowable range and specific values used for the parameters taken from Liu et al. [19].

2.1.3 Equation Descriptions

In general, positive terms indicate a contribution of cells to a population and negative terms indicate a decrease in the number of cells from a population. Each state equation includes growth and natural death terms, and certain parameters exist to represent how the chemotherapy is killing cells in the system.

The Tumor Equations

The α_i terms, for $i = 1, 2, 3$, are transition terms from one tumor phase to another, while the σ_i terms, for $i = 1, 2, 3$, are natural death terms for their respective phases. The destruction caused by drugs to the mitotic cancer cell population is given by $(1 - e^{-k_5 u(t)})$, as seen in [8]. The chemotherapy in use is cycle-specific, so the mitotic phase is the only one affected directly.

The Lymphocyte Equation

The nonlinear growth term, $\dfrac{\rho I(t)(x + y + sz)^n}{a + (x + y + sz)^n}$, was chosen by Villasana and Radunskaya [25] to represent the immune cell dynamics. They chose a Michaelis–Menten term to represent the stimulation of the immune cells by the presence of cancer cells, but also to indicate that the immune cells may reach a saturation point. This form reflects that this term should be zero in the case of no cancer cells, but approaches the horizontal asymptote as the lymphocytes reach a saturation level. The destruction of the lymphocyte populations caused by the chemotherapy drug is given by the term $(1 - e^{-k_7 u(t)})$, [8].

Chemotherapy Drug Equation

The first term, $-\gamma u$, represents the natural decay of the drug in the bloodstream. The addition of the control term $v(t)$ will represent a direct application of the drug. The ex-

ponential kill terms due to the detrimental effects of chemotherapy are incorporated into the mitotic phase equation, as the chemotherapy is cycle–specific, and into immune system equation, as the chemotherapy drug destroys both tumor and healthy cells indiscriminately.

Parameter	Description
α_1	rate at which cells move into mitosis
α_2	rate at which cells move into the resting phase
α_3	rate at which cells leave resting and enter cell cycle
c_i for $i = 1, 2, 3$	binding losses with immune cells
σ_i for $i = 1, 2, 3, 4$	natural death proportions for x, y, z, and I
ρ	proportional growth of I due to interaction with cancer cells
n	fractional exponent of growth from stimulus of cancer cells
a	rate at which I reaches saturation without stimulus
k	growth rate of I with no cancer cells
k_i for $i = 1, 2, 3$	rate at which I destroys cells in different phases
k_4, k_6	proportion of removal of y and I
k_5, k_7	proportion of drugs in removal of y and I
γ	natural decay rate of chemotherapy
τ	time of cells in interphase (delay variable)

Table 2.2: Parameter Descriptions

Parameter	Allowable Range [19]	Value Used
α_1	$0 - 1$/day	1
α_2	$0 - 1$/day	0.6
α_3	$0 - 1$/day	0.9
c_1	$0.01 \times 10^{-6} - 1 \times 10^{-6}$/cell day	0.2×10^{-6}
c_2	$0.01 \times 10^{-6} - 1 \times 10^{-6}$/cell day	0.8×10^{-6}
c_3	$0.01 \times 10^{-6} - 1 \times 10^{-6}$/cell day	0.108×10^{-6}
σ_1	$0 - 1$/day	0.11
σ_2	$0 - 1$/day	0.28
σ_3	$0 - 1$/day	0.1×10^{-4}
σ_4	$0 - 1$/day	0.3
ρ	0.2/day	0.2
a	$0.5 \times (0.1 \times 10^6$ cells$)^3$	$0.5 \times (0.1 \times 10^6)^3$
k	0.15×10^6 cell/day	0.15×10^6
k_1	$0.1 \times 10^{-8} - 1 \times 10^{-8}$ /cell day	0.1×10^{-7}
k_2	$0.1 \times 10^{-8} - 1 \times 10^{-8}$ /cell day	0.4×10^{-8}
k_3	$0.1 \times 10^{-8} - 1 \times 10^{-8}$ /cell day	0.1×10^{-8}
k_4	$0 - 1$/day	0.25
k_5	$0.01 \times 10^{-2} - 1 \times 10^{-2}$ /mg	1×10^{-2}
k_6	$0 - 1$/day	0.3×10^{-1}
k_7	$0.01 \times 10^{-2} - 1 \times 10^{-2}$ /mg	0.5×10^{-2}
γ	$0.1 \times 10^{-2} - 1 \times 10^{-2}$ /day	0.3×10^{-2}

Table 2.3: Parameter Ranges and Values

Chapter 3

Optimal Control

Optimal control theory evolved from an older branch of mathematics called calculus of variations. Different problems in this field, such as the brachistochrone and the Bolza problems, eventually developed the techniques that we call optimal control theory today. A typical problem starts with a system of differential equations modeling a physical process. We then wish to find a control belonging to some admissible control set that causes the system to follow an ideal pattern. We quantify "ideal" by the objective functional, and seek to find the control that minimizes or maximizes said objective functional.

In this chapter, we extend Pontryagin's Minimum Principle as taken from Kamien and Schwartz [14] to analyze the optimal control problem with an incorporated delay. We consider two objective functionals to quantify a "best" scenario, implementing a quadratic control to make the analysis more straightforward. A future analysis might include examining a linear control, but for the purposes of this study we limit ourselves to the quadratic case. We then define the respective Hamiltonians to obtain a characterization of the control. From the Hamiltonians, a system of initial state equations coupled with the adjoint equations result to be used in the numerical approximations to update the control.

3.1 Objective Functionals

We seek to minimize both objective functionals. The first is given by

$$J_1(v) = \int_0^{t_f} \left[\frac{\epsilon}{2}v^2(t) + x(t) + y(t) + sz(t)\right] \mathrm{d}t \tag{3.1.1}$$

over the set $\mathbb{V} = \{t \in [0, t_f] | 0 \leq v(t) \leq 1\}$, where x, y, and z are the cancer cells in their respective cycles and ϵ is a weight parameter that allows us to emphasize the cost of the chemotherapy drug to the system. Here, we wish to minimize the cost of the chemotherapy and the cell counts throughout the entire time frame.

We also wish to minimize a second objective functional

$$J_2(v) = \int_0^{t_f} \frac{\epsilon}{2}v^2(t)\mathrm{d}t + [x(t_f) + y(t_f) + sz(t_f)] \tag{3.1.2}$$

over the same set $\mathbb{V}$ with the same weight factor ϵ. Here, we minimize the cost associated with the drug throughout, but only minimize the cancer cells x, y, and z at the final time.

3.1.1 Existence

Existence of an optimal control in the case of the second objective functional (3.1.2) is given in [3], using a theorem from Das and Sharma [6]. Existence for the first objective functional (3.1.1) is shown by a similar argument.

3.1.2 Characterization of the Optimal Control

With the existence of an optimal control, we may obtain the analytic representation of the control for the objective functionals. In a standard optimal control setting, the form of the adjoint equations and the transversailty conditions follows from Pontryagin's Minimum Principle [14]. However, the presence of the delay necessitates modifications to this standard

approach. An analysis presented in [14] shows that the presence of the delay adds terms to the necessary conditions obtained in the nondelay case. We note that since the deviated argument does not appear in the control, the necessary conditions for optimality reduce to those in the standard case. The adjoint equations, on the other hand, will include additional terms as the deviated argument does appear in the state equations. We note that the analysis presented in Kamien and Schwartz [14] covers only the case of constant delay. More general cases are covered in [15], [13], [12], [4], [11].

The first step is to form the Hamiltonian, which relates the integrand of the objective functional to the state equations using adjoint variables λ_i, $i = 1, ..., 5$. Since the control is bounded we construct the Lagrangian, which combines the Hamiltonian and the optimal control with penalty multipliers. Taking partial derivatives of the Lagrangian with respect to each of the state variables will lead us to the representation of the optimal control. We emphasize that the partial derivative with respect to the terms involving the state variable, x, will have two forms, as the presence of the delay adds terms to the necessary conditions that would vanish in the case of no delay [14].

Theorem 3.1.1 (Characterization of the Optimal Control for Objective Functional 3.1.1)**.** *Given an optimal control, $v^*(t)$, and solutions to the corresponding state system, there exist*

adjoint variables λ_i *for* $i = 1, 2, ..., 5$ *satisfying the following:*

$$\begin{aligned} -\frac{\partial \mathcal{L}}{\partial x} - \frac{\partial \mathcal{L}}{\partial x(t-\tau)}\Big|_{t+\tau} &= \lambda_1' = -1 + \lambda_1(\alpha_1 + \sigma_1) + \lambda_1 k_1 I - \lambda_4 \left(\frac{\rho a I n (x+y+sz)^{(n-1)}}{(a + (x+y+sz)^n)^2} \right) \\ &+ \lambda_4 c_1 I - \lambda_2 \alpha_2|_{t+\tau}, \end{aligned}$$

for $0 \leq t < t_f - \tau$

$$\begin{aligned} -\frac{\partial \mathcal{L}}{\partial x_t} &= \lambda_1' = -1 + \lambda_1(\alpha_1 + \sigma_1) + \lambda_1 k_1 I - \lambda_4 \left(\frac{\rho a I n (x+y+sz)^{(n-1)}}{(a + (x+y+sz)^n)^2} \right) \\ &+ \lambda_4 c_1 I, \end{aligned}$$

for $t_f - \tau \leq t \leq t_f$.

For the last four adjoints, the interval for t *is* $[0, t_f]$*, and we have*

$$\begin{aligned} -\frac{\partial \mathcal{L}}{\partial y} &= \lambda_2' = -1 + \lambda_1(\alpha_1 + \sigma_1) + \lambda_2 k_2 I + \lambda_2 k_2 I + \lambda_2 k_4 (1 - e^{-k_5 u(t)}) \\ &+ \lambda_2(\alpha_2 + \sigma_2) - \lambda_3(2s^{-1}\alpha_2) - \lambda_4 \left(\left(\frac{\rho a I n (x+y+sz)^{(n-1)}}{(a + (x+y+sz)^n)^2} \right) - c_2 I \right) \\ -\frac{\partial \mathcal{L}}{\partial z} &= \lambda_3' = -s - \lambda_1 s \alpha_3 + \lambda_3(\alpha_3 + \sigma_3 + I(t) k_3) \\ &- \lambda_4 \left(\frac{\rho a I(t) n a s (x+y+sz)^{(n-1)}}{(a + (x+y+sz)^n)^2} \right) + \lambda_4 c_3 I(t) \\ -\frac{\partial \mathcal{L}}{\partial I} &= \lambda_4' = \lambda_1 k_1 x + \lambda_2 k_2 y + \lambda_3 k_3 z \\ &- \lambda_4 \left(\frac{\rho (x+y+sz)^n}{a + (x+y+sz)^n} + \sigma_4 + c_1 x + c_2 y + c_3 z + k_6(1 - e^{-k_7 u}) \right) \\ -\frac{\partial \mathcal{L}}{\partial u} &= \lambda_5' = \lambda_2 k_4 k_5 e^{-k_5 u(t)} y + \lambda_4 k_6 k_7 e^{-k_7 u(t)} I + \lambda_5 \gamma \end{aligned}$$

where $\lambda_i(t_f) = 0$ *for* $i = 1, 2, ..., 5$. *Furthermore,* $v^*(t)$ *can be represented by*

$$v^*(t) = \min\left(\max\left(0, \frac{-\lambda_5(t)}{\epsilon}\right), 1\right).$$

Proof. We begin by forming the Lagrangian. Since $0 \leq v(t) \leq 1$, the controls are bounded; thus, the Lagrangian takes the following form:

$$\mathcal{L} = H_1 - W_1(t)v(t) - W_2(t)(1 - v(t))$$

where H_1 is the Hamiltonian given by

$$\begin{aligned}
H_1 &= x(t) + y(t) + sz(t) + \frac{\epsilon}{2}v^2(t) \\
&+ \lambda_1[-(\alpha_1 + \sigma_1)x(t) + s\alpha_3 z(t) - k_1 x(t)I(t)] \\
&+ \lambda_2[\alpha_1 x(t-\tau) - (\alpha_2 + \sigma_2)y(t) - k_2 y(t)I(t) - k_4(1 - e^{-k_5 u(t)})y(t)] \\
&+ \lambda_3[2s^{-1}\alpha_2 y(t) - (\alpha_3 + \sigma_3)z(t) - k_3 z(t)I(t)] \\
&+ \lambda_4[k + \frac{\rho I(t)(x + y + sz)^n}{(a + (x + y + sz)^n)} - (\sigma_4 + c_1 x(t) + c_2 y(t) + c_3 z(t))I(t) - k_6(1 - e^{-k_7 u(t)})I(t)] \\
&+ \lambda_5[-\gamma u(t) + v(t)]
\end{aligned}$$

and $W_i(t) \geq 0$, for $i = 1, 2$, are penalty multipliers such that

$$\left.\begin{aligned} W_1(t)v(t) &= 0 \\ W_2(t)(1 - v(t)) &= 0 \end{aligned}\right\} \text{at } v^*(t). \tag{3.1.3}$$

Here, the penalty terms are subtracted from the Hamiltonian, as we are solving a minimization problem. To find the representation for $v^*(t)$, we analyze the necessary condition

for optimality. From Kamien and Schwartz [14], we see that the optimality conditions are

$$\frac{\partial \mathcal{L}}{\partial v(t)} + \frac{\partial \mathcal{L}}{\partial v(t-\tau)} = 0, \qquad \text{for } 0 \leq t < t_f - \tau$$

$$\frac{\partial \mathcal{L}}{\partial v(t)} = 0, \qquad \text{for } t_f - \tau \leq t \leq t_f.$$

However, since the delay does not appear as an argument in the control, the above conditions reduce to $\dfrac{\partial \mathcal{L}}{\partial v(t)} = 0$ (for $t_0 \leq t \leq t_f$). We then have

$$\begin{aligned} \frac{\partial \mathcal{L}}{\partial v} &= \frac{\partial H}{\partial v} - W_1 + W_2 = 0 \\ \Rightarrow \epsilon v + \lambda_5 - W_1 + W_2 &= 0. \end{aligned}$$

To determine an explicit expression for v, consider three cases:

1. Suppose $0 < v(t) < 1$. Then $W_1 = W_2 = 0$, so

$$v = \frac{-\lambda_5}{\epsilon}.$$

2. Suppose $v(t) = 1$. Then $W_1 = 0$, so

$$v + \frac{W_2}{\epsilon} = \frac{-\lambda_5}{\epsilon} \geq 1.$$

3. Suppose $v(t) = 0$. Then $W_2 = 0$, so

$$v - \frac{W_1}{\epsilon} = \frac{-\lambda_5}{\epsilon} \leq 0.$$

Combining these cases gives the characterization for the optimal control $v^*(t)$ as

$$v^*(t) = \min\left(\max\left(0, \frac{-\lambda_5(t)}{\epsilon}\right), 1\right). \tag{3.1.4}$$

□

In a similar manner, we obtain the analytic representation for the control for the second objective functional.

Theorem 3.1.2 (Characterization of the Optimal Control for Objective Functional 3.1.2)**.** *Given an optimal control, $v(t)$, and solutions to the corresponding state system, there exist adjoint variables λ_i for $i = 1, 2, ..., 5$ satisfying the following:*

$$\begin{aligned} -\frac{\partial \mathcal{L}}{\partial x} - \frac{\partial \mathcal{L}}{\partial x(t-\tau)}\Big|_{t+\tau} &= \lambda_1' = \lambda_1(\alpha_1 + \sigma_1) + \lambda_1 k_1 I - \lambda_4\left(\frac{\rho a I n (x+y+sz)^{(n-1)}}{(a+(x+y+sz)^n)^2}\right) \\ &+ \lambda_4 c_1 I - \lambda_2 \alpha_2|_{t+\tau}, \end{aligned}$$

for $0 \le t < t_f - \tau$

$$\begin{aligned} -\frac{\partial \mathcal{L}}{\partial x_t} &= \lambda_1' = \lambda_1(\alpha_1 + \sigma_1) + \lambda_1 k_1 I - \lambda_4\left(\frac{\rho a I n (x+y+sz)^{(n-1)}}{(a+(x+y+sz)^n)^2}\right) \\ &+ \lambda_4 c_1 I, \end{aligned}$$

for $t_f - \tau \le t \le t_f$

For the last four adjoints, the interval for t is $[0, t_f]$, and we have

$$
\begin{aligned}
-\frac{\partial \mathcal{L}}{\partial y} &= \lambda_2^{'} = \lambda_1(\alpha_1+\sigma_1) + \lambda_2 k_2 I + \lambda_2 k_2 I + \lambda_2 k_4(1-e^{-k_5 u(t)}) \\
&+ \lambda_2(\alpha_2+\sigma_2) - \lambda_3(2s^{-1}\alpha_2) - \lambda_4\left(\left(\frac{\rho a I n (x+y+sz)^{(n-1)}}{(a+(x+y+sz)^n)^2}\right) - c_2 I\right) \\
-\frac{\partial \mathcal{L}}{\partial z} &= \lambda_3^{'} = s - \lambda_1 s\alpha_3 + \lambda_3(\alpha_3+\sigma_3+I(t)k_3) \\
&- \lambda_4\left(\frac{\rho a I(t) n a s (x+y+sz)^{(n-1)}}{(a+(x+y+sz)^n)^2}\right) + \lambda_4 c_3 I(t) \\
-\frac{\partial \mathcal{L}}{\partial I} &= \lambda_4^{'} = \lambda_1 k_1 x + \lambda_2 k_2 y + \lambda_3 k_3 z \\
&- \lambda_4\left(\frac{\rho(x+y+sz)^n}{a+(x+y+sz)^n} + \sigma_4 + c_1 x + c_2 y + c_3 z + k_6(1-e^{-k_7 u})\right) \\
-\frac{\partial \mathcal{L}}{\partial u} &= \lambda_5^{'} = \lambda_2 k_4 k_5 e^{-k_5 u(t)} y + \lambda_4 k_6 k_7 e^{-k_7 u(t)} I + \lambda_5 \gamma
\end{aligned}
$$

where $\lambda_i(t_f) = 1$ *for* $i = 1, 2$, $\lambda_3(t_f) = s$, *and* $\lambda_i(t_f) = 0$ *for* $i = 4, 5$. *Again,* $v^*(t)$ *can be represented by*

$$v^*(t) = \min\left(\max\left(0, \frac{-\lambda_5(t)}{\epsilon}\right), 1\right). \tag{3.1.5}$$

Proof. We note that the transversality conditions take a different form due to the presence of the salvage terms in the objective functional. The form of these conditions is taken from [14]. As before, we begin by forming the Lagrangian. Since $0 \leq v(t) \leq 1$, the controls are bounded; thus, the Lagrangian takes the following form:

$$\mathcal{L} = H_2 - W_1(t)v(t) - W_2(t)(1 - v(t))$$

where H_2 is the Hamiltonian given by

$$\begin{aligned}
H_2 &= \frac{\epsilon}{2}v^2(t) \\
&+ \lambda_1[-(\alpha_1 + \sigma_1)x(t) + s\alpha_3 z(t) - k_1 x(t)I(t)] \\
&+ \lambda_2[\alpha_1 x(t-\tau) - (\alpha_2 + \sigma_2)y(t) - k_2 y(t)I(t) - k_4(1 - e^{-k_5 u(t)})y(t)] \\
&+ \lambda_3[2s^{-1}\alpha_2 y(t) - (\alpha_3 + \sigma_3)z(t) - k_3 z(t)I(t)] \\
&+ \lambda_4[k + \frac{\rho I(t)(x + y + sz)^n}{(a + (x + y + sz)^n)} - (\sigma_4 + c_1 x(t) + c_2 y(t) + c_3 z(t))I(t) - k_6(1 - e^{-k_7 u(t)})I(t)] \\
&+ \lambda_5[-\gamma u(t) + v(t)]
\end{aligned}$$

and $W_i(t) \geq 0$, for $i = 1, 2$, are penalty multipliers such that

$$\left.\begin{aligned} W_1(t)v(t) &= 0 \\ W_2(t)(1 - v(t)) &= 0 \end{aligned}\right\} \text{at } v^*(t) \tag{3.1.6}$$

Again, the penalty terms are subtracted from the Hamiltonian, as we are solving a min-

imization problem. To find the representation for $v^*(t)$, we analyze the necessary condition for optimality. From Kamien and Schwartz [14], we see that the optimality conditions are

$$\frac{\partial \mathcal{L}}{\partial v(t)} + \frac{\partial \mathcal{L}}{\partial v(t-\tau)} = 0, \qquad \text{for } 0 \leq t < t_f - \tau$$

$$\frac{\partial \mathcal{L}}{\partial v(t)} = 0, \qquad \text{for } t_f - \tau \leq t \leq t_f.$$

However, since the delay does not appear as an argument in the control, the above conditions reduce to $\dfrac{\partial \mathcal{L}}{\partial v(t)} = 0$ (for $t_0 \leq t \leq t_f$). We then have

$$\frac{\partial \mathcal{L}}{\partial v} = \frac{\partial H}{\partial v} - W_1 + W_2 = 0$$

$$\Rightarrow \epsilon v + \lambda_5 - W_1 + W_2 = 0.$$

To determine an explicit expression for v, consider three cases:

1. Suppose $0 < v(t) < 1$. Then $W_1 = W_2 = 0$, so

$$v = \frac{-\lambda_5}{\epsilon}.$$

2. Suppose $v(t) = 1$. Then $W_1 = 0$, so

$$v + \frac{W_2}{\epsilon} = \frac{-\lambda_5}{\epsilon} \geq 1.$$

3. Suppose $v(t) = 0$. Then $W_2 = 0$, so

$$v - \frac{W_1}{\epsilon} = \frac{-\lambda_5}{\epsilon} \leq 0.$$

Combining these cases gives the characterization for the optimal control $v^*(t)$ as

$$v^*(t) = \min\left(\max\left(0, \frac{-\lambda_5(t)}{\epsilon}\right), 1\right). \tag{3.1.7}$$

□

By comparing (3.1.4) and (3.1.5), we see that our representations for the quadratic controls are the same for these cases regardless of the choice of objective functionals (3.1.1) and (3.1.2). Future work could include the investigation of a linear control term.

Chapter 4

Numerical Methods

In a typical delay differential equation (DDE) setting, MATLAB offers a built-in solver called `dde23` [23]. This would accommodate the delay nicely, considering our case of a constant delay. However, the implementation of the control in the model makes `dde23` incredibly difficult to edit for our purposes. We therefore construct our own solver, which incorporates a modified Runge-Kutta method, and utilize the forward-backward sweep method provided by Lenhart and Workman [18] to update the control and obtain analytical representations of the system.

4.1 Forward–Backward Sweep Method

We take our approach for numerical solutions from Lenhart and Workman [18], using RK4 as the initial value problem solver. We solve the state system forward in time using the initial conditions, then the adjoint system backward in time using the transversality conditions. Each iteration of the sweeps updates the control and checks convergence. There are several stopping criteria for this method, including observing the averages of previous and current iterations. However, we choose to stop the sweeps when the difference between the values

of the control before and after the sweep are negligable. If this were the case, the control is stored using its analytical representation. Otherwise, the process repeats.

4.2 The Delay

The delay in the model represents the lag between shifting from the interphase to the division phase for the cancer cells and is an important distinction from the model presented by Villasana and Radunskaya [25]. Liu et al. [19] argue that the quiescent phase is the most important compartment for cancer treatment, as studies have shown that these cells can avoid the chemotherapy. Thus, inclusion of this delay presents an insightful aspect for treatment. Due to this presence, accommodations must be made for the analysis.

Several cases for the delay could have been chosen, but our case incorporates a constant delay, τ. A standard implementation of RK4 does not account for the delay, leading to an adjusted time mesh for the analysis. Here, this means that the deviated argument $(t - \tau)$ found in Equation (2.1.2) will store the information from the appropriate lagged time step, and that this lag will have the same size throughout the process. A visual representation of the difficulty posed by the presence of the delay is shown in Figure 4.2.1. Storing previous information only holds when the lag has passed a threshold where the lag $(t - \tau)$ would hit t_1 going forward, or $(t_f - \tau)$ would hit (t_{f-1}) going backward. Before this threshold, we have an initial function that extends behind the inital time, [2]. In our case, this initial function has a constant value equal to the initial condition for $x(t)$ in the forward sweep, and zero or one for the backward sweep, with respect to the appropriate adjoint system.

These initial functions can cause points of discontinuity when solving the system, as the right-hand derivative may not equal the left-hand derivative at t_0 or t_f. Discontinuities such as these can not only cause issues with the first derivative, but can propogate throughout future integration intervals [2]. Due to this, these possible points of discontinuity must be

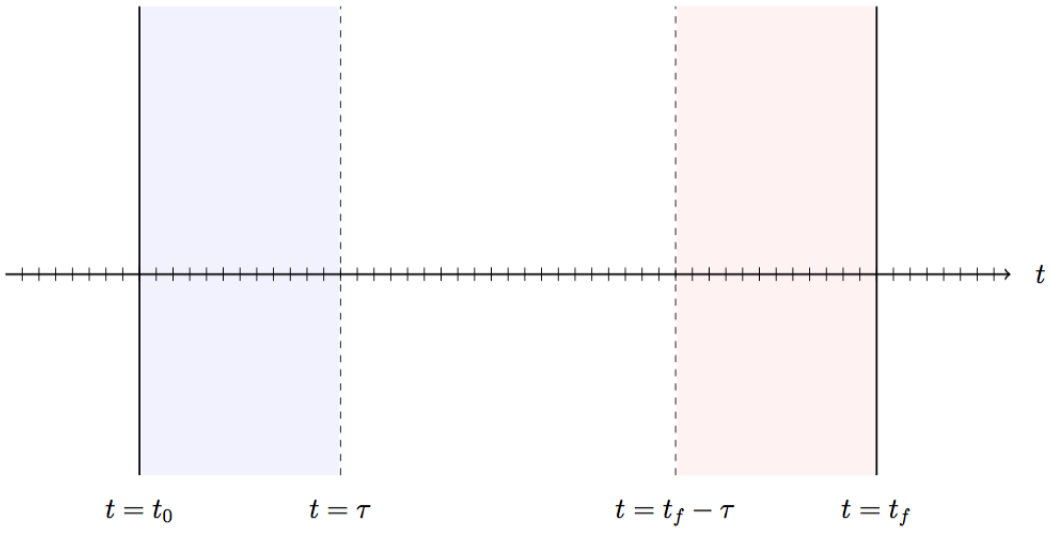

Figure 4.2.1: Thresholds for delays

included in our time mesh to accommodate the numerical methods. Since our initial functions are mathematically "nice," we do not encounter issues of irregularity, which could cause a loss of uniqueness [2].

In the case of our constant delay, the Runge-Kutta method takes the form

$$\eta(t_n + \theta h_{n+1}) = y_n + h_{n+1} \sum_{i=1}^{s} b_i(\theta) f(t_{n+1}^i, Y_{n+1}^i, \eta(t_{n+1}^i - \tau)), 0 \leq \theta \leq 1, \tag{4.2.1}$$

$$Y_{n+1}^i = y_n + h_{n+1} \sum_{j=1}^{s} a_{ij} f(t_{n+1}^j, Y_{n+1}^j, \eta(t_{n+1}^j - \tau)), i = 1, 2, ..., s \tag{4.2.2}$$

where, for $h_{n+1} \leq \tau$, $\eta(t_{n+1}^j - \tau)$ is known for any j. Thus, we get the following theorem from Bellen and Zennaro [2].

Theorem 4.2.1 (Global Order of Delay Differential Equation Method [2])**.** *Consider the*

Delay Differential Equation (DDE) with a constant delay

$$\begin{cases} y'(t) &= f(t, y(t), y(t-\tau)), t_0 \le t \le t_f, \\ y(t) &= \phi(t), t \le t_0, \end{cases} \tag{4.2.3}$$

where $f(t, y, x)$ is C^p–continuous in $[t_0, t_f] \times \mathbb{R}^d \times \mathbb{R}^d$ and the initial function $\phi(t)$ is C^p–continuous. Moreover, assume that the mesh $\Delta = \{t_0, t_1, ..., t_n, ..., t_N = t_f\}$ includes the discontinuity points $\xi_i = i\tau$, $i = 1, ..., p$, lying in $[t_0, t_f]$ and that the underlying continuous Runge-Kutta (CRK) method has discrete order p and uniform order q. Then the DDE method for (4.2.1), (4.2.2) has discrete global order and uniform global order $q' = \min\{p, q+1\}$; that is

$$\max_{1 \le n \le N} ||y(t_n) - y_n|| = O(h^{q'})$$

and

$$\max_{t_0 \le t \le t_f} ||y(t) - \eta(t)|| = O(h^{q'}),$$

where $h = \max_{1 \le n \le N} h_n$.

Since the algorithm proceeds with constant stepsize $h = \tau/m$ for some integer $m \ge 1$, the deviated arguments take the values

$$t_{n+1}^j - \tau = t_{n+1-m}^j = t_{n-m} + c_j h, j = 1, ..., s.$$

Also, since the CRK method is natural, $\eta(t_{n+1}^j) = Y_{n+1}^j$ and $\eta(t_{n+1}^j - \tau) = Y_{n+1-m}^j$. Thus, we get the simplified method

$$y_{n+1} = y_n + h \sum_{i=1}^s b_i f(t_{n+1}^i, Y_{n+1}^i, Y_{n+1-m}^i) \tag{4.2.4}$$

$$Y^i_{n+1} = y_n + h\sum_{j=1}^{s} a_{ij} f(t^j_{n+1}, Y^j_{n+1}, Y^j_{n+1-m}), \quad i = 1, 2, ..., s. \tag{4.2.5}$$

This theorem outlines the method we implement for our specific delay case. The continuous RK method uses interpolants to connect discrete values of the solution. In other words, the RK method makes distinct approximations for each time step, and then interpolates between approximations to get a continuous RK solution. Additionally, since RK4 is a one–step solver, we get the natural continuous extension automatically, as defined in Appendix A. With these methods in place, we may analyze our model, using the modified RK4 as the appropriate solver.

Chapter 5

Results

Each simulation uses the initial conditions $x(0) = y(0) = 0.1 \times 10^6$ cells, $z(0) = 0.2 \times 10^6$ cells, $I(0) = 2 \times 10^6$ cells, and $u(0) = 8$. We first replicate the results in Liu et al. [19], then analyze the cases of continuous treatment and two scheduled treatment approaches. The function `trapz` in MATLAB is used to obtain the area under the curve for the amount of treatment administered to compare treatment applications.

Previous Results

Our first goal was to replicate the work done by Liu et al. [19]. This verified that the implementation created here was consistent with the one used in [19]. Figure 5.0.1 shows the growth of the tumor with and without initial drug, but does not include the implementation of the control. We see that our method successfully duplicates the results of Liu et al. [19], which shows a significant decrease in the number of cancer cells in the treatment schedule that consists only of an initial dose of the chemotherapy drug.

New Results

We then incorporated the control to determine how it affected the model. Figure 5.0.2

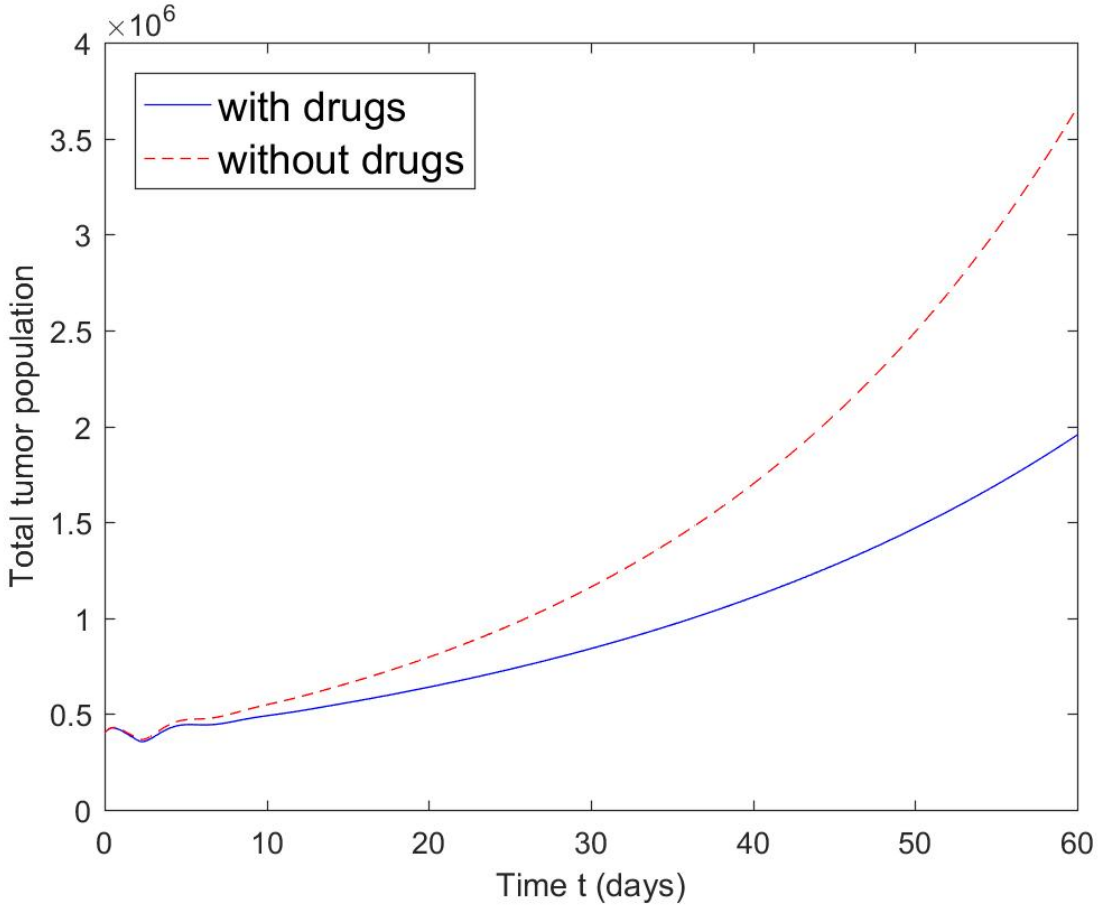

Figure 5.0.1: Replication of Liu et al. [19] results

shows the results with respect to the first objective functional. We see that the cancer follows an exponential growth pattern in the case of no drug. With the inital dosage of chemotherapy, but still no control, the cancer cells are reduced, as we saw from [19], but we see greater reduction of cells in the case with both the initial drug and the optimal control.

The lymphocytes, shown in Figure 5.0.3, exhibit a bit of growth when more cancer cells die in the case of initial dose with the control, as the parameters treat the cancer cells as a larger threat to the lymphocytes than the chemotherapy. The optimal treatment schedule is shown in Figure 5.0.4, following an almost on/off pattern starting with no drug. Analyses performed on the second objective functional provided results that were very similar in nature.

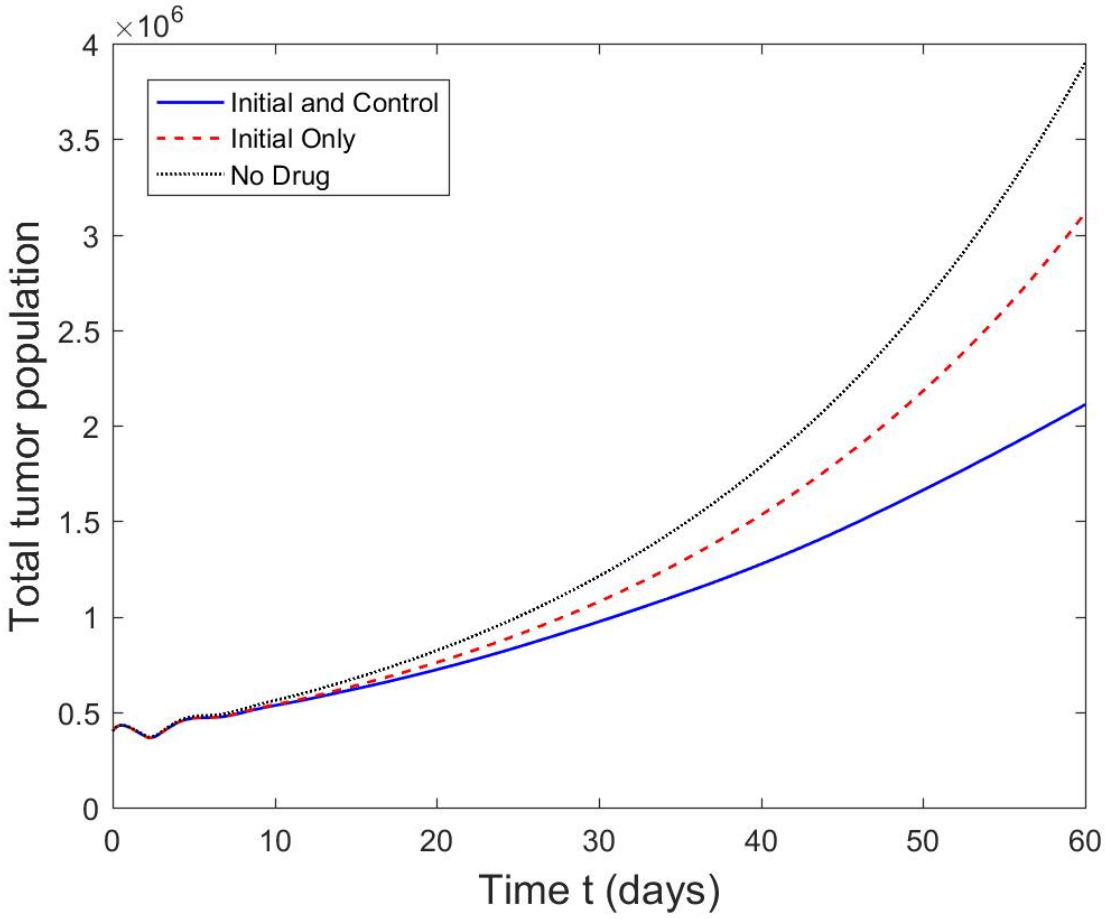

Figure 5.0.2: Total Number of Cancer Cells for Continuous Treatment

Schedule One: Four Days of Treatment

Next, we examine a more realistic approach to chemotherapy treatment. In this case, a patient would receive a scheduled drug administration of 4 days of treatment, 26 days of rest, receive another 4 days of treatment, and rest the last 26 days, shown by Figure 5.0.8. This schedule gives the body time to rest between treatments, but doesn't allow the cancer cells as much time to recover. The two cases considered here were the cases of initial dosage only and including the optimal control with respect to the first objective functional.

Figure 5.0.5 shows that with the control, the cancer cells drop at the second treatment

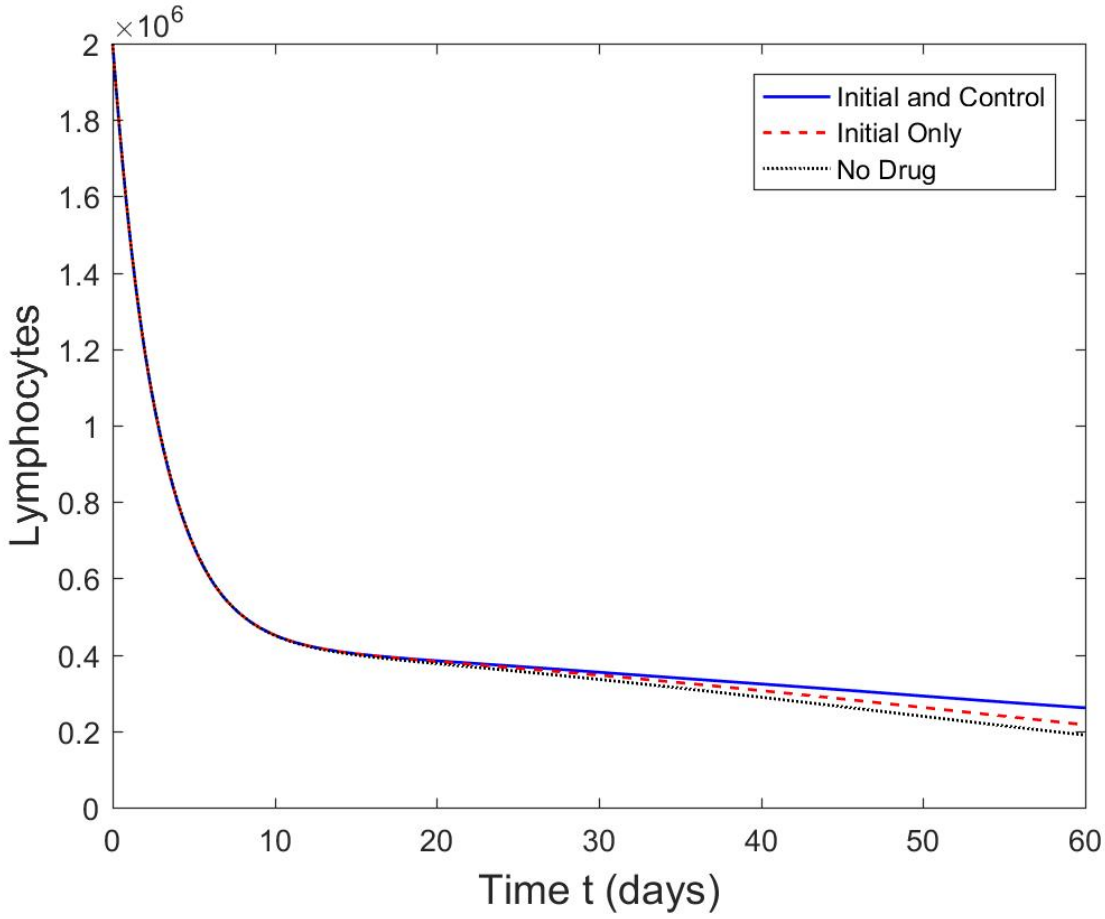

Figure 5.0.3: Total Number of Lymphocytes for Continuous Treatment

iteration, and never fully recover when compared to the initial dose only. The cancer cells end at 2.5×10^6 number of cells in the control case and 2.9×10^6 in the initial dose only case. Thus, their final cell count decreases by 16.6 percent in the case of control over the case of initial dose only. In Figure 5.0.6, the lymphocytes pick up slightly after the first round of treatment is over, and again after the second treatment. We see a fluctuation in the middle where the lymphocytes start to die off more as more cancer cells grow, but then recover after the second treatment is administered for a higher final cell count than in the case of the inital drug only.

The amount of drug in the system over 60 days is given by Figure 5.0.7. In the case

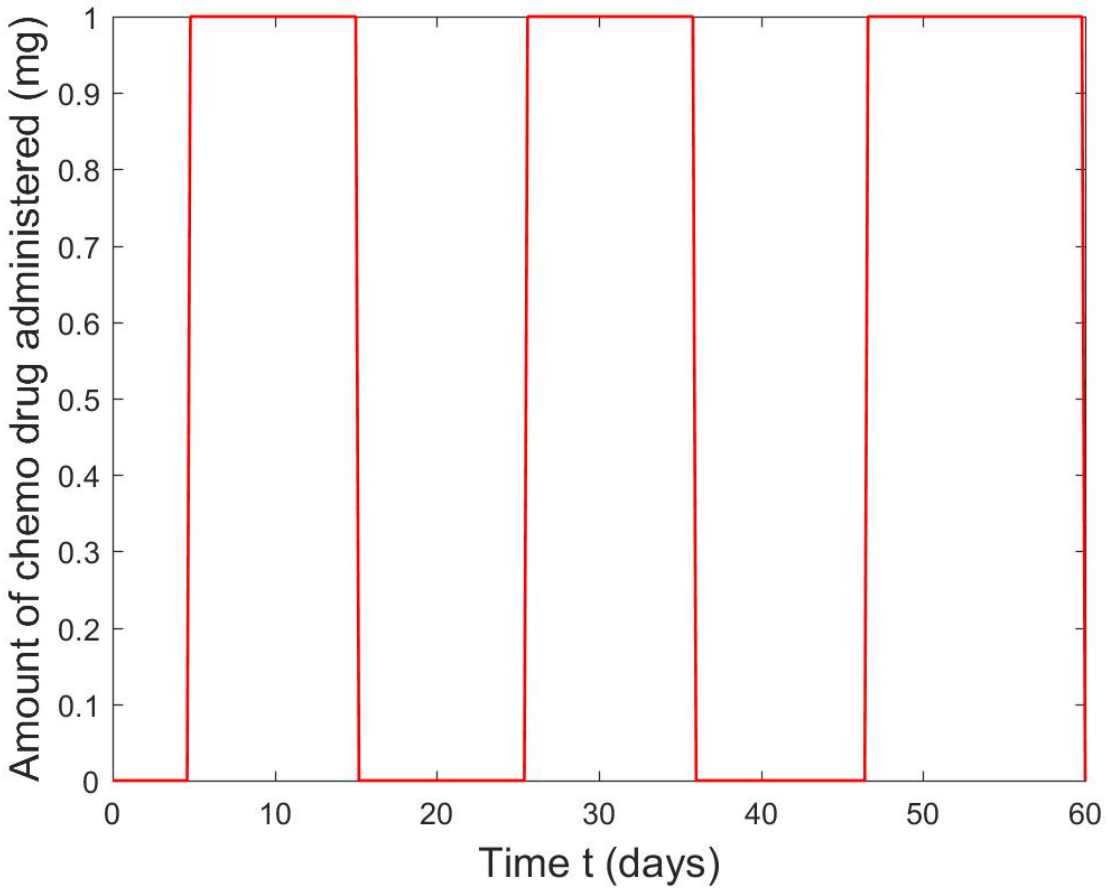

Figure 5.0.4: Continuous Treatment Schedule

of initial drug only, we administer the allotted dosage at the start time, and the amount of chemotherapy drug in the system steadily decreases over time. With the control, we never exceed the amount of drug given by the initial dose only case. At the final time, the inital dose case has an AUC (area under the curve) of 493.3 mg, while the control case has a AUC of 293.5 mg. Thus, there is a decrease of 33.2 percent in the total amount of chemotherapy in the system given by the optimal control case over the amount given by only the initial dosage. This treatment schedule produced lower cancer cell counts, higher final lymphocyte counts, and less total drug in the system than in the case of initial dosage only. This supports the hypothesis that incorporating an optimal control to the model will mini-

mize the cost associated with chemotherapy while also minimizing the number of cancer cells.

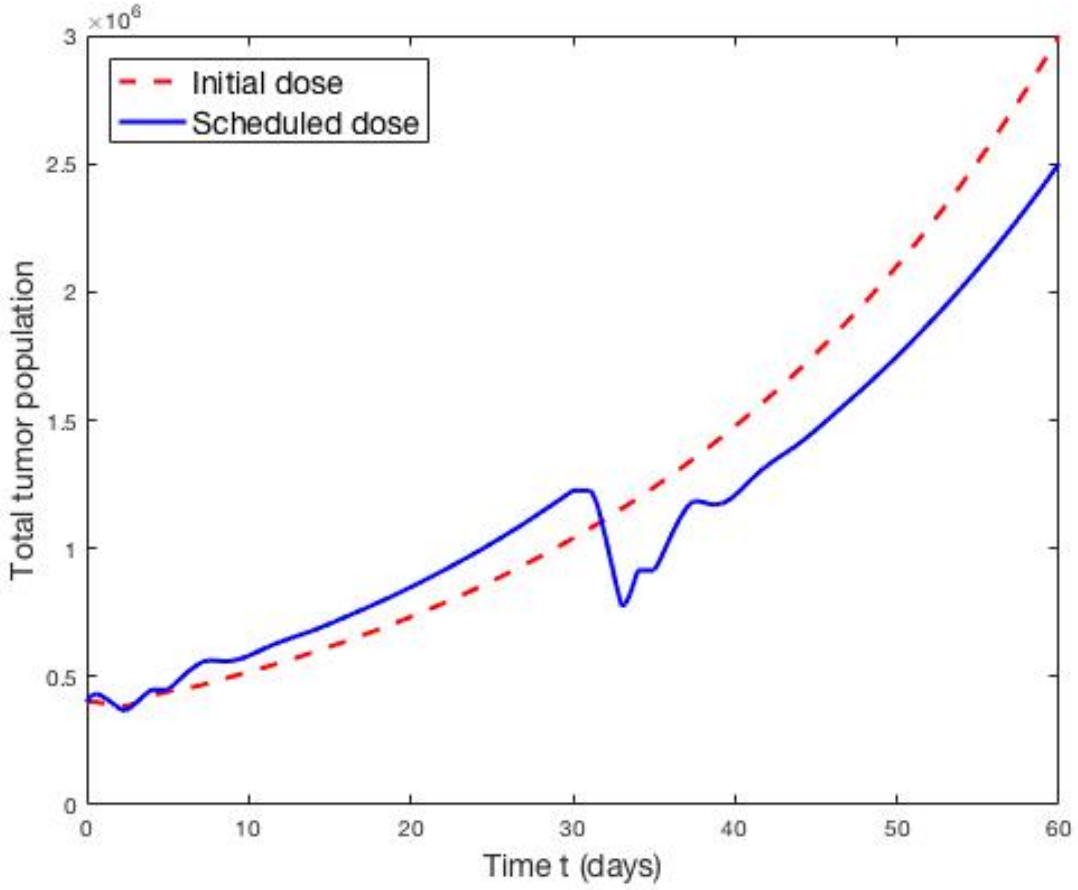

Figure 5.0.5: Total Number of Cancer Cells for Treatment Schedule One

Schedule Two: Two Days of Treatment

We also consider the case of two days of treatment and thirteen days of rest, repeated four times, with respect to the first objective functional. This treatment schedule is more plausible than the first, as this allows patients to leave the hospital during the sixty days. However, we do not see improved results when compared to Schedule One. Figure 5.0.9 shows that there are decreases in the number of cancer cells when the drug is administered, but they recover too quickly before the next iteration of treatment. The final cancer cell count

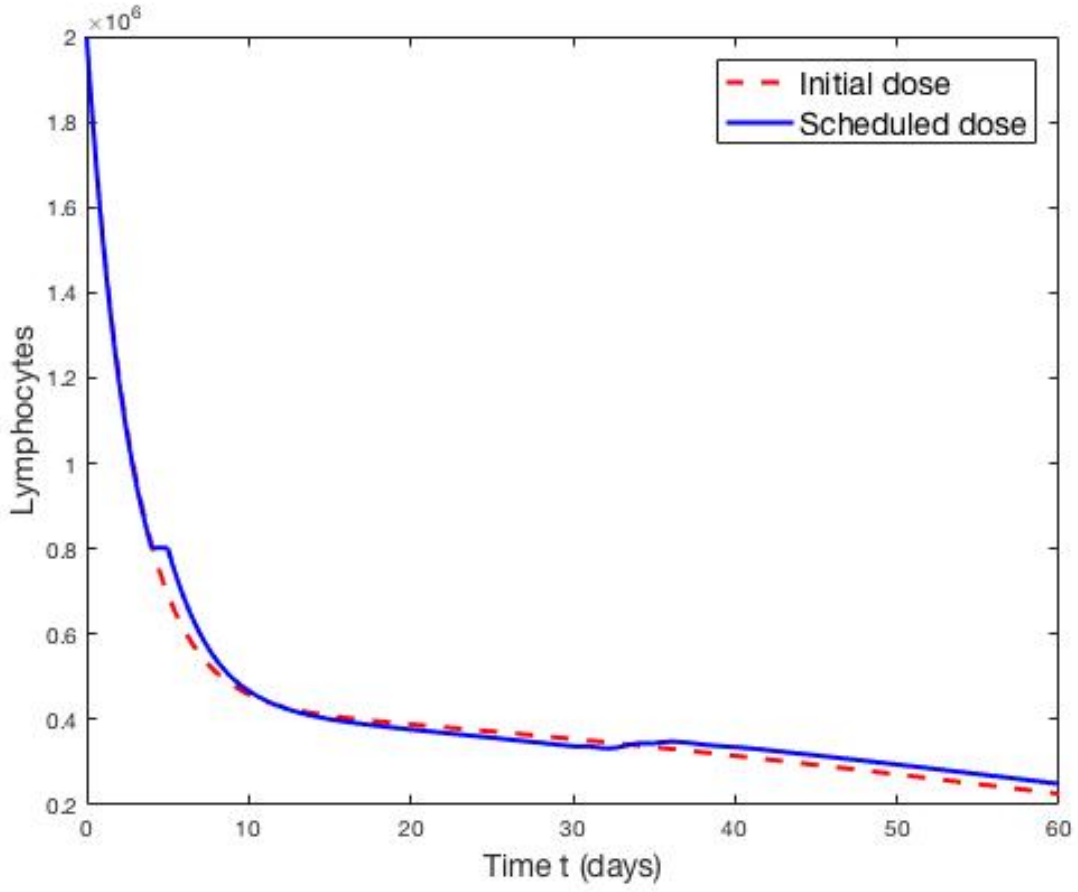

Figure 5.0.6: Total Number of Lymphocytes for Treatment Schedule One

actually increases by 20.9 percent in the two day schedule over the initial dose case.

Figure 5.0.10 shows that this treatment schedule does not help the lymphocyte population when compared to the initial dose case. This is due to the increased number of cancer cells that survived. The overall amount of chemotherapy in the system, as shown in Figure 5.0.12, is 56.5 percent less than the initial dose only, with an AUC of 191.2 mg. However, this amount of treatment does not show improved results for cancer cell count over Schedule One. These results imply that two days of treatment is not enough to harm the cancer cells to the point where they never fully recover. The four day treatment seems to be the experiment that provided the most beneficial outcome in terms of minimizing cancer cell

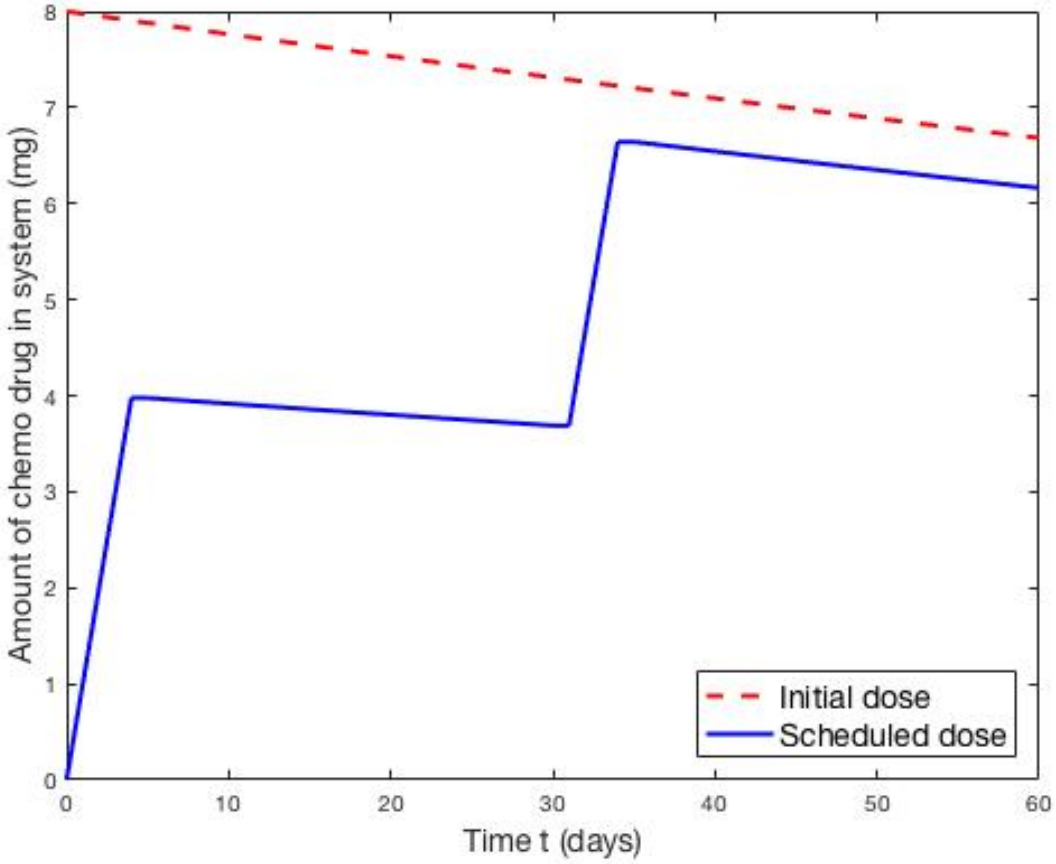

Figure 5.0.7: Amount of Drug in the System for Treatment Schedule One

count and the negative effects of chemotherapy.

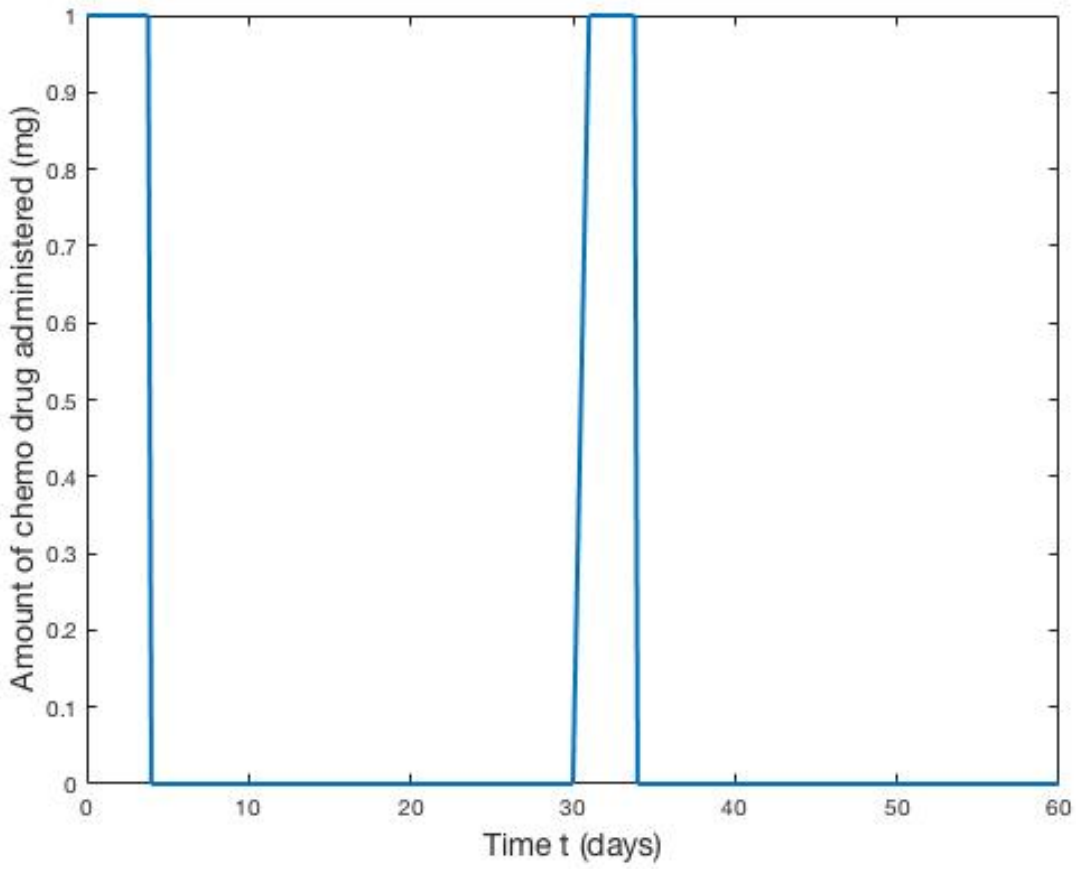

Figure 5.0.8: Drug Administration for Treatment Schedule One

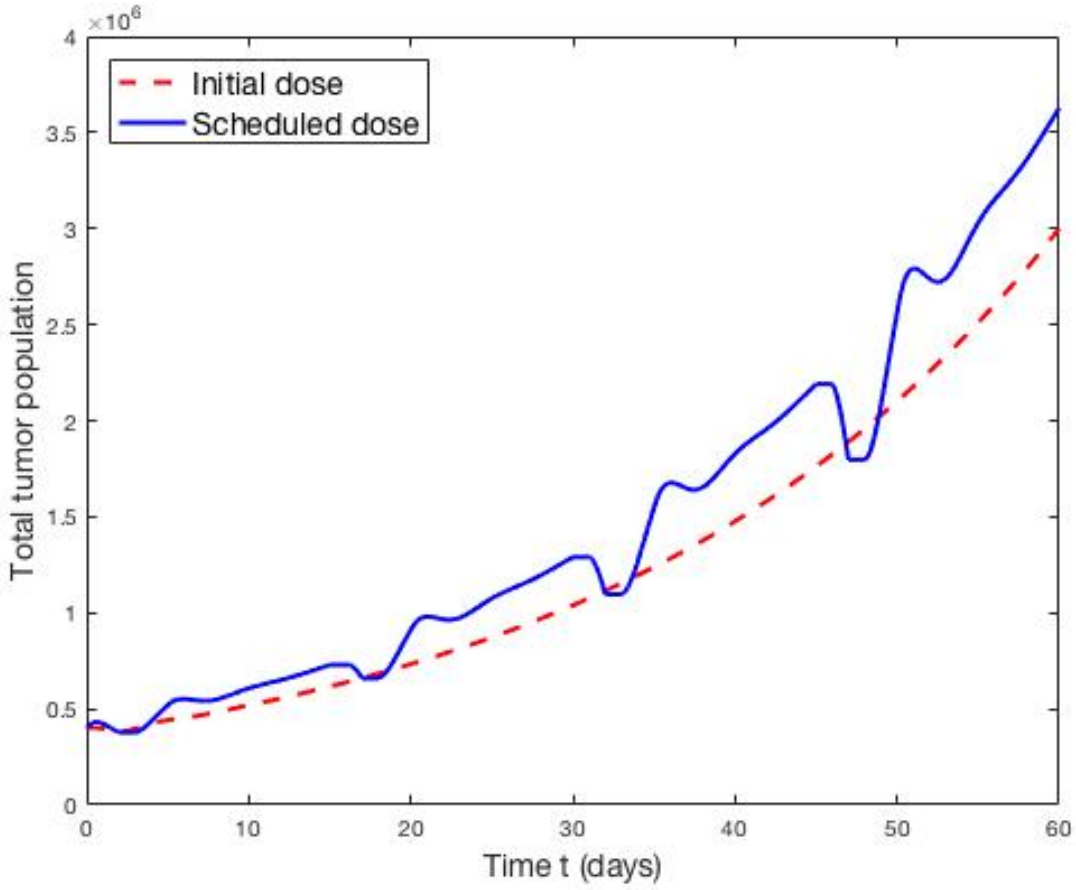

Figure 5.0.9: Total Number of Cancer Cells for Treatment Schedule Two

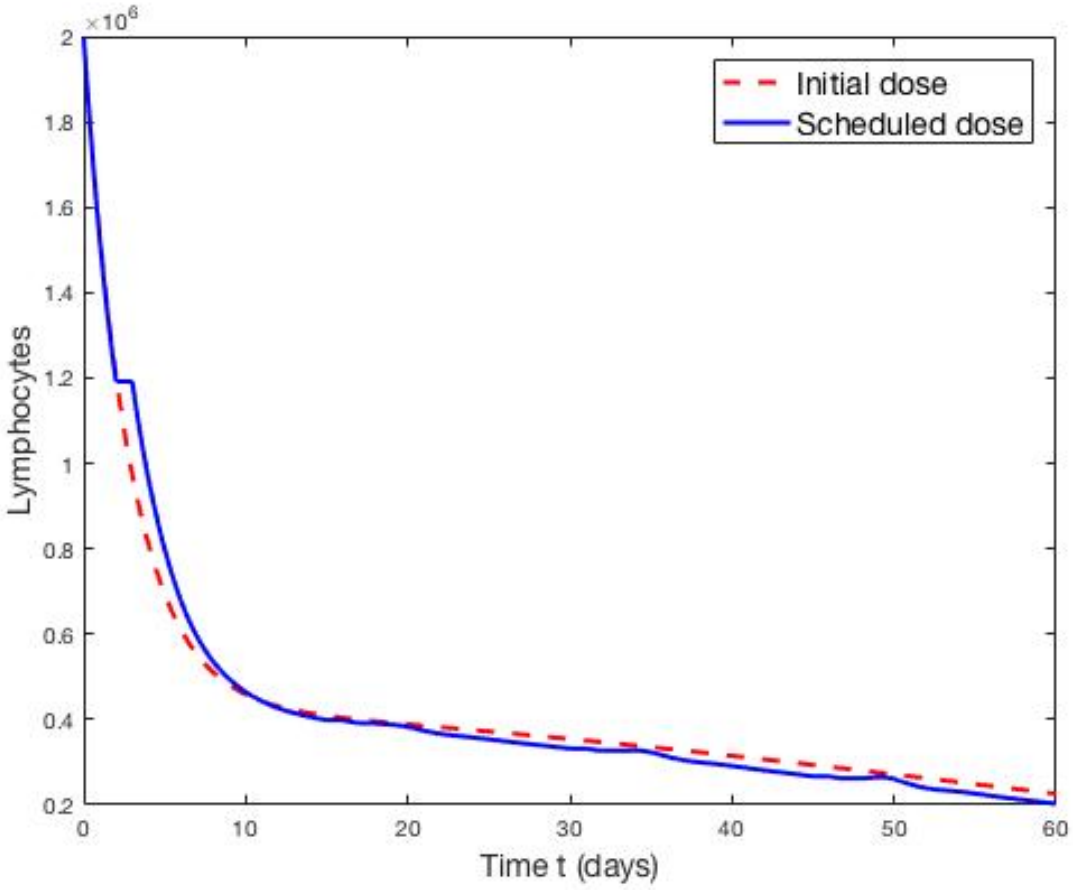

Figure 5.0.10: Total Number of Lymphocytes for Treatment Schedule Two

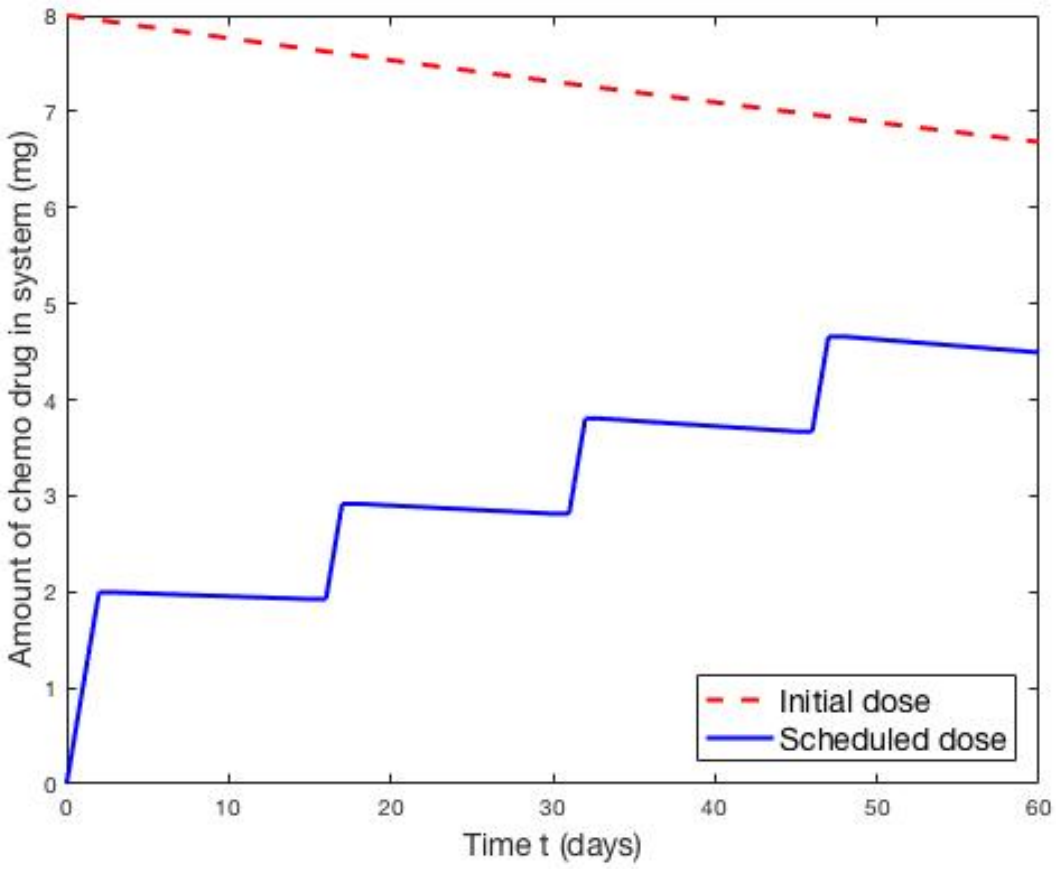

Figure 5.0.11: Amount of Drug in the System for Treatment Schedule Two

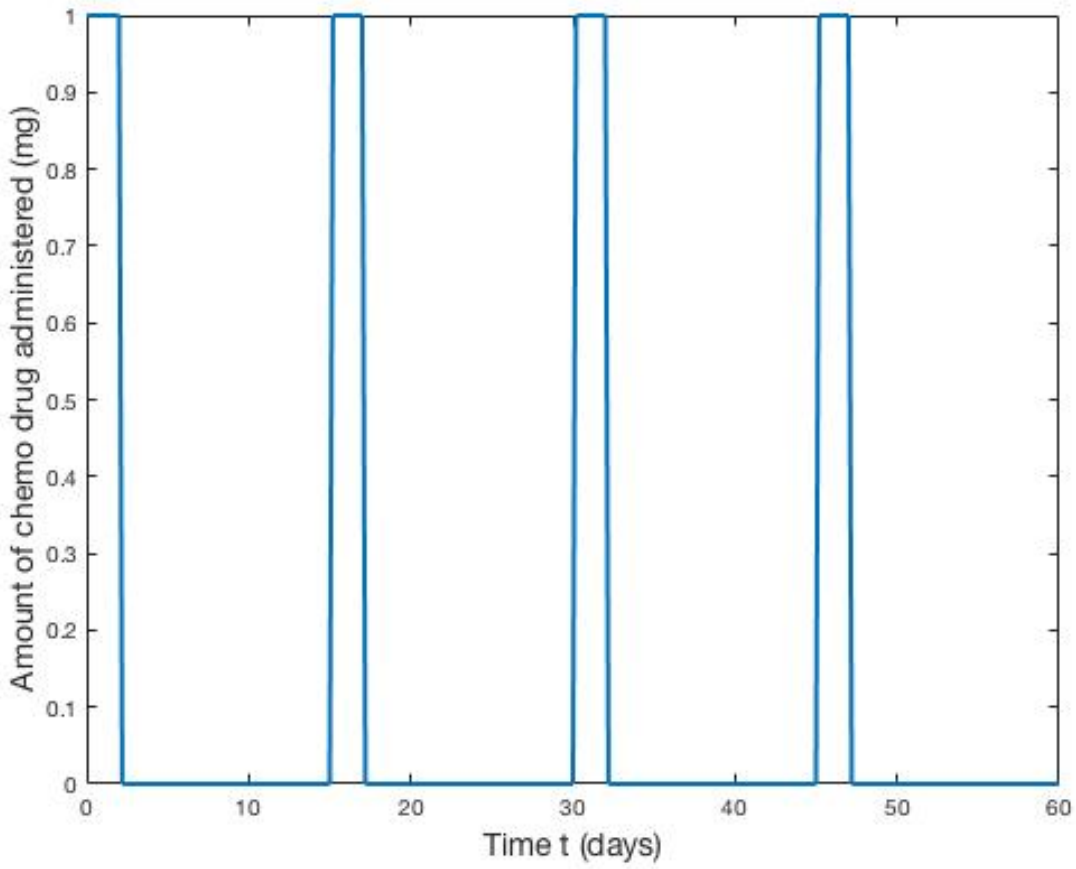

Figure 5.0.12: Drug Administration for Treatment Schedule Two

Chapter 6

Discussion

This thesis shows the numerical analysis of the delay differential equation system given by Liu et al. [19] with the addition of an optimal control. Existence of such a system and control is established from Collins et al. [3]. Analysis techniques included modifying Pontryagin's Minimum Principle [14] for the representation of an optimal control, a forward-backward sweep method utilizing RK4 as the solver, taken from Lenhart and Workman [18], and adjusted analyses to incorporate the delay given by Bellen and Zennaro [2].

The numerical simulations indicated that the particular treatments outlined here with the specified parameters did not kill the cancer cells entirely. However, we do see that the implementation of the control significantly reduced the number of cells in the system in the continuous and four–day treatments while also administering less chemotherapy drug in each case. However, in the case of two–day treatment, the cancer cells were able to rebound, which had worsened effects for the lymphocytes. Overall, the continuous treatment approach provided the best results in terms of minimizing cancer cell count throughout the time frame and at the final times. We note, too, that the experiments for the second objective functional were very similar to each respective experiment here. Thus, investigating this model with a delay and a control was insightful for future work.

Other implementations or delay cases could improve the results we see here. Including more delays in the cancer system would better model how the cancer behaves, which could provide more realistic results. The delay could also be a function of the drug, as there exists a lag between when the drug is administered and when the drug attacks the tumor cells [19]. Other components of the immune system could be incorporated, instead of only one factor. The immune system as a whole is very complicated and this model does not encompass that complexity. One interesting direction for future work could involve using optimal control theory to minimize the time of treatment instead of the drug administration, resulting in a different objective functional. Instead of optimizing the amount of drug administered, we could consider optimizing the amount of time when the drug is administered. Investigation of a control term in the immune system, or control terms in both the immune system and applied drug, could also provide interesting results.

Appendix A

Definitions

In this section, we give a precise statement of the definition of a *natural* continuous extension of a Runge–Kutta method.

Definition A.0.1 (Natural Continuous Extension [2])**.** *We say that the interpolant $\eta(t)$ in*

$$\eta(t_n + \theta h_{n+1}) = y_n + h_{n+1} \sum_{i=1}^{v} b_i(\theta) g(t_{n+1}^i, Y_{n+1}^i), 0 \leq \theta \leq 1$$

of order (and degree) q is a natural continuous extension (NCE) *of the RK method*

$$Y_{n+1}^i = y_n + h_{n+1} \sum_{j=1}^{v} a_{ij} g(t_{n+1}^i, Y_{n+1}^i), i = 1, ..., v, y_{n+1} = y_n + h_{n+1} \sum_{i=1}^{v} b_i g(t_{n+1}^i, Y_{n+1}^i)$$

of order p if the polynomials $b_i(\theta), i = 1, ..., v$, are such that $\eta(t)$ satisfies the additional asymptotic orthogonality condition

$$\left|\left| \int_{t_n}^{t_{n+1}} G(t)[z'_{n+1}(t) - \eta'(t)]\mathrm{d}t \right|\right| = O(h_{n+1}^{p+1})$$

for every sufficiently smooth matrix–valued function G, uniformly with respect to

$n = 1, ..., N-1$, *where* $z_{n+1}(t)$ *is the solution to the local problem*

$$\begin{cases} z'_{n+1}(t) &= g(t, z_{n+1}(t)), t_n \leq t \leq t_{n+1}, \\ z_{n+1}(t_n) &= y^*_n. \end{cases}$$

We note that for any one–step collocation method, the collocation polynomial is an NCE of degree $q = v$.

Appendix B

Theorems

In this section, we give a more precise statement of Pontryagin's Maximum (Minimum) Principle.

Theorem B.0.1 (Pontryagin's Minimum Principle [14])**.** *Let* $\boldsymbol{u}(t) = [u_1(t), \ldots, u_m(t)]$ *be a piecewise continuous control vector and* $\boldsymbol{x}(t) = [x_1(t), \ldots, x_n(t)]$ *be an associated continuous and piecewise differentiable state vector defined on the fixed time interval* $[t_0, t_1]$ *that minimizes*

$$\int_{t_0}^{t_1} f(t, \boldsymbol{x}(t), \boldsymbol{u}(t))dt$$

subject to the differential equations

$$x_i(t) = g_i(t, \boldsymbol{x}(t), \boldsymbol{u}(t)), \quad i = 1, \ldots, n,$$

initial conditions

$$x_i(t_0) = x_{i0}, \quad i = 1, \ldots, n \quad (x_{i0} \textit{ fixed}),$$

terminal conditions

$$x_i(t_1) = x_{i1}, \quad i = 1, \ldots, p,$$
$$x_i(t_1) \geq x_{it}, \quad i = p+1, \ldots, q \quad (x_{i1}, i = 1, \ldots, q \textit{ fixed}),$$
$$x_i(t_1) \textit{ free}, \quad i = q+1, \ldots, n,$$

and control variable restriction

$$X\,\boldsymbol{u}(t) \in U, \quad U \textit{ a given set in } \mathbb{R}^m.$$

We assume that $f, g, \partial f/\partial x_j$, *and* $\partial g_i/\partial x_j$ *are continuous functions of all their arguments, for all* $i = 1, \ldots, n$ *and* $j = 1, \ldots, n$. *Then there exists a constant* λ_0 *and continuous functions* $\lambda(t) = (\lambda_1(t), \ldots, \lambda_n(t))$, *where for all* $t_0 \leq t \leq t_1$ *we have* $(\lambda_0, \lambda(t)) \neq (0, 0)$ *such that for every* $t_0 \leq t \leq t_1$

$$H(t, \boldsymbol{x}^*(t), \boldsymbol{u}(t), \lambda(t)) \leq H(t, \boldsymbol{x}^*(t), \boldsymbol{u}^*(t), \lambda(t)),$$

where the Hamiltonian function H *is defined by*

$$H(t, \boldsymbol{x}, \boldsymbol{u}, \lambda) = \lambda_0 f(t, \boldsymbol{x}, \boldsymbol{u}) + \sum_{i=1}^{n} \lambda_i g_i(t, \boldsymbol{x}, \boldsymbol{u}).$$

Except at points of discontinuity of $\boldsymbol{u}^*(t)$,

$$\lambda'(t) = -\partial H(t, \boldsymbol{x}^*(t), \boldsymbol{u}^*(t), \lambda(t))/\partial x_i, \quad i = 1, \ldots, n.$$

Finally, the following transversality conditions are satisfied:

$$\begin{aligned} &\lambda_i(t_1) \text{ no conditions}, && i = 1, \ldots, p, \\ &\lambda_i(t_1) \geq 0 \quad (= 0 \text{ if } x_i^*(t_1) > x_{i1})) && i = p+1, \ldots, q, \\ &\lambda_i(t_1) = 0, && i = q+1, \ldots, n. \end{aligned}$$

In addition, the modifications to (B.0.1) generated by the terminal inequalities are given in Kamien and Schwartz [14], p. 160:

If $K(x_q(t_1), \ldots, x_n(t_1)) \geq 0$ *is required, then the transversality conditions*

$$\begin{aligned} \lambda_i(t_1) &= p\ \partial K/\partial x_1, \quad i = q, \ldots, n, \\ p &\leq 0, \\ pK &= 0 \end{aligned}$$

are necessary.

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