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OPTIMAL CONTROL APPLIED TO IMMUNOTHERAPY

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Abstract. We investigate a mathematical model for the dynamics between tumor cells, immune-effector cells, and the cytokine interleukin-2 (IL-2). In order to better determine under what circumstances the tumor can be eliminated, we implement optimal control theory. We design the control functional to maximize the effector cells and interleukin-2 concentration and to minimize the tumor cells. Next, we show that an optimal control exists for this problem. After which, we characterize our unique optimal control in terms of the solutions to the optimality system, which is the state system coupled with the adjoint system. Finally, we analyze the optimal control and optimality system using numerical techniques.

1. **Introduction.** Cancer is the second leading cause of death in the United States. More than 500,000 Americans die of cancer annually, and twice that number are diagnosed each year. Surgery, chemotherapy, hormone therapy, and radiation therapy are among the effective treatments for cancer patients. The specific method of treatment used is determined by the cancer's type, stage, and location. Recently, treatment efforts implementing immunotherapy are being investigated.

Immunotherapy refers to the use of natural and synthetic substances to stimulate the immune response. This treatment regimen is also effective in treating immune deficiencies and interfering with the growth of malignancies. Immunological therapies include antigen specific and non-antigen specific agents such as cytokines and heat shock proteins, among others. Of particular interest is the use of cytokines, which are proteins that aid in regulating aspects of cell growth and function during specific immune response. They act by changing the cells that produce them and altering the cells near them. These actions are referred to as the autocrine and

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panacrine effect. Interleukin-2 is an important cytokine in mediating cell proliferation, promoting production of other cytokines, and enhancing natural killer cell function.

This use of cytokines to treat cancer is usually done in conjunction with adoptive cellular immunotherapy (ACI). During ACI, T-cells are taken from cancer patients, then grown and activated in a manner which stimulates them to react to certain antigens. These cells are then infused into the patient. The adopted T-cells invade the tumor cite and immunologically reject it.

Some theoretical studies and mathematical works have been conducted in order to investigate this method of cancer treatment. For information on T cell sensitivity, see Chan, George, and Stark [9]. For other models, see Panetta and Kirschner [5], Swan [10],[11], and Murray [7],[8]. We will apply the method of optimal control theory to address this topic. We will discuss a system of differential equations which model tumor-immune dynamics (Section 2). We then analyze the existence, characterization, and uniqueness of the optimal control in Sections 4, 5, and 6 respectively. In Section 7, numerical analysis and results are then given with explanations relating the numerical results to clinical findings.

2. **The Model.** We analyze the model originally discussed in Panetta and Kirschner [5]. We define three populations. These include: x(t), the activated immune system cells, or effector cells; y(t), the tumor cells; z(t), the concentration of IL-2 in the single tumor-site compartment we are modeling. Our model has the form

$$\frac{dx}{dt} = cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + u(t)s_1 \tag{1}$$

$$\frac{dy}{dt} = r_2 y(1 - by) - \frac{axy}{g_2 + y} \tag{2}$$

$$\frac{dz}{dt} = \frac{p_2 xy}{g_3 + y} - \mu_3 z \tag{3}$$

with normalized initial conditions ,$x(0) = 1$, $y(0) = 1$, and $z(0) = 1$.

The parameters are all considered positive constants where the model terms are described as follows. Our first differential equation depicting the rate of change for the effector cell population consists of a recruitment term due to the presence of the tumor where c models the antigenicity of the tumor. The second term represents the natural death of the effector cells at a rate of μ_2. Our third term is of Michaelis-Menton form to indicate the saturated effects of the immune response, whereby effector cells are stimulated by IL-2. The final term in this equation involves the strength of the treatment, s_1 and the control $u(t)$ that represents an external source of effector cells. The term, s_1, is found to be a critical parameter in [5]. It is the main factor in determining the stability properties of the effector and cancer cells. Equation (2) includes a logistic term in order to model the rate of change of tumor cells. The loss of tumor cells is represented by a Michaelis-Menton term to indicate the limited interaction between the tumor and effector cells. Equation (3) gives the rate of change for the concentration of IL-2. The IL-2 source is modelled by another Michaelis-Menton term in which the tumor cells stimulate the interaction with the effector cells to produce more IL-2. The last term represents the loss of these cells at a rate of μ_3. The units for the parameters are in $days^{-1}$ except for g_1, g_2, g_3, and b whose units are volume. The function u(t) is the control describing the percentage of adoptive cellular immunotherapy given.

We choose as our control class piecewise continuous functions defined for all t such that $0 \leq u(t) \leq 1$ where u(t)= 1 represents maximal immunotherapy and u(t)= 0 represents no immunotherapy. Thus, we depict the class of admissible controls as

$$U = \{u(t) \text{ piecewise continuous} | 0 \leq u(t) \leq 1, \forall t \in [0, T]\}$$

Next, we define the objective functional. We would like to maximize the effects of the immunotherapy while minimizing the cost of the control. Therefore, we define the objective functional as

$$J(u) = \int_0^T [x(t) - y(t) + z(t) - \frac{1}{2}B(u(t))^2]dt \tag{4}$$

Here we are maximizing the amount of effector and interleukin-2 cells and minimizing the number of tumor cells and the cost of the control. B is a weight factor that represents a patient's level of acceptance of the treatment. If we consider the objective functional as a function of u, it can be seen that J is concave. Hence, a maximum value can be obtained. The goal is to characterize the optimal control u* satisfying

$$\max_{0 \leq u \leq 1} J(u) = J(u^*)$$

3. **Parameter estimation.** The basic model parameters are obtained from Panetta and Kirschner [5] and are given in the following table.

$units = days^{-1}$	$units = days^{-1}$	$units = volume$
$0 \leq c \leq 0.05$	$r_2 = 0.18$	$g_1 = 2 \times 10^7$
$\mu_2 = 0.03$	$\mu_3 = 10$	$g_2 = 1 \times 10^5$
$p_1 = 0.1245$	$p_2 = 5$	$g_3 = 1 \times 10^3$
$a = 1$		$b = 1 \times 10^{-9}$

By considering parameter choices in several studies, values that were most appropriate for this model were chosen. However, no previous study had investigated values for rate constants in equation (3). Thus, these values were determined by current medical literature and sensitivity analyses found in [5]. For instance, a wide range of values for c are explored, because the antigenicity of the tumor varies between patient cases. Large c values represent tumor cells that present a well-recognized antigen while small values represent tumor cells that present a weak antigen.

4. **Existence of optimal control.** The existence of an optimal control for the state system (Eq. 1, 2, 3) is analyzed. The existence of an optimal control can be determined from the theory developed by Fleming and Rishel [3]. The boundedness of solutions of the system for finite time is needed to obtain the existence of an optimal control and the uniqueness of the optimality system.

This can be completed using the fact that the supersolutions $\bar{x}$, $\bar{y}$, $\bar{z}$ of

$$\begin{aligned} \frac{d\bar{x}}{dt} &= c\bar{y} + p_1\bar{x} + s_1, \\ \frac{d\bar{y}}{dt} &= r_2\bar{y}, \\ \frac{d\bar{z}}{dt} &= p_2\bar{x}. \end{aligned} \tag{5}$$

are bounded on a finite time interval. We see that equation (5) can be written, where $\prime = d/dt$,

$$\begin{pmatrix} \bar{x} \\ \bar{y} \\ \bar{z} \end{pmatrix}' = \begin{pmatrix} p_1 & c & 0 \\ 0 & r_2 & 0 \\ p_2 & 0 & 0 \end{pmatrix} \begin{pmatrix} \bar{x} \\ \bar{y} \\ \bar{z} \end{pmatrix} + \begin{pmatrix} s_1 \\ 0 \\ 0 \end{pmatrix}$$

Since we have a linear system in finite time with bounded coefficients, then the supersolutions $\bar{x}$, $\bar{y}$, $\bar{z}$ are uniformly bounded. Using that the solution to each state equation is bounded, we now prove the existence of an optimal control.

Theorem 4.1. *Given the objective functional,* $J(u) = \int_0^T [x(t) - y(t) + z(t) - \frac{1}{2}B(u(t))^2]dt$, *where* $U = \{u(t)$ *piecewise continuous* $\mid 0 \leq u(t) \leq 1\ \forall t \in [0,T]\}$ *subject to Eq. (1) , (2), (3) with* $x(0) = 1$, $y(0) = 1$, *and* $z(0) = 1$, *then there exists an optimal control* u^* *such that* $\max_{0\leq u\leq 1} J(u) = J(u*)$ *if the following conditions are met.*

1. *The class of all initial conditions with a control u in the admissible control set along with each state equation being satisfied is not empty.*
2. *The admissible control set U is closed and convex.*
3. *Each right hand side of Eq. (1), (2), (3) is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of u with coefficients depending on time and the state.*
4. *The integrand of J(u) is concave on U and is bounded above by* $c_2 - c_1u^2$ *with* $c_1 > 0$.

Proof. Since the system Eq. 1, 2, 3 has bounded coefficients and any solutions are bounded on the finite time interval, we can use a result from Lukes [6] to obtain the existence of the solution of the system Eq. 1, 2, 3. Secondly, we note that U is closed and convex by definition. For the third condition, the right hand side of Eq. 1, 2, 3 is continuous since each term which has a denominator is nonzero. Also, the system is bilinear in the control and can be rewritten as

$$\overrightarrow{f}(t, \overrightarrow{X}, u) = \overrightarrow{\alpha}(t, \overrightarrow{X}) + s_1u$$

where $\overrightarrow{X} = (x, y, z)$ and $\overrightarrow{\alpha}$ is a vector valued function of $\overrightarrow{X}$.

Using that the solutions are bounded, we see that

$$\left|\vec{f}(t, \vec{X}, u)\right| \leq \left| \begin{pmatrix} p_1 & c & 0 \\ 0 & r_2 & 0 \\ p_2 & 0 & 0 \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix} \right| + \left| \begin{pmatrix} s_1u \\ 0 \\ 0 \end{pmatrix} \right| \leq C_1 \left|\vec{X}\right| + s_1 |u|$$

where C_1 depends on the coefficients on the system.

We note that the integrand of J(u) is concave in U. Also, $x(t) - y(t) + z(t) - \frac{B}{2}[u(t)]^2 \leq x(t) + z(t) - \frac{B}{2}[u(t)]^2 \leq C_2 - C_1 \mid u(t) \mid^2$ where C_2 depends on the upper bounds on x, y, and z and $C_1 = \frac{B}{2}$.

5. **Characterization of Optimal Control.** Since an optimal control exists for maximizing the functional (4) subject to equations (1-3), then a version of Pontryagin's maximum principle is used to derive necessary conditions for the optimal control, Kamien and Schwartz [4]. In order to do this, we define the Lagrangian as

$$\begin{aligned} L(x,y,z,\lambda_1,\lambda_2,\lambda_3) &= x(t)-y(t)+z(t)-\frac{B[u(t)]^2}{2} \\ &+ \lambda_1\left(cy-\mu_2 x+\frac{p_1xz}{g_1+z}+u(t)s_1\right) \\ &+ \lambda_2\left(r_2y(1-by)-\frac{axy}{g_2+y}\right) \\ &+ \lambda_3\left(\frac{p_2xy}{g_3+y}-\mu_3 z\right) \\ &+ w_1(t)u(t)+w_2(t)(1-u(t)) \end{aligned}$$

where $w_1(t)\geq 0$, $w_2(t)\geq 0$ are penalty multipliers satisfying

$$\begin{aligned} w_1(t)u(t) &= 0 \\ w_2(t)(1-u(t)) &= 0 \end{aligned} \tag{6}$$

at the optimal u^*.

Theorem 5.1. *Given an optimal control u^* and solutions of the corresponding state system, there exist adjoint variables λ_i for $i=1,2,3$ satisfying the following:*

$$\begin{aligned} \frac{d\lambda_1}{dt} &= -\frac{\partial L}{\partial x} = -\left[1+\lambda_1\left(-\mu_2+\frac{p_1z}{g_3+z}\right)-\frac{\lambda_2 ay}{g_2+y}+\frac{\lambda_3 p_2 y}{g_3+y}\right] \\ \frac{d\lambda_2}{dt} &= -\frac{\partial L}{\partial y} = -\left[-1+\lambda_1 c+\lambda_2(r_2-2r_2by)-\frac{\lambda_2 g_2 ax}{(g_2+y)^2}+\frac{\lambda_3 g_3 p_2 x}{(g_3+y)^2}\right] \\ \frac{d\lambda_3}{dt} &= -\frac{\partial L}{\partial z} = -\left[1+\frac{\lambda_1 p_1 x g_1}{(g_1+z)^2}-\lambda_3\mu_3\right] \end{aligned} \tag{7}$$

where $\lambda_i(T)=0$ for $i=1,2,3$. Further, u^* is represented by

$$u^*=\min\left(1,\left(\frac{\lambda_1 s_1}{B}\right)^+\right)$$

Proof. A version of the maximum principle gives existence of the adjoint variables satisfying (7) since the state variables are bounded. To complete the representation for u^* we analyze the optimality condition $\frac{\partial L}{\partial u}=0$. Upon algebraic manipulation, the representation of u^* becomes $u^*(t)=\frac{w_1(t)-w_2(t)+\lambda_1 s_1}{B}$. To determine an explicit expression for the optimal control, without w_1 and w_2, a standard optimality technique is utilized. Therefore, the optimal control is characterized as

$$u^*=\min\left(1,\left(\frac{\lambda_1 s_1}{B}\right)^+\right). \tag{8}$$

Also, it is noted that $u^*(T)=0$ since $\lambda_1(T)=0$. After obtaining an explicit expression for the control, the adjoint equations coupled with the state equations and the initial and transversality conditions form the following optimality system.

$$\begin{aligned}
\frac{dx}{dt} &= cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + \min\left(1, \left(\frac{\lambda_1 s_1}{B}\right)^+\right) s_1 \\
\frac{dy}{dt} &= r_2 y(1 - by) - \frac{axy}{g_2 + y} \\
\frac{dz}{dt} &= \frac{p_2 xy}{g_3 + y} - \mu_3 z \\
\frac{d\lambda_1}{dt} &= -\frac{\partial L}{\partial x} = -\left[1 + \lambda_1\left(-\mu_2 + \frac{p_1 z}{g_3 + z}\right) + -\frac{\lambda_2 ay}{g_2 + y} + \frac{\lambda_3 p_2 y}{g_3 + y}\right] \\
\frac{d\lambda_2}{dt} &= -\frac{\partial L}{\partial y} = -\left[-1 + \lambda_1 c + \lambda_2(r_2 - 2r_2 by) - \frac{\lambda_2 g_2 ax}{(g_2 + y)^2} + \frac{\lambda_3 g_3 p_2 x}{(g_3 + y)^2}\right] \\
\frac{d\lambda_3}{dt} &= -\frac{\partial L}{\partial z} = -\left[1 + \frac{\lambda_1 p_1 x g_1}{(g_1 + z)^2} - \lambda_3 \mu_3\right] \qquad (9)
\end{aligned}$$

with $x(0) = 1$, $y(0) = 1$, $z(0) = 1$, $\lambda_i(T) = 0$ for $i = 1, 2, 3$. In addition, the second derivative of the Lagrangian with respect to u is negative, indicating a maximum at u^*.

6. **Uniqueness.** Using the bounds for the state equations, the adjoint system has bounded coefficients and is linear in each adjoint variable. Hence, the solutions of the adjoint system are bounded.

Theorem 6.1. *For T sufficiently small, the solution to the optimality system is unique.*

Proof. We suppose that (x,y,z,λ_1,λ_2,λ_3) and ($\bar{x}$,$\bar{y}$,$\bar{z}$,$\bar{\lambda_1}$,$\bar{\lambda_2}$,$\bar{\lambda_3}$) are two distinct solutions to the optimality system (9). Let $m > 0$ be chosen such that $x = e^{mt}h$, $y = e^{mt}q$, $z = e^{mt}f$, $\lambda_1 = e^{-mt}w$, $\lambda_2 = e^{-mt}v$, $\lambda_3 = e^{-mt}j$, $\bar{x} = e^{mt}\bar{h}$, $\bar{y} = e^{mt}\bar{q}$, $\bar{z} = e^{mt}\bar{f}$, $\bar{\lambda_1} = e^{-mt}\bar{w}$, $\bar{\lambda_2} = e^{-mt}\bar{v}$, and $\bar{\lambda_3} = e^{-mt}\bar{j}$. In addition,

$$u = \min\left(1, \left(\frac{e^{-mt} w s_1}{B}\right)^+\right) \qquad (10)$$

and

$$\bar{u} = \min\left(1, \left(\frac{e^{-mt}\bar{w} s_1}{B}\right)^+\right). \qquad (11)$$

For example, substitution of $z = e^{mt}f$ and $\lambda_3 = e^{-mt}j$ into the third and the sixth differential equation of the optimality system yields the following where $\cdot = \frac{d}{dt}$

$$\begin{aligned}
\dot{f} + mf &= \frac{p_2 hqe^{mt}}{g_3 + qe^{mt}} - \mu_3 f \\
\dot{j} - mj &= -e^{mt} - \frac{wp_1 hg_1 e^{mt}}{(g_1 + fe^{mt})^2} - j\mu_3
\end{aligned}$$

Next, we subtract the equations for h and $\bar{h}$, q and $\bar{q}$, etc. The resulting equation is then multiplied by an appropriate function and integrated from zero to T. Consider the $j - \bar{j}$ equation after multiplying by $j - \bar{j}$ and integrating from zero to the final time.

$$\begin{aligned}
\frac{1}{2}\left[j(0)-\bar{j}(0)\right]^2+(m-\mu_3)\int_0^T(j-\bar{j})^2dt &= \\
p_1g_1\int_0^T e^{mt}(j-\bar{j})\left[\frac{g_1^2(wh-\bar{w}\bar{h})}{(g_1+e^{mt}f)^2(g_1+e^{mt}\bar{f})^2}\right]dt &+ \\
p_1g_1\int_0^T e^{mt}(j-\bar{j})\left[\frac{e^{3mt}(\bar{f}^2wh-f^2\bar{w}\bar{h})}{(g_1+e^{mt}f)^2(g_1+e^{mt}\bar{f})^2}\right]dt &+ \\
2p_1g_1^2\int_0^T e^{mt}(j-\bar{j})\left[\frac{e^{mt}(\bar{f}wh-f\bar{w}\bar{h})}{(g_1+e^{mt}f)^2(g_1+e^{mt}\bar{f})^2}\right]dt &
\end{aligned}$$

Now we must find bounds on the right-hand sides of the integral equations. Since $f,\bar{f}\geq 0$, we can estimate the denominator of the fraction in the integral as follows.

$$\begin{aligned}
(g_1+e^{mt}f)^2 &\geq g_1^2, \\
(g_1+e^{mt}\bar{f})^2 &\geq g_1^2
\end{aligned}$$

Thus, we have

$$\begin{aligned}
\frac{1}{2}\left[j(0)-\bar{j}(0)\right]^2+(m-\mu_3)\int_0^T(j-\bar{j})^2dt &\leq \frac{p_1e^{mT}}{g_1}\int_0^T(j-\bar{j})(wh-\bar{w}\bar{h})dt \\
&+ \frac{p_1e^{3mT}}{g_1^3}\int_0^T(j-\bar{j})(\bar{f}^2wh-f^2\bar{w}\bar{h})dt \\
&+ \frac{2e^{2mT}}{g_1^2}\int_0^T(j-\bar{j})(\bar{f}wh-f\bar{w}\bar{h})dt
\end{aligned}$$

We will now specifically analyze $\int_0^T(j-\bar{j})(\bar{f}^2wh-f^2\bar{w}\bar{h})dt$. To obtain this estimate, we use Cauchy's inequality in order to separate the linear terms into quadratic terms. Also, we recognize that $\bar{f}^2wh-f^2\bar{w}\bar{h}=\bar{f}^2(wh-\bar{w}\bar{h})+\bar{w}\bar{h}(f^2-\bar{f}^2)$. Therefore, we obtain

$$\begin{aligned}
\int_0^T(j-\bar{j})(\bar{f}^2wh-f^2\bar{w}\bar{h})dt &\leq \int_0^T\bar{f}^2(wh-\bar{w}\bar{h})(j-\bar{j})dt+\int_0^T\bar{w}\bar{h}(f^2-\bar{f}^2)(j-\bar{j}) \\
&\leq M_1^2\int_0^T(j-\bar{j})(wh-\bar{w}\bar{h})dt \\
&\quad +2M_7M_2M_1\int_0^T(j-\bar{j})(f-\bar{f})dt \\
&\leq \frac{M_1^2M_7}{2}\int_0^T(h-\bar{h})^2dt+\frac{M_1^2M_2}{2}\int_0^T(w-\bar{w})^2dt \\
&\quad +\frac{M_1^2M_7+M_1^2M_2+2M_7M_2M_1}{2}\int_0^T(j-\bar{j})^2dt \\
&\quad +M_7M_2M_1\int_0^T(f-\bar{f})^2dt
\end{aligned}$$

where M_1, M_7, M_2 are the upper bounds for $\bar{f},\bar{w},\bar{h}$ respectively.

To complete the proof for the uniqueness of the optimal control, the integral representations of $(h-\bar{h})$, $(q-\bar{q})$, $(f-\bar{f})$, $(w-\bar{w})$, $(v-\bar{v})$, and $(j-\bar{j})$ are combined, and estimates are utilized to obtain the following inequality:

$$\frac{1}{2}[h(T)-\bar{h}(T)]^2+\frac{1}{2}[q(T)-\bar{q}(T)]^2+\frac{1}{2}[f(T)-\bar{f}(T)]^2+\frac{1}{2}[w(T)-\bar{w}(T)]^2 \quad +$$

$$\frac{1}{2}[v(T)-\bar{v}(T)]^2+\frac{1}{2}[j(T)-\bar{j}(T)]^2+(m+\mu_2)\int_0^T(h-\bar{h})^2dt \quad +$$

$$(m-r_2)\int_0^T(q-\bar{q})^2dt+(m+\mu_3)\int_0^T(f-\bar{f})^2dt+(m+\mu_2)\int_0^T(w-\bar{w})^2dt \quad +$$

$$(m-r_2)\int_0^T(v-\bar{v})^2dt+(m-\mu_3)\int_0^T(j-\bar{j})^2dt \quad \leq$$

$$C_{21}e^{mT}\int_0^T[(f-\bar{f})^2+(q-\bar{q})^2]dt+\frac{T}{2}e^{mT}+C_{22}\int_0^T[(q-\bar{q})^2+(w-\bar{w})^2]dt \quad +$$

$$C_{23}e^{2mT}\int_0^T[(h-\bar{h})^2+(q-\bar{q})^2+(f-\bar{f})^2+(w-\bar{w})^2+(v-\bar{v})^2+(j-\bar{j})^2]dt \quad +$$

$$C_{24}e^{3mT}\int_0^T[(h-\bar{h})^2+(q-\bar{q})^2+(f-\bar{f})^2+(w-\bar{w})^2+(v-\bar{v})^2+(j-\bar{j})^2]dt$$

Using the nonnegativity of the variable expressions evaluated at the initial and the final time and simplifying, the inequality is reduced to the following:

$$(m-D_1-\tilde{C}e^{3mT})\int_0^T[(h-\bar{h})^2+(q-\bar{q})^2+(f-\bar{f})^2+(w-\bar{w})^2+(v-\bar{v})^2+(j-\bar{j})^2]dt\leq 0$$

where $D_1, \tilde{C}$ depend on all coefficients and bounds on all solution variables.

We choose m such that $m > \tilde{C}+D_1$ and thus, $m-D_1-\tilde{C}e^{3mT}>0$. Since the natural logarithm is an increasing function, then

$$ln\left(\frac{m-D_1}{\tilde{C}}\right)>3mT \tag{12}$$

Thus, this gives that $T<\frac{1}{3m}ln\left(\frac{m-D_1}{\tilde{C}}\right)$.

Based on the uniqueness of the optimality system, the optimal control is thus unique. Therefore, the optimal control is characterized in terms of λ_1.

7. **Numerical Results of Immunotherapy.**

7.1. **Discussion.** In papers by Fister and Panetta [1],[2] there were systems of differential equations mentioned that consisted of a combination of factors which could be analyzed numerically to determine the solution. In this particular case the desired solution is that cancer cells are eradicated producing a state of remission based upon the optimal control of immunotherapy.

There are three factors in this system of differential equations which can be altered: s_1, B, c. The first variable, s_1, is described best as the strength of the dosage of the given drug. A drug amount of 1000 units is the maximum dosage available and zero is the minimum. The second factor, B, is the weight associated with the drug component. The third variable, c, is the variable of antigenicity, which coincides with *the ability to provoke an immune response.* Zero is no ability to provoke such a response while one is the greatest ability to provoke a response.

7.2. **Explanation of the Code.** There are two systems of differential equations, the first system being the state equations involving the control and the second being the adjoint equations (λ's). An initial guess was made for the λ's gives and an initial guess for the control. From here the state equations were solved using the initial condition. Since the adjoint equations depend upon the state equations, the adjoint equations use the updated state variables to determine new solutions for the adjoints. Then update the solutions to which a new control is formulated. The process continues until the difference in the current and previous values for the states, adjoints and control are within an acceptable error range. The time frame used for this algorithm is 350 days.

We consider several scenarios below.

Case 1. $s_1 = 500$, **B = 5, c = .025**

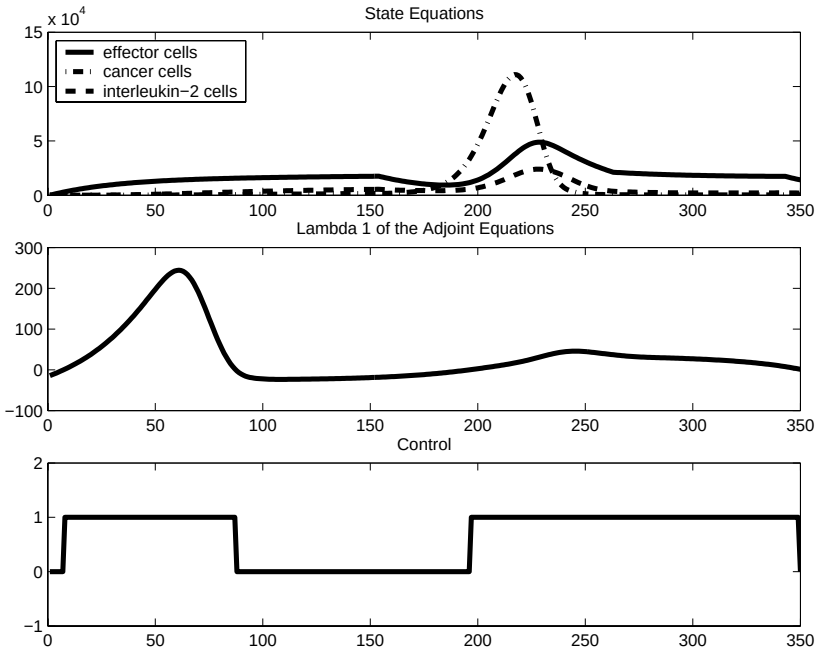

FIGURE 1. s_1=500,B=5,c=.025

In *Figure 1*, notice that s_1 is less than that desired 540 range (a critical value for the stability of the cancer based upon drug dosage given by Panetta and Kirschner for the positive steady states for x, y, and z). Also notice that regardless of the s_1 in an unstable range, we have taken advantage of it's instability and pushed the system to a status that we approve.

There are relatively small amounts of effector, cancer and IL-2 cells present when running these simulations. As is typical of situations with a similar outcome, at first the control bounces to a maximum amount and then slacks off. The cancer cells are control momentarily.

Later, as the control has been delinquent in activity, the cancer, effector and IL-2 cells rise in number. As the model compensates, the control once again activates, and the cancer cells are brought back under rule.

Case 2. $s_1 = 500$, **B = 1, c = .04**

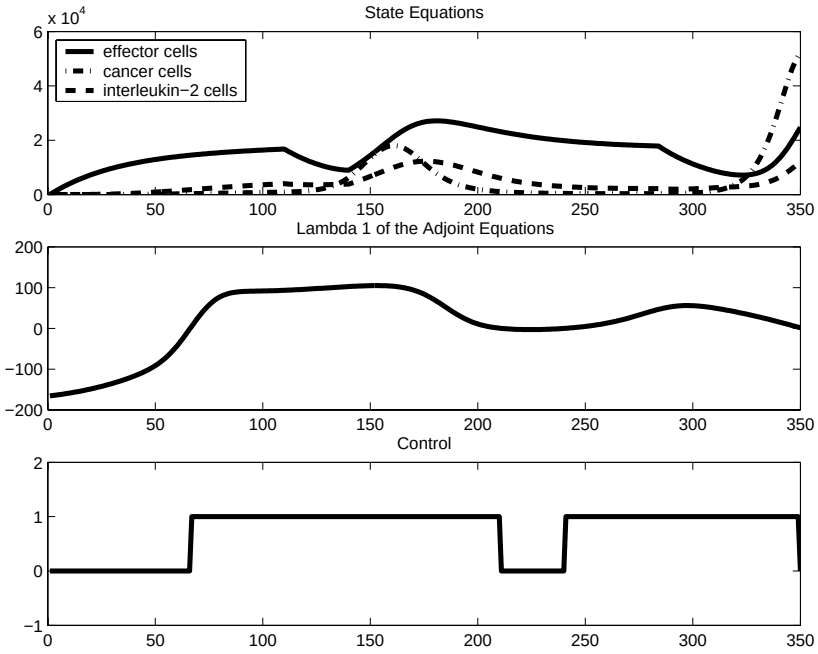

FIGURE 2. s_1=500,B=1,c=.04

In *Figure 2* we will notice several things. Of particular interest is to observe the λ_1 (first adjoint). Since the control depends heavily upon the value of the λ_1, the value of the control becomes one when λ_1 is positive. The control vanishes between days 200 and 250 due to the fact that our adjoint goes to zero. Since the adjoint is directly related to the number of the effector cells, this effects them and the cancer dynamics due to the coupled nature of the system of equations.. When the cancer increases, the first adjoint causes the control (drug) to adjust and effectively lowers the cancer cells from days 200 to 320. Notice there is a delayed reaction between the administration in drug and the reduction of the cancer cells. Eventually the cancer grows again because of the unstable dynamics.

Case 3. $s_1 = 550$, **B = 1, c = .025**

Once again λ_1 becomes positive in *Figure 3*. In turn, the control is maximized to 1. But at days 100 to 200 the λ_1 drops to nonpositive values and the control drops to zero. The maximum drug from day 5 to day 100 keeps the cancer within the acceptable level. However at approximately day 200 to day 250 the cancer resurges. Notice the control in this situation is immediately maximized to 1. Unlike Figure 2, there is no delay. Also, the cancer can be controlled without further growth at the end of the time interval. This situation seems to predict possible resistance.

Case 4. $s_1 = 550$, **B = 10000, c = .04**

This is a particularly interesting situation in *Figure 4*. Notice that s_1 is in the acceptable range for this situation. Yet, we see that slowly and surely he cancer cells (although low) are on the rebound at the end of the time period.

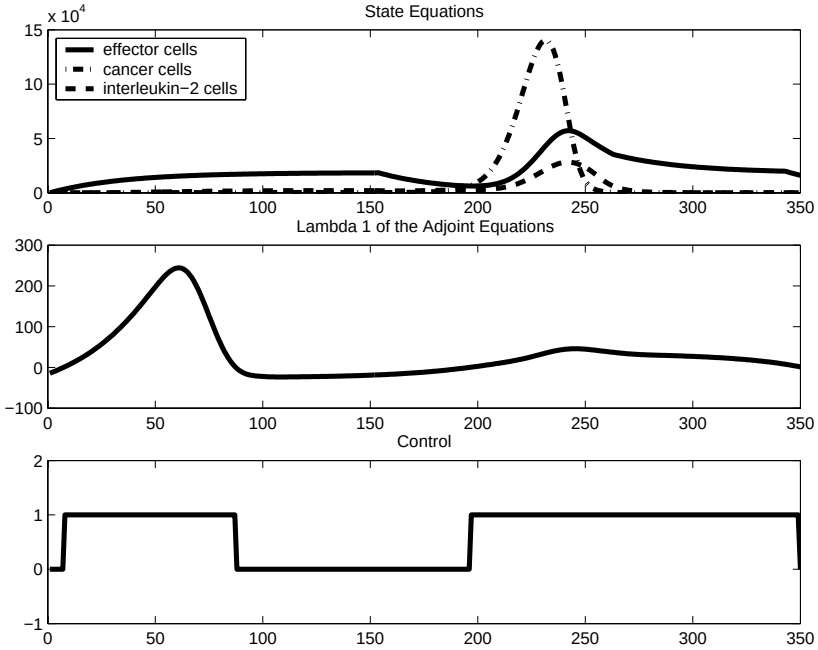

FIGURE 3. s_1=550,B=1,c=.025

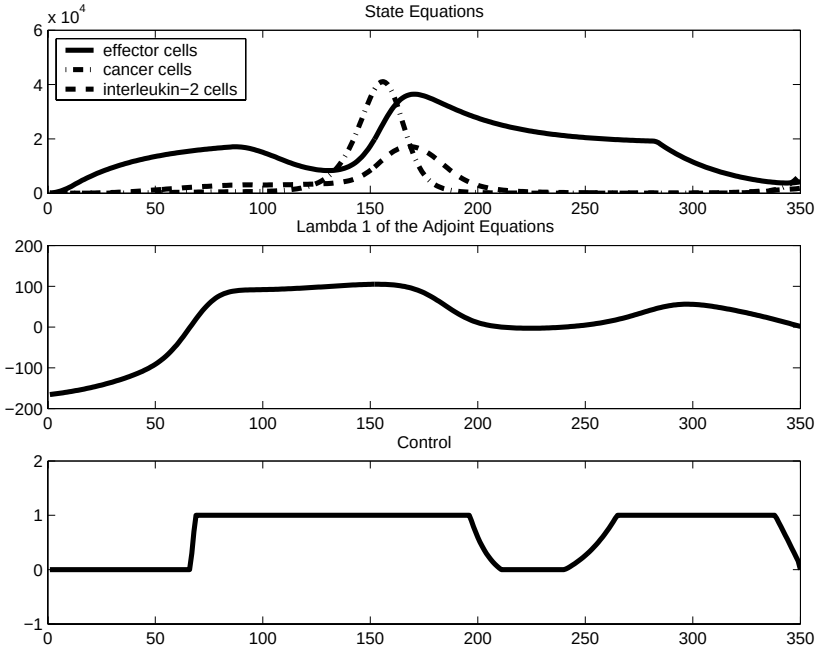

FIGURE 4. s_1=550,B=10000,c=.04

This is definitely a case where the potential of a more "long-term" study might be desirable.

8. **Conclusion.** This model seems to produce not only logical but reasonable output. Since the system of equations that are used to model this also includes factors that influence a standard cancer patient's life, we see the different effects that critical parameters illicit from the graphs in the previous section. Also, the uniqueness of the optimality system, guarantees that the optimal control is unique in the depictions.

As seen in Figures 1 and 2, the resurgence of the cancer at the end of the time frame is a problem. In future work, implementation of a state constraint on the cancer cell population will aid in reduction of the cancer at the final time. Also, further discussion of the introduction of delay and drug resistance into this model could give us a better understanding of our results depicted in Figures 3 and 4.

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