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IMMUNOTHERAPY: AN OPTIMAL CONTROL THEORY APPROACH

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Abstract. We investigate mathematical models for the dynamics between tumor cells, immune-effector cells, and cytokine interleukin-2 (IL-2). To better determine under what circumstances the tumor can be eliminated, we implement optimal control theory. We design two control functionals, the first functional having one control and the second having two controls, to maximize the effector cells and interleukin-2 concentration and to minimize the tumor cells. Next, we show that bang-bang optimal controls exist for each problem. Then, we characterize our optimal controls in terms of the solutions to the optimality system, which is the state system coupled with the adjoint system. Finally, we analyze the various optimal controls and optimality systems using numerical techniques.

1. **Introduction.** According to the American Cancer Society, the number of new cancer cases in 2003 was estimated to be about 1,334,100. Since 1990, there have been over 17 million new cases. Deaths from cancer in 2003 will total approximately 556,500[14]. Cancer accounts for one in four deaths in the United States. Surgery, chemotherapy, and radiation therapy are most commonly used to treat cancer. Recently, immunotherapy has become a viable treatment option.

Immunotherapy refers to the use of natural and synthetic substances to stimulate the immune response. This involves stimulating the immune system to work harder or using an outside source of cells, such as synthesized immune system proteins. Immunological therapies include the use of antigen and nonantigen specific agents such as cytokines. Cytokines are hormones produced in the immune system that regulate the growth and activity of other immune system cells and blood cells. Cytokines alone can give the immune system a boost or given with other immunotherapies they can be used as adjuvants[15]. Cytokines have been used to treat melanoma, leukemia, lymphoma, neuroblastoma, Kaposi's sarcoma, mesothelioma, brain cancer, cancer of the kidney, and cancer of the cervix.

Interleukin-2 (IL-2) is a cytokine that was approved by the FDA in 1992 for treatment of metastatic renal cell (kidney) cancer. IL-2 became the first cytokine approved for use alone in treating advanced cancer. Since that time, it has also been approved to treat people with metastatic melanoma. IL-2 can be used as a

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single-drug treatment for these cancers, or it may be combined with other forms of immunotherapy, such as vaccines. IL-2 helps immune system cells reproduce more rapidly once they are in the patient. The use of IL-2 together with chemotherapy or with other cytokines (such as interferon-alpha) may increase their effectiveness against some cancers, but the side effects of the combined treatment are also increased.

Some theoretical studies and mathematical works have been conducted to investigate this method of cancer treatment. For information on T cell sensitivity, see Chan, George, and Stark [10]. For other models, see Panetta and Kirschner [7]; Swan [12], [13]; DePillis and Radunskaya [2]; and Murray [8], [9]. Also, see Fister and Panetta [3], [4] for optimal control applied to cancer strategies. We apply the method of optimal control theory to address this topic. We discuss a system of differential equations that model tumor-immune dynamics (section 2). In section 3, parameter identification is briefly discussed. We then analyze the existence and characterization of the optimal control in sections 4 and 5, respectively. In section 6, numerical results are given.

2. **The models.** We analyze the model originally discussed in Panetta and Kirschner [7]. We define three populations for each model. 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 first model has the form

$$\frac{dx}{dt} = cy - \mu_2 x + \frac{p_1 xz}{g_1 + z,} \tag{1}$$

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

$$\frac{dz}{dt} = \frac{p_2 xy}{g_3 + y} - \mu_3 z + v(t)s_2. \tag{3}$$

Our second model has the form

$$\frac{dx}{dt} = cy - \mu_2 x + \frac{p_1 xz}{g_1 + z} + u(t)s_1, \tag{4}$$

$$\frac{dy}{dt} = r_2 y(1 - by) - \frac{axy}{g_2 + y,} \tag{5}$$

$$\frac{dz}{dt} = \frac{p_2 xy}{g_3 + y} - \mu_3 z + v(t)s_2, \tag{6}$$

where $u(t)$ and $v(t)$ are controls. Both models have normalized initial conditions, $x(0) = 1$, $y(0) = 1$, and $z(0) = 1$.

The parameters are all considered positive constants. The model terms are described as follows for equations (4)–(6) and similarly in equations (1)–(3). 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 the 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 terms, s_1 and s_2, are found to be critical parameters in [7]. They are the main factors in determining the stability properties of the effector and cancer cells. To model the rate of change of tumor cells, equation (5) includes a logistic term. The loss of tumor cells is represented by a Michaelis-Menton term to indicate the limited interaction between the tumor and effector cells. Equation (6) gives the rate of change for the concentration of IL-2. The IL-2 source is modeled by another Michaelis-Menton term in which the tumor cells stimulate the interaction with the effector cells to produce more IL-2. The next-to-last term represents the loss of these cells at a rate of μ_3. The final term in this equation involves the strength of the treatment, s_2. The units for the parameters are in $days^{-1}$ except for g_1, g_2, g_3, and b, whose units are volume. The functions $u(t)$ and $v(t)$ are the controls describing the percentage of adoptive cellular immunotherapy (ACI) given. We have two controls, because ACI has two approaches [7]. In the lymphokine-activated killer cell therapy, the cells are derived from the in vitro combination with IL-2. These are then injected back at the cancer site and are thought to mainly aid the effector cells. We refer to this control as $u(t)$. In the second approach of tumor infiltrating lymphocyte therapy, the cells are derived from the lymphocytes recovered from the tumors. They are combined with IL-2. We have included the $v(t)$ control to represent the inclusion of IL-2 that is cultured in vitro with the lymphocytes. This directly increases the rate of change of the IL-2 population while having an indirect effect on the immune system cells, $x(t)$.

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

$$\begin{aligned} U_1(t) &= \{v(t) \text{ piecewise continuous} | 0 \leq v(t) \leq 1, \forall t \in [0,T]\}, \\ U_2(t) &= \{u(t), v(t) \text{ piecewise continuous} | 0 \leq u(t), v(t) \leq 1, \forall t \in [0,T]\}. \end{aligned}$$

Next, we define the objective functionals. We desire to maximize the effects of the immunotherapy while minimizing the cost of the control. Therefore, we define the objective functionals as

$$J_1(v) = \int_0^T [x(t) - y(t) + z(t) - B(v(t))]dt, \tag{7}$$

$$J_2(u,v) = \int_0^T [x(t) - y(t) + z(t) - B_1(u(t)) - B_2(v(t))]dt. \tag{8}$$

Here we are maximizing the amount of effector and interleukin-2 cells and minimizing the number of tumor cells and the cost of the controls. B, B_1, and B_2 are weight factors that represent a patient's level of acceptance of the treatment. The goal is to characterize the optimal controls u^* and v^* satisfying

$$\begin{aligned} \max_{0 \leq u \leq 1} J_1(v) &= J_1(v^*), \\ \max_{0 \leq u,v \leq 1} J_2(u,v) &= J_2(u^*, v^*). \end{aligned}$$

As a remark, if $s_1 = 0$ and $B_1 = 0$ in $J_2(u,v)$, then the second model becomes the first model associated with $J_1(v)$. Throughout this paper, most of the analysis is completed for the first model so that the proofs are more insightful.

3. **Parameter estimation.** The basic model parameters are obtained from Panetta and Kirschner [7] and are given in the following table.

TABLE 1. Table 1: Model parameters

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

Values that were most appropriate for these models were chosen. Since no previous study had investigated values for rate constants in equation (6), these values were determined by current medical literature and sensitivity analyses found in [7]. 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 (1)–(3) associated with $J_1(v)$ is analyzed. The existence of an optimal control can be determined from the Filippov-Cesari theorem ([11], p. 132, Theorem 8).

For the theorem, the following notation is used. Here,

$$\vec{K} = \begin{pmatrix} x \\ y \\ z \end{pmatrix}$$

and

$$\begin{aligned} N(\vec{K}, U_1, t) &= \{x(t) - y(t) + z(t) - B(v(t)) + \gamma, cy - \mu_2 x + \frac{p_1 xz}{g_1 + z}, \\ r_2 y(1 &- by) - \frac{axy}{g_2 + y}, \frac{p_2 xy}{g_3 + y} - \mu_3 z + v(t)s_2\}, \end{aligned}$$

where $\gamma \leq 0$ and $v \in U_1$.

Theorem 1. *Consider the objective functional, $J_1(v)$ subject to equations (1)–(3). Assume that*

- *there exists an admissible pair $(\vec{K}, v(t))$;*
- *$N(\vec{K}, U_1, t)$ is convex in U_1 for each $(\vec{K}, t)$;*
- *U_1 is closed and bounded;*
- *there exists a number θ such that $\|\vec{K}\| \leq \theta$ $\forall t \in [t_0, t_1]$ and all admissible pairs $(\vec{K}, v(t))$.*

Then there exists an optimal control pair $(\vec{K}^*, v^*)$ that maximizes $J_1(v)$.

Proof. An admissible pair $(\vec{K}, v(t))$ is needed to obtain the existence of an optimal control. From the discussion of existence in Burden et al. [1], we know that an admissible pair exists. Second, we need $N(\vec{K}, U_1, t)$ to be convex in U_1 for each $(\vec{K}, t)$.

We define

$$w_1 = (x-y+z-Bv_1+\gamma_1, cy-\mu_2 x+\frac{p_1xz}{g_1+z}, r_2y(1-by)-\frac{axy}{g_2+y}, \frac{p_2xy}{g_3+y}-\mu_3 z+v_1s_2)$$

for some $\gamma_1 \leq 0$ and $v_1 \in U_1$,

$$w_2 = (x-y+z-Bu_2+\gamma_2, cy-\mu_2 x+\frac{p_1xz}{g_1+z}, r_2y(1-by)-\frac{axy}{g_2+y}, \frac{p_2xy}{g_3+y}-\mu_3 z+v_2s_2)$$

for some $\gamma_2 \leq 0$ and $v_2 \in U$, and $w_3 = (\lambda)(w_1) + (1-\lambda)w_2$, where $\lambda \in [0,1]$.

We need to prove that

$$w_3 = (\lambda(w_1) + (1-\lambda)w_2) \in (N(\vec{K}, U, t)).$$

To do this, we let

$$\begin{aligned} z_1 &= (\lambda)(x-y+z-Bv_1+\gamma_1) + (1-\lambda)(x-y+z-Bv_2+\gamma_2) \\ &= x-y+z-B((1-\lambda)v_2+\lambda(v_1)) + (\lambda)(\gamma_1) + (1-\lambda)(\gamma_2), \end{aligned}$$

and define

$$\gamma_3 = z_1 - (x-y+z) + Bv_3,$$

where $v_3 = (1-\lambda)(v_2) + \lambda v_1$.

Then $\gamma_3 = \lambda\gamma_1 + (1-\lambda)\gamma_2 \leq 0$, since $\gamma_1, \gamma_2 \leq 0$ and $\lambda \in [0,1]$.

We see that

$$\begin{aligned} z_2 &= \lambda(cy-\mu_2 x+\frac{p_1xz}{g_1+z}) + (1-\lambda)(cy-\mu_2 x+\frac{p_1xz}{g_1+z}) \\ &= cy-\mu_2 x+\frac{p_1xz}{g_1+z}, \\ z_3 &= \lambda(r_2y(1-by)-\frac{axy}{g_2+y}) + (1-\lambda)(r_2y(1-by)-\frac{axy}{g_2+y}) \\ &= r_2y(1-by)-\frac{axy}{g_2+y,} \end{aligned}$$

and

$$\begin{aligned} z_4 &= \lambda(\frac{p_2xy}{g_3+y}-\mu_3 z+v_1s_2) + (1-\lambda)(\frac{p_2xy}{g_3+y}-\mu_3 z+v_2s_2) \\ &= \frac{p_2xy}{g_3+y}-\mu_3 z+v_3s_2. \end{aligned}$$

Combining this information, we find a $v_3 \in [0,1]$ and $\gamma_3 \leq 0$ such that

$$\begin{aligned} (\lambda)w_1 \quad + \quad & (1-\lambda)w_2 = (x-y+z-Bv_3+\gamma_3, \\ & cy-\mu_2 x+\frac{p_1xz}{g_1+z}, r_2y(1-by)-\frac{axy}{g_2+y}, \frac{p_2xy}{g_3+y}-\mu_3 z+v_3s_2). \end{aligned}$$

Hence, $((\lambda)w_1 + (1-\lambda)w_2) \in N(\vec{K}, U_1, t)$. Thus, $N(\vec{K}, U_1, t)$ is convex in U_1.

A third requirement for the existence of an optimal control is that U is closed and bounded, which it is by definition. Finally, there exists a number θ such that $\|\vec{K}\| \leq \Theta$ for all $t \in [t_0, t_1]$and all admissible pairs $(\vec{K}, v(t))$. See Burden et al. [1] for a boundedness argument. □

A similar argument holds for the existence of an optimal control pair associated with $J_2(u,v)$ subject to equations (4)–(6).

5. **Characterization of optimal control.** Since an optimal control exists for maximizing the functionals in (7) and (8) subject to equations (1)–(3) and (4)–(6), then a version of Pontryagin's maximum principle is used to derive necessary conditions for the optimal control. See Kamien and Schwartz [6]. We analyze the characterization for an optimal control associated with $J_1(v)$.

For the characterization, we define the Hamiltonian associated with $J_1(v)$ and equations (1)–(3) as

$$\begin{aligned} H &= x - y + z + \lambda_1(cy - \mu_2 x + \frac{p_1 xz}{g_1 + z}) + \lambda_2(r_2 y(1 - by) - \frac{axy}{g_2 + y}) \\ &+ \lambda_3(\frac{p_2 xy}{g_3 + y} - \mu_3 z) + (\lambda_3 s_2 - B)v. \end{aligned}$$

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

$$\begin{aligned} \frac{d\lambda_1}{dt} &= \frac{-\partial H}{\partial x} = -[1 - \lambda_1\mu_2 + \frac{\lambda_1 p_1 z}{g_1 + z} - \frac{\lambda_2 ay}{g_2 + y} + \frac{\lambda_3 p_2 y}{g_3 + y}], \\ \frac{d\lambda_2}{dt} &= \frac{-\partial H}{\partial y} = -[-1 + \lambda_1 c + \lambda_2 r_2 - 2\lambda_2 r_2 by - \frac{g_2\lambda_2 ax}{(g_2 + y)^2} + \frac{\lambda_3 g_3 p_2 x}{(g_3 + y)^2}], \\ \frac{d\lambda_3}{dt} &= \frac{-\partial H}{\partial z} = -[1 + \frac{\lambda_1 g_1 p_1 x}{(g_1 + z)^2} - \lambda_3\mu_3], \end{aligned}$$

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

$$v^* = \begin{cases} 1, & \text{if } \lambda_3 s_2 - B > 0, \\ 0, & \text{if } \lambda_3 s_2 - B < 0. \end{cases}$$

Proof. From the Hamiltonian, the derivatives of the adjoints are easily determined. In addition, we see that

$$v^*(t) = \begin{cases} 1, & \text{if } \lambda_3 s_2 - B > 0, \\ 0, & \text{if } \lambda_3 s_2 - B < 0, \\ \textit{singular}, & \text{if } \lambda_3 s_2 - B = 0. \end{cases}$$

at the optimal v^*. We next determine the representation of the control by excluding the singular case.

We suppose the control is singular; that is, $\lambda_3 s_2 - B = 0$ on $(t_1, t_2) \subset [0, T]$.This says that $\lambda_3 = \frac{B}{s_2}$ on this interval. If we take a time derivative of $\lambda_3 s_2 - B = 0$, we obtain $\lambda_3'(t)s_2 = 0$ or $\lambda_3' = 0$. This means $\lambda_3(t) = C$ where C is a constant. Since $\lambda_3(t)$ can be shown to be continuous on $[0, T]$ and $\lambda_3(T) = 0$, then $\lambda_3(t) = 0$ on any subset of $[0, T]$. Yet, $\lambda_3 = \frac{B}{s_2} > 0$. This is a contradiction to our assumption.

Consequently, the control is of bang-bang type; that is,

$$v^*(t) = \begin{cases} 1, & \text{if } \lambda_3 s_2 - B > 0, \\ 0, & \text{if } \lambda_3 s_2 - B < 0. \end{cases} \square$$

Similarly, the necessary conditions for $J_2(u, v)$ give

$$\begin{aligned} \lambda_1' &= \frac{-\partial H}{\partial x} = -[1 - \lambda_1\mu_2 + \frac{\lambda_1 p_1 z}{g_1 + z} - \frac{\lambda_2 ay}{g_2 + y} + \frac{\lambda_3 p_2 y}{g_3 + y}], \\ \lambda_2' &= \frac{-\partial H}{\partial y} = -[-1 + \lambda_1 c + \lambda_2 r_2 - 2\lambda_2 r_2 by - \frac{g_2\lambda_2 ax}{(g_2 + y)^2} + \frac{\lambda_3 g_3 p_2 x}{(g_3 + y)^2}], \\ \lambda_3' &= \frac{-\partial H}{\partial z} = -[1 + \frac{\lambda_1 g_1 p_1 x}{(g_1 + z)^2} - \lambda_3\mu_3], \end{aligned}$$

where

$$u^*(t) = \begin{cases} 1, & \text{if } \lambda_1 s_1 - B_1 > 0, \\ 0, & \text{if } \lambda_1 s_1 - B_1 < 0, \end{cases}$$

and

$$v^*(t) = \begin{cases} 1, & \text{if } \lambda_3 s_2 - B_2 > 0, \\ 0, & \text{if } \lambda_3 s_2 - B_2 < 0. \end{cases}$$

For the case of two controls, we note that if it is assumed that both controls are singular on the same or even distinct subsets of $[0, T]$ and take time derivatives, then $\lambda_1(t) = 0$ and $\lambda_3(t) = 0$ on $[0, T]$, using the continuity of $\lambda_1(t)$ and $\lambda_3(t)$. This contradicts the facts that $\lambda_1 = \frac{B_1}{s_1}$ and $\lambda_3 = \frac{B_2}{s_2}$. Consequently, both controls cannot be singular. If it is assumed that one is singular and the other is bang-bang, then a contradiction similar to the above is found. Therefore, both controls are bang-bang.

We can establish uniqueness of the solution to the state system and its associated adjoint system. Note that the state system and its associated adjoint system are referred to as the optimality system. Thus, we obtain the uniqueness of the optimal control for each system associated with its respective objective functional.

Theorem 3. *For T sufficiently small, the solution to each optimality system is unique.*

In [1] and [5], similar proofs are given for the uniqueness. We note that the condition that T be sufficiently small is needed because the state system is moving forward in time and the adjoint system is moving backward in time.

6. **Numerical results.** In this section, the graphical results are analyzed. To solve each optimality system, first an initial guess is made for the control(s). Then the state system is solved forward in time while the adjoint system is solved backward in time. The controls are then updated. This process continues until the error in the iterates is less than a prescribed epsilon.

Using the bifurcation analysis that Kirschner and Panetta [7] have provided, we have chosen parameters that lie in stable or unstable regions. With these parameters, we determine the optimal control situation (i.e., the drug strategy) that develops. We also depict the evolution of the cancer cells, effector cells, and interleukin-2 cells within the context of each control strategy. We note that we include the graphs of the adjoints that are directly related to the controls. As the adjoint moves above or below 1, the control changes from off to on or vice versa.

Figure 1 represents the results for the $J_1(v)$ objective functional associated with equations (1)–(3). The values for s_2 and c are in the stable range per Kirschner and Panetta [7]. The cancer cells increase rapidly around day 100. The effector cells and interleukin-2 cells do not appear to respond at a level that has any affect on the cancer cells. The cancer continues to grow at the end of the time interval, with the effector and interleukin-2 cells being virtually nonexistent in comparison. About day 180, the control switches on, but the cancer has been growing since about day 100. The control stays on until about day 340, at which time the cancer has reached a plateau.

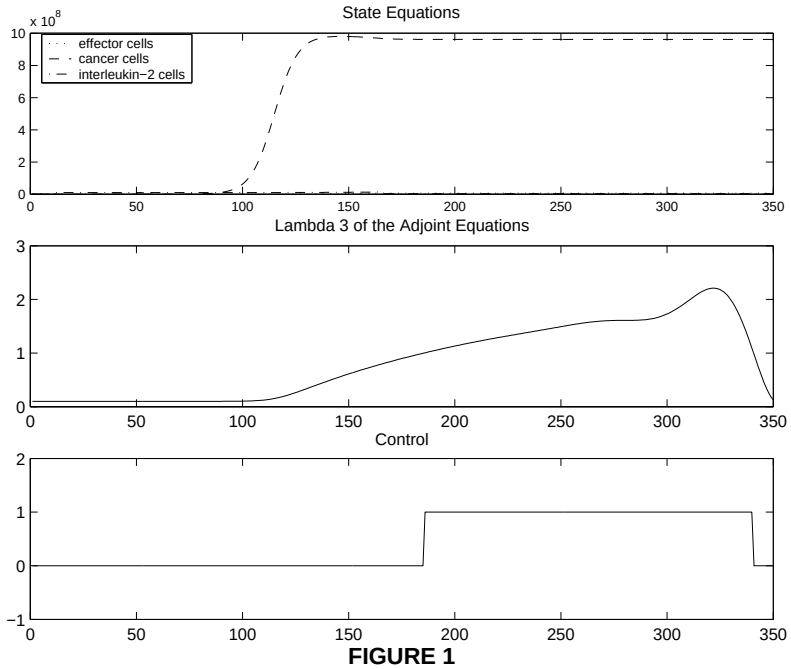

FIGURE 1. $s_2 = 100,000,000$, $B = 100,000,000$, $c = .000085$. This represents the results for the $J_1(v)$ functional subject to equations (1)–(3) with the parameter s_2 chosen so that the cancer cells lie in a region of stability.

Figure 2 represents the results for the $J_1(v)$ objective functional also associated with equations (1)–(3). The s_2 value in this case is not in the stable range. The cancer grows uncontrolled, even though the drug is given at its maximum level for the entire period. The effector cells and interleukin-2 cells are unable to affect the cancer cell growth. The cancer continues to grow at the end of the time interval.

Figures 1 and 2 have the same dynamics for the effector, cancer, and IL-2 cells. However, the drug strategy is different. Less therapy is needed in Figure 1. But sadly, the cancer cells in both situations overpower the treatment efforts.

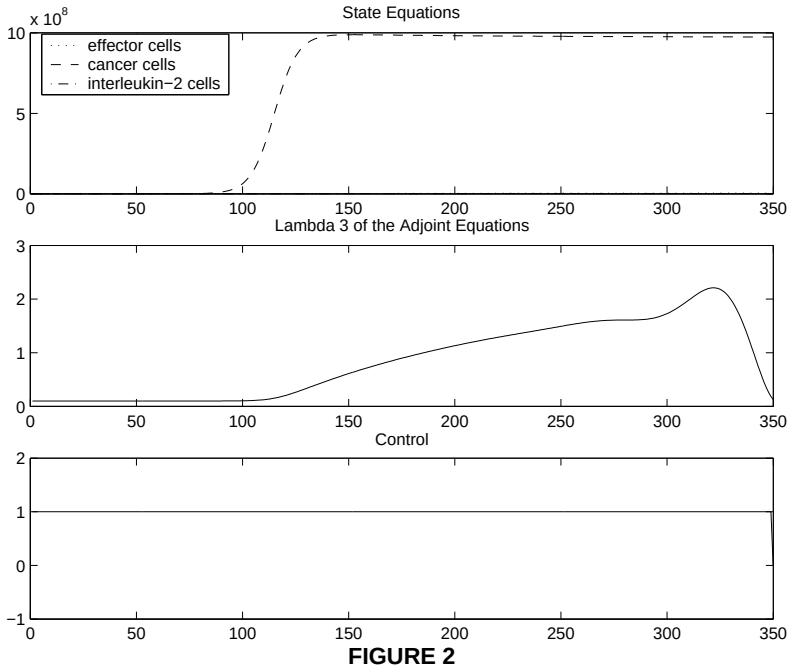

FIGURE 2

FIGURE 2. $s_2 = 10,000$, $B = 5$, $c = .000085$. The represents the results for $J_1(v)$ functional subject to equations (1)–(3) with the s_2 parameter lying in a region of instability.

Figure 3 represents the results for the $J_2(u, v)$ objective functional associated with equations (4)–(6). The values for s_1, s_2, and c are in the cancer-free state range. The cancer cells surge around day 50. The effector and interleukin-2 cells have a delayed response. Around day 90 when the cancer cells are eliminated, they are at their highest concentration. The second surge of cancer cell growth occurs around day 225. Again, the effector and interleukin-2 respond, and the cancer is reduced to undetectable levels at day 270. The cancer is not growing at the end of the time interval. Control $1(u)$ responds to the surges of cancer growth by switching on. Control $2(v)$ is always on at the highest level. The controls remain on until the end of the time interval at which time the cancer cells are virtually nonexistent.

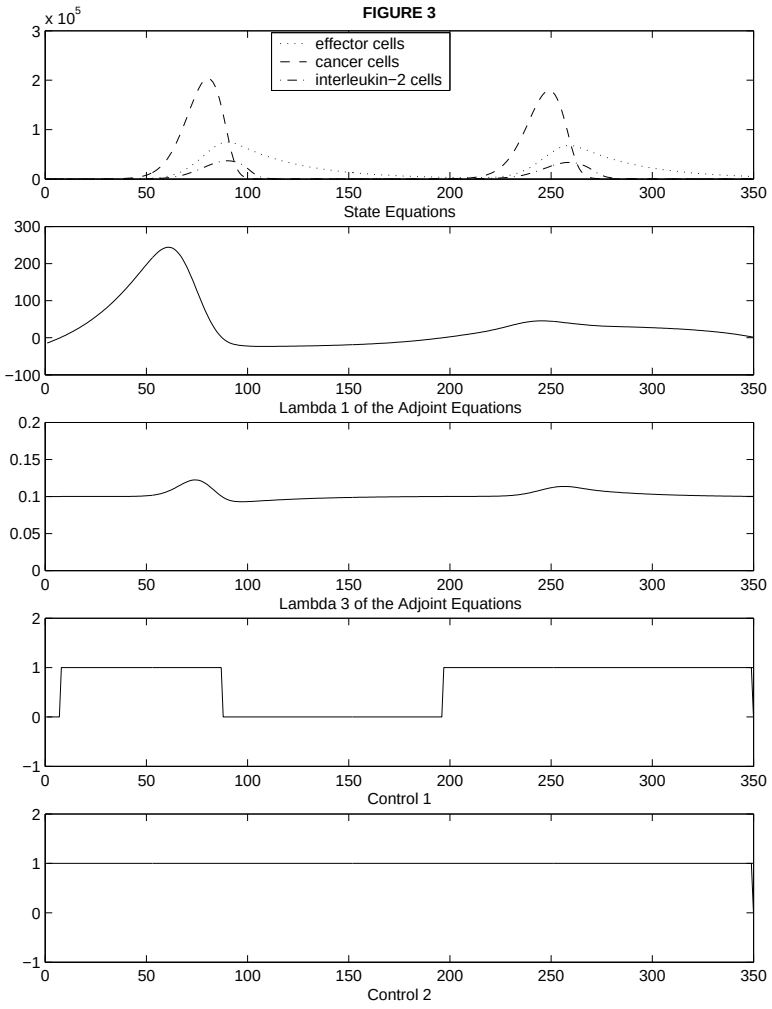

FIGURE 3. $s_1 = 500$,$s_2 = 70,000,000$, $B_1 = 50$,$B_2 = 10,000,000$,$c = .025$. This represents the results for the $J_2(u, v)$ objective functional associated with equations (4)–(6). The values for s_1,s_2 and c are in the cancer free state region.

Figure 4 represents the results for the $J_2(u, v)$ objective functional associated with equations (4)–(6). The s_1 value is not in the cancer-free state range, although at the end of the time interval, the cancer cells are not present. Each time the cancer cells increase, the effector cells and interleukin-2 cells also increase in response. In this case, Control 1(u) is always off and Control 2(v) is always on.

Figures 3 and 4 are similar except in the form of the controls. In Figure 3, a combination of the two strategies is employed, whereas in Figure 4 only one drug protocol is used. Depending on the side-effects of these treatments to the patient, the drug program that minimizes those effects should be chosen, because in both cases the cancer resurges but at a lower maximum level than before. This cyclic nature of the cancer resurgence is present even if the time period is increased. As

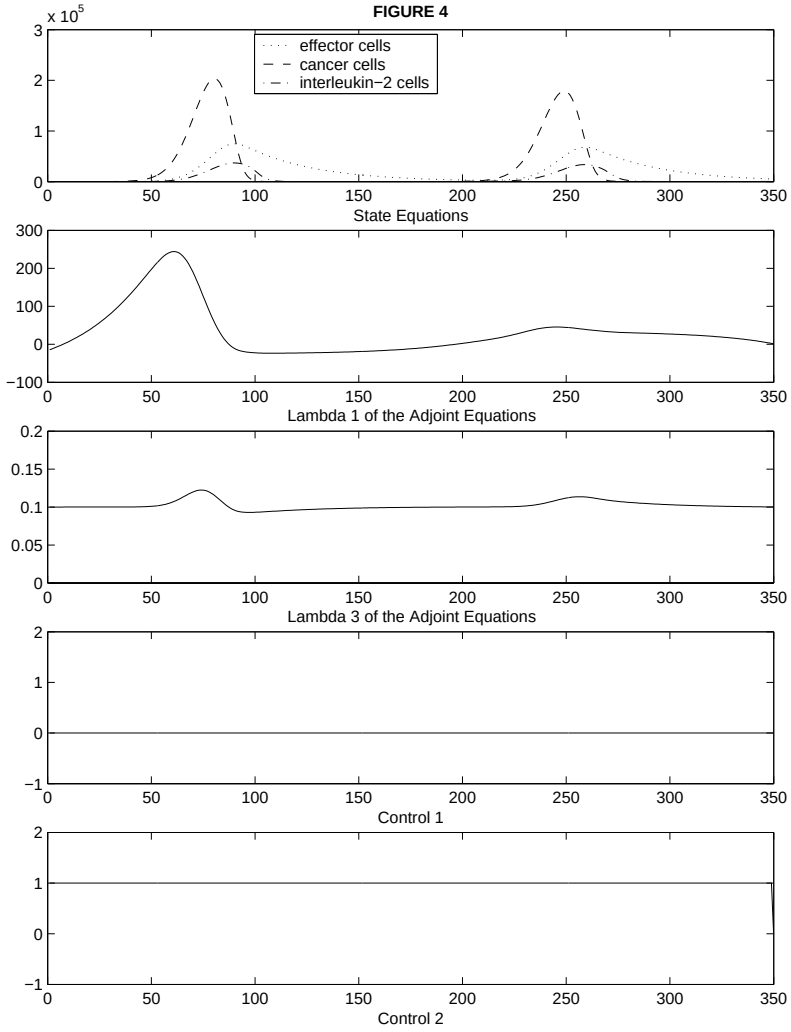

FIGURE 4. $s_1 = .000000025$,$s_2 = 70,000,000$, $B_1 = 1$,$B_2 = 5$,$c = .025$. This figure represents the results for the $J_2(u, v)$ objective functional associated with equations (4)–(6). The s_1 value is not in the cancer free state region.

the time period increases to two years, the maximum level at which the cancer reappears has been reduced by two orders of magnitude.

7. **Conclusion.** Numerical results are obtained for the two optimality systems. Bang-bang optimal controls are found to exist for each problem. The effects of altering the strength of the treatment(s_1 and s_2) and also the antigenicity of the tumor(c) are seen in the controls' response. We observe the growth of cancer cells and the response of the interleukin-2 and effector cells as the controls changed from maximum level to minimum level and vice versa. The results show that cancer cells can have a cyclic nature (see Figs. 3 and 4) even when the drug therapy is at a

maximum level. Thus, even though the tumor burden in the objective functional is minimized, the cancer cells are reduced but may not be totally eliminated from the system.

We observe qualitatively different treatment strategies based on the use of different objective functionals. These differences show the importance of defining an objective functional that most accurately reflects the toxicities of a particular drug along with the objective of the treatment strategy. In future work, different objective functionals will be evaluated. A next step will include the study of optimal control applied to immunotherapy and vaccination strategies of ordinary differential equation models and age-dependent partial differential equation models.

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REFERENCES

[1] T. Burden , J. Ernstberger, and R. Fister, 2004, *Optimal Control Applied to Immunotherapy*, Discrete and Continuous Dynamical Systems, Series B 4, 1, pp. 135–146.

[2] L. DePillis, and A. Radunskaya, 2001, *A Mathematical Tumor Model with Immune Resistance and Drug Therapy: An Optimal Control Approach*, J.Theoret. Med. 3, pp. 79–100.

[3] K. R. Fister and J. C. Panetta, 2000, *Optimal Control Applied to Cell-Cycle-Specific Cancer Chemotherapy*, SIAM J. Appl. Math. 60, pp. 1059–1072.

[4] K. R. Fister and J. C. Panetta, 2003, *Optimal Control Applied to Competing Chemotherapeutic Cell-Kill Strategies*, SIAM J. Appl. Math. 63, 6, pp. 1954–1971.

[5] K. R. Fister, S. Lenhart, and J. McNally, December 1998, *Optimizing Chemotherapy in an HIV* , Elec. J.DE , 1998, 32, pp. 1–12.

[6] M. I. Kamien and N. L. Schwartz, 1991, *Dynamic Optimization: The Calculus of Variations and Optimal Control in Economics and Management*, North-Holland, Amsterdam.

[7] D. Kirschner and J. C. Panetta, 1998, *Modeling Immunotherapy of the Tumor-Immune Interaction*, J. Math. Biol. 37, pp. 235–252.

[8] J. M. Murray, 1990, *Optimal Control for a Cancer Chemotherapy Problem with General Growth and Loss Functions*, Math. Biosci. 98, pp. 273–287.

[9] J. M. Murray, 1990, *Some Optimal Control Problems In Cancer Chemotherapy With a Toxicity Limit*, Math. Biosci. 100, pp. 49–67.

[10] C. Chan, A. George, and J. Stark, 2003, *T Cell Sensitivity and Specificity —Kinetic Proofreading Revisited* Discrete and Continuous Dynamical Systems - Series B 3, pp. 343–360.

[11] A. Seierstad and K. Sydsaeter, 1987, *Optimal Control Theory with Economic Applications*, Elsevier, Amsterdam, pp. 131.

[12] G. W. Swan, 1986, *Optimal Control Using the Verhulst-Pearl Equation*, Bull. Math. Bio., 48, pp. 381-404.

[13] G. W. Swan, 1990, *Role of Optimal Control Theory in Cancer Chemotherapy*, Math. Biosci.,101, pp. 237-284.

[14] American Cancer Society, 2003, "ACS Cancer Facts and Figures 2003 Released", http://www.cancer.org/docroot/NWS/content/NWS 1 1 x ACS Cancer Facts and Figures 2003 Released.asp

[15] American Cancer Society, 2003, "Immunotherapy for Specific Cancers", http://www.cancer.org/docroot/ETO/content/ETO 1 4 X Immunotherapy for Specific Cancers.asp sitearea=ETO.

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