Optimal treatments in cancer immunotherapy involving CD4$^+$ T cells

XIAOCHUAN HU and SOPHIA R.-J. JANG
Department of Mathematics and Statistics
Texas Tech University
Lubbock, Texas 79409
USA
sophia.jang@ttu.edu   http://www.math.ttu.edu/ sjang/

Abstract:- We apply optimal control theory to a model of interactions between cancer cells, CD4$^+$ T cells, cytokines and host cells to devise best immunotherapies for treating cancer. The CD4$^+$ T cells cannot kill cancer cells directly but use the cytokines produced to suppress tumor growth. The immunotherapy implemented is modeled as a control agent and it can be either transferring of CD4$^+$ T cells, cytokines or both. We establish existence and uniqueness of the optimal control. The optimal treatment strategy is then solved numerically under different scenarios. Our numerical results provide best protocols in terms of strengths and timing of the treatments.

Key-words:- Cytokine, Immunotherapy, Ordinary Differential equations, Optimal Control, Tumor

1 Introduction

Cancer is a leading cause of death worldwide. It is a broad group of diseases involved with unregulated cell growth. In particular, cancer cells have defects in regulatory circuits that govern normal cell proliferation and homeostasis. It is suspected that growth signaling pathways suffer deregulation in all human tumors [1]. On the other hand, many tumors express antigens that can be recognized by the adaptive immune system and therefore can be used to induce an anti-tumor immune response. The Tumor Immuno-Surveillance Hypothesis states that the immune system is capable of inhibiting the growth of very small tumors and eliminating them before they become clinically evident [2].

Cancer immunotherapy is the use of immune system to treat cancer. It frequently involves adopted cellular transfers of T cells and/or cytokines. Researchers designing anti-tumor treatments involving transfers of activated anti-tumor cells have long focused on the methods to elicit tumor-specific CD8 CTLs [3]. Although many of the resulting treatments have indeed been able to exploit CTLs that recognize tumor cells and/or tu-

mor antigens in vitro, complete tumor regression has been achieved only in a minority of patients and animal models [3]. Over the last few decades, a few studies have shown that CD4 T cells can also clear tumors completely and independently of CD8, including Corthay et al. [4], Fernandez et al. [5], Greenberg et al. [6], Mumberg et al. [7], and Qin et al. [8]. In addition to these references just mentioned, several more recent experiments reconfirm the effector roles of CD4$^+$ without CD8$^+$. In the following, we briefly discuss each of these research works.

To elucidate the direct anti-tumor activity of Th1 and Th2 cells, particularly against tumors resistant to CTL lysis, Mattes et al. [3] design experiments using B16 mouse melanoma, a highly metastatic and CTL-resistant tumor cell line. Their results demonstrate that CD4$^+$T cells can recognize a secreted tumor-specific antigen and exhibit a cytokine secretion profile characteristic of Th2 cells. The cytokines are capable of clearing established lung and visceral metastases of a CTL-resistant melanoma. This work provides the basis for a new approach to adoptive T cell immunotherapy of can-

cer using CD4$^+$ T cells.

Using TCR Tg mice, Perez-Diez et al. [9] in a recent study perform a direct comparison between CD4 and CD8 T cells specific for the same tumor containing pure populations of CD4 or CD8 T cells in order to test each type of effector role alone without the effects of potential contaminants. Their study shows that CD4 cells are actually better than CD8 cells at rejecting tumors in every case tested using six different tumors. They conclude that CD4 cells are better effector cells even when the CD4 effectors exhibited minimal in vitro or in vivo lytic activity against the tumor cells and even when the tumor expressed major histocompatibility complex (MHC) class I but not class II molecules.

Motivated by an increasing evidence indicating that CD4$^+$ T cells are able to mediate tumor destruction without direct interaction with tumor cells and that CD4$^+$ T cells may provide even greater anti-tumor effect than CD8$^+$ T cells, Zhang et al. [10] test CD8-depleted, B-cell-deficient mice for induction of the anti-tumor immunity of CD4$^+$ T cells. Zhang et al further confirm the role of CD4$^+$ T cells as effectors.

The interactions between tumor cells and other components of the tumor microenvironment are very complex and continuously changing. Therefore devising cancer immunotherapies to treat or to cure cancer is a very challenging task. Mathematical modeling provides a valuable tool for understanding the complicated interactions among the many components of the tumor microenvironment. See [11], [12], [13] and [14]. There are many mathematical models of tumor-immune interactions with different complexities in the literature. For example, Forys et al. [15], Kuznetsov et al. [16], Michelson et al. [17], and de Vladar and Gonzalez [18] use models of ordinary differential equations to understand the interactions between tumor and effector cells. Kirschner and Panetta [19] investigate asymptotic dynamics between cytokines and CTL cells, where the CTL cells are directly killing cancer cells. The article by Eftimie et al. [2] provides a very thorough review of the research in this area.

To further study the effector roles of CD4$^+$ T cells via cytokines discovered recently, Eftimie et al. [20] construct models of interactions between tumor, CD4$^+$ and cytokines to investigate the role of CD4$^+$ cells on skin tumor rejection. In [21], mathematical models of tumor, CD4$^+$ T cells, and cytokines with continuous treatments are proposed to explore the effects of different immunotherapies. It is known that tumor cells and normal tissue cells compete for resources and space [1]. Further, the signaling interactions between the stromal and neoplastic tissues are important in driving tumor cell proliferation [22]. As a consequence, host cells play important roles on tumor evolution. A mathematical model of tumor and normal tissue cells with another component of generic immune cells such as CD8$^+$ T cells or NK cells is proposed in [11] to study various optimal treatment strategies. More recently, mathematical models of tumor cells, normal tissue cells, CD4$^+$T cells and cytokines with continuous and pulsed treatments are investigated to study the possible effects of CD4$^+$ on tumor regression and dormancy [23].

In this work, we apply optimal control theory to devise the best immunotherapy strategies for treating cancer. The optimal control theory has been applied to study cancer immunotherapy by many researchers such as Burden et al. [24], Castiglione and Piccoli [25], Khajanchi and Ghosh [26], Minelli et al. [27], and Sharma and Samanta [28]. In these studies by [24, 25, 26, 27, 28], objective functionals may be defined differently depending on the goal of the treatment outcomes. Our model with no treatments is based on a system of ordinary differential equations studied in [23] where the model may have two interior steady states in the absence of any treatments. It is shown in [23] that if the tumor has a small intrinsic growth rate and is also less competitive than the host cells, then the cancer cells can be eradicated completely independent of the tumor size. Since continuous treatments may have serious side effects on the patients who receive

the treatments, our goal of this research is to derive a best immunotherapy by taking patient's tolerance of treatment into consideration. For our purpose, we aim to derive a best strategy under which the tumor size is small and the number of normal cells are large during the whole treatment period.

The remainder of this manuscript is organized as follows. In the following section, a brief review of the mathematical model investigated in [23] is presented. Section 3 uses optimal control theory to provide optimal treatment strategies. In particular, we show that the optimal control exists, and is unique if in addition the treatment period is small. Numerical simulations under different scenarios are performed in Section 4. The final section provides a brief summary and discussion.

2 The model with no treatment

In this section, we briefly review the model studied by Hu and Jang [23]. Recall that we focus on the effector role of $CD4^+$ T cells. Let $x(t)$, $y(t)$, $z(t)$ and $w(t)$ denote the tumor cells, $CD4^+$ T cells, cytokines, and the normal tissue cells at time $t \geq 0$, respectively. The cytokine in this study is based on IL-4 or more broadly any cytokines produced by the Th2 cells. The time unit is a day. It is assumed that both the tumor and normal tissue cells grow logistically with intrinsic growth rates r_1 and r_2 and carrying capacities $1/b_1$ and $1/b_2$, respectively. In the absence of $CD4^+$ T cells and cytokines, the interaction between tumor and normal tissue cells is described by the classical Lotka-Volterra competition equation with competition coefficients δ_1 and δ_3. These two types of cells compete for space and resources for growth. The simple Lotka-Volterra interaction is also assumed in [11] and [29] for studying competition between tumor and host tissue cells.

Unlike $CD8^+$ T cells, $CD4^+$ T cells cannot kill tumor cells directly but through the cytokines they produced [3, 10]. The Michaelis Menten kinetics, $\dfrac{c_1 xz}{a_1 + x}$, is used to model the killing of tumor cells due to cytokines, where c_1 is the maximum killing

rate by cytokines and a_1 is the half saturation constant. This tumor killing rate is also adopted in [20] and [21]. The activation of $CD4^+$ T cells is through tumor cells and cytokines but is also limited by the cancer cells and is described by $\dfrac{\beta_1 xz}{\alpha_1 + x}$. The parameter β_1 is the maximum $CD4^+$ production rate and α_1 is the half saturation constant, where β_1 may be interpreted as the antigenicity of the tumor. The immune system produces $CD4^+$ T cells more effectively if β_1 is larger. The rate of change of $CD4^+$ T cells increases with increasing tumor cells but is also limited by the tumor cells. The activation of $CD4^+$ T cells is similar to the model discussed in [20] but is different from that in [21].

In addition to the apoptosis, denoted by μ_1, $CD4^+$ T cells are inactivated due to interaction with the tumor cells and this loss rate is given by δ_2. This inactivation of $CD4^+$ T cells is also assumed in [20] but not in [21]. The production of cytokines depends on both the tumor and the $CD4^+$ T cells and is also modeled by the Michaelis-Menten kinetics. Therefore, the production of cytokines is also limited by the cancer cells as in [21] and [20]. Let β_2 denote the maximum production rate of cytokine and α_2 be the half saturation constant. The cytokine decays naturally at a rate μ_2. These parameters are positive constants and the model without any treatment is given by

$$
\begin{cases}
x' = r_1 x(1 - b_1 x) - \dfrac{c_1 xz}{a_1 + x} - \delta_1 xw \\[2mm]
y' = \dfrac{\beta_1 xz}{\alpha_1 + x} - \mu_1 y - \delta_2 xy \\[2mm]
z' = \dfrac{\beta_2 xy}{\alpha_2 + x} - \mu_2 z \\[2mm]
w' = r_2 w(1 - b_2 w) - \delta_3 xw \\[2mm]
x(0) > 0, y(0) \geq 0, z(0) \geq 0, w(0) > 0.
\end{cases}
\tag{1}
$$

System (1) can have at most two interior steady states and bistability exhibits in the interaction. It is proven that if $r_2 > \delta_3/b_1$ and $r_1 < \delta_1/b_2$, then steady state $E_2 = (0, 0, 0, 1/b_2)$ is globally

asymptotically stable for (1) in $int(\mathbb{R}^4_+)$ so that the tumor can be eradicated completely. On the other hand, if the product of the natural loss rates of CD4$^+$ T cells and cytokines are large, $\mu_1\mu_2 > \dfrac{\beta_1\beta_2}{(b_1\alpha_1+1)(b_1\alpha_2+1)}$, then the immune system is not effective and whether the tumor can establish itself or not depends solely on its interaction with the host cells. Although oscillations are frequently observed in some previous models such as [19] and [21] in which the host cells are not incorporated, oscillations are rarely present in model (1). When oscillations do exist in the dynamic interaction, then long periodicity and small amplitude are obtained and thus such an oscillatory behavior is not easily observed clinically. It is widely believed that solid tumor cells do not oscillate over time [2]. Therefore, the study in [23] suggests that host cells along with the mechanism of production of CD4$^+$ T cells play important roles on regulating tumor dynamics.

In the experiment carried out by Mattes et al. [3], 10^5 tumor cells are injected in the mouse on day zero and adopted transfer of 10^7 CD4$^+$ T cells is administered on day 7. The model (1) is validated in [23] with a single treatment of CD4+ T cells on day 7. It is concluded that the experimental result of Mattes et al. [3] can be achieved if the immune system of the subject is strong [23].

3 The optimal strategy of immunotherapy

In this section, we devise the best treatment strategies using optimal control theory. We introduce the control terms u_i, $i = 1, 2$, and formulate the treatment problem in an optimal control setting. Section 3.1 establishes existence of the optimal control and the uniqueness of the control pair is given in Section 3.2.

Before presenting our model, we briefly review some optimal control models involving immunotherapies. Burden, Ernstberger and Fister [24] propose a model of cancer cells $T(t)$, effector cells $E(t)$ and cytokines $C(t)$ with optimal control. The control

is added to the equation of the effector cells using the term $su(t)$, where s denotes strength and u is the control with $0 \le u \le 1$. Their objective functional is given by $J(u) = \int_0^{t_f}(E(t) - T(t) + C(t) - \dfrac{1}{2}Bu^2(t))dt$, $B > 0$, and they seek to maximize J subject to the state equations. Minelli et al. study a five-dimensional ordinary differential equations including effector cells E, help cells H, dendritic cells D, tumor cells T and cytokines C with a control term $u(t)$ added to the equation of dendritic cells. The objective functional is given by $J(u) = \rho T(f_f) + \dfrac{1}{2}\int_0^{t_f} u^2(t)dt$, where ρ is a weighted factor and their goal is to minimize J subject to the state equations. Notice that the term t_f appeared in the integral of both models denotes final time. That is, the control is applied over the finite time span $[0, t_f]$. Engelhart, Lebiedz and Sager [30] study several published models of tumor-immune interactions by applying optimal controls to these models. We refer the reader to [24, 27, 30] and their references for optimal controls in the setting of cancer treatments by immunotherapies.

Let $T > 0$ be the fixed treatment period. Using the same notations for the state variables in (1), the state equations are given by

$$
\begin{cases}
x' = r_1 x(1 - b_1 x) - \dfrac{c_1 xz}{a_1 + x} - \delta_1 xw \\[2mm]
y' = \dfrac{\beta_1 xz}{\alpha_1 + x} - \mu_1 y - \delta_2 xy + s_1 u_1(t) \\[2mm]
z' = \dfrac{\beta_2 xy}{\alpha_2 + x} - \mu_2 z + s_2 u_2(t) \\[2mm]
w' = r_2 w(1 - b_2 w) - \delta_3 xw
\end{cases} \tag{2}
$$

with initial conditions $x(0) = x_0 > 0, y(0) = y_0 \ge 0, z(0) = z_0 \ge 0$, and $w(0) = w_0 > 0$. Parameters $s_i \ge 0$, $i = 1, 2$, are the strengths of the immunotherapies by CD4$^+$ T cells and cytokines respectively, and $(u_1(t), u_2(t)) \in U$ represents time dependent external source of treatments with U defined below. There is no treatment by CD4$^+$ T cells if $u_1(t) = 0$ and the immunotherapy of CD4$^+$ cells is

maximal if $u_1(t) = 1$. Similar interpretations hold for $u_2(t)$. The admissible control class for our problem is

$$U = \{(u_1, u_2) : u_i(t) \text{ is piecewise continuous and }$$
$$0 \leq u_i(t) \leq 1 \text{ on } [0, T], \ i = 1, 2\}. \tag{3}$$

We assume the strengths of the treatments satisfying $s_1 + s_2 > 0$ so that at least one kind of immunotherapy is performed. If $s_1 = 0$, then the immunotherapy by CD4$^+$ T cells is not implemented, and the immunotherapy of cytokines is not adopted if $s_2 = 0$.

The goal of the treatment is to maximize the normal tissue cells and minimize the cancer cells along with the treatments during the whole treatment period $[0, T]$ and so the objective functional is given by

$$J(u_1, u_2) = \int_0^T \left(w(t) - x(t) - \frac{1}{2}B_1 u_1^2(t) - \frac{1}{2}B_2 u_2^2(t) \right) dt, \tag{4}$$

where $B_i \geq 0$, $i = 1, 2$, are weighted constants used to balance the contributions between the treatments. We assume $B_i > 0$ if $s_i > 0$ for $i = 1, 2$. The optimal control problem consists of

$$\max_{(u_1, u_2) \in U} J(u_1, u_2) \tag{5}$$

subject to the state equations (2).

Notice that our objective functional (4) is different from those in [24] and [27]. We shall make a remark on the numerical results later in the next section if we choose a slightly different objective functional. There are theory and techniques developed in Fleming and Rishel [31] and Lenhart and Workman [32] for studying the optimal control problem formulated above. We first provide existence of the control pair and then prove that the control is unique if in addition the treatment period T is small. These proofs are provided in Appendix.

3.1 Existence of Optimal Control

In this subsection we study existence of an optimal control and derive the necessary conditions. Our proof of the existence follows from Fleming and Rishel [31, pages 68-69].

Theorem 3.1 *There exists an optimal control for the problem* (2)–(5).

Once the existence of an optimal control is shown, we proceed to apply the Pontryagin's Maximum Principle [32] to derive necessary conditions. Let $(\lambda_1, \lambda_2, \lambda_3, \lambda_4)$ denote the adjoint vector. The Hamiltonian of the optimal control problem (2)–(5) is

$$H(x, y, z, w, \lambda_1, \lambda_2, \lambda_3, \lambda_4, u_1, u_2)$$

$$= w - x - \frac{1}{2}B_1 u_1^2 - \frac{1}{2}B_2 u_2^2$$

$$+ \lambda_1 \left(r_1 x(1 - b_1 x) - \frac{c_1 xz}{a_1 + x} - \delta_1 xw \right)$$

$$+ \lambda_2 \left(\frac{\beta_1 xz}{\alpha_1 + x} - \mu_1 y - \delta_2 xy + s_1 u_1 \right) \tag{6}$$

$$+ \lambda_3 \left(\frac{\beta_2 xy}{\alpha_2 + x} - \mu_2 z + s_2 u_2 \right)$$

$$+ \lambda_4 \left(r_2 w(1 - b_2 w) - \delta_3 xw \right),$$

where the adjoint variables satisfy $\lambda_1' = -\dfrac{\partial H}{\partial x}$, $\lambda_2' = -\dfrac{\partial H}{\partial y}$, $\lambda_3' = -\dfrac{\partial H}{\partial z}$, $\lambda_4' = -\dfrac{\partial H}{\partial w}$ with the transversality conditions $\lambda_i(T) = 0$ for $1 \leq i \leq 4$. Applying the optimality condition $\dfrac{\partial H}{\partial u_i} = 0$, we obtain $u_1 = \dfrac{\lambda_2 s_1}{B_1}$ and $u_2 = \dfrac{\lambda_3 s_2}{B_2}$ provided B_1 and B_2 are positive. Since the control u_1 and u_2 are bounded, the characterization of the optimal control pair (u_1^*, u_2^*) is therefore

$$u_1^*(t) = \begin{cases} \dfrac{\lambda_2(t)s_1}{B_1} & 0 < \dfrac{\lambda_2 s_1}{B_1} < 1 \\[2mm] 0 & \text{if} \quad \dfrac{\lambda_2 s_1}{B_1} \leq 0 \\[2mm] 1 & \dfrac{\lambda_2 s_1}{B_1} \geq 1, \end{cases}$$

$$u_2^*(t) = \begin{cases} \dfrac{\lambda_3(t)s_2}{B_2} & 0 < \dfrac{\lambda_3 s_2}{B_2} < 1 \\ 0 & \text{if} \quad \dfrac{\lambda_3 s_2}{B_2} \le 0 \\ 1 & \dfrac{\lambda_3 s_2}{B_2} \ge 1, \end{cases}$$

i.e., if $B_1 > 0$ and $B_2 > 0$

$$
\begin{aligned}
u_1^*(t) &= \min\{\max\{0, \frac{\lambda_2(t)s_1}{B_1}\}, 1\}, \\
u_2^*(t) &= \min\{\max\{0, \frac{\lambda_3(t)s_2}{B_2}\}, 1\}.
\end{aligned}
\tag{7}
$$

We summarize the above discussion as follows.

Proposition 3.2 *Given an optimal control pair* (u_1^*, u_2^*) *and solutions of the corresponding state equations* (2), *there exist adjoint variables* λ_i, $1 \le i \le 4$, *satisfying*

$$
\begin{aligned}
\lambda_1' &= 1 - \lambda_1[r_1(1 - 2b_1 x) - \frac{c_1 a_1 z}{(a_1 + x)^2} - \delta_1 w] \\
&\quad - \lambda_2[\frac{\alpha_1 \beta_1 z}{(\alpha_1 + x)^2} - \delta_2 y] - \frac{\lambda_3 \alpha_2 \beta_2 y}{(\alpha_2 + x)^2} + \lambda_4 \delta_3 w \\
\lambda_2' &= \mu_1 \lambda_2 + \delta_2 \lambda_2 x - \frac{\lambda_3 \beta_2 x}{\alpha_2 + x} \\
\lambda_3' &= \frac{\lambda_1 c_1 x}{a_1 + x} - \frac{\lambda_2 \beta_1 x}{\alpha_1 + x} + \lambda_3 \mu_2 \\
\lambda_4' &= -1 + \lambda_1 \delta_1 x - \lambda_4[r_2(1 - 2b_2 w) - \delta_3 x],
\end{aligned}
\tag{8}
$$

with $\lambda_i(T) = 0, 1 \le i \le 4$. *Moreover,* u_1^* *and* u_2^* *are represented by* (7).

Once the optimal control pair is characterized, the optimality system consists of the state and ad-

joint equations and is given as

$$
\begin{aligned}
x' &= r_1 x(1 - b_1 x) - \frac{c_1 xz}{a_1 + x} - \delta_1 xw \\
y' &= \frac{\beta_1 xz}{\alpha_1 + x} - \mu_1 y - \delta_2 xy + s_1 \min\{\max\{0, \frac{\lambda_2(t)s_1}{B_1}\}, 1\} \\
z' &= \frac{\beta_2 xy}{\alpha_2 + x} - \mu_2 z + s_2 \min\{\max\{0, \frac{\lambda_3(t)s_2}{B_2}\}, 1\} \\
w' &= r_2 w(1 - b_2 w) - \delta_3 xw \\
\lambda_1' &= 1 - \lambda_1[r_1(1 - 2b_1 x) - \frac{c_1 a_1 z}{(a_1 + x)^2} - \delta_1 w] \\
&\quad - \lambda_2[\frac{\alpha_1 \beta_1 z}{(\alpha_1 + x)^2} - \delta_2 y] - \frac{\lambda_3 \alpha_2 \beta_2 y}{(\alpha_2 + x)^2} + \lambda_4 \delta_3 w \\
\lambda_2' &= \mu_1 \lambda_2 + \delta_2 \lambda_2 x - \frac{\lambda_3 \beta_2 x}{\alpha_2 + x} \\
\lambda_3' &= \frac{\lambda_1 c_1 x}{a_1 + x} - \frac{\lambda_2 \beta_1 x}{\alpha_1 + x} + \lambda_3 \mu_2 \\
\lambda_4' &= -1 + \lambda_1 \delta_1 x - \lambda_4[r_2(1 - 2b_2 w) - \delta_3 x],
\end{aligned}
\tag{9}
$$

with $x(0) = x_0 > 0$, $y(0) = y_0 \ge 0$, $z(0) = z_0 \ge 0$, $w(0) = w_0 > 0$, and $\lambda_i(T) = 0$, $1 \le i \le 4$. The optimality system (9) yields a two-point boundary value problem, which will be studied numerically.

3.2   Uniqueness of the Optimal Control

We prove uniqueness of the solution of (9) in this subsection, and, as a result, the optimal control pair is unique. Since the adjoint differential equations (8) are linear in the adjoint variables λ_i, $1 \le i \le 4$, with bounded state coefficients, the adjoint variables are therefore bounded on $[0, T]$. Using these bounds along with the bounds of the state variables and the control pair, we prove that the optimality system (9) has a unique solution if $T > 0$ is sufficiently small. Our proof is similar to the proof in Burden et al. [24] and Fister et al. [33].

Theorem 3.3 *For* $T > 0$ *sufficiently small, the solution to the optimality system* (9) *is unique.*

From the uniqueness of solution of the optimality system, the optimal control pair (u_1^*, u_2^*) given in (7) is therefore unique if $T > 0$ is small.

4 Numerical Investigations

In this section, we study the optimal control problem (2)–(5) numerically and compare the three different immunotherapies, namely the infusion of CD4$^+$ T cells, cytokines, or a combination of these two. The optimality system is solved using a forward-backward sweep method described in Lenhart and Workman [32] with an iterative procedure combined with the fourth order Runge-Kutta scheme. Specifically, we adopt the following algorithm:

Step 1. We choose an initial guess for the control u_1 (u_2).

Step 2. We solve the state equations using a forward Runge-Kutta approximation with the initial conditions and the initial guess of the control.

Step 3. We then solve the adjoint equations backward by the Runge-Kutta approximation with the transversality condition and the state solutions from step 2.

Step 4. We update u_1^* (u_2^*) by using the characterization of the control.

Step 5. We repeat the same procedure until convergence of the states, adjoints, and the control is achieved.

The parameter values, their units and references are presented in Table 1. Notice that β_1, the tumor's antigenicity, lies in the range between 0.008 and 1.008 according to Eftimie et al. [20]. The value depends on the individual who carries the disease. In this numerical investigation, we let $\beta_1 = 0.835$. If β_1 is larger, then the immune system is more effective in producing the CD4$^+$ T cells. Local sensitivity analysis provided in Table 5 of [23] showing that parameters r_1, b_1, δ_1 and b_2 have the most significant impact on tumor size. Other parameters such as c_1, r_2 and β_1 are also important.

Using these parameter values, the tumor's carrying capacity is $1/b_1 \approx 9.8039 \times 10^8$ and the carrying capacity of the host cells is $1/b_2 = 10^9$. System (1) has boundary steady states $E_0 = (0, 0, 0, 0)$, $E_1 = (1/b_1, 0, 0, 0) = (9.8039 \times 10^8, 0, 0, 0)$, $E_2 = (0, 0, 0, 1/b_2) = (0, 0, 0, 10^9)$ and $\bar{E} = (\bar{x}, 0, 0, \bar{w}) = (8.053071806 \times 10^8, 0, 0, 8.3449 \times 10^8)$, where E_i is unstable for $i = 0, 1, 2$, and $\bar{E}$ is asymptotically stable. There are two interior steady states $E_1^* = (6.770 \times 10^3, 1.559 \times 10^6, 2.157 \times 10^5, 9.99998 \times 10^8)$ and $E_2^* = (3.179 \times 10^5, 5.329 \times 10^6, 8.438 \times 10^5, 9.9993 \times 10^8)$. The Jacobian matrix of (1) evaluated at E_2^* has three negative real eigenvalues and one positive real eigenvalue. Hence E_2^* is a saddle point with a three-dimensional stable manifold. The Jacobian matrix at E_1^* on the other hand has four complex eigenvalues with negative real parts and E_1^* is asymptotically stable. Therefore, model (1) exhibits bistability since there are two local attractors $\bar{E}$ and E_1^*.

If initial condition $X_0 = (6.77 \times 10^4, 10^6, 10^5, 10^9)$ is used, then the solution converges to $\bar{E} = (\bar{x}, 0, 0, \bar{w}) = (8.053071806 \times 10^8, 0, 0, 8.3449 \times 10^8)$ in the absence of treatment. Figures 1 and 2 provide the simulation results for X_0. Figure 1(a) illustrates that the tumor grows to a huge size of 8.053071806×10^8 if no treatment is administered. Let $s_1 = 5 \times 10^5$ be the strength of treatment by CD4$^+$ T cells. The time evolutions of the tumor cells and optimal control are given in Fig. 1(b) where $B_1 = 150$. When the same strength of cytokine treatment is applied, $s_2 = 5 \times 10^5$, the tumor size grows to the order of 8.0529995×10^8. This result is not presented. Figure 1(c) uses $s_2 = 5 \times 10^6$ with $B_2 = 150$. The combined treatment with $s_1 = 3 \times 10^5 = s_2$ and $B_1 = B_2 = 150$ is presented in Fig. 1(d). The final tumor sizes in (b)–(d) are about 379, 914 and 415 cells respectively. In this example, the treatment by CD4$^+$ T cells shows a better result than using cytokines alone. Although the tumor increases its size more sharply initially with the treatments by CD4$^+$ T cells, the final tumor size is smaller and the full strength of the treatment only lasts for about 90 days.

Table 1. Parameter values and their sources

Parameter	Value	Unit	Reference
r_1	0.514	day^{-1}	[20]
b_1	1.02×10^{-9}	day^{-1}	[20]
c_1	0.2	$\text{cell} \cdot (\text{day})^{-1} \cdot (\text{pg/ml})^{-1}$	[20]
a_1	10^5	cell	[19]
δ_1	1.1×10^{-10}	$(\text{cell} \cdot \text{day})^{-1}$	[29]
β_1	$(0.008, 1.008)$	$\text{cell} \cdot (\text{day})^{-1}$	[20]
α_1	10^3	cell	[34]
μ_1	0.1	day^{-1}	[21]
δ_2	10^{-7}	$(\text{cell} \cdot \text{day})^{-1}$	[20]
β_2	5.4	$\text{pg/ml} \cdot (\text{cell} \cdot \text{day})^{-1}$	[20]
α_2	10^3	cell	[20]
μ_2	34	day^{-1}	[20]
r_2	0.2822	day^{-1}	[29]
b_2	10^{-9}	day^{-1}	[29]
δ_3	0.58×10^{-10}	$(\text{cell} \cdot \text{day})^{-1}$	[29]

In Fig. 2(a), the strength s_1 is increased to 5×10^6 and the final tumor size is about 68 cells. Notice that as s_1 is increased, the full strength of treatment only last for about five days which is considerably shorter than the the smaller strength used in Fig. 1(b). If we increase s_2 to $s_2 = 5 \times 10^7$, then the tumor can be completely eradicated. The optimal control u_2 varies with the tumor size as shown in Fig. 2(b). A combined treatment is presented in Fig. 2(c), where $s_1 = s_2 = 6 \times 10^5$. The final tumor size is about 226 cells. In these examples, we used $B_1 = B_2 = 150$.

Let $X_1 = (10^7, 10^6, 10^5, 10^9)$ be the initial condition so that the tumor size is larger. Then the solution also converges to $\bar{E}$ as for the initial condition X_0 when there is no treatment. That is, both X_0 and X_1 lie in the basin of attraction of $\bar{E}$. Figures 3 and 4 present the simulation results with different treatment strategies. In Fig. 3(a), $s_1 = 5 \times 10^8$, where the final tumor size is about 3 cells. Fig. 3(b) adopts $s_2 = 6.4 \times 10^8$ and the tumor cells can be eradicated completely. Comparing the two treatment options, there is a tradeoff between the two. The use of CD4$^+$ T cells requires a smaller strength s_1 than the use of cytokines, s_2. Indeed, CD4$^+$ can reduce the number of tumor cells to 25 with $s_1 = 2.14 \times 10^8$. But $u_1(t)$ is larger than $u_2(t)$ for more than 90 days even if we increase s_1 up to 6.4×10^8. In this instance there are 2 cells at the end of the treatment. Moreover, there is a sharp drop of the tumor cells in the first five days if CD4$^+$ T cells are adopted with $s_1 = 5 \times 10^8$. A combination of the two therapies is given in Fig. 3(c) where $s_1 = 2 \times 10^8$ and $s_2 = 10^8$, and the final tumor size is about 144 cells. One can see that the full strengths of the treatments last for only about five days and

then half of the maximum strengths are used for the remaining days. This is different from Fig. 1(d) and 2(c) where full treatment of $CD4^+$ T cells are needed. On the other hand, the final tumor size is about 8×10^8 if $s_1 = 10^8$ and $s_2 = 3 \times 10^8$. This is not presented. The tumor is completely eradicated if $s_1 = s_2 = 2 \times 10^8$, see Fig. 3(d).

Figure 4 uses smaller B_i with $B_1 = 15 = B_2$. In Fig. 4(a), $s_1 = 2.5 \times 10^8$ and the final tumor size is around 2. With $s_2 = 6 \times 10^8$, the tumor grows to 7.9×10^8. This strength of cytokines is not sufficient to suppress the tumor. Fig. 4(b) provides time evolutions of the cancer cells along with the optimal control u_2 when $s_2 = 6.32 \times 10^8$. Comparing Fig. 4(a) and 4(b), the treatment by $CD4^+$ T cells seems better than adopting cytokines since in the later case the final tumor size is about 2. The optimal combined treatments is given in Fig. 4(c), where $s_1 = 2.5 \times 10^8$ and $s_2 = 1.5 \times 10^8$, and in Fig. 4(d) where s_1 is decreased to $s_1 = 2 \times 10^8$. In this later case, larger values of u_1 and u_2 last longer.

Suppose now the tumor killing rate c_1 is increased to 0.3. Then the magnitudes and local stability of E_i, $i = 0, 1, 2$, and $\bar{E} = (\bar{x}, 0, 0, \bar{w})$ remain the same since they are independent of c_1. System (1) has two interior steady states $E_1^* = (6.769605 \times 10^3, 1.039022 \times 10^6, 1.437819 \times 10^5, 9.999986 \times 10^8)$ and $E_2^* = (3.178716 \times 10^5, 3.552882 \times 10^6, 5.625116 \times 10^5, 9.999347 \times 10^8)$, where E_1^* is locally asymptotically stable and E_2^* is a saddle point with a three-dimensional stable manifold. The tumor size in E_i^*, $i = 1, 2$, is smaller than the tumor size of the corresponding interior steady states with $c_1 = 0.2$. The solution converges to $\bar{E}$ if X_1 is used as the initial condition. Figure 5 provides the simulation results for $B_1 = 150 = B_2$. In particular, $s_1 = 2 \times 10^8$ and $s_2 = 4.5 \times 10^8$ are given in Fig. 5(a) and Fig. 5(b) respectively. The final tumor size is about 4 in (a) and the tumor cells are eradicated completely in (b). A combined treatments is given in Fig. 5(c)-(d). In (c), $s_1 = 1.5 \times 10^8$ and $s_2 = 10^8$ with $x(100) \approx 0$. In (d), $s_1 = 10^8$ and $s_2 = 1.5 \times 10^8$ with $x(100) \approx 0$. We see that as c_1 is increased, then the cytokines

are more effective in killing the cancer cells so that the strength needed to control the tumor is smaller.

Remark. If the goal of the treatment is to minimize the final tumor size, and maximize the normal tissue cells and minimize the cancer cells along with the cost or tolerance for the whole treatment period, then the objective functional is given by

$$J(u_1, u_2) \quad = \quad -x(T) + \qquad (10)$$
$$\int_0^T \quad (w(t) \quad -x(t) - \frac{1}{2}B_1 u_1^2(t) - \frac{1}{2}B_2 u_2^2(t))dt,$$

where $B_i \geq 0$, $i = 1, 2$, are the weighted constants representing either a patient's level of treatments tolerance or costs associated with the treatment, and $(u_1, u_2) \in U$. Comparing the objective functional (10) with that of (4), the extra payoff term $-x(T)$ is added here. The optimal control problem consists of

$$\max_{(u_1, u_2) \in U} J(u_1, u_2) \qquad (11)$$

subject to the state equations (2).

The Hamiltonian of the optimal control problem (10)–(11) subject to the state equations (2) is given by (3.5). The adjoint variables λ_i, $1 \leq i \leq 4$, satisfy $\lambda_1' = -\frac{\partial H}{\partial x}$, $\lambda_2' = -\frac{\partial H}{\partial y}$, $\lambda_3' = -\frac{\partial H}{\partial z}$, $\lambda_4' = -\frac{\partial H}{\partial w}$ with the transversality conditions $\lambda_1(T) = -1$ and $\lambda_i(T) = 0$ for $2 \leq i \leq 4$. The condition $\lambda_1(T) = -1$ results from the extra payoff term $-x(T)$ given in (10). Applying the optimality condition, we obtain an optimal control pair (u_1^*, u_2^*) that maximizes $J(u_1, u_2)$, where u_1^* and u_2^* are given by (7). The optimality system is then numerically solved using the same algorithm but with a different transversality condition, namely $\lambda_1(T) = -1$. If the objective functional (10) is considered for those parameter values and initial conditions given in Fig. 1–5, then although the final tumor size is somewhat smaller but it is not significantly smaller. The difference of final tumor size between the two objective functionals is only between 0 to 50 cells depending on the

parameter values and initial conditions. However, the tumor size usually increases slightly at the end of the treatment period if objective functional (4) is considered.

5 Conclusion

In this work, we apply optimal control theory to provide a best immunotherapy for treating cancer. The treatment period is fixed and the optimal immunotherapy is defined as the therapy that maximizes the host cells and minimizes the cancer cells along with the costs or tolerance associated with the treatments during the whole treatment period. The model of tumor-immune interaction without the control is based on a system of ordinary differential equations studied in [23]. Using the classical theory, we show that an optimal control pair exists and is given explicitly in terms of the parameters and adjoints. We prove that the optimal control pair is unique if the treatment period is small.

The optimal control pair is numerically solved using a forward-backward Runge-Kutta sweep method. We investigate the optimal treatment strategies with two different initial conditions. One initial condition has a small tumor size while the tumor size is large in the other initial condition. The strategy of using CD4$^+$ T cells or cytokines alone or a combination of these two is investigated. The treatment by CD4$^+$ performs better than using cytokines alone when the tumor size is small as shown in Figures 1 and 2. The dose of CD4$^+$ T cells and the final tumor size are smaller. Moreover, the schedule of adopting maximum dose of CD4$^+$ T cells is considerably shorter than using of cytokines. If the tumor size is large, then a large dose s_i of the treatment is needed and there is a tradeoff between the two immunotherapies. A combined treatment of CD4$^+$ and cytokines seem to be more effective than using a single type of treatment alone. Further, if cytokines are more effective in killing the cancer cells, that is, if c_1 is larger, then a smaller strength of the treatment is needed.

In this study we do not consider any negative effect on the host cells when immunotherapies are applied. In a future research project, we plan to incorporate side effects of the immunotherapy into the host cells and to provide a best protocol for treating cancer under this additional scenario.

A Appendix

A. Proof of Theorem 3.1 To prove existence, it is enough to verify the following five conditions given in Corollary 4.1 of [31]:

(a) The class of all initial conditions with a control pair $(u_1, u_2) \in U$ for which the state equations being satisfied is nonempty.

(b) U is closed and convex.

(c) The right hand side of each of the state equations is continuous, bounded above by the sum of the control and the state, and can be written as a linear function of u_i, $i = 1, 2$.

(d) For fixed x and w, the integrand of $J(u_1, u_2)$ is convex on U.

(e) The integrand of $J(u_1, u_2)$ is concave in u_i, $1 \le i \le 2$, and is bounded above by $C_2 - C_1||(u_1, u_2)||^\gamma$ for some $C_1 > 0$ and $\gamma > 1$.

Given any initial condition (x_0, y_0, z_0, w_0) and a control pair $(u_1, u_2) \in U$, we have from the state equations (2) that $x' \le r_1 x$, $y' \le \beta_1 z + s_1$, $z' \le \beta_2 y + s_2$ and $w' \le r_2 w$. Consider the linear system

$$\begin{cases} \bar{x}' = r_1 \bar{x} \\ \bar{y}' = \beta_1 \bar{z} + s_1 \\ \bar{z}' = \beta_2 \bar{y} + s_2 \\ \bar{w}' = r_2 \bar{w} \\ \bar{x}(0) = x_0, \bar{y}(0) = y_0, \bar{z}(0) = z_0, \bar{w}(0) = w_0. \end{cases}$$

Since the solution of the above linear system is bounded on $[0, T]$, the solution of (2) exists and condition (a) is satisfied. Moreover, as $x'|_{x=0} = 0$, $y'|_{y=0, x, z \ge 0} \ge 0$, $z'|_{z=0, x, y \ge 0} \ge 0$ and $w'|_{w=0}$, solutions of (2) remain nonnegative on $[0, T]$ by Theorem A.4 of [35].

It is clear that condition (b) is trivially true. To verify condition (c), we let $X = (x, y, z, w)$ and let $f(t, X, u_1, u_2)$ denote the right hand side of (2). Then there exists $M_0 > 0$ such that

$$
\begin{aligned}
\|f(t, X, u_1, u_2)\| &\leq \left\| \begin{pmatrix} r_1 & 0 & 0 & 0 \\ 0 & 0 & \beta_1 & 0 \\ 0 & \beta_2 & 0 & 0 \\ 0 & 0 & 0 & r_2 \end{pmatrix} \right\| \\
\times \|X\| + s\|u\| &\leq M_0\|X\| + s\|u\|, \quad (12)
\end{aligned}
$$

where $s = \max\{s_1, s_2\} > 0$ and $u = (u_1, u_2)$. Moreover, the right hand side of each of the state equations is continuous and can be written as a linear function of u_i, $i = 1, 2$. Therefore condition (c) is proved. For each fixed x and w, we let $g(u_1, u_2) = w - x - \frac{1}{2}B_1 u_1^2 - \frac{1}{2}B_2 u_2^2$. Then by a direct computation, we have $ag(u_1, u_2) + (1-a)g(v_1, v_2) \leq g(a(u_1, u_2) + (1-a)(v_1, v_2))$ for any a, $0 \leq a \leq 1$, and $(u_1, u_2), (v_1, v_2) \in U$. Hence $g(u_1, u_2)$ is convex on U and condition (d) is satisfied.

Clearly the integrand of $J(u_1, u_2)$ is concave in u_i, $i = 1, 2$, and $w(t) - x(t) - \frac{1}{2}B_1 u_1^2(t) - \frac{1}{2}B_2 u_2^2(t) \leq w(t) - \frac{1}{2}B_1 u_1^2(t) - \frac{1}{2}B_2 u_2^2(t) \leq C_2 - C_1(u_1^2 + u_2^2) = C_2 - C_1\|(u_1, u_2)\|^\gamma$, where C_2 depends on the upper bound of $w(t)$ on $[0, T]$, $C_1 = \min\{B_1/2, B_2/2\} > 0$ and $\gamma = 2 > 1$, i.e., condition (e) is verified. Therefore, an optimal control pair exists for the control problem (2)–(5) by Corollary 4.1 of [31]. ∎

B. Proof of Theorem 3.3

Suppose $(x, y, z, w, \lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and $(\bar{x}, \bar{y}, \bar{z}, \bar{w}, \bar{\lambda}_1, \bar{\lambda}_2, \bar{\lambda}_3, \bar{\lambda}_4)$ are two solutions of the optimality system (9). Similar to the proof in [24] and [33], we let $m > 0$ be such that

$$
\begin{aligned}
x &= e^{mt}p, \ y = e^{mt}q, \ z = e^{mt}v, \ w = e^{mt}g, \\
\lambda_1 &= e^{-mt}j, \ \lambda_2 = e^{-mt}k, \ \lambda_3 = e^{-mt}l, \ \lambda_4 = e^{-mt}f, \\
\bar{x} &= e^{mt}\bar{p}, \ \bar{y} = e^{mt}\bar{q}, \ \bar{z} = e^{mt}\bar{v}, \ \bar{w} = e^{mt}\bar{g}, \\
\bar{\lambda}_1 &= e^{-mt}\bar{j}, \ \bar{\lambda}_2 = e^{-mt}\bar{k}, \ \bar{\lambda}_3 = e^{-mt}\bar{l}, \ \bar{\lambda}_4 = e^{-mt}\bar{f}.
\end{aligned}
$$

Substituting the above expressions into the x equation in (9) and simplifying, yields

$$
mp + p' = r_1 p(1 - b_1 e^{mt}p) - \frac{c_1 e^{mt}pv}{a_1 + e^{mt}p} - \delta_1 e^{mt}pe^{mt}g, \quad (13)
$$

and

$$
m\bar{p} + \bar{p}' = r_1 \bar{p}(1 - b_1 e^{mt}\bar{p}) - \frac{c_1 e^{mt}\bar{p}\bar{v}}{a_1 + e^{mt}\bar{p}} - \delta_1 e^{mt}\bar{p}e^{mt}\bar{g}. \quad (14)
$$

Subtracting (14) from (13), multiplying the resulting equation by $p - \bar{p}$ and integrating from 0 to T, we have

$$
\begin{aligned}
m\int_0^T (p - \bar{p})^2 dt &+ \frac{1}{2}[p(T) - \bar{p}(T)]^2 \\
= \quad \delta_1 \int_0^T & e^{mt}(\bar{p}\bar{g} - pg)(p - \bar{p})dt \quad (15) \\
+ \quad r_1 \int_0^T & (p - \bar{p})^2 dt + r_1 b_1 \int_0^T e^{mt}(\bar{p}^2 - p^2)(p - \bar{p})dt \\
+ \quad c_1 \int_0^T & e^{mt}\left[\frac{\bar{p}\bar{v}}{a_1 + e^{mt}\bar{p}} - \frac{pv}{a_1 + e^{mt}p}\right](p - \bar{p})dt.
\end{aligned}
$$

We next use the bounds of the state and adjoint variables to provide a bound for the right hand side of (15). Specifically, the following inequality is used frequently in obtaining the estimates

$$
\begin{aligned}
\int |f(t)g(t)|dt &\leq \left(\int f^2(t)dt\right)^{1/2}\left(\int g^2(t)dt\right)^{1/2} \\
&\leq \frac{\int f^2(t)dt + \int g^2(t)dt}{2}.
\end{aligned}
$$

For example, in the last term of (15) where

$$
\begin{aligned}
& \left[\frac{\bar{p}\bar{v}}{a_1 + e^{mt}\bar{p}} - \frac{pv}{a_1 + e^{mt}p}\right] \\
= & \frac{a_1\bar{p}(\bar{v} - v) + a_1 v(\bar{p} - p) + a_1 \bar{p}pe^{mt}(\bar{v} - v)}{(a_1 + e^{mt}p)(a_1 + e^{mt}\bar{p})},
\end{aligned}
$$

and hence

$$c_1 \quad \int e^{mt}[\frac{\bar{p}\bar{v}}{a_1 + e^{mt}\bar{p}} - \frac{pv}{a_1 + e^{mt}p}](p - \bar{p})dt$$

$$\leq \quad c_1 e^{mT} \times [M_1 \frac{\int (v - \bar{v})^2 + \int (p - \bar{p})^2}{2a_1}$$

$$+ \quad M_3 \int (p - \bar{p})^2/a_1$$

$$+ \quad M_1^2 e^{mT} \frac{\int (v - \bar{v})^2 + \int (p - \bar{p})^2}{2a_1}]dt.$$

Here we have used the bounds $p, \bar{p} \leq M_1$ and $v, \bar{v} \leq M_3$ and without writing out the lower and upper limits of the integral. We apply a similar procedure to other terms of (15) and simplifying, yields

$$(m - r_1) \int_0^T (p - \bar{p})^2 dt + \frac{1}{2}[p(T) - \bar{p}(T)]^2$$

$$\leq (E_1 e^{mT} + E_2 e^{2mt}) \int (p - \bar{p})^2 dt$$

$$+ (E_3 e^{mT} + E_4 e^{2mT}) \int (v - \bar{v})^2 dt \quad (16)$$

$$+ E_5 e^{mT} \int (g - \bar{g})^2 dt,$$

where E_i, $1 \leq i \leq 5$, depend on the bounds of the state variables and parameters.

For the y equation in (9), we let $h^*(k) = \min\{\max\{0, \frac{s_1 e^{-mt}k}{B_1}\}, 1\}$. Observe that $|h^*(k) - h^*(\bar{k})| \leq |k - \bar{k}| \leq e^{mt}|k - \bar{k}|$ since $m > 0$ and $0 \leq t \leq T$. We apply a similar technique as in the x equation to obtain

$$mq + q' = \frac{\beta_1 e^{mt}pv}{\alpha_1 + e^{mt}p} - \mu_1 q - \delta_2 e^{mt}pq + e^{-mt}s_1 h^*(k),$$
$$(17)$$

and

$$m\bar{q} + \bar{q}' = \frac{\beta_1 e^{mt}\bar{p}\bar{v}}{\alpha_1 + e^{mt}\bar{p}} - \mu_1 \bar{q} - \delta_2 e^{mt}\bar{p}\bar{q} + e^{-mt}s_1 h^*(\bar{k}).$$
$$(18)$$

Subtracting (18) from (17), multiplying the resulting equation by $q - \bar{q}$ and integrating from 0 to T,

the last term becomes

$$s_1 \quad \int e^{-mt}(h^*(k) - h^*(\bar{k}))(q - \bar{q})dt$$

$$\leq \quad s_1 e^{mT} \frac{\int (k - \bar{k})^2 + \int (q - \bar{q})^2}{2}.$$

The procedure yields

$$(m - \mu_1) \int_0^T (q - \bar{q})^2 dt + \frac{1}{2}[q(T) - \bar{q}(T)]^2$$

$$\leq F_1 e^{mT} \int (p - \bar{p})^2 dt + F_2 e^{mT} \int (q - \bar{q})^2 dt$$

$$+ F_3 e^{mT} \int (v - \bar{v})^2 dt \quad (19)$$

$$+ F_4 e^{mT} \int (k - \bar{k})^2 dt,$$

where F_i, $1 \leq i \leq 4$, depend on the bounds of the state variables and the parameters. The z and w equations can be treated similarly.

For the adjoint variables, say λ_2, we have

$$-mk + k' = \mu_1 k + \delta_2 e^{mt}kp - \frac{\beta_2 e^{mt}lp}{\alpha_2 + e^{mt}p}$$

and

$$-m\bar{k} + \bar{k}' = \mu_1 \bar{k} + \delta_2 e^{mt}\bar{k}\bar{p} - \frac{\beta_2 e^{mt}\bar{l}\bar{p}}{\alpha_2 + e^{mt}\bar{p}}.$$

Subtracting the first equation from the second, multiplying the resulting equation by $k - \bar{k}$ and integrating from 0 to T, we obtain

$$m \int (k - \bar{k})^2 dt + \frac{1}{2}[k(0) - \bar{k}(0)]^2$$

$$= -\mu_1 \int (k - \bar{k})^2 dt + \delta_2 \int e^{mt}(\bar{k}\bar{p} - kp)(k - \bar{k})dt$$

$$+ \beta_2 \int e^{mt}(\frac{lp}{\alpha_2 + e^{mt}p} - \frac{\bar{l}\bar{p}}{\alpha_2 + e^{mt}\bar{p}})(k - \bar{k})dt.$$
$$(20)$$

We then have the following estimates

$$(m + \mu_1) \int (k - \bar{k})^2 dt + \frac{1}{2}[k(0) - \bar{k}(0)]^2$$

$$\leq \tilde{B}_1 e^{mt} \int (p - \bar{p})^2 dt \quad (21)$$

$$+ (\tilde{B}_2 e^{mt} + \tilde{B}_3 e^{2mt}) \int (k - \bar{k})^2 dt$$

$$+ (\tilde{B}_4 e^{mT} + \tilde{B}_5 e^{2mt}) \int (l - \bar{l})^2 dt,$$

where $\tilde{B}_i$, $1 \le i \le 5$, depend on the bounds of the state and adjoint variables and the parameters.

We perform the same procedure to other adjoint and state variables and then adding the eight estimates of the equations in (9) and obtain

$$\frac{1}{2}([p(T) - \bar{p}(T)]^2 + [q(T) - \bar{q}(T)]^2$$
$$+ \quad [v(T) - \bar{v}(T)]^2 + [g(T) - \bar{g}(T)]^2)$$
$$+ \quad \frac{1}{2}([j(0) - \bar{j}(0)]^2 + [k(0) - \bar{k}(0)]^2$$
$$+ \quad [l(0) - \bar{l}(0)]^2 + [f(0) - \bar{f}(0)]^2)$$
$$+ \quad (m - r_1) \int (p - \bar{p})^2 dt$$
$$+ \quad (m - \mu_1) \int (q - \bar{q})^2 dt + (m - \mu_2) \int (v - \bar{v})^2 dt$$
$$+ \quad (m - r_2) \int (g - \bar{g})^2 dt + (m - r_1) \int (j - \bar{j})^2 dt$$
$$+ \quad (m + \mu_1) \int (k - \bar{k})^2 dt + (m + \mu_2) \int (l - \bar{l})^2 dt$$
$$+ \quad (m - r_2) \int (f - \bar{f})^2 dt$$
$$\le \quad (J_{11}e^{mT} + J_{12}e^{2mT} + J_{13}e^{3mT}) \int (p - \bar{p})^2 dt$$
$$+ \quad J_{21}e^{mT} \int (v - \bar{v})^2 dt$$
$$+ \quad (J_{31}e^{mT} + J_{32}e^{2mT} + J_{33}e^{3mT}) \int (v - \bar{v})^2 dt$$

$$+ \quad (J_{41}e^{mT} + J_{42}e^{2mT}$$
$$+ \quad J_{43}e^{3mT}) \times \int (q - \bar{q})^2 dt \qquad (22)$$
$$+ \quad (J_{51}e^{mT} + J_{52}e^{2mT} + J_{53}e^{3mT}) \int (k - \bar{k})^2 dt$$
$$+ \quad J_{71}e^{mT} \int (f - \bar{f})^2 dt$$
$$+ \quad (J_{81}e^{mT} + J_{82}e^{2mT} + J_{83}e^{3mT}) \int (l - \bar{l})^2 dt,$$

where J_{ij} depends on the bounds of the state and adjoint variables and the parameters. Simplifying (22), we have

$$(m - \tilde{M}_1 - \tilde{M}_2 e^{3mT}) \int_0^T [(p - \bar{p})^2 + (g - \bar{g})^2$$
$$+ (v - \bar{v})^2 + (q - \bar{q})^2 + (j - \bar{j})^2 \qquad (23)$$
$$+ (k - \bar{k})^2 + (f - \bar{f})^2 + (l - \bar{l})^2] dt \le 0,$$

where $\tilde{M}_i$, $i = 1, 2$, depend on the bounds of the state and adjoint variables and the parameters. We can choose $m > 0$ such that $m > \tilde{M}_1 + \tilde{M}_2$. Then $T_0 := \frac{1}{3m} \ln(\frac{m - \tilde{M}_1}{\tilde{M}_2}) > 0$. Therefore if $T < T_0$, then $m - \tilde{M}_1 - \tilde{M}_2 e^{3mT} > 0$ and from (23) we must have $0 = (p - \bar{p})^2 = (g - \bar{g})^2 = (v - \bar{v})^2 = (q - \bar{q})^2 = (j - \bar{j})^2 = (k - \bar{k})^2 = (l - \bar{l}))^2 = (f - \bar{f})^2$ on $[0, T]$. Therefore for $T > 0$ small, $T < T_0$, the solution to the optimality system (9) is unique. ∎

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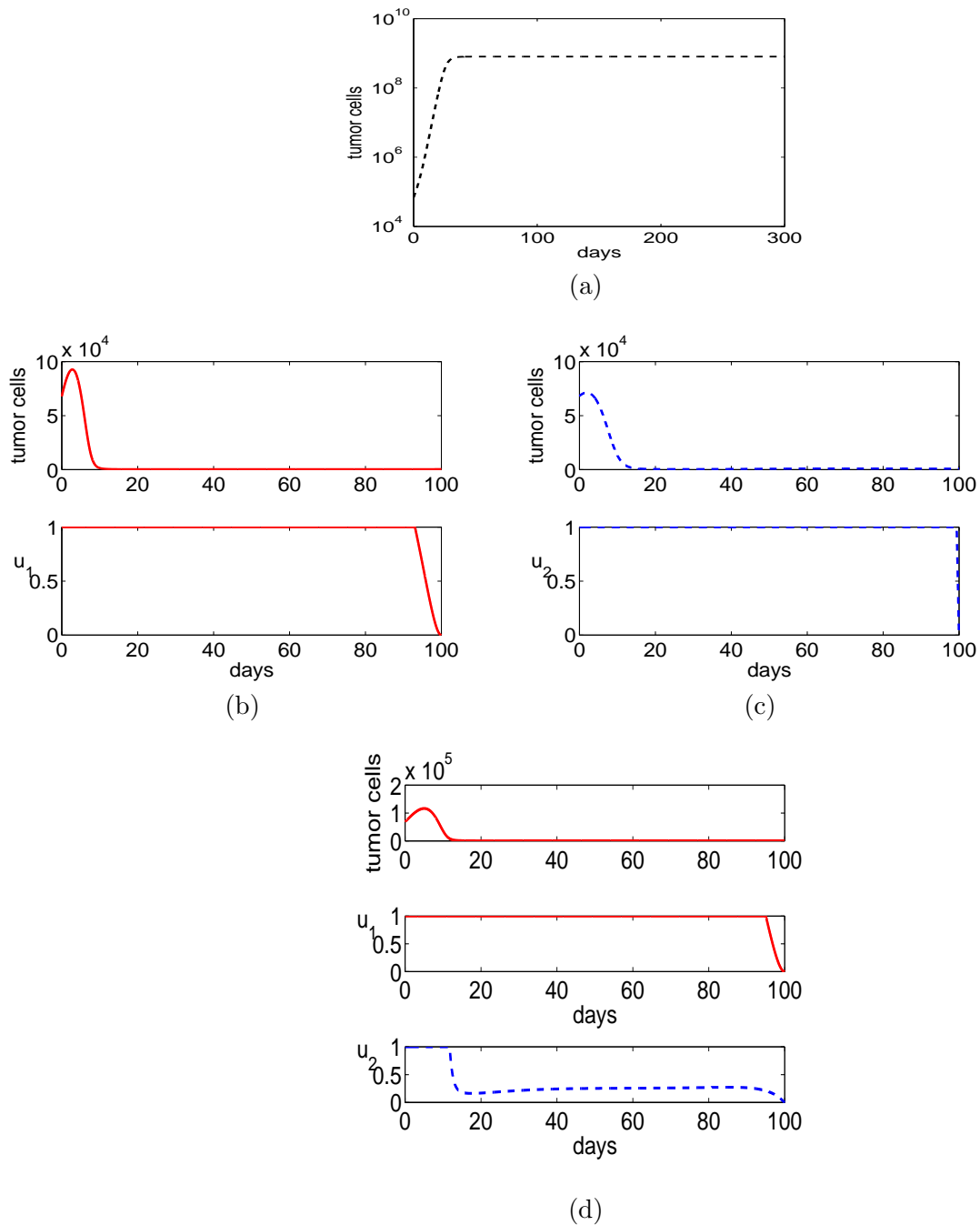[35] H,R. Thieme, *Mathematics in Population Biology*, Princeton University Press: New Jersey, 2003.

Figure 1: The parameter $\beta_1 = 0.835$ and the initial condition is $X_0 = (6.77 \times 10^4, 10^6, 10^5, 10^9)$. In (a) no treatment is adopted and the tumor grows to 8.05307181×10^8. Plots (b) and (c) apply the treatment of CD4$^+$ and cytokines respectively with $s_1 = 5 \times 10^5$, $s_2 = 5 \times 10^6$, and $B_i = 150$ for $i = 1, 2$. The number of tumor at the end of the treatment period is about 379 and 914, respectively. In (d), a combined treatment with $s_1 = 3 \times 10^5 = s_2$ and $B_1 = 150 = B_2$ is given. The final tumor size is about 415.
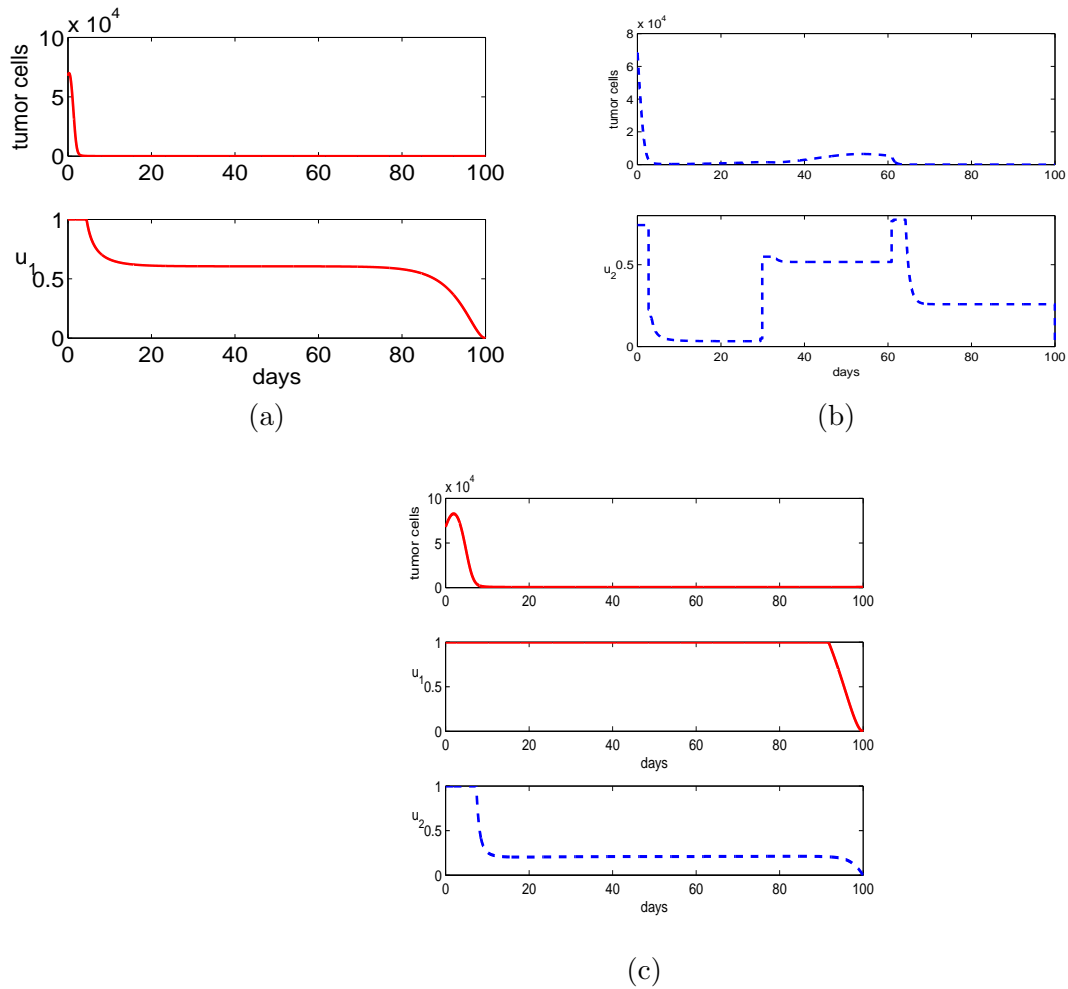
Figure 2: The parameter $\beta_1 = 0.835$ and the initial condition is $X_0 = (6.77 \times 10^4, 10^6, 10^5, 10^9)$ with $B_1 = 150 = B_2$. In (a) $s_1 = 5 \times 10^6$, in (b) $s_2 = 5 \times 10^7$, and in (c) $s_1 = s_2 = 6 \times 10^5$.
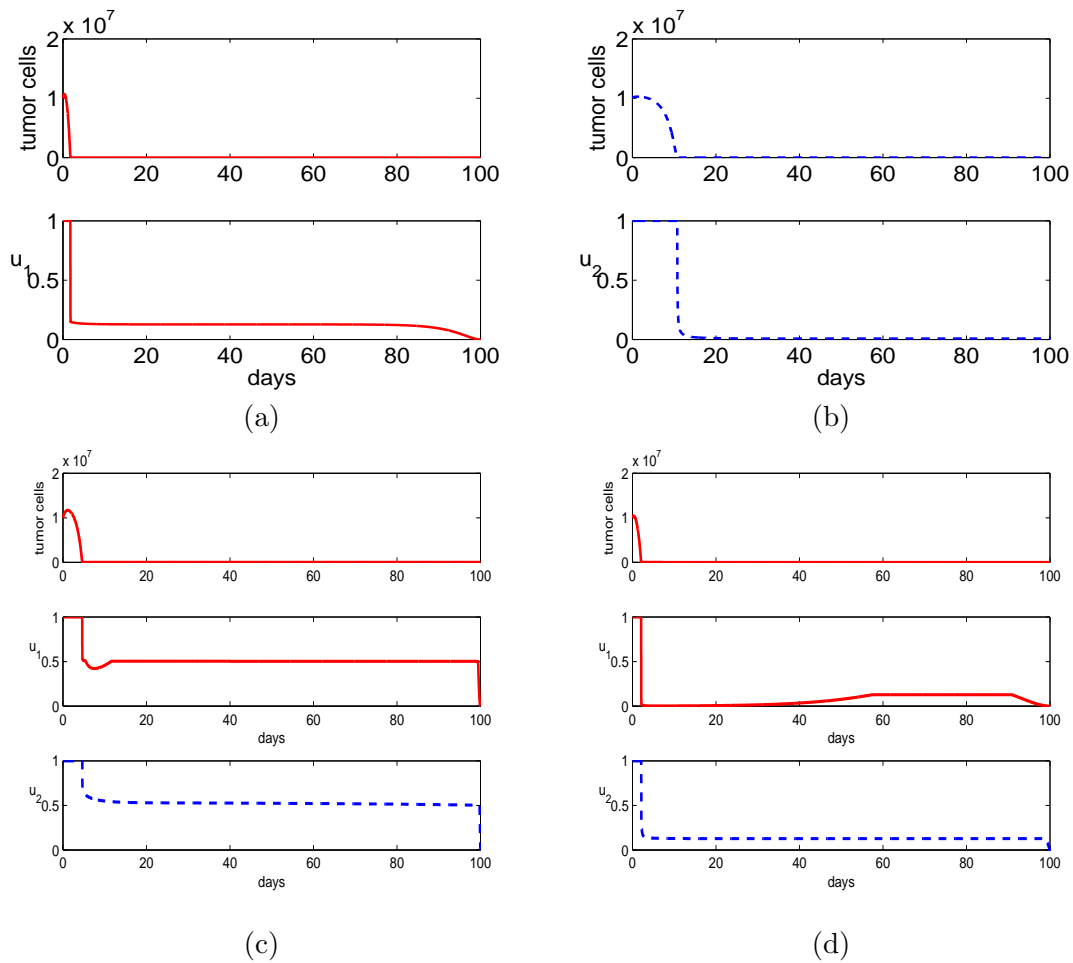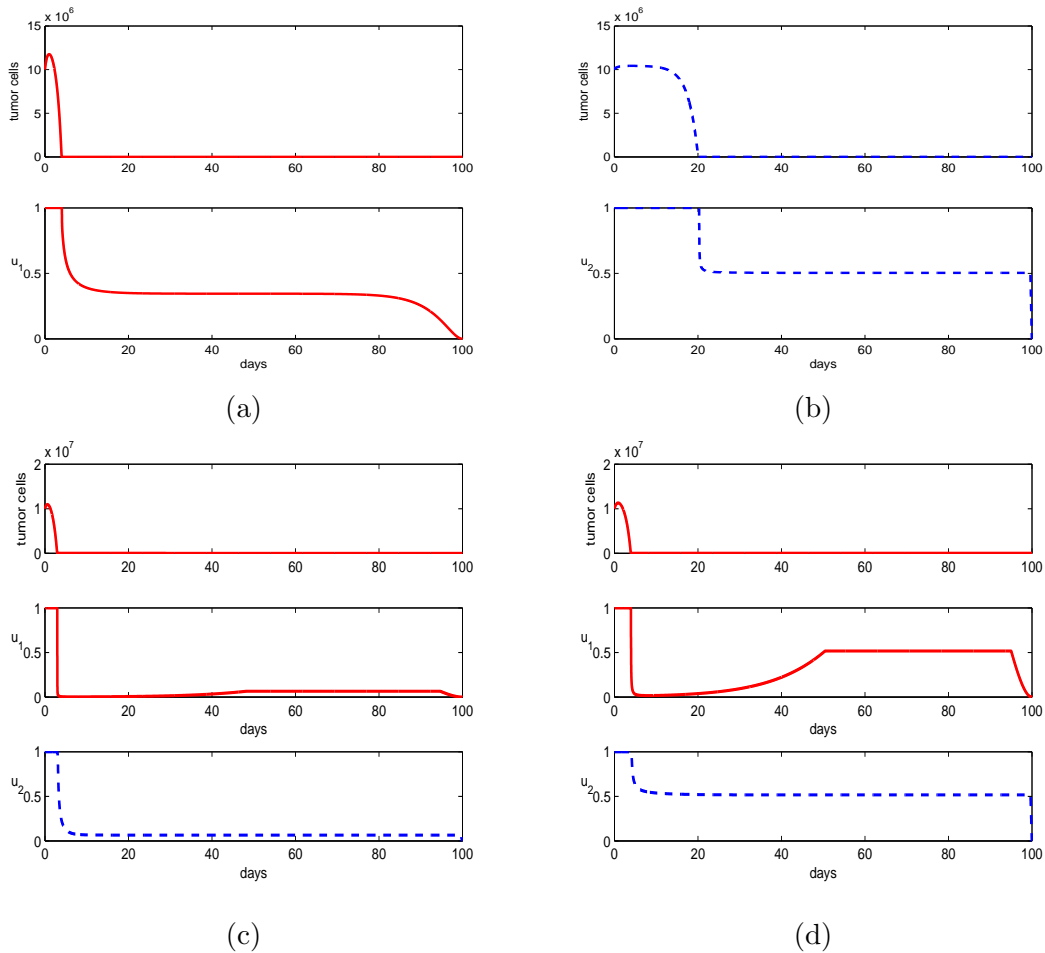
Figure 3: This figure uses the same parameter values as in Fig. 1 with initial condition $X_1 = (10^7, 10^6, 10^5, 10^9)$ and $B_1 = 150 = B_2$. In (a) $s_1 = 5 \times 10^8$, (b) $s_2 = 6.4 \times 10^8$, (c) $s_1 = 2 \times 10^8$ and $s_2 = 10^8$, and (d) $s_1 = 2 \times 10^8$ and $s_2 = 2 \times 10^8$.

Figure 4: This figure uses the same parameter values as in Fig. 1 with initial condition $X_1 = (10^7, 10^6, 10^5, 10^9)$ and $B_1 = 15 = B_2$. In (a), $s_1 = 2.5 \times 10^8$ with $x(100) \approx 2$, (b) $s_2 = 6.32 \times 10^8$ and $x(100) \approx 1$, (c) $s_1 = 2.5 \times 10^8$ and $s_2 = 1.5 \times 10^8$ with $x(100) \approx 0$, and in (d) $s_1 = 2 \times 10^8$, $s_2 = 1.5 \times 10^8$ and $x(100) \approx 5$.
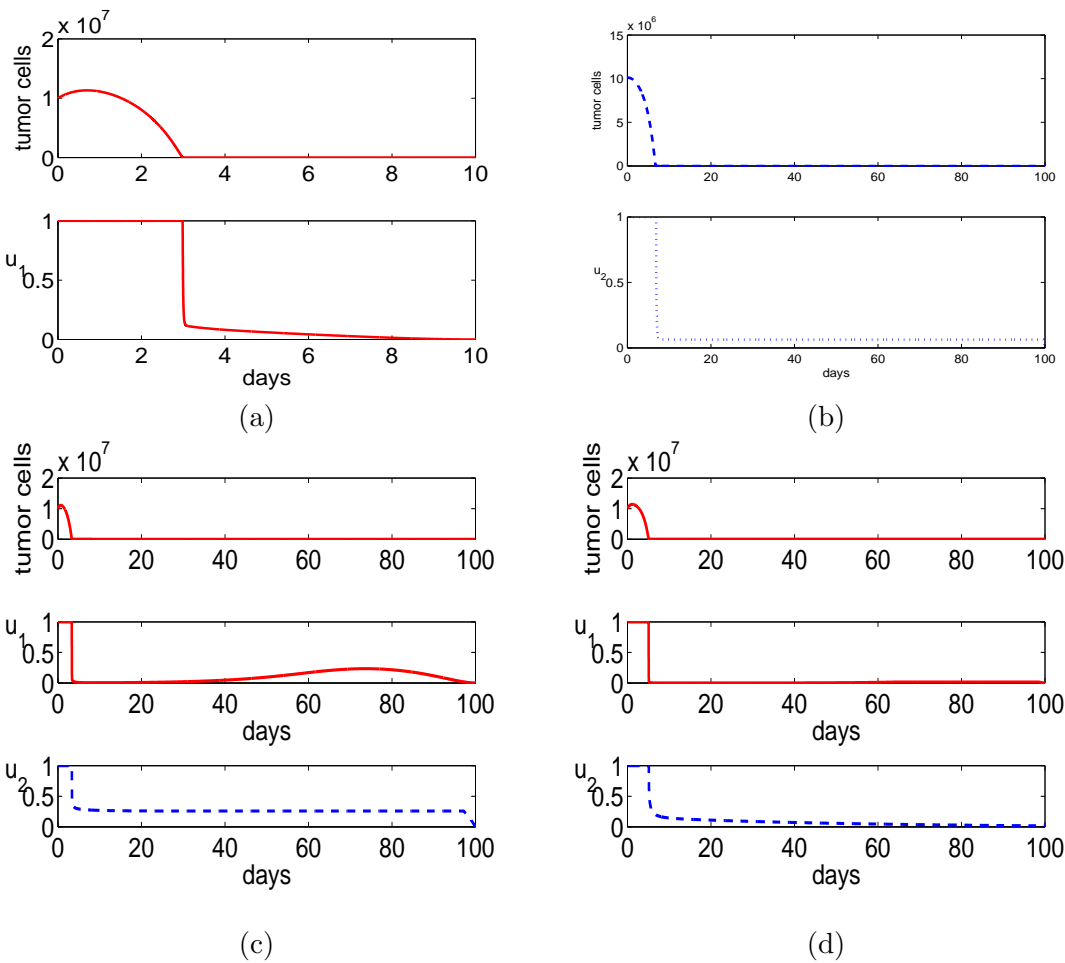
Figure 5: This figure adopts $\beta_1 = 0.835$, $c_1 = 0.3$, initial condition $X_1 = (10^7, 10^6, 10^5, 10^9)$ and $B_1 = 150 = B_2$. In (a), $s_1 = 2 \times 10^8$ with $x(100) \approx 4$, (b) $s_2 = 4.5 \times 10^8$ and $x(100) \approx 0$, (c) $s_1 = 1.5 \times 10^8$ and $s_2 = 10^8$ with $x(100) \approx 0$, and in (d) $s_1 = 10^8$, $s_2 = 1.5 \times 10^8$ and $x(100) \approx 0$.