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Research Article

Optimal Feedback Control of Cancer Chemotherapy Using Hamilton–Jacobi–Bellman Equation

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Cancer chemotherapy has been the most common cancer treatment. However, it has side effects that kill both tumor cells and immune cells, which can ravage the patient's immune system. Chemotherapy should be administered depending on the patient's immunity as well as the level of cancer cells. Thus, we need to design an efficient treatment protocol. In this work, we study a feedback control problem of tumor-immune system to design an optimal chemotherapy strategy. For this, we first propose a mathematical model of tumor-immune interactions and conduct stability analysis of two equilibria. Next, the feedback control is found by solving the Hamilton–Jacobi–Bellman (HJB) equation. Here, we use an upwind finite-difference method for a numerical approximate solution of the HJB equation. Numerical simulations show that the feedback control can help determine the treatment protocol of chemotherapy for tumor and immune cells depending on the side effects.

1. Introduction

Cancer is known as one of leading causes of death worldwide. While many studies are under way to understand the tumor-immune interactions, it is the challenging problem to find an efficient cancer treatment in modern medicine. Chemotherapy has been one of the most common cancer treatment options, but because it kills both tumor cells and immune cells, it has side effects that destroy the patient's immune system. Immunotherapy compensates for the deficiencies of chemotherapy by raising the effectiveness of immunity against tumor cells, so it is one of the most prominent cancer treatments, especially in a multifaceted approach [1]. However, immunotherapy may make immune cells over-activated, potentially causing autoimmune diseases. Furthermore, it is limited to cancer types and has expensive costs. Thus, chemotherapy is still being used as a common cancer treatment.

There exist many research papers on mathematical modeling about tumor-immune system interactions [2–13]. De Boer et al. [14] presented a mathematical model based on ordinary differential equations (ODEs), which is for the macrophage T lymphocyte interactions generating an immune response against tumors. Furthermore, there are many studies on analyzing various cancer treatments through mathematical modeling [15–23]. De Pillis et al. [18] explored a computationally optimal strategy combining chemotherapy and immunotherapy treatments to minimize tumors and toxicity to patients while maximizing the immunity. Rihan et al. [15] studied an optimal control problem using a delay differential model (DDE) describing the tumor-immune interactions in presence of immuno-chemotherapy.

Most of the papers mentioned above are related to the results of open-loop control which is a function of time. By solving the optimality system from Pontryagin's maximum principle (PMP) [24], the control can be obtained. However,

the principle is only a necessary condition for the control to be optimal and the change of states is not reflected in the open-loop control, so there are the difficulties in applying these results to biological phenomena practically.

On the contrary, in the case of feedback control, since the perturbation of the state is considered, the shortcomings of open-loop control can be compensated. Feedback control can be found by solving a nonlinear partial differential equation called Hamilton–Jacobi–Bellman (HJB) equation which arises from the idea of dynamic programming [25]. Because the value function, which is the solution of HJB equation, was not generally guaranteed to be smooth, the concept of viscosity solution came up as an alternative [26], but this also could not be obtained analytically. Thus, numerical approximation method is needed to solve the problem.

In this paper, we study an optimal feedback control problem of a tumor-immune model. To minimize tumor cells and cost associated with chemotherapy while reducing immune cells destroyed by chemotherapy, we find an optimal chemotherapy strategy that is dependent on tumor and immune cells. Furthermore, we investigate the change of optimal chemotherapy strategy according to the level of side effects and cost. For this, we derive the HJB equation through Bellman's principle. As a numerical approximation method for the viscosity solution, an approximated solution for the HJB equation, an upwind finite-difference method [27], is used.

The organization of this study is as follows. In Section 2, we propose a mathematical model of the tumor-immune system and explain the parameters used in the model. In addition, we study the positiveness and boundedness of solutions of the model. In Section 3, we conduct the stability analysis for two equilibria. In Section 4, the optimal control problems are discussed. To design the feedback control problem, we define a value function and then derive the HJB equation. For solving this problem numerically, the upwind finite-difference method is described. Also, an open-loop control problem is considered for comparison with the feedback control. Numerical simulation results of the optimal chemotherapy strategy are presented in Section 5. Finally, we provide discussion and conclusions in Section 6.

2. Mathematical Model

2.1. Tumor-Immune Dynamics.
We consider a mathematical model for tumor-immune dynamics, as represented by the scheme in Figure 1. The model is given by the following differential equations:

$$
\begin{cases}
\dfrac{dE}{dt} = \sigma + cT - \delta E, \\[2mm]
\dfrac{dT}{dt} = \alpha T(1 - \beta T) - \omega ET.
\end{cases}
\tag{1}
$$

Tumor cells (T) are assumed to grow in a logistic fashion. α is a growth rate of tumor cells and β is the inverse

of carrying capacity for tumor cells. Effector cells (E) kill tumor cells at a net rate ω [7]. We assume that the effector cells are produced at a constant rate σ [28]. δ denotes the rate of effector cell turnover. Furthermore, it is assumed that, due to the direct presence of tumor cells, the effector cells grow at a rate c. The explanation of the parameters used in model (1) is in Table 1.

2.2. Positiveness and Boundedness.
To validate the mathematical model biologically, we should prove that solutions to system (1) are positive and bounded. For instance, it is not biologically feasible that a cell is negative. Furthermore, because the human body is made up of a finite number of cells, the cells should remain finite. These are summarized in the following theorems.

Theorem 1. *Let $(E(t), T(t))$ be a solution of model (1). If the initial conditions satisfy $E(0) > 0$ and $T(0) > 0$, then the solution will remain positive, for all $t > 0$.*

Proof. Assume that there exists $t^* = \inf\{t > 0 \mid E(t) \cdot T(t) = 0\}$. First, we consider the case of $E(t^*) = 0$. Then, we know that $E(t) \geq 0$ and $T(t) > 0$, for all $t \in [0, t^*]$. It follows that, for all $t \in [0, t^*]$,

$$
\frac{dE}{dt} = \sigma + cT - \delta E > -\delta E.
\tag{2}
$$

By Gronwall's inequality, we obtain the inequality as follows. For all $t \in [0, t^*]$,

$$
E(t) > E(0)e^{\delta t}.
\tag{3}
$$

This is a contradiction with the fact that $E(t^*) = 0$.

Now, suppose that $T(t^*) = 0$ and note that $E(t) > 0$, for all $t \in [0, t^*]$. It is followed from the extreme value theorem that E has positive maximum value E_M. Then, it is obtained that, for all $t \in [0, t^*]$,

$$
\begin{aligned}
\frac{dT}{dt} &= \alpha T(1 - \beta T) - \omega ET \\[2mm]
&\geq -\alpha \beta T^2 - \omega E_M T \\[2mm]
&= -\alpha \beta T\left(T + \frac{\omega E_M}{\alpha \beta}\right).
\end{aligned}
\tag{4}
$$

By the partial fraction decomposition, we obtain the inequality as follows; for all $t \in [0, t^*]$,

$$
T(t) \geq \frac{B(\omega E_M/\alpha\beta)e^{-\omega E_M t}}{1 - Be^{-\omega E_M t}} > 0,
\tag{5}
$$

where $B = T_0/T_0 + \omega E_M/\alpha\beta$. This contradicts the assumption of $T(t^*) = 0$. Thus, $E(t), T(t)$ will remain positive. □

Theorem 2. *Let $(E(t), T(t))$ be a solution of model (1). If $E(0) \geq 0$ and $T(0) \geq 0$, then $E(t)$ and $T(t)$ are bounded.*

Proof. Suppose $T(t)$ is unbounded. First, we consider the case of $T(0) > 1/\beta$. Let $t_1 = \inf\{t > 0 \mid T(t) = 1/\beta\}$. Then, it
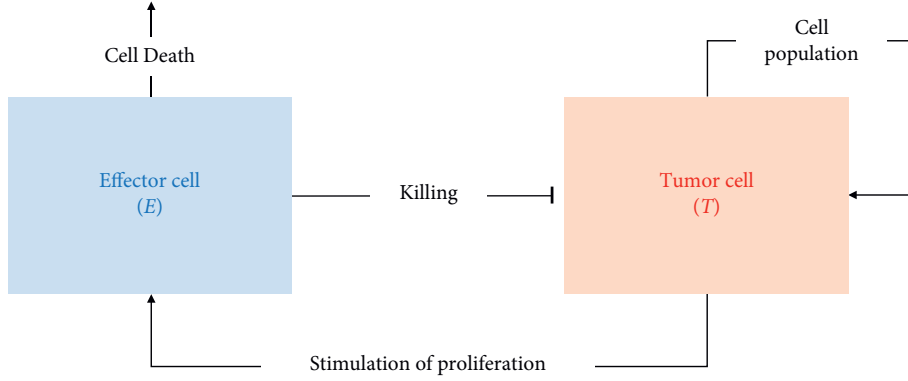
FIGURE 1: Schematic diagram of model (1) for interaction of tumor cells and immune cells (commonly called effector cells).

TABLE 1: Variables and parameters in model (1).

Symbol	Description	Unit
σ	The rate of effector cell proliferation	cells day^{-1}
c	The antigenicity of tumor cell	day^{-1}
δ	The rate of effector cell turnover	day^{-1}
α	The growth rate of tumor cell	day^{-1}
β	The inverse of tumor cell's carrying capacity	cells^{-1}
ω	The death rate of tumor cell by the interaction with an effector cell	cells^{-1} day^{-1}

follows that $dT/dt|_{t=t_1} < 0$. However, since $T(t)$ is unbounded, there exists $t_2 > t_1$ such that $T(t_2) = 1/\beta$, which also implies that $dT/dt|_{t=t_2} < 0$. By the recursive procedures, we obtain that $T(t) \leq 1/\beta$ for $t \geq t_1$. This contradicts the assumption. So, $T(t) \leq T(0)$, for all $t > 0$. Now, consider $T(0) \leq 1/\beta$. Let $t^* = \inf\{t > 0 | T(t) > 1/\beta\}$. Then, there exists $\bar{t} \in (0, t^*)$ such that $T(\bar{t}) = 1/\beta$. It follows that $dT/dt|_{t=\bar{t}} < 0$. The remaining proof is similar to the first case. Thus, $T(t) \leq 1/\beta$, for all $t > 0$. Therefore, $T(t)$ is bounded. Then, we can obtain the following inequality:

$$\frac{dE}{dt} = \sigma + cT - \delta E < \sigma + cT_M - \delta E, \tag{6}$$

where $T_M = \max\{T(0), 1/\beta\}$. It is followed that

$$E(t) < \frac{\sigma + cT_M}{\delta} + \left(E(0) - \frac{\sigma + cT_M}{\delta}\right)e^{-\delta t}. \tag{7}$$

Taking the limsup of both sides, we obtain

$$\limsup_{t \to \infty} E(t) \leq \frac{\sigma + cT_M}{\delta}. \tag{8}$$

Therefore, $E(t)$ is also bounded. □

3. Stability Analysis

3.1. Local Stability. From model (1), two equilibria can be obtained. One of these is the tumor-free equilibrium, that is,

$$P_0 = (E_0, T_0)$$

$$= \left(\frac{\sigma}{\delta}, 0\right). \tag{9}$$

To check the local stability, we compute the Jacobian at P_0 as follows:

$$J(P_0) = \begin{pmatrix} -\delta & c \\ 0 & \alpha - \dfrac{\sigma\omega}{\delta} \end{pmatrix}. \tag{10}$$

If the trace is negative and the determinant is positive, then P_0 is locally asymptotically stable. Thus, the condition $\alpha\delta - \sigma\omega > 0$ should be satisfied. We define the criterion K as follows:

$$K = \frac{\alpha\delta}{\sigma\omega}. \tag{11}$$

The local stability of P_0 is summarized in the following theorem.

Theorem 3. If $K < 1$, model (1) has an tumor-free equilibrium P_0 which is locally asymptotically stable.

The other equilibrium is $P_1 = (E_1, T_1)$, where

$$E_1 = \frac{\sigma + cT_1}{\delta},$$

$$T_1 = \frac{\alpha\delta - \sigma\omega}{\alpha\beta\delta + c\omega}. \tag{12}$$

If $K > 1$, the positiveness of P_1 is guaranteed. Note that if $K < 1$, the equilibrium P_1 does not exist and $P_0 = P_1$ when $K = 1$. The local stability of the equilibrium P_1 is summarized in the next theorem.

Theorem 4. If $K > 1$, model (1) has an unstable equilibrium P_0 and a locally asymptotically stable positive equilibrium P_1.

Proof. Computing the Jacobian at P_1 gives

$$J(P_1) = \begin{pmatrix} -\delta & c \\ \omega T_1 & \alpha - 2\alpha\beta T_1 - \omega E_1 \end{pmatrix}. \tag{13}$$

To show that P_1 is locally asymptotically stable, we compute the following conditions:

$$\begin{aligned} TrJ(P_1) &= -\delta + \alpha - 2\alpha\beta T_1 - \omega E_1 \\ &= \frac{-\delta^2 + \alpha\delta - 2\alpha\beta\delta T_1 - c\omega T_1 - \sigma\omega}{\delta} \\ &= -\delta - \frac{\alpha\beta(K-1)}{\alpha\beta\delta + c\omega}, \end{aligned} \tag{14}$$

$$\begin{aligned} DetJ(P_1) &= -\alpha\delta + 2\alpha\beta\delta T_1 + \omega\delta E_1 + c\omega T_1 \\ &= (\alpha\delta - \sigma\omega) + 2\alpha\beta\delta T_1 + 2c\omega T_1 \\ &= \alpha\delta - \sigma\omega. \\ &= \sigma\omega(K-1). \end{aligned}$$

Since $K > 1$, the trace is negative and the determinant is positive. Therefore, the equilibrium P_1 is locally asymptotically stable. In this case, the tumor-free equilibrium P_0 is unstable, which is a saddle. □

3.2. Global Stability. Furthermore, we investigate the global stability of the equilibria P_0 and P_1. These are summarized in the following theorems.

Theorem 5. *If $K \leq 1$, the tumor-free equilibrium P_0 of model (1) is globally asymptotically stable.*

Proof. Consider the following Lyapunov function on $\mathbb{R}_+^2$:

$$L = \left(E - E_0 - E_0 \ln\frac{E}{E_0}\right) + \frac{c}{\alpha}T. \tag{15}$$

It is easy to see that $L = 0$ at the equilibrium P_0 and $L > 0$, for all $(E, T) \neq (\sigma/\delta, 0)$. Thus, L is positively definite and is also clearly radially unbounded. Taking the derivative of L with respect to t, we obtain that

$$\begin{aligned} \frac{dL}{dt} &= \left(1 - \frac{E_0}{E}\right)E' + \frac{c}{\alpha}T' \\ &= \left(1 - \frac{E_0}{E}\right)(\sigma + cT - \delta E) + cT(1 - \beta T) - \frac{c\omega}{\alpha}ET \\ &= -c\beta T^2 + \left(\sigma + \delta E_0 - \delta E - \frac{\sigma E_0}{E}\right) + \left(2cT - \frac{cE_0 T}{E} - \frac{c\omega}{\alpha}ET\right) \\ &= -c\beta T^2 + \sigma\left(2 - \frac{\delta E}{\sigma} - \frac{\sigma}{\delta E}\right) + cT\left(2 - \frac{\sigma}{\delta E} - \frac{\delta E}{\sigma K}\right). \end{aligned} \tag{16}$$

By the arithmetic-geometric mean and the assumption $K \leq 1$, we obtain the following inequality:

$$\frac{dL}{dt} \leq -c\beta T^2 < 0. \tag{17}$$

Hence, we have $L' < 0$, for all $(E, T) \neq (\sigma/\delta, 0)$. Therefore, by Lyapunov's theorem, the tumor-free equilibrium P_0 is globally asymptotically stable. □

Theorem 6. *Assume $K > 1$; the equilibrium P_1 of model (1) is globally asymptotically stable whenever $T(0) > 0$.*

Proof. Let $X = \mathbb{R}_+^2$ and set the functions:

$$\begin{aligned} F_1(E, T) &= \sigma + cT - \delta E, \\ F_2(E, T) &= \alpha T(1 - \beta T) - \omega ET. \end{aligned} \tag{18}$$

Define the function $D(E, T) = 1/T$ on X. Then, D is continuously differentiable on X. Furthermore, we obtain that

$$\frac{\partial(DF_1)}{\partial E} + \frac{\partial(DF_2)}{\partial T} = -\frac{\delta}{T} - \alpha\beta < 0. \tag{19}$$

Applying Dulac–Bendixson criterion, system (1) has no periodic orbits or graphics on X. Since Theorem 2 guaranteed the boundedness of solutions of system (1), X is positively invariant and contains an omega limit set of every initial conditions. Thus, Poincaré–Bendixson theorem can be applied. When $K > 1$, if $T(0) = 0$, then the solutions will remain on the E-axis in (E, T)-plane and converge to P_0. If $T(0) > 0$, that is, $(E(0), T(0)) \in X$, then we want to show that the equilibrium P_0 does not belong to the omega limit set of the point $(E(0), T(0))$. Suppose the omega limit set contains P_0. By Theorem 4, P_0 is unstable saddle, and so it has stable manifold which is given by the E-axis. Because each solution starting from $T(0) = 0$ remains on the E-axis and converges to P_0, thus, the stable manifold of P_0 is not in X. Hence, the omega limit set should contain another equilibrium P_1. But, since P_1 is locally asymptotically stable, the solutions starting close to P_1, approach to it. So, the equilibrium P_0 is not in the omega limit set. Therefore, the omega limit set of $(E(0), T(0))$ contains only P_1. □ □

4. Optimal Control Problems

In this section, we consider optimal control problems of model (1) to investigate the optimal chemotherapy strategy depending on the level of effector cells and tumor cells. To begin with, we design a feedback control problem. Additionally, an open-loop control problem of chemotherapy is considered for comparison with the feedback control.

First, we simplify model (1) into the nondimensional form through the following process:

$$\begin{aligned} x &= (x_1, x_2) \\ &= \left(\frac{E}{E^*}, \frac{T}{T^*}\right), \end{aligned} \tag{20}$$

where $E^* = \sigma + c/\beta/\delta$ and $T^* = 1/\beta$. Then, the new dependent variables $x_1(t)$ and $x_2(t)$ are dimensionless quantities. Hence, the system for them becomes

$$\begin{cases} \dfrac{dx_1}{dt} = f_1(t,x) = \overline{\sigma} + \overline{c}x_2 - \delta x_1, \\[2mm] \dfrac{dx_2}{dt} = f_2(t,x) = \alpha x_2(1-x_2) - \overline{\omega}x_1 x_2, \end{cases} \quad (21)$$

where $\overline{\sigma} = \sigma/E^*$, $\overline{c} = cT^*/E^*$, and $\overline{\omega} = \omega E^*$.

4.1. Feedback Control Problem

4.1.1. Hamilton–Jacobi–Bellman Equation.

Let τ and t_f be an initial time and a final time, respectively, and let u be a measurable function from $[\tau, t_f]$ to $[0,1]$. The control $u(t)$ means the treatment effort in time t, which represents the intensity of chemotherapy. The class of all admissible controls is denoted by

$$\mathcal{U}_f = L^\infty\left([\tau, t_f]; [0,1]\right). \quad (22)$$

Then, the system with the control is as follows:

$$\begin{cases} \dfrac{dx_1}{dt} = f_1(t,x,u) = \overline{\sigma} + \overline{c}x_2 - \delta x_1 - q_E u x_1, \\[2mm] \dfrac{dx_2}{dt} = f_2(t,x,u) = \alpha x_2(1-x_2) - \overline{\omega}x_1 x_2 - q_T u x_2, \end{cases} \quad (23)$$

where q_E and q_T are the chemotherapy-induced death coefficients of effector cell and tumor cell, respectively. Especially, the coefficient q_E is related to the side effect of chemotherapy. Thus, to reduce tumor cells and death of effector cells via chemotherapy while minimizing the cost to chemotherapy, we consider the following objective functional:

$$\mathcal{J}(\tau, a, b, u) = \int_\tau^{t_f} L(t, x(t), u(t))dt, \quad (24)$$

where the Lagrangian $L(t, x(t), u(t)) = q_E u(t) x_1(t) + (1 - q_T u(t)) x_2(t) + B/2u(t)^2$ and $x(\tau) = (x_1(\tau), x_2(\tau)) = (a,b)$ is an initial condition. In the Lagrangian L, first and second terms mean the death of effector cells due to side effects and the tumor cells remaining after chemotherapy, respectively. The last term represents the cost of chemotherapy.

Define the value function:

$$v(\tau, x(\tau)) = \min_{u \in \mathcal{U}_f} \mathcal{J}(\tau, x(\tau), u). \quad (25)$$

The optimal control problem can be formulated as the HJB equation via Bellman's principle of the dynamic programming. Thus, we can obtain the HJB equation as follows:

$$v_t + \min_{u \in \mathcal{U}_f}[\nabla_x v \cdot f(t,x,u) + L(t,x,u)] = 0, \quad \forall (t,x) \in [0, t_f] \times \mathbb{R}^2, \quad (26)$$

where $f = (f_1, f_2)$ and the initial condition $v(t_f, x) = 0$. The value function in characterizing the optimal feedback law is described in the following two propositions [29].

Proposition 1. *Let $v \in C^1([0, t_f] \times \mathbb{R}^n)$ be the value function. Then, if there exists a control $u^*(\cdot) \in \mathcal{U}_f$ such that*

$$\nabla_x v(t, x^*(t)) \cdot f(t, x^*(t), u^*(t)) + L(t, x^*(t), u^*(t))$$
$$= \min_{u \in \mathcal{U}_f}\{\nabla_x v(t, x^*(t)) \cdot f(t, x^*(t), u) + L(t, x^*(t), u)\}. \quad (27)$$

then $u^*(\cdot)$ is an optimal control, where $x^* = (x_1^*, x_2^*)$ is the state corresponding to u^*.

The optimal control is denoted as

$$u^*(t) \in \arg\min_{u \in \mathcal{U}_f}\{\nabla_x v(t, x^*(t)) \cdot f(t, x^*(t), u) + L(t, x^*(t), u)\}, \quad (28)$$

for almost all $t \in [0, T]$.

Proposition 2. *Let $v \in C^1([0, t_f] \times \mathbb{R}^2)$ be the value function. Then, $(u^*(t), x^*(t))$ is an optimal control-trajectory pair in feedback form if and only if*

$$v_t(t, x^*(t)) + \nabla_x v(t, x^*(t)) \cdot f(t, x^*(t), u^*(t))$$
$$+ L(t, x^*(t), u^*(t)) = 0, \quad (29)$$

for almost all $t \in [0, T]$.

By Propositions 1 and 2, the feedback law via the value function can be constructed. This is summarized in the following theorem.

Theorem 7. *Let $v \in C^1([0, t_f] \times \mathbb{R}^2)$ be the value function. Suppose $u(t,x)$ satisfies*

$$\nabla_x v(t,x) \cdot f(t, x, u(t,x)) + L(t, x, u(t,x))$$
$$= \min_{u \in \mathcal{U}_f}\{\nabla_x v(t,x) \cdot f(t, x, u(t,x)) + L(t, x, u(t,x))\}. \quad (30)$$

Then, $u_z^*(t) = u(t, x_z(t))$ is the feedback law of the optimal control problem, where $x_z(t)$ is the solution of the following control system:

$$x_z'(t) = f(t, x_z(t), u(t, x_z(t))), \quad \forall x_z(0) = z, t \in [0, t_f]. \quad (31)$$

4.1.2. Upwind Finite-Difference Method.

Solutions of HJB equation are continuous, but nonsmooth in $\mathbb{R}^n$. In order to complement the nonsmooth, the idea of viscosity solutions is used by Lions [26]. The idea is to consider the convection-diffusion equation by adding the diffusion term $\epsilon\nabla^2 v$, where $\epsilon > 0$ is the viscosity. Then, the solution of this equation becomes smooth and converges to the viscosity solution of original HJB equation as $\epsilon \longrightarrow 0$ [30]. It can be shown that the existence and uniqueness of viscosity solution to HJB equation are guaranteed [30, 31]. However, this equation generally is not analytically solvable and so we use the upwind finite-difference method as a numerical approximation method.

Before addressing this method, we settle for computational problems that arise from using the finite-difference method. Since the variables of model (1) have wide ranges of numbers, solving a feedback control problem requires a high amount of numerical computations. So, by scaling the

variables to the appropriate level, we transformed model (1) to dimensionless model (21). Assuming that $E(0) \leq E^*$ and $T(0) \leq T^*$, it is followed from Theorem 2 that $x(t) = (x_1(t), x_2(t)) \in [0, 1] \times [0, 1]$, for all $t > 0$. Therefore,

we restrict the feedback control problem to the domain $[0, t_f) \times \Omega$, where $\Omega = [0, 1] \times [0, 1]$. Then, we can reformulate equation (26) as follows:

$$\varepsilon \nabla^2 v + v_t + \min_{u \in \mathcal{U}_f} \left[\nabla_x v(t, x) \cdot f(t, x, u) + L(t, x, u) \right] = 0, \quad \forall (t, x) \in [0, t_f) \times \Omega,$$

$$v(t, x) = g(t, x), \quad \forall (t, x) \in [0, t_f) \times \partial \Omega ,$$

$$v(t_f, x) = 0, \quad \forall x \in \Omega.$$

(32)

We need to be determine a suitable boundary condition, for $(t, x) \in [0, t_f) \times \partial \Omega$. Since the only possible information is the value function at the final time t_f, we pose the Dirichlet boundary condition, that is, $g(t, x) = v(t_f, x)$ [32].

Here, we apply the upwind finite-difference method to (32) with $\epsilon \ll 1$ [33, 34]. Let $i = (i_1, i_2), i_1^+ = (i_1 + 1, i_2), i_1^- = (i_1 - 1, i_2), i_2^+ = (i_1, i_2 + 1)$, and $i_2^- = (i_1, i_2 - 1)$. To discretize (32), we assume that, for $k = 1, 2$, $x_{k, i_k} = i_k \Delta x_k$, $i_k = 0, 1, \ldots, M_k$, with $\Delta x_k = 1/M_k$, and $t_j = (j - 1) \Delta t$, $j = 1, 2, \ldots, M_t + 1$, with $\Delta t = t_f / M_t$, are the partitions

along the x_k and t axes, respectively. Here, we assume the meshes for state variables are uniform, that is, $M_1 = M_2 = M$. Then, two stencils can be considered. One consists of the six vertices $(x_{1, i_1 - 1}, t_j)$, (x_{1, i_1}, t_j), $(x_{1, i_1 + 1}, t_j)$, $(x_{1, i_1 - 1}, t_{j+1})$, (x_{1, i_1}, t_{j+1}), and $(x_{1, i_1 + 1}, t_{j+1})$. The other consists of the six vertices $(x_{2, i_2 - 1}, t_j)$, (x_{2, i_2}, t_j), $(x_{2, i_2 + 1}, t_j)$, $(x_{2, i_2 - 1}, t_{j+1})$, (x_{2, i_2}, t_{j+1}), and $(x_{2, i_2 + 1}, t_{j+1})$. On the cuboid consisting these stencils, (32) can be approximated by the difference equations as follows; for $i_1, i_2 = j, \ldots, M - j$ and $j = 1, 2, \ldots, M_t$,

$$\frac{v_i^{j+1} - v_i^j}{\Delta t} = \sum_{k=1}^{2} \left(\frac{1 + \text{sgn}\left(f_{k,i}^j(u_i^j)\right)}{2} f_{k,i}^j(u_i^j) \frac{v_{i_k^+}^j - v_i^j}{\Delta x_k} + \frac{1 - \text{sgn}\left(f_{k,i}^j(u_i^j)\right)}{2} f_{k,i}^j(u_i^j) \frac{v_i^j - v_{i_k^-}^j}{\Delta x_k} \right) + L_i^j(u_i^j),$$

$$u_i^j = \arg\sup_{u \in \mathcal{U}_f} \left[-\sum_{k=1}^{2} \left(\frac{1 + \text{sgn}\left(f_{k,i}^j(u)\right)}{2} f_{k,i}^j(u) \frac{v_{i_k^+}^j - v_i^j}{\Delta x_k} + \frac{1 - \text{sgn}\left(f_{k,i}^j(u)\right)}{2} f_{k,i}^j(u) \frac{v_i^j - v_{i_k^-}^j}{\Delta x_k} \right) - L_i^j(u) \right],$$

(33)

where

$$f_{1,i}^j(u_i^j) = f_1(t_j, x_{1,i_1}, x_{2,i_2}, u_i^j),$$

$$f_{2,i}^j(u_i^j) = f_2(t_j, x_{1,i_1}, x_{2,i_2}, u_i^j),$$

$$L_i^j(u_i^j) = L(t_j, x_{1,i_1}, x_{2,i_2}, u_i^j).$$

(34)

Based on the upwind finite-difference method, the algorithm for solving HJB equation is summarized in Algorithm 1.

4.2. Open-Loop Control Problem.

In open-loop control problem, t_f and u are the same as meanings in the feedback control problem. Then, an objective functional for open-loop control problem is given by

$$\mathcal{G}(u) = \int_0^{t_f} L(t, x(t), u(t)) \mathrm{d}t,$$

(35)

where $x(0) = (x_1(0), x_2(0))$ is an appropriate initial condition. Similarly, the open-loop control problem is to find an optimal control u^* such that

$$\mathcal{G}(u^*) = \min\{\mathcal{G}(u), u \in \mathcal{U}_o\}.$$

(36)

subject to system (23), where the control set is defined as

$$\mathcal{U}_o = \{u | u(t) \text{ is Lebesgue measurable}, \quad 0 \leq u(t) \leq 1 \, \forall t \in [0, t_f] \}.$$

(37)

First, an existence of optimal control for problem (36) and the optimality system is derived.

Theorem 8. *Given the objective functional $\mathcal{G}(u)$ and the control set $\mathcal{U}_o$, there exist an optimal control u^* such that $\mathcal{G}(u^*) = \min\{\mathcal{G}(u), \quad u \in \mathcal{U}_o\}$.*

Proof. From [35], we prove the existence of an optimal control. By Theorem 1, the state variables are nonnegative. Note that the control is also nonnegative. The set of all controls u in $\mathcal{U}_o$ is convex and closed. For the minimizing problem, the convexity of $\mathcal{G}$ in u is satisfied and the optimality system is bounded. So, the compactness necessary for the existence of optimal control is guaranteed. Furthermore, the Lagrangian L is convex on the control set $\mathcal{U}_o$. Since the state variables are bounded, we can easily confirm that there exist a constant $\kappa > 1$ and numbers ρ_1, ρ_2 such that

$$\mathcal{G}(u) \geq \rho_1 \left(u^2\right)^{\kappa/2} - \rho_2 = \rho_1 u^\kappa - \rho_2.$$

(38)

Set the initial condition $\{v_i^1\}_{i_k=0}^{M_k}$ and the feedback control $\{u_i^1\}_{i_k=0}^{M_k}$ for $k = 1, 2$
for $j = 1, 2, \ldots, M_t$ do
    for $i_1 = j, j + 1, \ldots, M_1 - j$ do
        for $i_2 = j, j + 1, \ldots, M_2 - j$ do
        $W_i^j(u) = -\sum_{k=1}^2 (1 + \text{sgn}(f_{k,i}^j(u))/2) f_{k,i}^j(u)(v_{i_k^+}^j - v_i^j/\Delta x_k) + (1 - \text{sgn}(f_{k,i}^j(u))/2) f_{k,i}^j(u)(v_i^j - v_{i_k^-}^j/\Delta x_k) - L_i^j(u)$
        $u_i^j = \arg\sup_{u \in \mathcal{U}_f} W_i^j(u)$
        $v_i^{j+1} = v_i^j - \Delta t W_i^j(u_i^j)$
        end
    end
end

ALGORITHM 1: Algorithm for solving HJB equation

If follows the existence of an optimal control.

In order to find a minimal value of the Lagrangian, we define a Hamiltonian:

$$H = x_2 + q_E u x_1 - q_T u x_2 + \frac{B}{2}u^2 + \lambda_1[\overline{\sigma} + \overline{c}x_2 - \delta x_1 - q_E u x_1]$$

$$+ \lambda_2[\alpha x_2(1 - x_2) - \overline{\omega}x_1 x_2 - q_T u x_2],$$

(39)

where λ_1 and λ_2 are the adjoint variables. To derive a necessary conditions for the optimal solution of optimal control problem (23) and (35), we use Pontryagin's Maximum Principle [24]. The adjoint system and control characterization are described in the following theorem. □

Theorem 9. *Given an optimal control u^* and a solution $x^* = (x_1^*, x_2^*)$, there exist adjoint variables λ_1 and λ_2 satisfying*

$$\lambda_1'(t) = -\frac{\partial H}{\partial x_1} = q_E u(t) + \lambda_1(t)[\delta + q_E u(t)] + \lambda_2(t)[\overline{\omega}x_2(t)],$$

$$\lambda_2'(t) = -\frac{\partial H}{\partial x_2} = -1 + q_T u(t) - \overline{c}\lambda_1(t) - \lambda_2(t)[\alpha - 2\alpha x_2(t) - \overline{\omega}x_1(t) - q_T u(t)].$$

(40)

under transversality conditions,

$$\lambda_i(t_f) = 0, \quad i = 1, 2.$$

(41)

Moreover, the control function u^* is given by

$$u^* = \min\{1, \max\{0, R\}\},$$

(42)

where $R = (\lambda_1 - 1)q_E x_1 + (\lambda_2 + 1)q_T x_2/B$.

Proof. From Pontryagin's Maximum Principle [24], the adjoint system can be obtained:

$$\lambda_1'(t) = -\frac{\partial H}{\partial x_1},$$

$$\lambda_2'(t) = -\frac{\partial H}{\partial x_2}.$$

(43)

with $\lambda_i(t_f) = 0$ for $i = 1, 2$. By solving the equation

$$\frac{\partial H}{\partial u} = 0$$

(44)

and using properties of the control set $\mathcal{U}_o$, we can characterize the optimal control (42). □

5. Numerical Results

In numerical simulations of feedback control and open-loop control problems, we set the case where the criterion K is greater than 1, i.e., tumor survive persistently. The parameter values are summarized in Table 2. Because chemotherapy usually proceeds only for the initial about 5 days due to toxicity, we assume that model (23) is defined over a time interval [0, 5]. Also, we set weight constant $B = 1$. In particular, for the feedback control problem, we solve the HJB equation numerically by using mesh size for state variables and time with $\Delta x_1 = \Delta x_2 = 0.02$ and $\Delta t = 0.01$, respectively.

We consider two scenarios for q_E. One is $q_E = 0.2$, which is a case of lower side effects. Upper panels in Figure 2 represent values of feedback control $u(t, x_1, x_2)$ on the domain Ω at $t = 0$ and 2 with $q_E = 0.2$. At $t = 0$, there are higher control values if effector cells are low and tumor cells are high. The controls are not required in the opposite case where tumor cells are high and effector cells are low. When the level of effector cells is fixed, the controls have higher values which decrease as the number of tumor cells increases. On the contrary, the control values become lower as tumor cells go higher. At $t = 2$, the controls are needed

Symbol	Value	References
σ	1.3×10^4	[7]
c	0.103	[12]
δ	0.0412	[7]
α	0.18	[7]
β	2.0×10^{-9}	[7]
ω	1.101×10^{-7}	[7]
q_E	—	
q_T	0.9	[19]
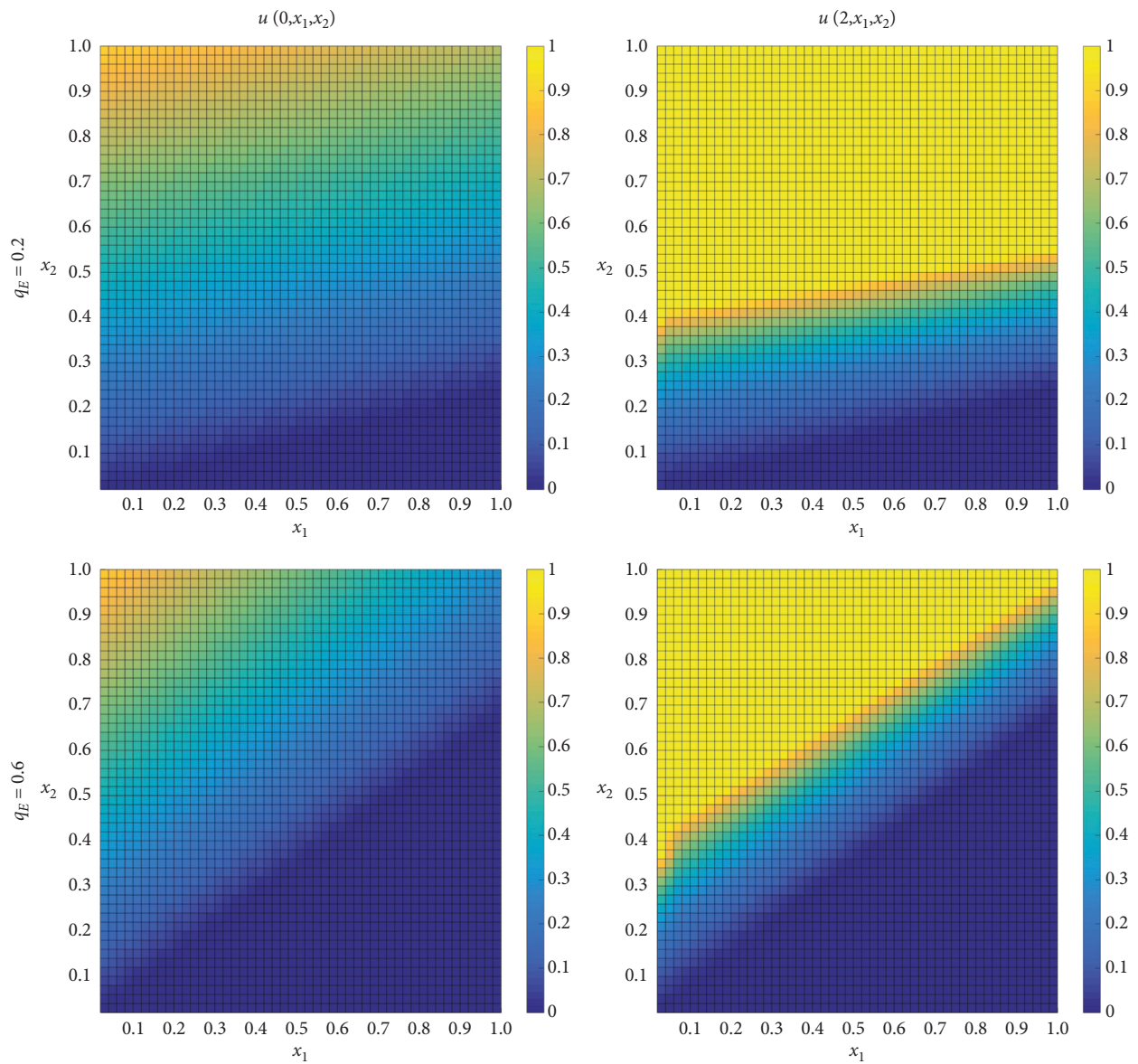
FIGURE 2: Feedback controls for initial time values $\tau = 0$ and 2 with $q_E = 0.2$ (upper panels) and with $q_E = 0.6$ (lower panels).
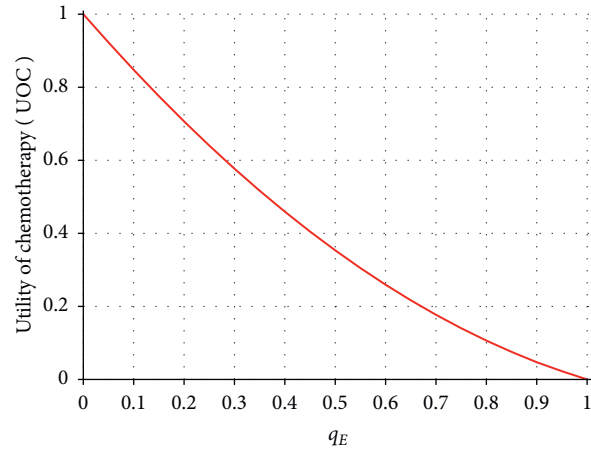
FIGURE 3: Utility of chemotherapy (UOC) for the chemotherapy-induced death coefficient of effector cell (q_E).
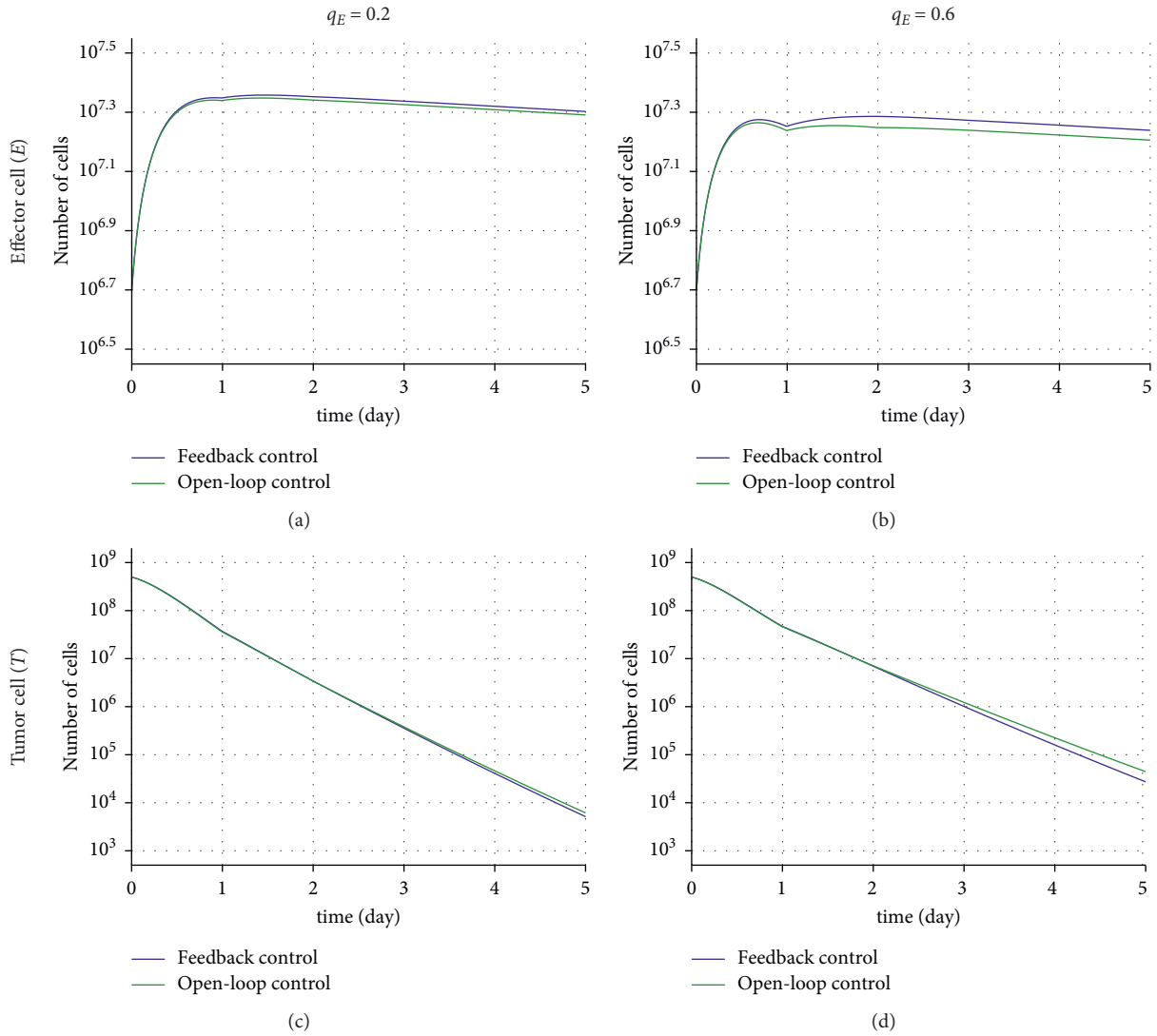

(a)

(b)

(c)

(d)

FIGURE 4: Numerical simulations of tumor-immune model (1) with chemotherapy. The blue line means the feedback control and the green line represents the open-loop control. The upper panels indicate the number of effector cells for $q_E = 0.2$ (a) and $q_E = 0.6$ (b), respectively. The lower panels indicate the number of tumor cells for $q_E = 0.2$ (c) and $q_E = 0.6$ (d), respectively. The initial values are assumed to be $(E(0), T(0)) = (5.0 \times 10^6, 5.0 \times 10^8)$.

highest when the level of tumor cells is more than about 0.4, which suggests that, in this case, the chemotherapy should depend on the level of tumor cells rather than the effector cells. The other is the case where $q_E = 0.6$, which is represented in the lower panels in Figure 2. Similar to the case of $q_E = 0.2$, the higher degree of chemotherapy is required when the effector cells are low and the tumor cells are

high. Compared to the case of lower side effects, the chemotherapy should be conducted when the immunity is much higher.

Furthermore, in order to investigate the utility of chemotherapy (UOC), we consider a measure, UOC, as the function of q_E which is defined by

$$\text{UOC}(q_E) = \frac{\iint_\Omega u_{q_E}(0, x_1, x_2)\mathrm{d}x_1\mathrm{d}x_2 - \iint_\Omega u_1(0, x_1, x_2)\mathrm{d}x_1\mathrm{d}x_2}{\iint_\Omega u_0(0, x_1, x_2)\mathrm{d}x_1\mathrm{d}x_2 - \iint_\Omega u_1(0, x_1, x_2)\mathrm{d}x_1\mathrm{d}x_2}, \tag{45}$$

where u_0 and u_1 represent feedback controls in the case of $q_E = 0$ and $q_E = 1$, respectively. The numerator describes the difference between the level of chemotherapy adapted when the degree of side effects is q_E and in the case of 100% side effects. The denominator indicates the difference between the level of chemotherapy adapted in the absence of side effects and the level of chemotherapy adapted when there are fully side effects. That is, UOC is the ratio of efficacy of chemotherapy according to the degree of side effects. Figure 3 shows UOC as the chemotherapy-induced death coefficient of effector cell, q_E, varies. UOC decreases from 1 to 0 as q_E increases and falls below 50% if q_E is higher than 0.4. A case with $q_E = 0.2$ has UOC as 70%, but it is about 30% when q_E is 0.6.

In addition, we examine the efficacy of feedback control for chemotherapy as compared to the open-loop control. This is shown in Figure 4. In the case of $q_E = 0.2$, the open-loop control initially reduces tumor cells slightly more than the feedback control, but, at the same time, the effector cells decrease more. Through the feedback control, it can be confirmed that effector cells survived more and the tumor cells were reduced more at the final time. However, in this case, there was no big difference between feedback control and open-loop control. Especially, considering the higher side effects, the difference became higher.

6. Discussion and Conclusion

Chemotherapy is known as the common cancer treatment, which can directly kill tumor cells. Since there are side effects of killing effector cells and alternative treatment such as immunotherapy have been introduced, the use of chemotherapy has decreased. However, due to the advantages of time and cost, it is still the most widely used. For the effective chemotherapy, we should take into account for not only the size of tumor cells but also the level of effector cells. Thus, in this study, we set up the mathematical model for tumor-immune system and considered feedback control problem using HJB equation to show the effective chemotherapy with simulation. The upwind finite-difference method was used to solve the problem numerically. As a result, the optimal chemotherapy was designed depending on the level of effector cells as well as the size of tumor cells. Also, we calculated the degree of chemotherapy according to the extent of side effects and then suggested the utility of chemotherapy (UOC).

Furthermore, considering the open-loop control for chemotherapy through PMP, we compared the results of feedback control with that. In the case of feedback control, the effector cells were reduced less and the tumor cells were decreased more at the same extent of side effects. Consequently, the feedback control could suggest the effective chemotherapy compared to the open-loop control. PMP is widely used as a conventional optimization method, but it is only a necessary condition for an optimum, which is just a local solution for optimal control problems. On the contrary, the dynamic programming can guarantee necessary and sufficient conditions for an optimum. However, it has also drawbacks of complicated process and a lot of computation times. We were able to reduce the complexity and computation times by using the simple model for tumor-immune system, but this is one of the limitations in our study. Therefore, in this regard, we plan two points as future works. First is to investigate more sophisticated biological mechanisms for the tumor-immune system and then establish a mathematical model for those. Secondly, we will improve the existing numerical method to effectively reduce the computation time of dynamic programming, which is expected to make it easier to apply mathematical models to feedback control problems.

Data Availability

No data have been used in this study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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