Combining a drug therapy and oncolytic virotherapy to treat cancer: an optimal control approach

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Abstract
Optimal control theory is applied to a controlled tumor model. Seeking to minimize the infected cells and to maximize uninfected cells, we use two controls representing drug therapy and oncolytic virotherapy. The Pontryagin's maximum principle is used to characterize the optimal controls. The optimal controls are obtained by solving the optimality system. The results are analyzed and interpreted numerically using MATLAB.

Keywords: *Optimal control, mathematical models, oncolytic virus, Pontryagin's maximum principle.*

1. Introduction

Cancer is a disease that begins as a renegade human cell over which the body has lost control. In order for the body and its organs to function properly, cell growth needs to be strictly regulated. Cancer cells, however, continue to divide and multiply at their own speed, forming abnormal lumps, or tumors.

Not all cancers are natural-born killers. Some tumors are referred to as benign because they don't spread elsewhere in the body. But cells of malignant tumors do invade other tissues and will continue to spread if left untreated, often leading to secondary cancers.

Cancers can start in almost any body cell, due to damage or defects in genes involved in cell division. Mutations build up over time, which is why people tend to develop cancer later in life. What actually triggers these cell changes remains unclear, but diet, lifestyle, viral infections, exposure to radiation or harmful chemicals, and inherited genes are among factors thought to affect a person's risk of cancer.

There are over 100 different types of cancer, affecting various parts of the body. Each type of cancer is unique with its own causes, symptoms, and methods of treatment. Like with all groups of disease, some types of cancer are more common than others. According to the World Health Organization (WHO), cancer is a leading cause of death worldwide and accounted for 7.6 million deaths (13% of all deaths) in 2008. The main types of cancer are: lung (1.37 million deaths), stomach (736 000 deaths), liver (695 000 deaths), colorectal (608 000 deaths), breast (458 000 deaths) and cervical cancer (275 000 deaths). Deaths from cancer worldwide are projected to continue to rise to over 13.1 million in 2030(WHO).

Knowledge about the causes of cancer, and interventions to prevent and manage the disease are extensive. Cancer can be reduced and controlled by implementing evidence-based strategies for cancer prevention, early detection of cancer and management of patients with cancer. Many cancers have a high chance of cure if detected early and treated adequately. The most common types of cancer treatment are surgery chemotherapy, radiation therapy, targeted therapy, and immunotherapy. The efficiency of cancer treatment has improved dramatically in the last decade. However, patients with certain forms of cancer are still left with limited options for therapy. Many tumors also remain completely incurable, creating a need for a broader spectrum of therapeutic strategies. One promising form of treatment is oncolytic virotherapy. This technique employs replication competent viral vectors as agents that preferentially attack and proliferate in cancerous cells, leaving most healthy cells uninjured. The result is the destruction of tumor populations without appreciable damage to normal tissue. Here are many oncolytic viruses which have demonstrated anti-tumor efficacy, including adenoviruses [1] Coxsackieviruses [2], herpes simplex viruses [3], measles viruses [4], Newcastle disease virus [5], reoviruses [6], Seneca Valley virus [7], vaccinia viruses [8], and vesicular stomatitis virus (VSV) [9].

Mathematical modeling of cancer treatment can illuminate the underlying dynamics of therapy systems and can lead to more optimal treatment strategies. A wide variety of models that study the tumors dynamics and treatment have been developed and analyzed (see for example [10, 11, 12, 13] and the reference in it).

In this paper we explore an optimal control strategy of tumor therapy. We use a controlled model of tumor dynamics that includes two controls representing drug therapy and oncolytic virotherapy; our goal is to maximize the number of susceptible cells and to minimize the number of infected cells.

The paper is organized as follows. In section 2, we present a mathematical model with two control terms. The analysis of optimization problem is presented in section 3. In section 4, we give a numerical appropriate method and the simulation corresponding results. Finally, the conclusions are summarized in section 5.

2. Mathematical model of cancers

We consider the model used in [14].The model considers two types of tumor cells (x) and (y) growing in logistic fashion. (x) is the density of the uninfected tumor cell population and (y) is the density of infected tumor cell population. The model has the following form

$$\begin{cases} \frac{dx}{dt} = r_1 x\left(1-\frac{x+y}{k}\right) - \frac{bxy}{x+y} \\ \frac{dy}{dt} = r_2 y\left(1-\frac{x+y}{k}\right) + \frac{bxy}{x+y} - ay \end{cases} \quad (1)$$

With initial conditions: $x(0) = x_0 > 0$ and $y(0) = y_0 > 0$
Here r_1 and r_2 are the maximum per capita growth rates of uninfected and infected cells correspondingly; K is the carrying capacity , b is the transmission rate and a is the rate of infected cell killing by the viruses. All the parameters of the model are supposed to be non-negative.

The model under consideration in this paper comprises of the following

$$\begin{cases} \frac{dx}{dt} = r_1 x\left(1-\frac{x+y}{k}\right) - \left(1-u_1(t)\right)\frac{bxy}{x+y} & (2.1) \\ \frac{dy}{dt} = r_2 y\left(1-\frac{x+y}{k}\right) + \left(1-u_1(t)\right)\frac{bxy}{x+y} - u_2(t)y & (2.2) \end{cases}$$

The modifications to the original model are the control terms comprising of u_1 and u_2. Here $u_1 = u_1(t)$ represents the efficiency of drug therapy in blocking new infection. Thus, the infection rate in the presences of drug is $\left(1-u_1(t)\right)\frac{bxy}{x+y}$. If $u_1 = 1$, the efficiency of drug therapy in blocking new infection is 100%, whereas if $u_1 = 0$ we find the same incidence term in the model (1). On the other hand the original model contained the term a which is assumed to be a constant, but it would be more biologically realistic if this rate depends on the injected dose of virus. Hence, we consider $u_2 = u_2(t)$ as the second control. It represents the efficiency of killing infected cells by the virus (cytotoxicity), which instead of being selected constant values would change over time.

The control function $u_1(t)$ and $u_2(t)$ are bounded, Lebesgue integral function.

3. The optimal problems

In this section we use the optimal control theory to analyze the behavior of the model (2.1), (2.2). Our goal is to maximize the number of the uninfected cells, to minimize the infected cells and the cost of treatment. Mathematically, for a fixed terminal time t_f, the problem is to maximize the objective functional defined by

$$J(u_1,u_2) = \int_0^{t_f} \left\{x(t) - y(t) - \left[\frac{A_1}{2}u_1^2(t) + \frac{A_2}{2}u_2^2(t)\right]\right\} dt$$

(3)

Where t_f is the period of treatment and the parameters $A_1 \geq 0$ and $A_2 \geq 0$ are based on the benefits and costs of the treatment.
In other words, we are seeking optimal control pair (u_1^*, u_2^*) so that

$$J(u_1^*, u_2^*) = max\{J(u_1,u_2)\,, (u_1,u_2) \in U\} \qquad (4)$$

Where U is the control set defined by

$$U = \begin{Bmatrix} u = (u_1,u_2)\,, u_i\, mesurable\,; 0 \leq u_i(t) \leq 1\,; \\ t \in [0,t_f]\,; i = 1,2 \end{Bmatrix}$$

3.1 Existence of an optimal control

Before to show the existence of the optimal control pair; we prove the existence of the solution for the controlled system (2.1), (2.2).
We rewrite our system (2.1), (2.2) following form

$$X_t = AX + F(X) \qquad (5)$$

Were : $X = (x,y)$, $A = \begin{bmatrix} r_1 & 0 \\ 0 & r_2 - u_2(t) \end{bmatrix}$,

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$$F = \begin{bmatrix} -r_1 x\left(\frac{x+y}{k}\right) - \left(1-u_1(t)\right)\frac{bxy}{x+y} \\ -r_2 y\left(\frac{x+y}{k}\right) + \left(1-u_1(t)\right)\frac{bxy}{x+y} \end{bmatrix}.$$

And X_t denote derivative of X with respect to time t.
Equation (3) is a non-linear system with a bounded coefficient.
We set:

$$D(X) = AX + F(X) \qquad (6)$$

And $\|X\| = max(|x|,|y|)$ we define:

$$\|F(X_1) - F(X_2)\| = max(|G_1(X_1,X_2)|, |G_2(X_1,X_2)|)$$

Where:

$$G_1(X_1,X_2) = \left\{r_1\left(x_2\left(\frac{x_2+y_2}{k}\right) - x_1\left(\frac{x_1+y_1}{k}\right)\right) + \left(1-u_1(t)\right)b\left(\frac{x_2y_2}{x_2+y_2} - \frac{x_1y_1}{x_1+y_1}\right)\right\}$$

And:

$$G_2(X_1,X_2) = \left\{r_2\left(y_2\left(\frac{x_2+y_2}{k}\right) - y_1\left(\frac{x_1+y_1}{k}\right)\right) - \left(1-u_1(t)\right)b\left(\frac{x_2y_2}{x_2+y_2} - \frac{x_1y_1}{x_1+y_1}\right)\right\}$$

It follows:

$$|G_1(X_1,X_2)| = \left|\frac{r_1}{k}(x_2^2 + x_2y_2 - x_1^2 - x_1y_1) + \left(1-u_1(t)\right)b\left(\frac{x_2y_2(x_1+y_1) - x_1y_1(x_2+y_2)}{(x_2+y_2)(x_1+y_1)}\right)\right|$$

$$= \left|\frac{r_1}{k}(x_2^2 + x_2y_2 - x_1y_2 + x_1y_2 - x_1^2 - x_1y_1) + \left(1-u_1(t)\right)b\left(\frac{x_2y_2(x_1+y_1) - x_1y_1(x_2+y_2)}{(x_2+y_2)(x_1+y_1)}\right)\right|$$

$$\le \left|\frac{r_1}{k}\left((x_2-x_1)(x_1+x_2) + y_2(x_2-x_1) + x_1(y_2-y_1)\right)\right|$$

$$+\left(1-u_1(t)\right)b\left|\left(\frac{x_2y_2x_1 + x_2y_2y_1 - x_1y_1x_2 - x_1y_1y_2}{(x_2+y_2)(x_1+y_1)}\right)\right|$$

$$\le 4r_1\|X_2 - X_1\| + b\left|\frac{x_2y_2x_1 + x_2y_2y_1 - x_1y_1x_2 - x_1y_1y_2}{(x_2+y_2)(x_1+y_1)}\right|$$

$$\le 4r_1\|X_2 - X_1\| + b\left|\frac{x_2x_1(y_2-y_1) + y_1y_2(x_2-x_1)}{(x_2+y_2)(x_1+y_1)}\right|$$

$$\le 4r_1\|X_2 - X_1\| + 2k^2b\|X_2 - X_1\|$$

$$\le (4r_1 + 2k^2b)\|X_2 - X_1\|$$

So we will

$$|G_1(X_1,X_2)| \le (4r_1 + 2k^2b)\|X_2 - X_1\| .$$

We get

$$|G_2(X_1,X_2)| \le (4r_2 + 2k^2b)\|X_2 - X_1\|.$$

Also we get

$$\|F(X_1) - F(X_2)\| \le M_1\|X_2 - X_1\|$$

Where

$$M_1 = max(4r_1 + 2k^2b, 4r_2 + 2k^2b) .$$

We get

$$\|D(X_1) - D(X_2)\| \le M\|X_2 - X_1\|$$

Where

$$M = max(\|A\|, M_1) .$$

Thus, it follows that the function D is uniformly Lipschitz continuous. From the definition of the control $u_1(t)$, $u_2(t)$, $x(t)$ and $y(t) \ge 0$, we see that a solution of the system (3) exists [15].

Now In order to find an optimal solution pair, we consider the optimal control problem ((2.1), (2.2).)– (4). First we should find the Lagrangian and Hamiltonian for the optimal control problem ((2.1), (2.2).)–(4). Actually, the Lagrangian of the optimal problem is given by

$$L(x,y,u_1,u_2) = x - y - \left(\frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2\right).$$

We seek the maximal value of the Lagrangian. To accomplish this, we define the Hamiltonian H for the control problem:

$$H(t,X,u,\lambda) = L(x,y,u_1,u_2) + \sum_{i=1}^{2} f_i$$

Where f_i is the right side of the differential equation of the i^{th} state variable.
This is written in our case:

$$\begin{aligned} &H(x,y,u_1,u_2,\lambda_1,\lambda_2) = L(x,y,u_1,u_2) \\ &+\lambda_1\left(r_1x\left(1-\frac{x+y}{k}\right) - \left(1-u_1(t)\right)\frac{bxy}{x+y}\right) \qquad (7) \\ &+\lambda_2\left(r_2y\left(1-\frac{x+y}{k}\right) + \left(1-u_1(t)\right)\frac{bxy}{x+y} - u_2(t)y\right) . \end{aligned}$$

Where λ_1 and λ_2 are the adjoint functions to be determined suitably.

Theorem 1:
There exists an optimal control $\left(u_1^*(t), u_2^*(t)\right)$ so that

$$J(u_1^*,u_2^*) = \max_{(u_1,u_2)\in U} J(u_1,u_2)$$

subject to the control system (2.1), (2.2).
<u>Proof</u>:
To use an existence result in [16], we must check the following properties.

1) The set U of controls and corresponding state variables is nonempty.
2) The control set U is convex and closed.
3) The right-hand side of the state system is bounded by a linear function in the state and control variables.

4) The integrand of the objective functional is concave on U .
5) There exist constants $c_1, c_2 > 0$ and $\rho > 1$ so that the integrand $L(x, y, u_1, u_2)$ of the objective functional satisfies:

$$L(x, y, u_1, u_2) \le c_1 - c_2 \left(|u_1|^2 + |u_1|^2\right)^{\frac{\rho}{2}}$$

An existence result by Lukes [17] is used to give the existence of system (2.1), (2.2).with bounded coefficients, which gives condition 1. The control set is convex and closed by definition. Since the state system is bilinear in u_1 and u_2, the right side of (2.1), (2.2).satisfies condition (3), using the boundedness of the solution. The integrand in the objective functional (4) is concave on U. In addition, we can easily see that there exist a constant $\rho > 1$ and positive numbers c_1 and $c_2 > 0$ satisfying :

$$L(x, y, u_1, u_2) \le c_1 - c_2 \left(|u_1|^2 + |u_1|^2\right)^{\frac{\rho}{2}}.$$

3.2 Characterization of the optimal control

In the previous section we showed the existence of the optimal control pair, which maximizes the functional (3) subject to the system (2.1), (2.2).In order to derive the necessary conditions for this optimal control pair, we apply Pontryagin's maximum principle to the Hamiltonian H (7).

If $(x^*(t), u^*(t))$ is an optimal solution of an optimal control problem, then there exists a non-trivial vector function $\lambda(t) = (\lambda_1(t), \lambda_2(t), \ldots, \lambda_n(t))$ satisfying the following equalities:

$$x'(t) = \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial \lambda},$$
$$\lambda'(t) = \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x},$$
$$0 = \frac{\partial H(t, x^*(t), u^*(t), \lambda(t))}{\partial x},$$

Now, we apply the necessary conditions to the Hamiltonian H . (7)

Theorem 2:

Let $x^*(t)$ and $y^*(t)$ be optimal state solutions with associated optimal control variable $u^*(t) = (u_1^*(t), u_2^*(t))$ for the optimal control problem (2.1), (2.2).and (4). Then, there exist adjoint variables $\lambda_1(t)$ and $\lambda_2(t)$ that satisfy the equations

$$\lambda'_1 = -1 + \lambda_1 \left\{ r_1\left(-1 + \frac{2x^* + y^*}{k}\right) + (1 - u_1(t)) b \left(\frac{y^*}{x^* + y^*}\right)^2 \right\}$$
$$+ \lambda_2 \left\{ \frac{r_2 y^*}{k} - (1 - u_1(t)) b \left(\frac{y^*}{x^* + y^*}\right)^2 \right\}$$
$$\lambda'_2 = 1 + \lambda_1 \left\{ \frac{r_1 x^*}{k} + (1 - u_1(t)) b \left(\frac{x^*}{x^* + y^*}\right)^2 \right\}$$
$$+ \lambda_2 \left\{ r_2\left(-1 + \frac{x^* + 2y^*}{k}\right) - (1 - u_1(t)) b \left(\frac{x^*}{x^* + y^*}\right)^2 + u_2(t) \right\}$$

With transversality conditions:

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

Furthermore, the optimal control $u^*(t) = (u_1^*(t), u_2^*(t))$ is given by

$$u^*_1 = min\left(1, max\left(0, \frac{(\lambda_1 - \lambda_2)}{A_1} \frac{b x^* y^*}{x^* + y^*}\right)\right)$$
$$u^*_2 = min\left(1, max\left(0, \frac{-\lambda_2 y^*}{A_2}\right)\right)$$

<u>Proof:</u>

We use the Hamiltonian (7) in order to determine the adjoint equations and the transversality conditions. By putting $x(t) = x^*(t)$ and $y(t) = y^*(t)$ differentiating the Hamiltonian with respect to x and y we obtain

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial x} = -1$$
$$+ \lambda_1 \left\{ r_1\left(-1 + \frac{2x + y}{k}\right) + (1 - u_1(t)) b \left(\frac{y}{x + y}\right)^2 \right\}$$
$$+ \lambda_2 \left\{ \frac{r_2 y}{k} - (1 - u_1(t)) b \left(\frac{y}{x + y}\right)^2 \right\}.$$
$$\frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial y} = 1 + \lambda_1 \left\{ \frac{r_1 x}{k} + (1 - u_1(t)) b \left(\frac{x}{x + y}\right)^2 \right\}$$
$$+ \lambda_2 \left\{ r_2\left(-1 + \frac{x + 2y}{k}\right) - (1 - u_1(t)) b \left(\frac{x}{x + y}\right)^2 + u_2(t) \right\}.$$

With transversality conditions:

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

And by using the optimality conditions we find

$$\frac{\partial H}{\partial u_1} = -A_1 u_1 + \lambda_1 \frac{bxy}{x + y} - \lambda_2 \frac{bxy}{x + y}.$$
$$\frac{\partial H}{\partial u_2} = -A_2 u_2 - \lambda_2 y .$$

By the bounds in U of the controls, it is easy to obtain $u_1^*$and u_1^*in the form:

$$u^*_1 = min\left(1, max\left(0, \frac{(\lambda_1 - \lambda_2)}{A_1} \frac{b x^* y^*}{x^* + y^*}\right)\right).$$
$$u^*_2 = min\left(1, max\left(0, \frac{-\lambda_2 y^*}{A_2}\right)\right).$$

4. Numerical simulations

The optimality system consists of the state system coupled with the adjoint system with the initial and transversality conditions together with the characterization of the optimal control. Utilizing the characterization of the optimal control, we have the following optimality system.

$$\frac{dx^*}{dt} = r_1 x^* \left(1 - \frac{x^* + y^*}{k}\right) - (1 - u_1^*(t)) \frac{b x^* y^*}{x^* + y^*}$$
$$\frac{dy}{dt} = r_2 y^* \left(1 - \frac{x^* + y^*}{k}\right) + (1 - u_1^*(t)) \frac{b x^* y^*}{x^* + y^*} - u_2^*(t) y^*$$

$$\lambda'_1 = -1 + \lambda_1 \left\{ r_1 \left(-1 + \frac{2x^* + y^*}{k} \right) + (1 - u_1^*(t)) b \left(\frac{y^*}{x^* + y^*} \right)^2 \right\}$$
$$+ \lambda_2 \left\{ \frac{r_2 y^*}{k} - (1 - u_1(t)) b \left(\frac{y^*}{x^* + y^*} \right)^2 \right\}$$

$$\lambda'_2 = 1 + \lambda_1 \left\{ \frac{r_1 x^*}{k} + (1 - u_1^*(t)) b \left(\frac{x^*}{x^* + y^*} \right)^2 \right\}$$
$$+ \lambda_2 \left\{ r_2 \left(-1 + \frac{x^* + 2y^*}{k} \right) - (1 - u_1^*(t)) b \left(\frac{x^*}{x^* + y^*} \right)^2 + u_2^*(t) \right\}$$

With $u^*_1 = min\left(1, max\left(0, \frac{(\lambda_1 - \lambda_2)}{A_1} \frac{b x^* y^*}{x^* + y^*}\right)\right)$

$$u^*_2 = min\left(1, max\left(0, \frac{-\lambda_2 y^*}{A_2}\right)\right)$$

$\lambda_1(t_f) = 0$, $\lambda_2(t_f) = 0$, $x(0) = x_0$ and $y(0) = y_0$.

In this formulation, there are initial conditions for the state variables and terminal conditions for the adjoints. That is, the optimality system is a two-point boundary value problem, with separated boundary conditions at times $t=0$ and t_f . An efficient method to solve two-point BVPs numerically is collocation. A convenient collocation code is the solver BVP4c Implemented under MATLAB, which can be used to solve nonlinear two-point BVPs. It is a powerful method to solve the two-point BVP resulting from optimality conditions.
The simulations are carried out using the following values taken from [18]:

$r_1=40$, $r_2=2$, k=100, and b=0.02

The figure 1 shows that, in case without control, the number of uninfected cells decreases sharply. However, it starts to increase since the first days of treatment.

In figure 2, the number of infected cells grows significantly in case without control. While in case with control we observe a steady decrease.

Figures 3-4-5 give the optimal control pair (u_1, u_2) and the optimal value of cost. We observe that the curves drop off steadily which is because of the constant and steady eradication of the infection.

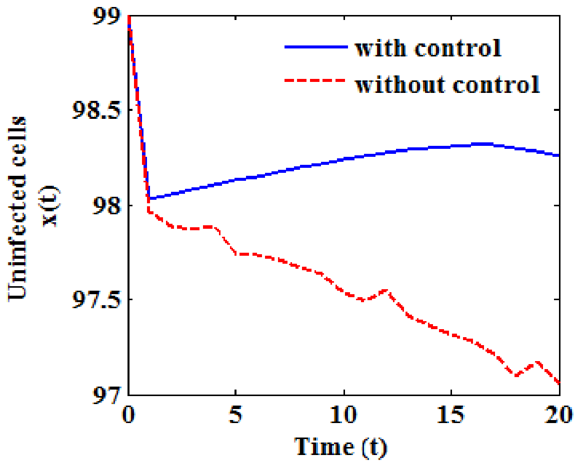

Fig. 1 The function *x* with and without controls

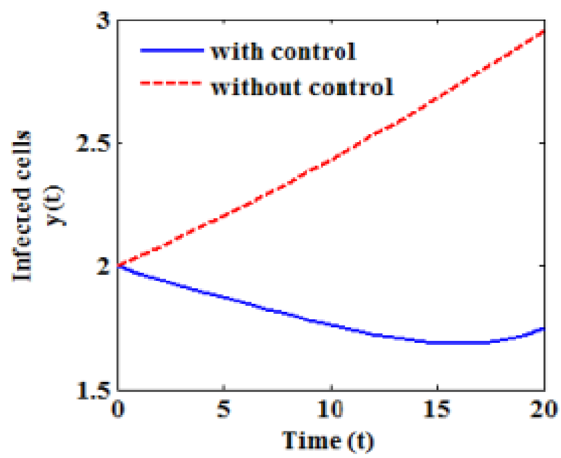

Fig. 2 The function *y* with and without controls

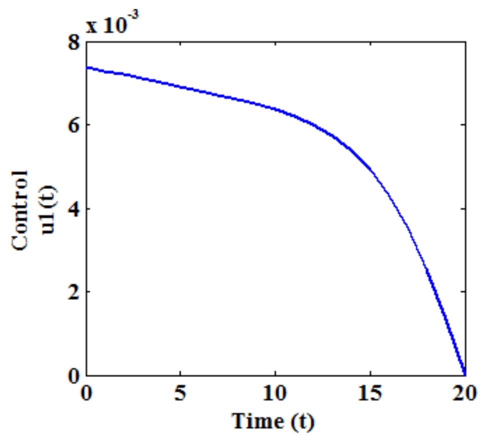

Fig. 3 The optimal control u_1

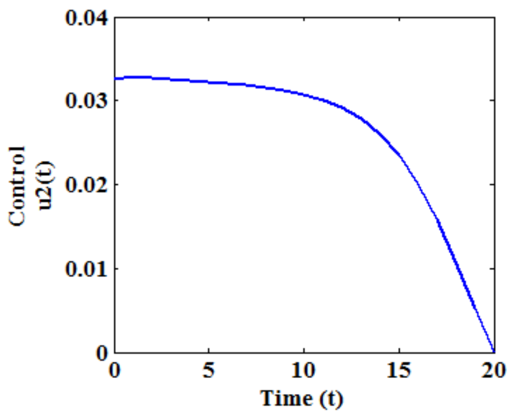

Fig. 4 The optimal control u_2

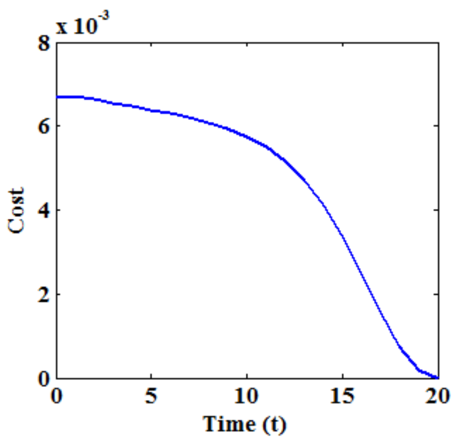

Fig. 5 The optimal value of the cost

4. Conclusion

In this work, we investigate an efficient optimal control strategy of cancer therapy, we use a controlled model of tumor dynamics that includes two controls representing drug therapy and oncolytic virotherapy; our goal is to maximize the number of susceptible cells and to minimize the number of infected cells. The optimal control theory is used to prove the existence and characterize of optimal control pair; the obtained results confirm the performance of our strategy.

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