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Optimal control of a basic model of oncolytic virotherapy

Abdullah Abu-Rqayiq[a,*], Haneen Alayed[b], Mohammad Zannon[c]

[a]Department of Mathematics & Statistics, Texas A&M University, Corpus Christi, Texas 78412, U.S.A.

[b]Department of Mathematical Sciences, New Mexico State University, Las Cruces 88003, U.S.A.

[c]Department of Mathematics & Statistics, Tafilah Technical University, At-Tafilah, Jordan.

Abstract

This paper applies an optimal control approach to study the dynamics of a basic Oncolytic Virotherapy model. This study applies mathematical modeling based on an established basic oncolytic virotherapy model for tumor growth. Choosing an appropriate control strategy is essential to reduce the cost of the therapy. By applying optimal control theory, we seek to minimize the cost of virotherapy and reduce the load of tumor cells. The existence of optimal control is proved. State solution given an optimal strategy and the optimal control is determined. Numerical simulation is carried out to visualize and support our results.

Keywords: Oncolytic virotherapy, optimal control, tumor cells, hamiltonian.

2020 MSC: 92C50, 93A30, 37N35, 34K28.

1. Introduction

Oncolytic virotherapy is a cancerous treatment using a native or programmed virus that has the potential to targeting and killing cancerous cells. This kind of treatment has a long history of research and clinical attempts. The results obtained so far are promising therapeutic. The treatment, at least theoretically, causes tumor cell lysis after oncolytic virus being replicated in the tumor cell. As a result, three main changes can occur; a local inflammation can occur causing a destruction of tumor micro invironment, release of virus progeny causing infecting more nearby tumor cells, and release of tumor antigens causing systematic anti-tumor immune response.

One of the main advantage of applying the oncolytic virotherapy is that it can selectively damage cancerous tissues leaving normal cells unharmed. In addition, oncolytic viruses can mediate the killing of the normal cells by indirect mechanisms such as the destruction of tumor blood vessels, the amplification of specific anticancer immune responses or through the specific activities of transgene-encoded proteins expressed from engineered viruses.

In recent years, several models were proposed to study the dynamics of oncolytic viruses, the main goal was to capture the behavior of the solutions and to study the role of some components of the

*Corresponding author

Email address: abdullah.aburqayiq@tamucc.edu (Abdullah Abu-Rqayiq)

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treatment, and the ultimate goal was to understand the cancer virus dynamics and find better treatment strategies. For example, Wu et al. [12] and Wein et al. [9] proposed and analyzed some partial differential equations models to study some aspects of cancer virotherapy. For ordinary differential equations models, Wodarz in [11] and [10], Komarova and Wodarz [5], Novozhilov et al. [7], Bajzer et al. [2], and Tian [8] studied ODE models. Abu-Rqayiq and Zannon [1] studied a fractional order version of Tian's proposed model. Tian's model was introduced to describe the development of a growing tumor and an oncolytic virus population. That basic model is given by the following system of ordinary differential equations

$$\begin{aligned} \frac{dx}{dt} &= \lambda x\left(1-\frac{x+y}{K}\right)-\beta x v,\\ \frac{dy}{dt} &= \beta x v-\delta y,\\ \frac{dv}{dt} &= b\delta y-\beta x v-\gamma v, \end{aligned} \tag{1.1}$$

where variables x, y and v stand for the population of uninfected cells, infected tumor cells, and oncolytic viruses (free viruses), respectively. The coefficient β represents the infection of the virus. The tumor growth is modeled by logistic growth, and K is the maximal tumor size (the carrying capacity). λ is the per capita tumor growth rate. δ means the lysis rate of the infected tumor cells. b represents the burst size of new viruses coming out from the lysis of an infected tumor cell. γ represents the death rate of the virus. See Table 1 for parameters' description. [12]

In [8], it was shown that when the threshold $b < 1+\frac{\gamma}{K\beta}$, the equilibrium solution $(K,0,0)$ is globally asymptotically stable, which indicates that the virotherapy does not have any affect, and unstable for $b > 1+\frac{\gamma}{K\beta}$.

In this paper we develop a model for the controlled infected brain tumor cells. Optimal control theory is applied to the cost functional and is supposed to achieve the ultimate goal of optimizing that functional and find a best strategy for minimizing the cost of the virotherapy. The goal of this paper is to model, analyze, and explore optimal ways that can minimize a tumor and the cost of the virotherapy.

This paper is organized as follows: Section 2 describes the controlled Oncolytic Virotherapy model with some background from the Control Theory. Our objective functional and the existence of the optimal control is also introduced and proved in this section. In Section 3, we carried out a numerical study of our controlled model followed by a discussion of our results.

2. The model with control

2.1. Introduction

Optimal control theory is a branch of the applied mathematics that deals with finding the best possible control that can take a dynamical system from one state to another.

The Hamiltonian of optimal control theory was developed by the Russian mathematician Lev Pontryagin as a part of his investigation into the maximum principle. Pontryagin proved that the necessary condition for solving certain optimal control problems is that the control should be chosen in such a way that minimizes the Hamiltonian.

A control function $u(t)$ is to be chosen so that it minimizes the objective function

$$J(u(t)) = \Psi(x(T)) + \int_0^T L(x(t),u(t),T(t))dt,$$

where $x(t)$ is the system state which evolves according to the state equation

$$\dot{x} = f(x(t),u(t),t), \quad x(0)=x_0, \quad t\in[0,T],$$

and the control $u(t)$ must satisfy the constraint $a \leqslant u(t) \leqslant b$. The purpose of introducing controls in the model is to find the optimal level of the intervention strategy to reduce the spreads of the disease and the cost of implementation of the control.

The Hamiltonan is defined as

$$H(x, \Psi, u, t) = \Psi^T(t) f(x, u, t) + L(x, u, t),$$

where $\Psi(t)$ is a vector of costate variables of the same dimension as the state variable $x(t)$ such that

$$\dot{\Psi}(t) = -\frac{\partial H}{\partial x}.$$

The basic steps to set up and to solve an optimal control problem should include [10]

- Modeling the situation with a system of ODEs.
- Choosing format and bounds of Controls.
- Designing an appropriate objective functional.
- Proving existence(and uniqueness) of the optimal control.
- Deriving necessary conditions for the optimal control.
- Characterizing the optimal control.
- Computing the optimal control numerically.

2.2. The model

Our goal is to formulate an optimal control problem to find the optimal oncolytic virotherapy cost strategy that (maximizes) the fraction of the normal cells with least infected cells and least cost associated with the control. We formulate model (1.1) by introducing a control function $u(t)$ which represents the efforts on damaging the tumor cells. Hence, $(1-u(t))$ represents the growth rate of the infected cells. The control u is adjusted in the dynamical system to achieve our goals. Therefore, the model under consideration is given by

$$\begin{aligned} \frac{dx}{dt} &= (1-u(t))\lambda x\left(1-\frac{x+y}{K}\right) - \beta x v, \\ \frac{dy}{dt} &= \beta x v - (1-u(t))\delta y, \\ \frac{dv}{dt} &= b\delta(1-u(t))y - \beta x v - \gamma v. \end{aligned} \tag{2.1}$$

The control $u(.)$ is bounded between 0 and u_{max} with $u_{max} < 1$. We assume that u_{max} is never equal to 1. In this study, the control is bounded as $0 \leqslant u(t) \leqslant 0.9$. This makes the model more realistic from a medical view point.

Table 1: Pameters' Description.

Parameter	Description	Value	Dimentions
λ	Tumor growth rate	2×10^{-2}	$1/h$
δ	Death rate of infected tumor cells	$1/18$	$1/h$
β	Infection rate of the virus	$7/10 \times 10^{-9}$	$mm^3h/$ virusl
k	Immune killing rate of virus	10^{-8}	$mm^3h/$ immune cell
b	Burst size of free virus	50	viruses/cell
γ	Clearance rate of virus	2.5×10^{-2}	$1/h$

We find the optimal value u^* of the control u along the time interval $[0, T]$ such that the associated state trajectories x^*, y^*, and v^* are solutions of the system in model (2.1) with the following initial conditions

$$x(0) \geqslant 0, \quad y(0) \geqslant 0, \quad v(0),$$

and $u^*(.)$ maximizes the objective functional given by

$$J(u(t)) = \int_0^T y(t) + \frac{1}{2} B u^2 dt, \tag{2.2}$$

where B is a measure of the relative cost of interventions associated to the control $u(t)$. We want to minimize the number infected tumor cells which can be established by choosing an appropriate control strategy that can result in lowering the number of free viruses as well, which leads to a lower cost of the treatment. The set of admissible control functions is [6]

$$\Omega = \{u(\cdot) \in L^\infty(0, t_f) : 0 \leqslant u(t) \leqslant u_{max}, \ \forall t \in [0, T]\}.$$

In order to make computations a bit easier, we non-dimensionalize the system by rescaling the parameters and variables. Setting $\tau = \delta t$ $x = Kx^*, y = Ky^*, v = Kv^*, r = \frac{\lambda}{\delta}$, $a = \frac{\beta K}{\delta}$, and $c = \frac{\gamma}{\delta}$ and dropping the stars over variables

$$\begin{aligned} \frac{dx}{dt} &= (1-u)rx(1-x-y) - axv, \\ \frac{dy}{dt} &= axv - (1-u)y, \\ \frac{dv}{dt} &= b(1-u)y - axv - cv, \end{aligned} \tag{2.3}$$

with the initial conditions $x(0) = x_0$, $y(0) = y_0$, and $v(0) = v_0$.

2.3. *Pontryagin's principle*

Pontryagin's maximum principle for fractional optimal control can be used to solve the problem. The Hamiltonian associated with our optimal control problem is

$$H = y(t) + \tfrac{B}{2}u^2 + \Psi_1((1-u)rx(1-x-y) - axv) + \Psi_2(axv - (1-u)y) + \Psi_3(b(1-u)y - axv - cv).$$

The adjoint system uphold that the co-state variables $\Psi_i(t)$, $i = 1, 2, 3$ verify the following system

$$\begin{aligned} \dot{\Psi}_1 &= -\Psi_1(1-u)(r - 2rx - ry) + av(\Psi_1 - \Psi_2 + \Psi_3), \\ \dot{\Psi}_2 &= -1 + rx(1-u)\Psi_1 + (1-u)(\Psi_2 - b\Psi_3), \\ \dot{\Psi}_3 &= ax(\Psi_1 - \Psi_2 + \Psi_3) + c\Psi_3. \end{aligned} \tag{2.4}$$

The condition of that establishes the optimal control is given by

$$u(t) = \min\left\{\max\left\{0, \frac{rx(1-x-y)\Psi_1 - y(\Psi_2 + b\Psi_3)}{B}\right\}, u_{max}\right\},$$

where B is the weight factor associated to the control $u(t)$. The optimal controls $u(.)$ maximize $\mathcal{H}$ as a function of $u(.)$ according to the Pontryagin's Maximum Principle. The existence of the optimal control $u(.)$ comes from the convexity of the integrand of the minimizer functional with respect to controls and regularity of the system.

According to The Pontryagin's Maximum Principle, if $u(.) \in \Omega$ is optimal for the problem under consideration, the minimizer with the initial conditions and fixed final time T, then there exists a nontrivial absolutely continuous mapping $\Psi : [0, 1] \longrightarrow \mathbb{R}^3$.

The minimization condition

$$H(x^*(t), y^*(t), v^*(t)) = \min_{0 \leqslant u_1, u_2 \leqslant 1} H(x^*(t), y^*(t), v^*(t), \Psi_i, u_1(t), u_2(t)),$$

holds almost everywhere on $[0, T]$. Moreover, the transversality conditions $\Psi_i(T) = 0,\ i = 1, 2, 3$ hold.

Now we state a main result of our work.

Theorem 2.1. *Problem* (2) *with fixed initial conditions* $x(0), y(0), v(0)$ *and a fixed final time* T*, admits a unique optimal solution* $(x^*(\cdot), y^*(\cdot), v^*(\cdot))$ *associated to an optimal control* (u^*) *on* $[0, T]$*. Moreover, there exists adjoint functions* Ψ_1^*, Ψ_1^**, and* Ψ_3^**, such that with transversality conditions* $\Psi_i^*(T) = 0$*, i=1, 2, 3. Furthermore,*

$$u^*(t) = \frac{rx(1 - x - y)\Psi_1 - y(\Psi_2 + b\Psi_3)}{B}. \tag{2.5}$$

Proof. By [9, Corollary 3.1], the existence of the optimal control exists due to the convexity of the integrand of (2.3) with respect to u, boundeness of the state solutions on the finite time interval $[0, T]$, and the Lipschitz property of the state system with respect to the state variables. Applying the Pontryagin's Maximum Principle, we obtain

$$\begin{aligned}
\dot{\Psi_1} &= -\frac{\partial H}{\partial x}, \Psi_1(T) = 0, \\
\dot{\Psi_2} &= -\frac{\partial H}{\partial y}, \Psi_2(T) = 0, \\
\dot{\Psi_3} &= -\frac{\partial H}{\partial v}, \Psi_3(T) = 0.
\end{aligned}$$

These are evaluated at $u^*$and the corresponding states, which implies the adjoint system (2.4). Now we obtain the characterization u^* by considering the optimality condition $\frac{\partial H}{\partial u} = 0$ and solving for u^*. This gives us the characterization in (2.5). □

3. Numerical simulations and discussion

3.1. Numerical simulations

Numerical simulations leading to the approximation of the optimal control are carried out by implementing a forward-backward fourth-order Runge-Kutta method. The state and adjoint differential equations together with the (2.5) control characterization are solved numerically to illustrate our control results.

We implement the forward fourth-order Runge-Kutta method for state system and the backward one for the adjoint system. We define the state, adjoint, and control variables at the mesh points. An initial guess is given for the control u which is then updated continuously until the objective functional satisfies the conditions. Given an initial guess for the control, to compute the optimal state values, the program solves (2.3) with initial its initial conditions forward in time using a fourth-order Runge-Kutta method. Resulting state values are placed in adjoint system (2.4). These adjoint equations with given final conditions are then solved backwards in time. Again, a fourth order Runge-Kutta method is employed. Both state and adjoint values are used to update the control using the characterization (2.5) and the entire process repeats itself.

For this purpose, we use the following parameter values: $r = 0.36$, $a = 0.11$, and $c = 0.44$. We also pick the weight factor $B = 500$.

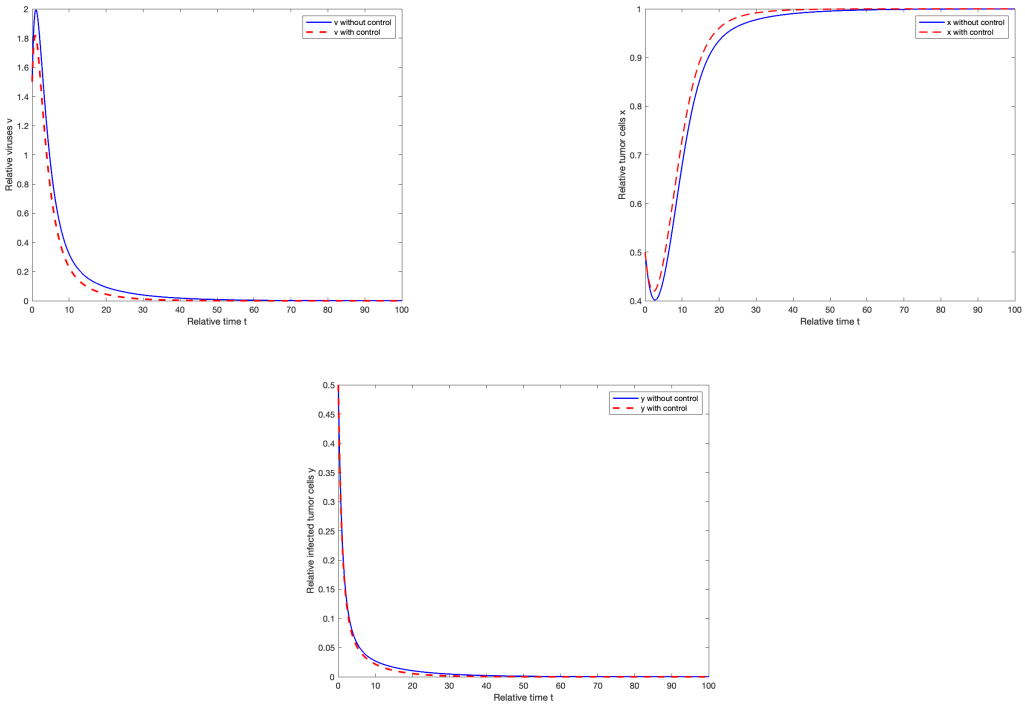

Figure 1: Optimal state variables for the controlled and the uncontrolled systems subject to the initial values $x = 0.5$, $y = 0.5$, and $\nu = 1.5$, $b = 4$, and the admissible control set versus trajectories without control measures.

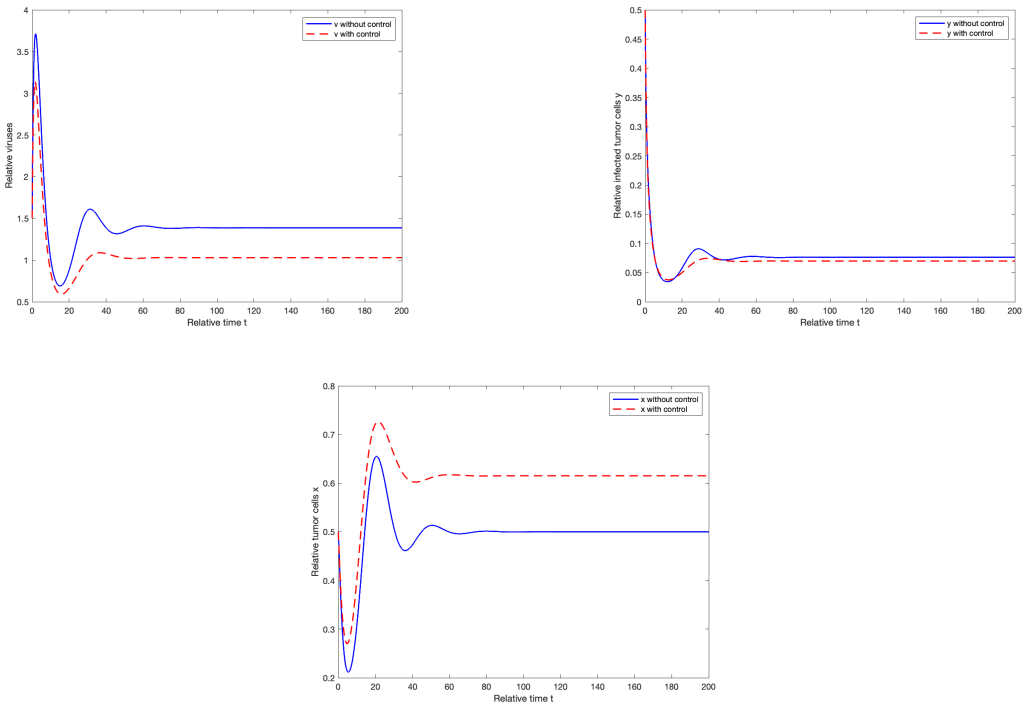

Figure 2: Optimal state variables for the controlled and the uncontrolled systems subject to the initial values $x = 0.5$, $y = 0.5$, and $\nu = 1.5$, $b = 9$, and the admissible control set versus trajectories without control measures.

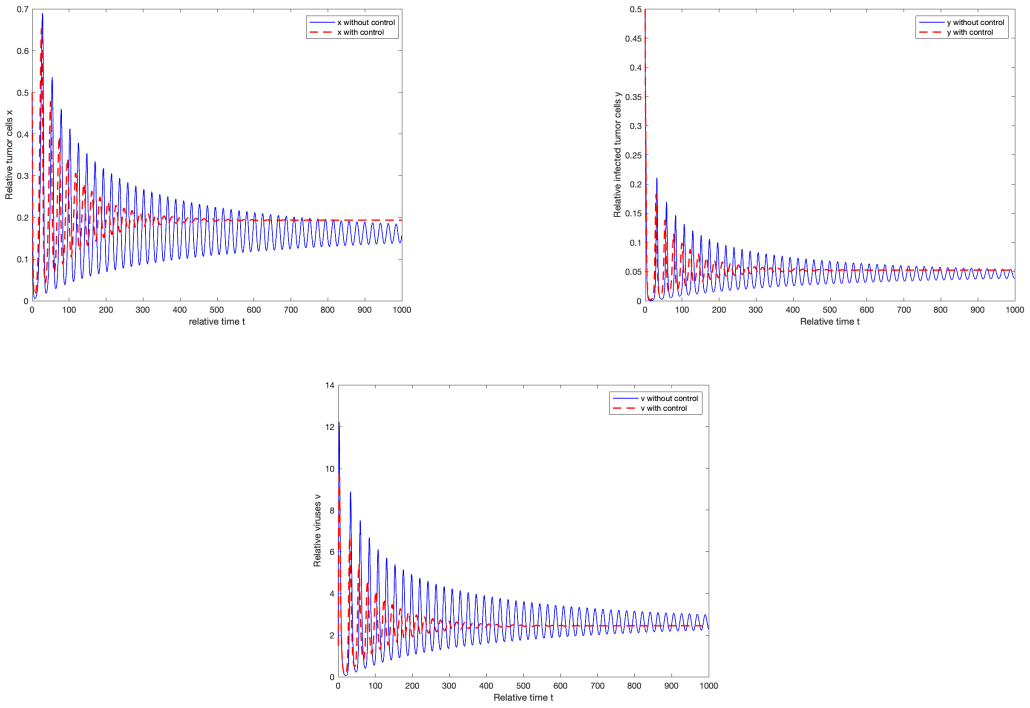

Figure 3: Damped oscillators appear for the controlled and the uncontrolled systems subject to the initial values $x = 0.5$, $y = 0.5$, and $v = 1.5$, $b = 26$, and the admissible control set versus trajectories without control measures.

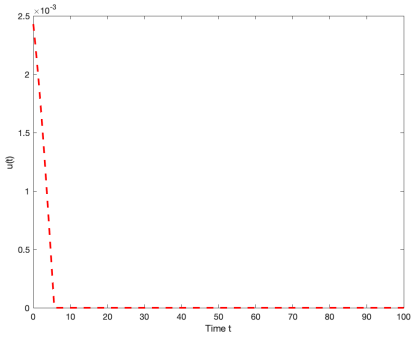

Figure 4: The optimal ontrol u^* for the Oncolytic virotherapy model subject to the initial values $x = 0.5$, $y = 0.5$, and $v = 1.5$, $b = 9$, and the admissible control.

3.2. Discussion and conclusion

In this paper, we studied an optimal control problem of a basic model of oncolytic virotherapy. The model was first introduced to present a better understanding of oncolytic virotherapy dynamics in the presence of burst size. Analysis of this model suggests that the tumor load can drop to a undetectable level either during the oscillation or when the burst size is large enough [8]. Controlled variables were introduced into the originally uncontrolled model. We considered a L^1 type objective functional to minimize the tumor cells and the therapy viruses which, in turns, minimizes the cost of the therapy. Through this study, we showed that an optimal control exists for this problem as stated in Theorem 2.1 and proved.

We estimated the optimality controlled system to determine the optimal control situation and predict the evolution of the tumors cells relative to specific choices of virus bust size in time scale of 100 days for burst size $b = 4$ as shown in Figure 1, 200 days for burst size $b = 9$ as shown in Figure 2, and 1000 days for the oscillation to capture that behavior as shown in Figure 3. Figure 1 shows that the existence

of the control can improve the growth of the normal cells population until approximately 60 days of the therapy and it will be stabilized after then. The number of infected cells will be dropped significantly after approximately the fifth day of the treatment until they are terminated in the 50th day of the treatment. Figure 2 shows more power of the existence of the control u in the system, where the number of the uninfected cells increases significantly, the size of the infected cells becomes less, and the number of free viruses is significantly less which results in minimizing the cost of the therapy. In figure 3 we notice the periodic behavior of the solution for both of the uncontrolled and controlled systems. The numerical simulations displayed in the paper validate the existence of optimality of the control variables and show that the virotherapy reduces the tumor load within days of the therapy and reduces number of viruses used in the therapy as well. As a result, the cost of the therapy is minimized.

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