Filomat 34:15 (2020), 5195–5206
https://doi.org/10.2298/FIL2015195S

Published by Faculty of Sciences and Mathematics,
University of Niš, Serbia
Available at: http://www.pmf.ni.ac.rs/filomat

Mathematical Model of Optimal Chemotherapy and Oncolytic Virotherapy

Elham Shamsara[a], Habibollah Esmaily[b], Abbas Bahrampour[c]

[a] *Social Determinants of Health Research Center, Mashhad University of Medical Sciences, 91778-99191 Mashhad, IRAN.*
School of Mathematics, Institute for Research in Fundamental Sciences (IPM), P.O. Box: 19395-5746, Tehran, IRAN
[b] *Corresponding author: Social Determinants of Health Research Center, Mashhad University of Medical Sciences, 91778-99191 Mashhad, IRAN.*
[c] *Modelling in Health Research Centre, Institute for Futures Studies in Health, Department of Biostatistics and Epidemiology, Faculty of Health, Kerman University of Medical Sciences, Kerman, IRAN.*
Centre of Applied Health Economics, School of Medicine, Griffith University, Nathan Campus, Brisbane, QLD, AUSTRALIA.

Abstract. In this paper, a mathematical model of fighting against cancer tumor growth by a combination of oncolytic virotherapy and chemotherapy is introduced. In this model, we considered two time delays τ_1 and τ_2. The time delay τ_1 shows the lag of transmission of infection from oncolytic virus to tumor cells. A lot of kind of cancers, symptoms are diagnosed at a late stage and as a consequence the chemotherapy approach start with a lag . Thus, we take this delay into account by presenting the time delay τ_2 in the control variable. Therefore, in this study, delay parameters are used for both state and control variables. The Pontryagin minimum principle with delays in both state and control is used to obtain an optimal model for the treatment to minimize the side effect as well as the cost of the treatment.

1. Introduction

A healthy human body is composed of more than ten million cells. An uncontrolled growth of the cells within the body of the patient is called cancer [1]. Healthy cells acquire a number of mutations that allow them to escape regulatory mechanisms. In many cancers, a cell has to accumulate several mutations in order to escape homeostasis, a process called multistep carcinogenesis [2]. When mutations occur, the normal control systems of cells can be damaged or lost. Most mutations that result in polyp formation only give the cell a small proliferation advantage and these polyps are considered benign. However, approximately %1 of these polyps will become cancerous, which will have unregulated proliferation. The cells from these cancerous polyps can break off into the bloodstream, and then acquire the ability to travel to a different site. There, they will start growing in a different organ to begin proliferating again. When this happens, the tumor is said to have metastasized, which can no longer be removed by surgery alone [3].
The main approaches of cancer treatments are to remove cancerous cells completely from the body of the patient. For types of cancer that are still largely not curable, the purpose is to improve the quality of life

2010 *Mathematics Subject Classification*. 49J15; 33E30
Keywords. Oncolytic virus, Cancer, Pontryagin minimum principle with delay, Optimal control
Received: 01 December 2018; Accepted: 22 March 2019
Communicated by Shuai Li, Predrag Stanimirović
Email addresses: elham.shamsara@mail.um.ac.ir (Elham Shamsara), EsmailyH@mums.ac.ir (Habibollah Esmaily), a_bahrampour@kmu.ac.ir, a.bahrampour@griffith.edu.au (Abbas Bahrampour)

and survival probabilities by avoiding life-threatening toxicity. In case of a solid tumor, if possible, the first choice of treatment is removal via surgery. Besides surgery, the main standard treatment approaches to destroy tumors are by radiotherapy and chemotherapy. In radiotherapy, it is attempted to destroy the tumor with directed radiation beams. But, the most common treatment approach, and in spite of its many negative side effects, still is chemotherapy. Especially, if cancer has already metastasized, chemotherapy often is used [4]. The disadvantage of chemotherapy is that drugs cannot recognize the difference between cancer cells and normal cells. Chemotherapy kills cells that are actively growing and dividing into new cells. Of course, cancer cells can grow and divide much more than normal cells, so they are more a target to be killed by the treatment. In addition, cancer cells are not as good at repairing themselves as normal cells. Normal cells have this ability to repair any damage caused by chemotherapy. Furthermore, in treatment, immunotherapies are also playing an important role in the duration of therapy. Through immunotherapy, the body's own natural ability can combat cancer by enhancing the effectiveness of the immune system. The importance of the immune system in fighting cancer has been verified by clinical experiments [5].
Another targeted treatment approach that is less established and is at an earlier stage of development is the use of oncolytic virotherapy. The first oncolytic virus was licensed by FDA (the food and drug administration of the United States) in October 2015 to Amgen (Thousand Oaks, CA, USA) for the treatment of advanced melanoma [6]. Oncolytic viruses specifically infect cancer cells and replicate in them, spreading from one tumor cell to the other. It is important to notice that, they do not infect healthy cells [2]. The combination of oncolytic virotherapy with existing radiotherapy and chemotherapy has the advantage to augment the antineoplastic activity [7, 8]. Mathematical and computational modeling has increasingly become a tool to study the dynamics of cancers. For example in [9, 10] the effect of obesity on the growth of cancer tumors was investigated. A 5-dimensional mathematical model for the effect of obesity on the tumor growth and consequently, for the optimal control of chemotherapy schedules has been discussed in [9]. komarova et al in [2] presented a 3-dimensional model which is studied the dynamics between the tumor cells, the oncolytic virus, and virus-specific CTL.

1.1. The optimal control model

In this paper, we considered a mathematical model of the interactions between tumor cells, immune cell populations, oncolytic virus, obesity, and chemotherapy. In this study, we coupled models in [2, 9]. Our extended model is a 7-dimensional model with control and delays. The newly introduced model has the advantage that not only considered the effect of obesity on the tumor growth but also a combination of chemotherapy and oncolytic virotherapy is investigated for therapy, which is a new approch in treatment [11–15]. Furthermore, time delay parameter τ_1 in state and time delay parameter τ_2 in control are added. For analyzing the treatment strategy we used the Pontryagin minimum principle with delays in both state and control. Our aim is to minimize the cost and side effects associated with the chemotherapy drugs and to minimize the tumor cells while maximizing the healthy cells.
The extended model with delays and control is as follows

$$\begin{cases} \dot{T}(t) = r_1 T(t)(1 - \frac{T(t)+V(t)}{w}) - \beta T(t)V(t) - p_T T(t) I_T(t) + k_4 T(t) F(t) - a_1(1 - e^{-u(t)})T(t), \\ \dot{V}(t) = \beta T(t-\tau_1)V(t-\tau_1) + r_2 V(t)(1 - \frac{T(t)+V(t)}{w}) - p_V V(t) I_V(t) - a_2(1 - e^{-u(t)})V(t), \\ \dot{N}(t) = r_3 N(t)(1 - b_1 N(t)) - k_1 T(t) N(t) - a_3(1 - e^{-u(t)})N(t), \\ \dot{F}(t) = r_4 F(t)(1 - b_2 F(t)) - k_3 F(t) T(t) - a_4(1 - e^{-u(t)})F(t), \\ \dot{I_V}(t) = s_1 + c_V V(t) I_V(t) - d_1 I_V(t) - a_5(1 - e^{-u(t)})I_V(t), \\ \dot{I_T}(t) = s_2 + c_T V(t) I_T(t)(V(t) + T(t)) - d_2 I_T(t) - a_6(1 - e^{-u(t)})I_T(t), \\ \dot{u}(t) = -d_3 u(t) + m(t - \tau_2). \end{cases} \tag{1.1}$$

Where, $T(t)$ denotes the number of the tumor cells at time t, $V(t)$ the oncolytic viruses at time t, $N(t)$ the normal cells at time t, $F(t)$ the obesity stored in the body at time t, $I_V(t)$ the virus-specific CTL at time t, $I_T(t)$ tumor specific CTL at time t and $u(t)$ is the biomass of chemotherapy drug in mg at time t. The drug is introduced to a patient at a variable rate $m(t)$ and is removed from the patient body through liver and kidney at a rate $d_3u(t)$. The constants r_1, r_2, r_3 and r_4 are the growth rates for the tumor cells, oncolytic viruses, the normal cells and the obesity, respectively. The constants b_1 and b_2 are the inverses of the carrying capacity of the populations of N and F, respectively. The coefficients of the competition terms among the different populations are the parameters k_1, k_3 and k_4. The parameters a_1, a_2, a_3, a_4, a_5 and a_6 are considered for the kill effectiveness of the drug on T, V, N, F, I_V and I_T populations, respectively. The tumor-specific CTL expand in response to tumor antigen, which is displayed both on uninfected and infected cells $(T + V)$, at a rate c_T. The tumor-specific CTL kill both uninfected and infected tumor cells at a rate p_T. The strength of the virus specific CTL response, or CTL responsiveness, is denoted by c_V. CTLs, I_V and I_T die at rates d_1 and d_2 respectively. p_V stands for the killing rate of the infected tumor cells by the specific virus CTL. The maximum size of the tumor is allowed to occupy by its carrying capacity w. The virus spreads to tumor cells at a rate β. s_1 and s_2 are the basal responses of specific CTLs. According to parameter τ_1, tumor cells become productive in a time period τ_1 after they are infected, provided they survive this interval. In fact, τ_1 is the viral replication time in a newly infected tumor cell [16]. In addition, most patients are diagnosed in a late-stage disease [17, 18]. In this study, we presented this delay of starting chemotherapy with τ_2.
This paper is organized as follows:
In Section 2, a brief explanation of the optimal control with delays in state and control is stated. In Section 3, the existence and uniqueness solution of system (1.1) is discussed. In Section 4, we pose the optimal control problem for our model by describing the objective function. Section 5 is devoted to numerical simulations. Finally, conclusions on the optimal control protocols are presented in Section 6.

2. Preliminary

The optimal control problem with delays in state and control

This section is devoted to some preliminaries of optimal control problem with delay, which is necessary in the next sections. For more details, one can see [19].
A quite general optimal control problem governed by a control state delay differential system can be formulated in the following form,

$$minimize\, L(m, \vartheta^m) = \int_0^T G(t, m(t), m(t-\tau_2), \vartheta^m(t), \vartheta^m(t-\tau_1))dt + \varphi(\vartheta^m(T)), \tag{2.1}$$

subject to $u \in K \subset \mathbb{L}^\infty(0, T; \mathbb{R}^M)$ $(T > 0)$, where ϑ^m is the solution to

$$\begin{cases} \dot{\vartheta}(t) = f(t, m(t), m(t-\tau_2), \vartheta(t), \vartheta(t-\tau_1)), \ t \in (0, T), \\ \vartheta(t) = (T(t), V(t), N(t), F(t), I_V(t), I_T(t), u(t))^T, \\ \vartheta(t) = \xi(t), \quad t \in [-\tau_1, 0], \\ m(t) = \psi(t), \quad t \in [-\tau_2, 0]. \end{cases} \tag{2.2}$$

Here

$$G : [0, T] \times \mathbb{R}^M \times \mathbb{R}^M \times \mathbb{R}^N \times \mathbb{R}^N \to \mathbb{R},$$

$$\varphi : \mathbb{R}^N \to \mathbb{R},$$

$$f : [0, T] \times \mathbb{R}^M \times \mathbb{R}^M \times \mathbb{R}^N \times \mathbb{R}^N \to \mathbb{R}^N,$$

$\vartheta_0 \in \mathbb{R}^N, M, N \in \mathbb{N}$ and $K \subset \mathbb{L}^\infty(0,T;\mathbb{R}^M)$ which is a closed convex subset.
We assume that for any $m \in \mathbb{L}^\infty\left(0,T;\mathbb{R}^M\right)$, system (2.2) admits a unique solution denoted by ϑ^m. Equation (2.2) is called the state problem. A pair of functions $(m,\vartheta^m) \in \mathbb{L}^\infty\left(0,T;\mathbb{R}^M\right) \times \mathbb{W}^{(1,\infty)}(0,T;\mathbb{R}^n)$ is called an admissible pair for optimal control problem with delays in state and control. An admissible pair (m^*,ϑ^{m^*}) is called a locally optimal pair or weak minimum for (2.1), if

$$L(m^*,\vartheta^{m^*}) \leq L(m,\vartheta^m),$$

for any $m \in K$. $L(m^*,\vartheta^{m^*})$ is the optimal value of the cost functional.
Pontryagin function with delay is given by:

$$H(t,m(t),m(t-\tau_2),\vartheta(t),\vartheta(t-\tau_1),p(t)) = G(t,m(t),m(t-\tau_2),\vartheta(t),\vartheta(t-\tau_2)) + f(t,m(t),m(t-\tau_2),\vartheta(t),\vartheta(t-\tau_1))p(t).$$

This function is Hamiltonian, if satisfies in the following relations

$$\dot{\vartheta}(t) = H_p,$$

and

$$\dot{p}(t) = -H_\vartheta,$$

$p(t)$ is defined as the adjoint function.
Since we are going to use optimal control, we state the following theorem which one can find the proof in [19].

Theorem 1. *(minimum principle for the retarded optimal control problem (ROCP)). Let $(m^*(t),\vartheta^*(t))$ be locally optimal for (ROCP) with delays for (2.1), then there exists a piecewise differentiable costate (adjoint) function $p(t)$ such that*

$$\begin{aligned}
&H(t,\vartheta^*(t),\vartheta^*(t-\tau_1),m^*(t-\tau_2),p(t)) + \\
&\chi_{[0,T-\tau_2]}(t)H(t+\tau_2,\vartheta^*(t+\tau_2),\vartheta^*(t+\tau_2-\tau_1),m^*(t+\tau_2),m^*(t),p(t+\tau_2)) \leq \\
&H(t,\vartheta^*(t),\vartheta^*(t-\tau_1),m(t),m^*(t-\tau_2),p(t)) + \\
&\chi_{[0,T-\tau_2]}(t)H(t+\tau_2,\vartheta^*(t+\tau_2),\vartheta^*(t+\tau_2-\tau_1),m^*(t+\tau_2),m(t),p(t+\tau_2)),
\end{aligned} \tag{2.3}$$

for all controls u at each time t, where H is the Hamiltonian previously defined and

$$\begin{aligned}
&\dot{p}(t) = -\frac{\partial H}{\partial \vartheta}(t,\vartheta(t),\vartheta(t-\tau_1),m(t),m(t-\tau_2),p(t)) - \\
&\chi_{[0,T-\tau_1]}(t)\frac{\partial H}{\partial \vartheta_{\tau_1}}(t+\tau_1,\vartheta(t+\tau_1),\vartheta(t),m(t+\tau_1),m(t+\tau_1-\tau_2),p(t+\tau_1)),
\end{aligned} \tag{2.4}$$

where $\vartheta_{\tau_1} = \vartheta(t-\tau_1)$.

$$p(T) = 0 \quad (\textit{transversality condition}), \tag{2.5}$$

the OCP must satisfy (optimality condition):

$$\frac{\partial H}{\partial m}(t) + \chi_{[0,T-\tau_2]}(t)\frac{\partial H}{\partial m_{\tau_2}}(t+\tau_2) = 0, \tag{2.6}$$

where $m_{\tau_2} = m(t-\tau_2)$ and for $i = 1,2$

$$\chi_{[0,T-\tau_i]}(t) = \begin{cases} 1, & t \in [0,T-\tau_i], \\ 0, & O.W. \end{cases} \tag{2.7}$$

3. Solution of system (1.1)

In the following by using technique [20, 21] in relation to our problem, we show the existence and uniqueness solution of system (1.1) in the entire interval $[-\tau, t_f]$, where $\tau = min\{\tau_1, \tau_2\}$. Let

$$f(\vartheta(t)) = \begin{pmatrix} r_1T(t)(1-\frac{T(t)+V(t)}{w}) - \beta T(t)V(t) - p_TT(t)I_T(t) + k_4T(t)F(t) - a_1(1-e^{-u(t)})T(t) \\ \beta T(t-\tau)V(t-\tau) + r_2V(t)(1-\frac{T(t)+V(t)}{w}) - p_VV(t)I_V(t) - a_2(1-e^{-u(t)})V(t) \\ r_3N(t)(1-b_1N(t)) - k_1T(t)N(t) - a_3(1-e^{-u(t)})N(t) \\ r_4F(t)(1-b_2F(t)) - k_3F(t)T(t) - a_4(1-e^{-u(t)})F(t) \\ s_1 + c_VV(t)I_V(t) - d_1I_V(t) - a_5(1-e^{-u(t)})I_V(t) \\ s_2 + c_TV(t)I_T(t)(V(t)+T(t)) - d_2I_T(t) - a_6(1-e^{-u(t)})I_T(t) \\ -d_3u(t) + m(t-\tau) \end{pmatrix}, \tag{3.1}$$

where $\vartheta(t) = (T(t), V(t), N(t), F(t), I_V(t), I_T(t), u(t))^T$. Let $\varrho : [t-\tau, t] \to \mathbb{R}$ be a function, then we define the function on $\varrho_t : [\tau, 0] \to \mathbb{R}$ by

$$\varrho_t(\sigma) = \varrho(t+\sigma),$$

for $-\tau \le \sigma \le 0$. Thus, system (1.1) can be rewritten as

$$\dot{X}(t) = F(t, T_t(\sigma), V_t(\sigma), N(t), F(t), I_V(t), I_T(t), u_t(\sigma)),$$

where $F : [0, \alpha) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^4 \times C([-\tau, 0], \mathbb{R}) \to \mathbb{R}^8$ for $\alpha \in [0, t_f]$. Furthermore, we consider $T_t(t-\tau-t) = T(t+t-\tau-t) = T(t-\tau)$, hence, $T_t(-\tau) = T(t-\tau)$, similarly $V_t(-\tau) = V(t-\tau)$ and $m_t(-\tau) = m(t-\tau)$. Since all the partial derivatives in the Jacobian matrix of $f(\vartheta(t))$ with respect to $\vartheta(t)$ are continuous, thus $f(\vartheta(t))$ is locally satisfied the Lipschitz condition. On $[0, \alpha] \times \mathbb{R}^7 \to \mathbb{R}^8$, then function F mapping $[0, \alpha) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^4 \times C([-\tau, 0], \mathbb{R}) \to \mathbb{R}^8$ is locally satisfied the Lipschitz condition.

Theorem 2. *Let $F(t, T_t, V_t, N, F, I_V, I_T, u) : [0, t_f) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^4 \times C([-\tau, 0], \mathbb{R} \to \mathbb{R}^8$ be continuous and be locally satisfied in Lipschitz condition. If*

$$\|F(t, \eta)\| \le M(t) + N(t)\|\eta\|,$$

on $[0, t_f) \times C([-\tau, 0], \mathbb{R}^2) \times \mathbb{R}^4 \times C([-\tau, 0], \mathbb{R})$, where $M(t)$ and $N(t)$ are continuous positive real valued function on $[0, t_f]$ and $\eta = (T_t, V_t, N, F, I_V, I_T, u)^T$, the unique noncontinuous solution exists on the interval $[-\tau, t_f]$.

Proof. $F(t, T_t, V_t, N, F, I_V, I_T, u)$ has already been shown to be locally Lipschitz. Also, with $g_1(t) = t - \tau$ and the right hand side of our differential equation system (3.1) being continuous, then $F(t, T(t-\tau), V(t-\tau), N(t), F(t), I_V(t), I_T(t), u(t))$ is a composition of continuous functions and hence is continuous on $[0, t_f)$. So, that's enough to show $\|F(t, \eta)\| \le M(t) + N(t)\|\eta\|$ is satisfied. Using the upper bound on our control, we find from (3.1) that

$$u(t) = (u_0 - 1)e^{-\gamma t} \le u_0, \tag{3.2}$$

γ is positive. Also, by system (3.1), we have

$$\begin{cases} \dot{T}(t) \le r_1T(t)(1-\frac{T(t)}{w}) + k_4T(t)F(t) + a_1e^{-u(t)}T(t), \\ \dot{V}(t) \le \beta T(t-\tau)V(t-\tau) + r_2V(t)(1-\frac{V(t)}{w}) + a_2e^{-u(t)}V(t) \\ \dot{N}(t) \le r_3N(t)(1-b_1N(t)) + a_3e^{-u(t)}N(t), \\ \dot{F}(t) \le r_4F(t)(1-b_2F(t)) + a_4e^{-u(t)}F(t), \\ \dot{I}_V(t) \le s_1 + c_VV(t)I_V(t) + a_5e^{-u(t)}I_V(t), \\ \dot{I}_T(t) \le s_2 + c_TV(t)I_T(t)(V(t)+T(t)) + a_6e^{-u(t)}I_T(t). \end{cases} \tag{3.3}$$

By (3.2), $u(t)$ is bounded so, third and forth terms of (3.3) are Bernoulli differential equations. Hence, the functions $N(t)$ and $F(t)$ are bounded on the interval $[-\tau, t_f]$. Now, since $F(t)$ is bounded, we consider a bound for the function $F(t)$ and thus, the first term of (3.3) is also a Bernoulli differential equation, that shows the function $T(t)$ is bounded. By the boundedness of $T(t)$ and the second term of (3.3), the boundedness of $V(t)$ is obvious. In addition, one can check easily the boundedness of $I_V(t)$ and $I_T(t)$. Thus, we define Q, R, J and H as the upper bounds for $k_4T(t)V(t)$, $\beta T(t-\tau)V(t-\tau)$, $c_V V(t)I_V(t)$ and $c_T V(t)I_T(t)(V(t)+T(t))$ respectively. So

$$\begin{pmatrix} \dot{T}(t) \\ \dot{V}(t) \\ \dot{N}(t) \\ \dot{F}(t) \\ \dot{I}_V(t) \\ \dot{I}_T(t) \end{pmatrix} \leq \begin{pmatrix} r_1 + a_1 e^{-u(t)} & 0 & 0 & 0 & 0 & 0 \\ 0 & r_2 + a_2 e^{-u(t)} & 0 & 0 & 0 & 0 \\ 0 & 0 & r_3 + a_3 e^{-u(t)} & 0 & 0 & 0 \\ 0 & 0 & 0 & r_4 + a_4 e^{-u(t)} & 0 & 0 \\ 0 & 0 & 0 & 0 & a_5 e^{-u(t)} & 0 \\ 0 & 0 & 0 & 0 & 0 & a_6 e^{-u(t)} \end{pmatrix} \begin{pmatrix} T(t) \\ V(t) \\ N(t) \\ F(t) \\ I_V(t) \\ I_T(t) \end{pmatrix} + \begin{pmatrix} Q \\ R \\ 0 \\ 0 \\ s_1 + J \\ s_2 + H \end{pmatrix}. \tag{3.4}$$

Therefore, $\|F(t,\eta)\| \leq M + N\|\eta\|$ where

$$M = \begin{pmatrix} Q \\ R \\ 0 \\ 0 \\ s_1 + J \\ s_2 + H \end{pmatrix}, \qquad N = \begin{pmatrix} r_1 + a_1 e^{-u(t)} & 0 & 0 & 0 & 0 & 0 \\ 0 & r_2 + a_2 e^{-u(t)} & 0 & 0 & 0 & 0 \\ 0 & 0 & r_3 + a_3 e^{-u(t)} & 0 & 0 & 0 \\ 0 & 0 & 0 & r_4 + a_4 e^{-u(t)} & 0 & 0 \\ 0 & 0 & 0 & 0 & a_5 e^{-u(t)} & 0 \\ 0 & 0 & 0 & 0 & 0 & a_6 e^{-u(t)} \end{pmatrix}.$$

Now, by application of this theorem and with the assumption of boundedness of admissible control, we have the uniqueness of a solution on $[-\tau, t_f)$. □

4. Optimal control for system (1.1)

In this section we determine the optimal control for our system (1.1).
Our aim is to look for protocols of administration, which are as much as drugs efficient as possible and not too toxic. So, we restrict the amount of drugs administered to the patient [22]. Thus, we consider a biological bound for the controller, as

$$0 \leq m(t) \leq m_{max}.$$

The lower bounds for $m(t)$ is corresponding to no therapy. Next, we determine the optimal control, which gives the optimal drug dosage for patient recovery.

$$U = \left\{ m(t) \mid m(t) \text{ is Lebesgue measurable}, \ 0 \leq m(t) \leq m_{max}, \ t \in [0, t_f] \right\}. \tag{4.1}$$

Our problem is to minimize the objective functional

$$\min_{m(.)\in U} \left\{ L = \int_0^{t_f} [T(t) - N(t) + Bm(t)]\, dt \right\}, \tag{4.2}$$

$T(t)$ and $N(t)$ are the solutions of system (1.1) and the parameters $B > 0$ represents the desired 'weight constant' on the benefit and cost.
The aim is to find an optimal control for minimizing the objective functional defined in (4.2) subject to the state system (1.1). In other words, we are seeking optimal control (m^*) such that

$$L(m^*) = min \left\{ L(m), \ m \in U \right\}. \tag{4.3}$$

4.1. Optimality conditions

We invoke Pontryagin's Maximum Principle to determine the precise formulation of our optimal control $m^*(t)$. To do this, we note that our Hamiltonian is given by

$$H = H(T(t), T(t-\tau_1), V(t), V(t-\tau_1), N(t), F(t), I_V, I_T, u(t), m(t-\tau_2), \psi_1(t), \psi_2(t), \psi_3(t), \psi_4(t), \psi_5(t), \psi_6(t), \psi_7(t)) = \dot{T}(t)\psi_1(t) + \dot{V}(t)\psi_2(t) + \dot{N}(t)\psi_3(t) + \dot{F}(t)\psi_4(t) + \dot{I_V}(t)\psi_5(t) + \dot{I_T}(t)\psi_6(t) + \dot{u}(t)\psi_7(t) + [T(t) - N(t) + Bm(t)], \tag{4.4}$$

with the optimality condition

$$\frac{\partial H}{\partial m}(t) + \chi_{[0,t_f-\tau_2]}(t)\frac{\partial H}{\partial m_{\tau_2}}(t+\tau_2) = 0, \tag{4.5}$$

where $m_{\tau_2} = m(t-\tau_2)$ and the adjoint equation

$$\begin{cases} \dot{\psi}_1 = -\frac{\partial H}{\partial T} - \chi_{[0,t_f-\tau_1]}(t)\frac{\partial H}{\partial T_{\tau_1}}(t+\tau_1), \\ \dot{\psi}_2 = -\frac{\partial H}{\partial V} - \chi_{[0,t_f-\tau_1]}(t)\frac{\partial H}{\partial V_{\tau_1}}(t+\tau_1), \\ \dot{\psi}_3 = -\frac{\partial H}{\partial N}, \\ \dot{\psi}_4 = -\frac{\partial H}{\partial F}, \\ \dot{\psi}_5 = -\frac{\partial H}{\partial I_V} \\ \dot{\psi}_6 = -\frac{\partial H}{\partial I_T}, \\ \dot{\psi}_7 = -\frac{\partial H}{\partial u}, \end{cases} \tag{4.6}$$

with transversality conditions $\psi_i(t_f) = 0, i = 1, ..., 7$ is a Hamiltonian function. Now we apply the necessary conditions to the Hamiltonian function H in (4.4).

Theorem 3. *Let $(T^*(t), V^*(t), N^*(t), F^*(t), I_V^*, I_T^*, u^*(t)) \in \mathbb{W}^{(1,\infty)}([0,t_f], \mathbb{R}^6) \times \mathbb{L}^\infty([0,t_f])$ be optimal state solutions associated with the optimal control $m^*(t)$ for the optimal control problem (1.1). Then, there exists an adjoint state $\psi(t) = (\psi_1, ..., \psi_7) \in \mathbb{W}^{(1,\infty)}([0,t_f], \mathbb{R}^6)$ defined by (4.6), such that $(T^*(t), V^*(t), N^*(t), F^*(t), I_V^*, I_T^*, u^*(t), \psi)$ satisfies the state equation*

$$\begin{cases} \dot{T}^*(t) = r_1 T^*(t)(1 - \frac{T^*(t)+V^*(t)}{w}) - \beta T^*(t)V^*(t) - p_T T^*(t) I_T^*(t) + k_4 T^*(t)F^*(t) - a_1(1 - e^{-u^*(t)})T^*(t), \\ \dot{V}^*(t) = \beta T^*(t-\tau_1)V^*(t-\tau_1) + r_2 V^*(t)(1 - \frac{T^*(t)+V^*(t)}{w}) - p_V V^*(t) I_V^*(t) - a_2(1 - e^{-u^*(t)})V^*(t), \\ \dot{N}^*(t) = r_3 N^*(t)(1 - b_1 N^*(t)) - k_1 T^*(t)N^*(t) - a_3(1 - e^{-u^*(t)})N^*(t), \\ \dot{F}^*(t) = r_4 F^*(t)(1 - b_2 F^*(t)) - k_3 F^*(t)T^*(t) - a_4(1 - e^{-u^*(t)})F^*(t), \\ \dot{I_V^*}(t) = s_1 + c_V V^*(t) I_V^*(t) - d_1 I_V^*(t) - a_5(1 - e^{-u^*(t)})I_V^*(t), \\ \dot{I_T^*}(t) = s_2 + c_T V^*(t) I_T^*(t)(V^*(t) + T^*(t)) - d_2 I_T^*(t) - a_6(1 - e^{-u^*(t)})I_T^*(t), \\ \dot{u}^*(t) = -d_3 u^*(t) + m^*(t-\tau_2). \end{cases} \tag{4.7}$$

With the initial conditions

$$\begin{cases} T^*(t) = \phi_1(t), \\ V^*(t) = \phi_2(t), \\ N^*(t) = N(0), \\ F^*(t) = F(0), \qquad t \in [-\tau, 0]; \tau = min\{\tau_1, \tau_2\} \\ I_V^*(t) = I_V(0), \\ I_T^*(t) = I_T(0), \\ u^*(t) = \phi_3(t). \end{cases} \tag{4.8}$$

The adjoint state equations are

$$\begin{cases} \dot{\psi}_1 = -\frac{\partial H}{\partial T^*} - \chi_{[0,t_f-\tau_1]}(t)\frac{\partial H}{\partial T^*_{\tau_1}}(t+\tau_1) = (\frac{2r_1}{w}T^* - r_1 + \beta V^* + p_T I^*_T - k_4 F^* + a_1(1-e^{-u^*}))\psi_1 + \\ (\frac{r_2}{w} - \beta)V^*\psi_2 + k_1 N^*\psi_3 + k_3 F^*\psi_4 - c_T V^* I^*_T\psi_6 - \chi_{[0,t_f-\tau_1]}(t)\beta V^*(t)\psi_2(t+\tau_1), \\ \dot{\psi}_2 = -\frac{\partial H}{\partial V^*} - \chi_{[0,t_f-\tau_1]}(t)\frac{\partial H}{\partial V^*_{\tau_1}}(t+\tau_1) = (\frac{r_1}{w} + \beta)T^*\psi_1 + (-\beta T^* - r_2 + \frac{2r_2}{w}V^* + p_V I^*_V + a_2(1-e^{-u^*}))\psi_2 + \\ k_2 N^*\psi_3 - c_V I^*_V\psi_5 - (c_T I^*_T(2V^* + T^*))\psi_6 - \chi_{[0,t_f-\tau_1]}(t)\beta T^*(t)\psi_2(t+\tau_1), \\ \dot{\psi}_3 = -\frac{\partial H}{\partial N^*} = (-r_3 + 2b_1 r_3 N^* + k_1 T^* + a_3(1-e^{-u^*}))\psi_3, \\ \dot{\psi}_4 = -\frac{\partial H}{\partial F^*} = -k_4 T^*\psi_1 + (-r_4 + 2r_4 b_2 F^* + k_3 T^* + a_4(1-e^{-u^*}))\psi_4, \\ \dot{\psi}_5 = -\frac{\partial H}{\partial I^*_V} = p_V V^*\psi_2 + (-c_V V^* + d_1 + a_5(1-e^{-u^*}))\psi_5, \\ \dot{\psi}_6 = -\frac{\partial H}{\partial I^*_T} = p_T T^*\psi_1 + (-c_T V^*(V^* + T^*) + d_2 + a_6(1-e^{-u^*}))\psi_6, \\ \dot{\psi}_7 = -\frac{\partial H}{\partial u^*} = e^{-u^*}(a_1 T^*\psi_1 + a_2 V^*\psi_2 + a_3 N^*\psi_3 + a_4 F^*\psi_4 + a_5 I^*_V\psi_5 + a_6 I^*_T\psi_6) + d_3\psi_7. \end{cases} \tag{4.9}$$

with transversality conditions

$$\psi_i(t_f) = 0, \quad i = 1, ..., 7. \tag{4.10}$$

Furthermore, the optimal control is given as follows:

$$m^*(t) = \begin{cases} 0 & if \ \ \chi_{[0,t_f-\tau_2]}(t)\psi_7(t+\tau_2) > -B, \\ m_{max} & if \ \ \chi_{[0,t_f-\tau_2]}(t)\psi_7(t+\tau_2) < -B. \end{cases} \tag{4.11}$$

Proof. By the theorem of existence and uniqueness in differential equation [23] and the Pontryagin maximum principle with delay given in [19], for $m^*(t)$ and the corresponding trajectory $(T^*(t), V^*(t), N^*(t), F^*(t), I^*_V(t), I^*_T(t), u^*(t))$, there exists a nontrivial solution $(\psi_1(t), ..., \psi_7(t))$ of the adjoint system (4.9). Now by condition (4.5), one can have

$$\begin{aligned} &\frac{\partial H}{\partial m}(t) + \chi_{[0,t_f-\tau_2]}(t)\frac{\partial H}{\partial m_{\tau_2}}(t+\tau_2) = B + \chi_{[0,t_f-\tau_2]}(t)\psi_7(t+\tau_2) = 0 \\ \Rightarrow &m^*(t) = \begin{cases} 0 & \text{if} \ \ \chi_{[0,t_f-\tau_2]}(t)\psi_7(t+\tau_2) > -B, \\ m_{max} & \text{if} \ \ \chi_{[0,t_f-\tau_2]}(t)\psi_7(t+\tau_2) < -B. \end{cases} \end{aligned} \tag{4.12}$$

Since $(\psi_1(t), ..., \psi_7(t))$ is a solution of (4.9), then $m^*(t)$ is the optimal control for system (1.1). □

5. Numerical simulation

In this section, we considered three different cases to show the effectivity of combination treetment of oncolytic virotherapy and chemotherapy numerically. In Case I, we assumed $\tau_1 = 6.5$ for the lag of viral transmission to tumor cells while the chemotherapy started after $\tau_2 = 10$ days. The numerical simulation shows that the treatment was succesful in this case. In Case II, we chose the same value for the parameter delay τ_1 as the previous case but, we increased the length of delay in chemotherapy to $\tau_2 = 50$ days. As it is shown in the simulations, a lot of unstable fluctuations imposed to all variables and the therapy method fails to control the tumor growth. In Case III, we assumed $\tau_2 = 50$, but we decreased the time delay of viral transmission to $\tau_1 = 1.5$. In this case, the solutions provide a promising results that could control the disease optimally.

In all cases, initial values are assumed the same and are as follows:

$$\begin{cases} T_0 = 19, \\ V_0 = 0.02, \\ N_0 = 881, \\ F_0 = 4, \\ I_V = 14, \\ I_T = 0.0001. \end{cases} \tag{5.1}$$

The values in (5.1) are the numerical approximations for one of the equilibrium point of the system (1.1) in the case there is no drug ($u(t) = 0$) with parameter values as in Table 1.

Table 1: List of parameters values.

Parameter	value	unit
r_1	1.5	$\text{day}^{-1}\text{cell}^{-1}$
r_2	0.5	$\text{day}^{-1}\text{cell}^{-1}$
r_3	1	$\text{day}^{-1}\text{cell}^{-1}$
r_4	0.5	$\text{day}^{-1}\text{cell}^{-1}$
b_1	0.001	day^{-1}
b_2	0.1	day^{-1}
k_1	0.001	$\text{day}^{-1}\text{cell}^{-1}$
k_3	0.01	$\text{day}^{-1}\text{cell}^{-1}$
k_4	1.5	$\text{day}^{-1}\text{cell}^{-1}$
a_1	9×10^{-1}	day^{-1}
a_2	1×10^{-1}	day^{-1}
a_3	1×10^{-1}	day^{-1}
a_4	1×10^{-1}	day^{-1}
a_5	6×10^{-1}	day^{-1}
a_6	6×10^{-1}	day^{-1}
d_1	1×10^{-1}	day^{-1}
d_2	0.1	day^{-1}
d_3	1×10^{-2}	day^{-1}
c_T	10	day^{-1}
c_V	0.002	day^{-1}
p_T	0.02	day^{-1}
p_V	0.2	day^{-1}
β	0.3	day^{-1}
ω	5	day^{-1}
s_1	10	day^{-1}
s_2	20	day^{-1}

Case I In the first case, we considered $\tau_1 = 6.5$, $\tau_2 = 10$ and $u_0 = 0.5$.

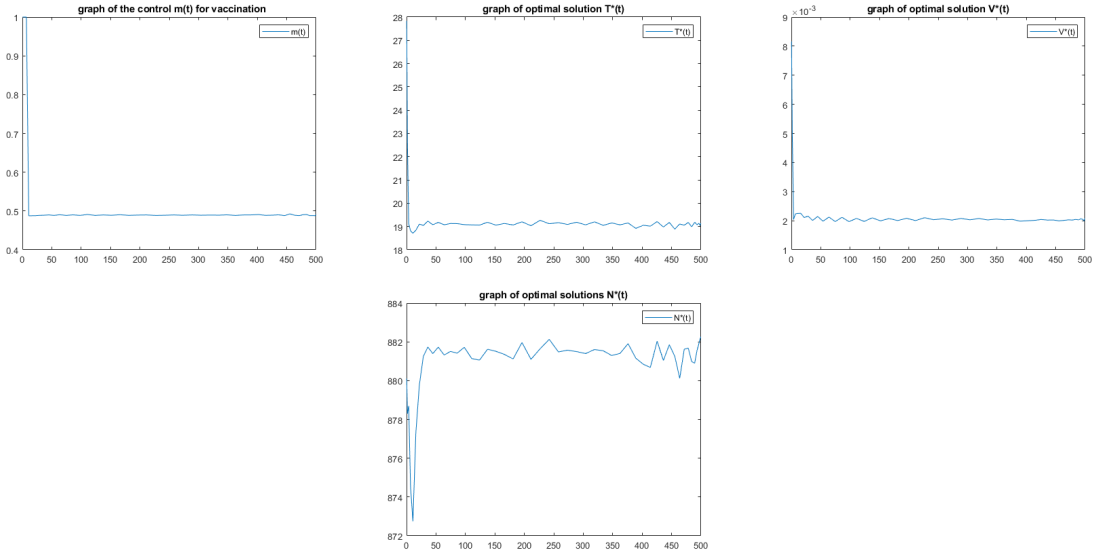

Figure 1: Optimal drug control and optimal tumor cells, oncolytic virus and normal cells are illustrated at $\tau_1 = 6.5$ and $\tau_2 = 10$.

Case II In this case, we increased the interruption of chemotherapy to $\tau_2 = 50$ and as it shown in Figure 2, solutions suffers more oscillations than the previous case and the chemotherapy cannot control the tumor cells well.

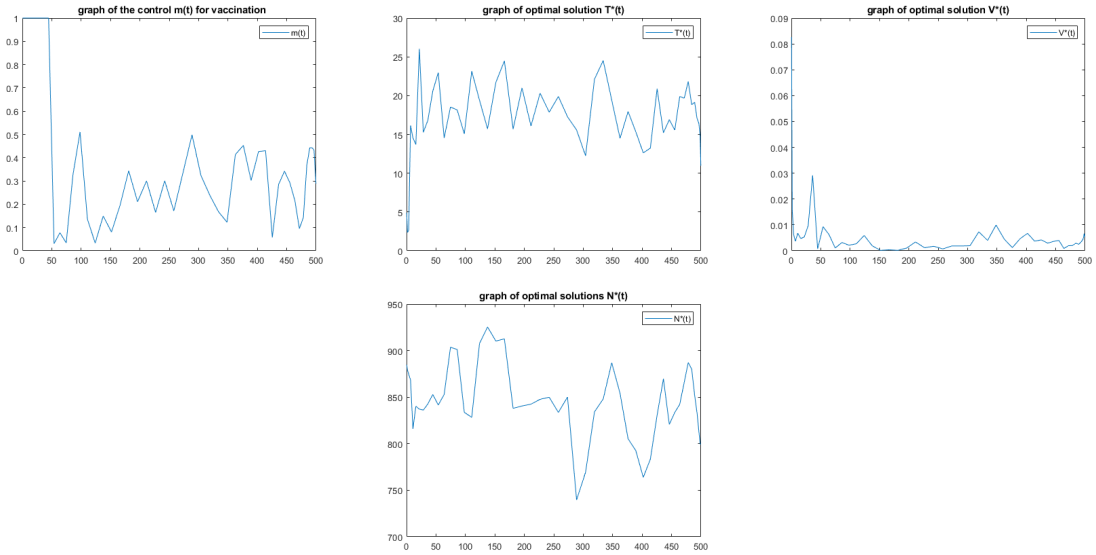

Figure 2: In this figure, optimal drug control and optimal tumor cells, oncolytic virus and normal cells are simulated at $\tau_1 = 6.5$ and $\tau_2 = 50$. The simulation shows tumor cells are not completely controllable.

Case III In this case, the time delay of chemotherapy is considered $\tau_2 = 50$ while, we decreased the delay of transmission of oncolytic virus to tumor cells and infecting them as $\tau_1 = 1.5$. Figure 3 displays the valuable effect of virotherapy.

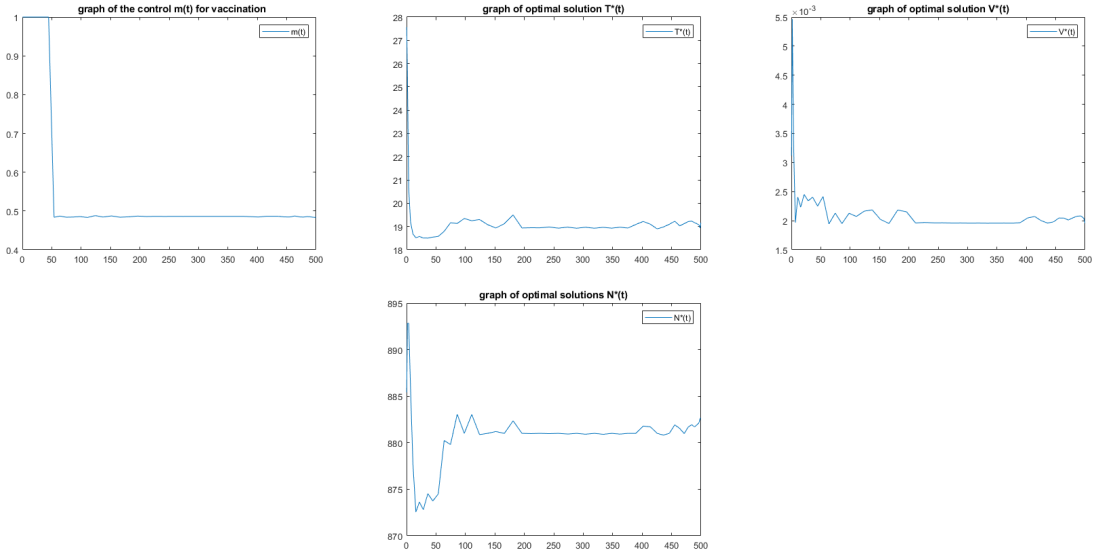

Figure 3: In this figure, optimal drug control and optimal tumor cells, oncolytic virus and normal cells are simulated at $\tau_1 = 1.5$ and $\tau_2 = 50$. The simulation displays the remarkable effect of virotherapy.

6. Conclusion

In this paper we introduced a nonlinear mathematical model that describes the interactions among tumor cells, oncolytic virotherapy, normall cells, obesity, immune cells with respect to virus and tumor cells and, chemotherapy as drug control of the system. We emphasis that this mathematical model has the advantage that could introduce a combination therapy. In treating cancer, specially at metastatic or progressed stages single therapies are hardly successful. Combination of oncolytic virotherapy with chemotherapy, besides that can reduce toxic side effects of chemotherapy also has shown that may lead to a synergistic interactions in increased therapeutic effects [11, 24].
In addition, two time delays are imposed to the system. τ_1 for the time needed that tumor cells become productive in order to infected by oncolytic virus. τ_2 is considered for the time delay of starting the chemotherapy. From biological point of view these so called delays are essential to consider for a more realistic model. Our model has this advantage that investigated the effect of delays in viral transmission and chemotherapy for treatment. In fact, we defined optimal control with delays in both state and control for our model. After characterizing the optimal control problem, numerical simulations has been done. Numerical simulations could help us to obtain a better overview of the problem. In simulation, we investigated a combination therapy. In the Case III, the solutions are modified in compare with the Case II where, the time delay of transmission of infection to tumor cells is decreased. The simulations implies that combinations has an increasing significance effect in cancer therapy. However, still the sensitivity of the model to time delay of therapy is obvious. If the delay is too large, it could be possible the response is out of clinical time for sufficient therapeutic conditions.

Acknowledgment

This research was in part supported by a grant from IPM. Grant number: 95920071

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Dominik Wodarz and Natalia L Komarova. *Dynamics of cancer: mathematical foundations of oncology*. World Scientific, 2014.
[2] N Komarova and Dominik Wodarz. Targeted cancer treatment in silico. In *Modeling and simulation in science, engineering and technology*. Springer, 2014.
[3] Hannah P Savage. A nonlinear ode model of tumor growth and effect of immunotherapy and chemotherapy treatment in colorectal cancer. 2010.
[4] Heinz Schättler and Urszula Ledzewicz. *Optimal Control for Mathematical Models of Cancer Therapies*. Springer, 2015.
[5] Lisette G de Pillis, Weiqing Gu, and Ami E Radunskaya. Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. *Journal of theoretical biology*, 238(4):841–862, 2006.
[6] Leonard W Seymour and Kerry D Fisher. Oncolytic viruses: finally delivering. *British journal of cancer*, 2016.
[7] Shantanu Kumar, Lu Gao, Brian Yeagy, and Tony Reid. Virus combinations and chemotherapy for the treatment of human cancers. *Current opinion in molecular therapeutics*, 10(4):371–379, 2008.
[8] Kathryn Ottolino-Perry, Jean-Simon Diallo, Brian D Lichty, John C Bell, and J Andrea McCart. Intelligent design: combination therapy with oncolytic viruses. *Molecular Therapy*, 18(2):251–263, 2010.
[9] Roberto A Ku-Carrillo, Sandra E Delgadillo, and BM Chen-Charpentier. Effects of the obesity on optimal control schedules of chemotherapy on a cancerous tumor. *Journal of Computational and Applied Mathematics*, 2016.
[10] Roberto A Ku-Carrillo, Sandra E Delgadillo, and BM Chen-Charpentier. A mathematical model for the effect of obesity on cancer growth and on the immune system response. *Applied Mathematical Modelling*, 40(7):4908–4920, 2016.
[11] Andrew Nguyen, Louisa Ho, and Yonghong Wan. Chemotherapy and oncolytic virotherapy: advanced tactics in the war against cancer. *Frontiers in oncology*, 4:145, 2014.
[12] Guy R Simpson, Kate Relph, Kevin Harrington, Alan Melcher, and Hardev Pandha. Cancer immunotherapy via combining oncolytic virotherapy with chemotherapy: recent advances. *Oncolytic virotherapy*, 5:1, 2016.
[13] Sonia Tusell Wennier, Jia Liu, and Grant McFadden. Bugs and drugs: oncolytic virotherapy in combination with chemotherapy. *Current pharmaceutical biotechnology*, 13(9):1817–1833, 2012.
[14] Ta-Chiang Liu, Evanthia Galanis, and David Kirn. Clinical trial results with oncolytic virotherapy: a century of promise, a decade of progress. *Nature Reviews Clinical Oncology*, 4(2):101, 2007.
[15] Stephen J Russell, Kah-Whye Peng, and John C Bell. Oncolytic virotherapy. *Nature biotechnology*, 30(7):658, 2012.
[16] Narendra M Dixit and Alan S Perelson. Complex patterns of viral load decay under antiretroviral therapy: influence of pharmacokinetics and intracellular delay. *Journal of Theoretical Biology*, 226(1):95–109, 2004.
[17] Fiona Mary Walter, Greg Rubin, C Bankhead, HC Morris, Nicola Hall, K Mills, C Dobson, RC Rintoul, W Hamilton, and J Emery. Symptoms and other factors associated with time to diagnosis and stage of lung cancer: a prospective cohort study. *British journal of cancer*, 112(s1):S6, 2015.
[18] AD Hartkopf, T Fehm, M Wallwiener, and U Lauer. Oncolytic viruses to treat ovarian cancer patients–a review of results from clinical trials. *Geburtshilfe und Frauenheilkunde*, 72(2):132, 2012.
[19] Laurenz Göllmann, Daniela Kern, and Helmut Maurer. Optimal control problems with delays in state and control variables subject to mixed control–state constraints. *Optimal Control Applications and Methods*, 30(4):341–365, 2009.
[20] C Collins, KR Fister, and M Williams. Optimal control of a cancer cell model with delay. *Mathematical Modelling of Natural Phenomena*, 5(3):63–75, 2010.
[21] Elham Shamsara, Jamal Shamsara, and Zahra Afsharnezhad. Optimal control therapy and vaccination for special HIV-1 model with delay. *Theory in Biosciences*, pages 1–14, 2016.
[22] Suzanne Lenhart and John T Workman. *Optimal control applied to biological models*. CRC Press, 2007.
[23] Jack K Hale and Sjoerd M Verduyn Lunel. *Introduction to functional differential equations*, volume 99. Springer Science & Business Media, 2013.
[24] Drew A Spencer, Jacob S Young, Deepak Kanojia, Julius W Kim, Sean P Polster, Jason P Murphy, and Maciej S Lesniak. Unlocking the promise of oncolytic virotherapy in glioma: combination with chemotherapy to enhance efficacy. *Therapeutic delivery*, 6(4): 453–468, 2015.