OPTIMAL CONTROL OF VIRAL INFECTION MODEL WITH SATURATED INFECTION RATE

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ABSTRACT. This paper deals with an optimal control problem for a viral infection model with cytotoxic T-lymphocytes (CTL) immune response. The model under consideration describes the interaction between the uninfected cells, the infected cells, the free viruses and the CTL cells. The two treatments represent the efficiency of drug treatment in inhibiting viral production and preventing new infections. Existence of the optimal control pair is established and the Pontryagin’s maximum principle is used to characterize these two optimal controls. The optimality system is derived and solved numerically using the forward and backward difference approximation. Finally, numerical simulations are performed in order to show the role of optimal therapy in controlling the infection severity.

1. Introduction. Despite advances in treatment and prevention, the epidemics still cause a significant number of deaths in world, and some diseases are eradicated. For example the Hepatitis B virus (HBV) infects more than 300 million people worldwide and is a common cause of liver disease and liver cancer [12]. Hepatitis C virus (HCV) is a liver disease caused by the hepatitis C virus (HCV). Approximately, between 130 and 150 million people globally have chronic hepatitis C infection. Then, HCV infection presents a significant global public health issue [21]. The human immunodeficiency virus (HIV) is a virus that gradually weakens the immune system. It is considered as the main cause for several deadly diseases after the resulting acquired immunodeficiency syndrome (AIDS) is reached. After this stage, the immune system fails to play a crucial role, which is to protect the whole body against harmful intruders, according to the world health organization [27], 36.7 million people living with HIV, 1.8 million people becoming newly infected with HIV and more than 1 million deaths annually. So, the HIV is becoming a major public health problem around the world. Thus, the mathematical modeling of viral infection is one of the current pertaining tools for predicting the evolution of infectious diseases [2, 6, 15–17]. The basic viral infection model with four dynamics components including the uninfected cells, the infected cells, the free viruses and the cellular immune response, also called the cytotoxic T-lymphocyte (CTL) response,
was first studied in [17]. Here we observe that, often, models introduce the effect of the CTL which attacks and kills the infected cells [5, 7, 9, 22, 28]. In [4], it is assumed that CTL proliferation depends, besides infected cells, as usual, also on healthy cells. Moreover, an optimal control problem associated with the suggested model is studied [4]. In 2016, the same problem was tackled by introducing time delays [20]. Recently, in [3] the authors continue the investigation of such kind of problems by introducing the free virus dynamics to the system of equations. This is important because uninfected cells must be in contact with the free virus before they become infected. This scenario is represented as follows:

\[
\begin{align*}
\frac{dx}{dt}(t) &= \lambda - dx(t) - \beta(1 - u_1)x(t)v(t), \\
\frac{dy}{dt}(t) &= \beta(1 - u_1)x(t - \tau)v(t - \tau) - ay(t) - py(t)z(t), \\
\frac{dv}{dt}(t) &= aN(1 - u_2)y(t) - \mu v(t), \\
\frac{dz}{dt}(t) &= cx(t)y(t)z(t) - hz(t).
\end{align*}
\]

(1)

In this model, \(x, y, v\) and \(z\) denote the concentration of uninfected cells, infected cells, free virus, and CTL cells, respectively. The two constants \(u_1\) and \(u_2\) stand for the efficiency of treatment in blocking new infection and in inhibiting viral production, respectively. The parameters of the system (1) are described in the following table:

| Parameters | Description | value | References |
|------------|-------------|-------|------------|
| \(\lambda\) | The birth rate of the uninfected cells | \([0, 10]\) | [3] |
| \(\beta\) | The infection rate | \([2.5 \times 10^{-4}, 0.5]\) | [3] |
| \(d\) | The natural mortality of the susceptible cells | \([7 \times 10^{-3}, 0.1]\) | [3] |
| \(a\) | The death rate of infected cells, not by CTL killing | \([0.2, 0.3]\) | [3] |
| \(N\) | Number of virions produced by infected cells | \([6.25, 23599.9]\) | [3] |
| \(\mu\) | The natural mortality of the free virus | \([2.06, 3.81]\) | [3] |
| \(p\) | Clearance rate of infection | \([10^{-4}, 4.048 \times 10^{-4}]\) | [3] |
| \(c\) | Activation rate CTL cells | \([5.1 \times 10^{-3}, 3.912]\) | [3] |
| \(h\) | Death rate of CTL cells | \([4 \times 10^{-4}, 8.087]\) | [3] |
| \(\tau\) | Time delay | \([7, 21]\) | [3] |

Noting that, the basic reproduction number of system (1) as follows:

\[ R_0^* = \frac{\lambda N \beta}{d \mu}, \]

we observe that \(R_0^*\) is proportional to \(\frac{\lambda}{d}\) which represents the total number of cells. This suggests that (1) may not be a reasonable model for describing the viral infection since it implies that an individual with a smaller total number of cells may be more resistant to the virus infection than an individual with a larger one. Therefore, in this paper, we try the problem (1) by using the saturated rate
of infection. For this purpose, we will consider the following nonlinear differential equations:

\[
\begin{align*}
\frac{dx}{dt}(t) &= \lambda - dx(t) - \frac{\beta(1 - u_1)x(t)v(t)}{x(t) + v(t)}, \\
\frac{dy}{dt}(t) &= \frac{\beta(1 - u_1)x(t-\tau)v(t-\tau)}{x(t-\tau) + v(t-\tau)} - ay(t) - py(t)z(t), \\
\frac{dv}{dt}(t) &= aN \left(1 - u_2\right)y(t) - \mu v(t), \\
\frac{dz}{dt}(t) &= cx(t)y(t)z(t) - hz(t).
\end{align*}
\]

Our model uses a more realistic saturated incidence function $\frac{\beta xv}{x + v}$ [2, 8, 23, 24]. This saturated incidence functional describes the infection rate taking into consideration the effect of free viruses crowd near the healthy cells.

In our case, the basic reproduction number is

\[R_0 = \frac{N\beta}{\mu}.\]

The paper is organized as follows. The next section is dedicated to the Positivity and boundedness, followed in Section 3 by the optimization analysis of the model. In Section 4, we construct an appropriate numerical algorithm and give some numerical simulations. We conclude in the last section.

2. **Positivity and boundedness.** The model (2) presents a system of delayed differential equations. For such problem, initial functions need to be stated and the functional framework needs to be specified. Let $X = C([-\tau, 0]; \mathbb{R}^4)$ be the Banach space of continuous mapping from $[-\tau, 0]$ to $\mathbb{R}^4$ equipped with the sup-norm $\|\varphi\| = \sup_{-\tau \leq t \leq 0} |\varphi(t)|$. The initial functions verify

\[(x(\theta), y(\theta), v(\theta), z(\theta)) \in X.\]

Also, for biological reasons, these initial functions $x(\theta)$, $y(\theta)$, $v(\theta)$ and $z(\theta)$ are non-negative:

\[x(\theta) \geq 0, y(\theta) \geq 0, v(\theta) \geq 0, z(\theta) \geq 0, \text{ for } \theta \in [-\tau, 0].\]

It is straightforward to show that the solutions of the system (2) are positive for any positive initial conditions. We examine the boundedness of the solutions to the system (2) with non-negative initial conditions. For this purpose, we introduce the variable $X(t) = x(t) + y(t + \tau) + \frac{1}{2N}v(t + \tau)$. Using the system (2), we have

\[\dot{X} = \lambda - dx(t) - \frac{a(1 - u_2)}{2}y(t + \tau) - \frac{\mu}{2N}v(t + \tau) - py(t + \tau)z(t + \tau),\]

since $0 \leq 1 - u_2 \leq 1$, we have

\[\dot{X} \leq \lambda - dx(t) - \frac{a}{2}y(t + \tau) - \frac{\mu}{2N}v(t + \tau),\]

if we set, $\rho = \min(d, a, \mu, h)$, we will have

\[\dot{X} \leq \lambda - \rho X(t),\]
then,
\[ X(t) \leq X(0)e^{-\rho t} + \frac{\lambda}{\rho} \left( 1 - e^{-\rho t} \right). \]

Since \( 0 \leq e^{-\rho t} \leq 1 \) and \( 1 - e^{-\rho t} \leq 1 \). So, \( X(t) \) is bounded, therefore the functions \( x(t), y(t) \) and \( v(t) \).

Now, we prove that \( z(t) \) is bounded. From the last equation of the system (2), we have
\[
\frac{dz}{dt}(t) + hz(t) = cx(t)y(t)z(t),
\]
using the second equation of (2), we have
\[
\frac{dz}{dt}(t) + hz(t) = \frac{c}{p} x(t) \left( \frac{\beta x(t-\tau)v(t-\tau)}{x(t-\tau) + v(t-\tau)} - ay(t) - \frac{dy}{dt}(t) \right),
\]
then,
\[
z(t) = z(0)e^{-ht + \frac{c}{p} \int_0^t x(s) \left( \frac{\beta x(s-\tau)v(s-\tau)}{x(s-\tau) + v(s-\tau)} - ay(s) - \frac{dy}{dt}(s) \right)e^{h(s-t)} ds},
\]
since \( x, y \) and \( v \) are bounded, it follows the boundedness of \( z(t) \). Therefore, every local solution can be prolonged up to any time \( t_m > 0 \), which means that the solution exists globally.

3. The optimal control problem. Now, to state the optimization problem, we first consider that \( u_1 \) and \( u_2 \) vary with time. The problem (2) becomes
\[
\begin{aligned}
\frac{dx}{dt}(t) &= \lambda - dx(t) - \frac{\beta(1-u_1(t))x(t)v(t)}{x(t) + v(t)}, \\
\frac{dy}{dt}(t) &= \frac{\beta(1-u_1(t))x(t-\tau)v(t-\tau)}{x(t-\tau) + v(t-\tau)} - ay(t) - py(t)z(t), \\
\frac{dv}{dt}(t) &= aN(1-u_2(t))y(t) - \mu v(t), \\
\frac{dz}{dt}(t) &= cx(t)y(t)z(t) - hz(t).
\end{aligned}
\]  

The objective functional that we seek to maximize is defined by the following quadratic costs:
\[
J(u_1, u_2) = \int_0^{t_f} \left( x(t) + z(t) - \frac{A_1}{2} u_1^2(t) - \frac{A_2}{2} u_2^2(t) \right) dt,
\]  
where \( t_f \) is the period of treatment, \( A_1 \) and \( A_2 \) represent the financial and physiological costs associated with the administration of the two treatments respectively. \( A_1 > 0, A_2 > 0 \) reflect the extent of toxicity of the administered drugs. The two control functions, \( u_1(t) \) and \( u_2(t) \) are assumed to be bounded and Lebesgue integrable. The quadratic terms \( u_1^2(t) \) and \( u_2^2(t) \) reflect the expectation that the side-effects of the drugs are nonlinear [1, 25]. Our target is to maximize the objective functional defined in equation (6) by increasing the number of the uninfected cells, the CTLs immune responses and the viral load and minimizing the cost of treatment. In other words, we are seeking optimal control pair \((u_1^*, u_2^*)\) such that:
\[
J(u_1^*, u_2^*) = \max \{ J(u_1, u_2) : (u_1, u_2) \in U \},
\]
where the control set \( U \) is defined by
\[ U = \{(u_1(t), u_2(t)) : u_i(t) \text{ measurable}, a_i \leq u_i(t) \leq b_i, t \in [0, t_f], i = 1, 2\}. \] (7)

where \(0 < a_i \leq u_i \leq b_i < 1\) for \(i = 1, 2\). Here \(a_i\) and \(b_i\) act as the lower and upper bound on the therapeutic efficacy \(u_i\) \((i = 1, 2)\).

### 3.1 Existence of an optimal control pair.

In order to prove the existence of an optimal control pair and the uniqueness of the optimal system, we need the upper bounds of the state variables [10]. Note that the super-solutions \(x(t), y(t), v(t)\) and \(z(t)\) are uniformly bounded.

Now, we prove the existence of an optimal control pair. We illustrate the sufficient condition using the result of Fleming and Rishel (see Theorem 4.1, pp 68–69 in [11]).

**Theorem 3.1.** There exists an optimal control pair \((u_1^*, u_2^*) \in U\) such that

\[ J(u_1^*, u_2^*) = \max_{(u_1, u_2) \in U} J(u_1, u_2). \]

**Proof.** To use the existence result in [11], we must check the following properties:

(P1) The set of controls and corresponding state variables is nonempty.

(P2) The control \(U\) set is convex and closed.

(P3) The right-hand side of each equation of (5) is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of a control pair \((u_1, u_2)\) with coefficients depending on time and state.

(P4) The integrand of the objective functional \(L(\vec{X}, \vec{u}, t)\) is concave on \(U\).

(P5) There exists constants \(c_1\) and \(c_2 > 0\), such that the integrand \(L(\vec{X}, \vec{u}, t)\) of the objective functional satisfies

\[ L(\vec{X}, \vec{u}, t) \geq -c_1 + c_2(|u_1|^2 + |u_2|^2). \]

Where

\[ L(\vec{X}, \vec{u}, t) = x(t) + z(t) - \frac{A_1}{2} u_1^2(t) - \frac{A_2}{2} u_2^2(t), \]

with \(\vec{X} = (x, y, v, z)\) and \(\vec{u} = (u_1, u_2)\).

(P1) The boundedness of the system of state equations under the two controls (5) ensures the existence of a solution. We can therefore conclude that the set of controls and the corresponding state variables is non-empty, which gives condition (P1).

(P2) The control set is convex and closed by definition, which gives condition (P2).

(P3) It can be easily seen that the right-hand side of the each equation of (5) is continuous and can be written as:

\[ \vec{f}(t, \vec{X}, \vec{u}) = \varphi(t, \vec{X}) + \psi(t, \vec{X})\vec{u}. \]

Since the system is bilinear in \(u_1, u_2\) and the solutions of the system (5) are bounded, we have

\[ |\vec{f}(t, \vec{X}, \vec{u})| \leq c_0(1 + |\vec{X}| + |\vec{u}|), \]

where \(\vec{X} = (x, y, v, z)\) and \(\vec{u} = (u_1, u_2)\) and \(c_0\) depends on the coefficients of the state system (5).
The Hessian matrix of the integrand \( L \) is given by

\[
M_L = \begin{pmatrix} -A_1 & 0 \\ 0 & -A_2 \end{pmatrix},
\]

then its determinant is given as follows

\[
det(M_L) = A_1 A_2 \geq 0, \quad \forall (u_1, u_2) \in U,
\]

which implies the concavity of the integrand on \( U \).

\( P_5 \) For the last part, we have

\[
L(\bar{X}, \bar{u}, t) = x(t) + z(t) - \frac{A_1}{2} u_1^2(t) - \frac{A_2}{2} u_2^2(t)
\]

\[
L(\bar{X}, \bar{u}, t) \leq c_2 - \sum_{i=1,2} \frac{A_i}{2} u_i^2(t)
\]

\[
L(\bar{X}, \bar{u}, t) \leq c_2 - c_1 (|u_1|^2 + |u_2|^2),
\]

where \( c_1 \) depends on the upper bound on \( x, z \) and \( c_2 = \min \left( \frac{A_1}{2}, \frac{A_2}{2} \right) \).

We conclude that there exists an optimal control pair \( \bar{u}^* = (u_1^*, u_2^*) \in U \) such that

\[
J(u_1^*, u_2^*) = \max_{(u_1, u_2) \in U} J(u_1, u_2).
\]

\[\square\]

3.2. Optimality system. We have already proved the existence of an optimal control pair which minimizes the functional (6) subject to (5). We now use Pontryagin’s minimum principle to derive the necessary conditions for the optimal control [19]. However, it will be worthy to notice that there exist other efficient optimal control methods for some problems dealing with switching or time-delay optimal control [13, 14, 26]. In our case the Hamiltonian is given by

\[
H(t, x, y, v, z, \tau, \nu, u_1, u_2, \lambda) = \frac{A_1}{2} u_1^2 + \frac{A_2}{2} u_2^2 - x - z + \sum_{i=1}^4 \lambda_i f_i
\]

\[
- w_{11}(t)(b_1 - u_1) - w_{12}(t)(u_1 - a_1)
\]

\[
- w_{21}(t)(b_2 - u_2) - w_{22}(t)(u_2 - a_2),
\]

with

\[
\begin{align*}
    f_1 &= \lambda - dx(t) - \frac{k_1(1 - u_1(t))x(t)v(t)}{x(t) + v(t)}, \\
    f_2 &= \frac{\beta(1 - u_1(t))x(t) - \nu(t)}{x(t) + v(t)} - a\nu(t) - p\nu(t)z(t), \\
    f_3 &= a\nu(1 - u_2(t))s(t) - \nu(t), \\
    f_4 &= cx(t)y(t)z(t) - hz(t),
\end{align*}
\]

with \( w_{11}(t), w_{12}(t), w_{21}(t), w_{22}(t) \geq 0 \) are penalty multipliers satisfying

\[
w_{11}(t)(b_1 - u_1) = 0, \quad w_{12}(t)(u_1 - a_1) = 0 \text{ at } u_1^* 
\]

\[
w_{21}(t)(b_2 - u_2) = 0, \quad w_{22}(t)(u_2 - a_2) = 0 \text{ at } u_2^*. 
\]

By applying Pontryagin’s minimum principle in state, we obtain the following theorem.
Theorem 3.2. For any optimal controls $u_1^*, u_2^*$, and solutions $x^*, y^*, v^*$ and $z^*$ of the corresponding state system (5), there exist adjoint variables, $\lambda_1, \lambda_2, \lambda_3$ and $\lambda_4$ satisfying the equations

\[
\begin{align*}
\lambda_1'(t) &= 1 + \lambda_1(t) \left( d + \beta (1 - u_1^*(t)) \left( \frac{v^*(t)}{x^*(t) + v^*(t)} \right)^2 \right) - \lambda_4 cy^*(t) z^*(t) \\
&\quad + \chi_{[0,t_f-\tau]}(t) \lambda_2(t + \tau) \left( u_1^*(t + \tau) - 1 \right) \beta e^{-k\tau} \left( \frac{v^*(t)}{x^*(t) + v^*(t)} \right)^2, \\
\lambda_2(t) &= \lambda_2(t) (a + pz^*(t)) - \lambda_3(t)aN \left( 1 - u_1^*(t) \right) - \lambda_4(t)cx^*(t)z^*(t), \\
\lambda_3(t) &= \lambda_1(t) \beta (1 - u_1^*(t)) \left( \frac{x^*(t)}{x^*(t) + v^*(t)} \right)^2 + \mu \lambda_3(t) \\
&\quad + \chi_{[0,t_f-\tau]}(t) \lambda_2(t + \tau) \left( u_1^*(t + \tau) - 1 \right) \beta e^{-k\tau} \left( \frac{x^*(t)}{x^*(t) + v^*(t)} \right)^2, \\
\lambda_4(t) &= 1 + \lambda_4(t) (b - cxy^*(t)) + \lambda_3(t)py^*(t),
\end{align*}
\]

with the transversality conditions

\[
\lambda_i(t_f) = 0, \quad i = 1, \ldots, 4.
\]

Moreover, the optimal control is given by

\[
\begin{align*}
\lambda_1^*(t) &= \min \left( b_1, \max \left( \frac{\beta}{A_1} \left( \lambda_2(t) \frac{v^*(t - \tau)x^*(t - \tau)}{v^*(t - \tau) + x^*(t - \tau)} - \lambda_1(t) k_1 v^*(t)x^*(t) \right) \right) \right), \\
\lambda_2^*(t) &= \min \left( b_2, \max \left( \frac{1}{A_2} \left( \lambda_3(t)aNy^*(t) \right) \right) \right).
\end{align*}
\]

Proof. The adjoint equations and transversality conditions can be obtained by using Pontryagin’s maximum principle [19], such that

\[
\begin{align*}
\lambda_1'(t) &= -\frac{\partial H}{\partial x^*} (t) - \chi_{[0,t_f-\tau]}(t + \tau) \frac{\partial H}{\partial x^*} (t + \tau), \quad \lambda_1(t_f) = 0, \\
\lambda_2'(t) &= -\frac{\partial H}{\partial y^*} (t), \quad \lambda_2(t_f) = 0, \\
\lambda_3'(t) &= -\frac{\partial H}{\partial v^*} (t) - \chi_{[0,t_f-\tau]}(t + \tau) \frac{\partial H}{\partial v^*} (t + \tau), \quad \lambda_3(t_f) = 0, \\
\lambda_4'(t) &= -\frac{\partial H}{\partial z^*} (t), \quad \lambda_4(t_f) = 0.
\end{align*}
\]

The optimal control $u_1^*$ and $u_2^*$ can be solved from the optimality conditions,

\[
\frac{\partial H}{\partial u_1} (t) = 0, \quad \frac{\partial H}{\partial u_2} (t) = 0.
\]
Then, by calculating the derivative of $H$, we obtain
\[
\frac{\partial H}{\partial u_1}(t) = A_1 u_1(t) + \lambda_1(t) \beta \frac{v^*(t)x^*(t)}{v^*(t) + x^*(t)} - \lambda_2(t) \beta \frac{v^*(t)x^*(t)}{v^*(t) + x^*(t)} + \frac{\partial H}{\partial u_2}(t) = A_2 u_2(t) - aN_3(t)y(t) + w_{21}(t) - w_{22}(t) = 0 \text{ at } u_1^*,
\]
using (10), (11) and the boundedness of the two controls in $U$, we obtain the following optimal control:
\[
u_1^* = \min \left( b_1, \max \left( \frac{\partial H}{\partial u_1}(t), \frac{\partial H}{\partial u_2}(t) \right) \right),
\]
\[
u_2^* = \min \left( b_2, \max \left( 1, \frac{1}{A_2} (3(t)aNy^*(t)) \right) \right).
\]
If we substitute $u_1^*$ and $u_2^*$ in the systems (5) and (12), we obtain the following optimality system:
\[
\begin{align*}
\frac{dx^*}{dt} &= \lambda - \frac{d}{dt} - \frac{\beta(1 - u_1^*)x(t)v^*(t)}{x^*(t) + v^*(t)}, \\
\frac{ds^*}{dt} &= \frac{\beta(1 - u_1^*)x(t)v^*(t)}{x^*(t) + v^*(t)} - ay^*(t) - py^*(t)z^*(t), \\
\frac{dv^*}{dt} &= aN(1 - u_2^*)y^*(t) - \mu v^*(t), \\
\frac{dz^*}{dt} &= cx^*(t)y^*(t)z^*(t) - b z^*(t),
\end{align*}
\]
Using the system (15), we obtain
\[
\begin{align*}
\lambda_1^*(t) &= 1 + \lambda_1(t) \left( d + \beta(1 - u_1^*) \left( \frac{v^*(t)}{x^*(t) + v^*(t)} \right)^2 \right) - \lambda_1 ay^*(t)z^*(t) \\
&\quad + \chi_{[0,t_f]}(t) \beta \left( u_1^*(t + \tau) - 1 \right) \beta e^{-k(t)} \left( \frac{v^*(t)}{x^*(t) + v^*(t)} \right)^2, \\
\lambda_2^*(t) &= \lambda_2(1 + \beta z^*(t)) - \lambda_3(t) aN(1 - u_2^*) - \lambda_4(t) cx^*(t)z^*(t), \\
\lambda_3^*(t) &= \lambda_3(t) \beta(1 - u_1^*) \left( \frac{x^*(t)}{x^*(t) + v^*(t)} \right) + \mu \lambda_3(t) \\
&\quad + \chi_{[0,t_f]}(t) \beta \left( u_1^*(t + \tau) - 1 \right) \beta e^{-k(t)} \left( \frac{x^*(t)}{x^*(t) + v^*(t)} \right)^2, \\
\lambda_4^*(t) &= 1 + \lambda_4(1 - b - cx^*(t)) + \lambda_5(t)py^*(t),
\end{align*}
\]
and the transversality conditions is given by
\[
\lambda_i(t_f) = 0, i = 1, ..., 4.
\]

4. Numerical Simulations. In order to solve our optimality system (5), we will use a numerical scheme based on forward and backward finite difference approximation. Hence, we will have the following numerical algorithm
Step 1: for $i = -m, \ldots , 0$, do:
\begin{align*}
x(i+1) &= x_i + h_t[\lambda - dx_i - \beta(1 - u_1^i) \frac{v_1 x_i}{v_1 + x_i}], \\
y(i+1) &= y_i + h_t[\beta(1 - u_1^i) \frac{x_{i-m} v_{i-m}}{x_{i-m} + v_{i-m}} - ay_i - py_i z_i], \\
v(i+1) &= v_i + h_t[(1 - u_2^i)aN_y i - \mu v_i], \\
z(i+1) &= z_i + h_t[c_y z_i - h z_i], \\
\lambda_1^{n-i-1} &= \lambda_1^{n-i} - h_t[1 + \lambda_1^{n-i}(d_1 + \beta(1 - u_1^i)(\frac{v_{i+1}}{x_{i+1} + v_{i+1}})^2) \\
&\quad + \chi_{[0,t_f-r]}(t_{n-i})\lambda_2^{n-i+m} \beta(u_1^i - 1)\frac{v_{i+1}}{x_{i+1-m} + v_{i+1-m}}^2], \\
\lambda_2^{n-i} &= \lambda_2^{n-i} - h_t[\lambda_2^{n-i}(a + p z_{i+1}) - \lambda_2^{n-i} a N (1 - u_2^i) - \lambda_4^{n-i} c z_{i+1}], \\
\lambda_3^{n-i} &= \lambda_3^{n-i} - h_t[\lambda_3^{n-i} \beta(1 - u_1^i)(\frac{v_{i+1}}{x_{i+1} + v_{i+1}})^2] \\
&\quad + \chi_{[0,t_f-r]}(t_{n-i})\lambda_2^{n-i+m} \beta(u_1^i - 1)(\frac{x_{i+1+m}}{x_{i+1-m} + v_{i+1-m}})^2], \\
\lambda_4^{n-i} &= \lambda_4^{n-i} - h_t[\lambda_4^{n-i}(h - c y_{i+1}) + \lambda_4^{n-i} p z_{i+1}] \\
R_1^{i+1} &= (b_1/A_1) (\lambda_2^{n-i} - \lambda_3^{n-i} a N y_{i+1}) \\
R_2^{i+1} &= (1/A_2) \lambda_3^{n-i} a N y_{i+1}, \\
u_1^{i+1} &= \min(b_1, \max(R_1^{i+1}, a_1)), \\
u_2^{i+1} &= \min(b_2, \max(R_2^{i+1}, a_2)),
\end{align*}
end for

Step 2:
for $i = 0, \ldots , n-1$, do:
\begin{align*}
x(i+1) &= x_i + h_t[\lambda - dx_i - \beta(1 - u_1^i) \frac{v_1 x_i}{v_1 + x_i}], \\
y(i+1) &= y_i + h_t[\beta(1 - u_1^i) \frac{x_{i-m} v_{i-m}}{x_{i-m} + v_{i-m}} - ay_i - py_i z_i], \\
v(i+1) &= v_i + h_t[(1 - u_2^i)aN_y i - \mu v_i], \\
z(i+1) &= z_i + h_t[c_y z_i - h z_i], \\
\lambda_1^{n-i-1} &= \lambda_1^{n-i} - h_t[1 + \lambda_1^{n-i}(d_1 + \beta(1 - u_1^i)(\frac{v_{i+1}}{x_{i+1} + v_{i+1}})^2) \\
&\quad + \chi_{[0,t_f-r]}(t_{n-i})\lambda_2^{n-i+m} \beta(u_1^i - 1)\frac{v_{i+1}}{x_{i+1-m} + v_{i+1-m}}^2], \\
\lambda_2^{n-i} &= \lambda_2^{n-i} - h_t[\lambda_2^{n-i}(a + p z_{i+1}) - \lambda_2^{n-i} a N (1 - u_2^i) - \lambda_4^{n-i} c z_{i+1}], \\
\lambda_3^{n-i} &= \lambda_3^{n-i} - h_t[\lambda_3^{n-i} \beta(1 - u_1^i)(\frac{v_{i+1}}{x_{i+1} + v_{i+1}})^2] \\
&\quad + \chi_{[0,t_f-r]}(t_{n-i})\lambda_2^{n-i+m} \beta(u_1^i - 1)(\frac{x_{i+1+m}}{x_{i+1-m} + v_{i+1-m}})^2], \\
\lambda_4^{n-i} &= \lambda_4^{n-i} - h_t[\lambda_4^{n-i}(h - c y_{i+1}) + \lambda_4^{n-i} p z_{i+1}] \\
R_1^{i+1} &= (b_1/A_1) (\lambda_2^{n-i} - \lambda_3^{n-i} a N y_{i+1}) \\
R_2^{i+1} &= (1/A_2) \lambda_3^{n-i} a N y_{i+1}, \\
u_1^{i+1} &= \min(b_1, \max(R_1^{i+1}, a_1)), \\
u_2^{i+1} &= \min(b_2, \max(R_2^{i+1}, a_2)),
\end{align*}
end for

Step 3:
for $i = 1, \ldots , n$, write:
\begin{align*}
x^*(t_i) &= x_i, \ y^*(t_i) = y_i, \ v^*(t_i) = v_i, \ z^*(t_i) = z_i, \ u_1^*(t_i) = u_1^i, \ u_2^*(t_i) = u_2^i.
\end{align*}
end for

The numerical algorithm.

The convergence of our numerical method is tested by successive decreasing of time steps.

For the purpose of this work, we will assume that the minimum and maximum of the controls to be $a_i = 0.01$ and $b_i = 0.99, i = 1, 2$. The optimal control pair $\bar{u}^* = (u_1^*, u_2^*)$ is obtained for a period of 200 days of observation. The parameters of our numerical simulations are taken from the works of [3], $\lambda = 1$, $d = 0.1, \beta = 0.00025$, $a = 0.2$, $p = 0.001$, $N = 1500$, $\mu = 3$, $c = 0.03$ and $h = 0.2$. The cost coefficients that were introduced in the definition of the objective functional (6) are $A_1 = 5000$ and $A_2 = 5000$ [18].

Figure 1 shows that with control the amount of the uninfected cells is higher than those observed for without control case.

Figure 2 shows that with control the number of infected cells vanishes after the first days of therapy. However, without control this number remains at positive level 0.35.

The role of therapy control is also observed in Fig. 3. It was shown that with control, the number of the virus dies out after the first days of therapy, while without
control it stays equal to 158.16. This indicates the impact of the administrated therapy in controlling viral replication.

The CTL cells are clearly affected by the control. This is shown in Fig. 4; indeed the curve of CTL cells converges towards zero with control, while without any control it converges towards $1.2 \times 10^4$ which reveals the importance of CTL component in viral dynamics.

**Figure 1.** The uninfected cells as function of time.

**Figure 2.** The infected cells as function of time.
The two optimal controls $u_1$ and $u_2$ corresponding to blocking new infections and inhibiting viral production are represented in Fig. 5. The two curves represent the drug administration schedule during the period of treatment. Both controls start from zero, after a few days, the first treatment reaches its maximum value one, the second drug reaches its maximum value one after the 145$^{th}$ days. In this case, the new infection is totally blocked.
5. Conclusion and discussion. In this paper, we have presented a model of the viral infection where the patient is subjected to the combination therapy. We have formulated an optimal control problem with the objective is minimizing the levels of infected cells and free virus as well as the therapeutic cost of the combination treatment. The existence and uniqueness of the optimal controls using Pontryagin’s maximum principle is established. The problem was solved numerically using backward and forward finite difference scheme. It was shown that with the two optimal treatments, the number of the healthy cells increases remarkably while the number of infected cells decreases significantly. In addition, it was also observed that, with the control strategy, the viral load decreases considerably compared with the model without control which can improve the patient’s life quality.

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