

Optimal control and infectiology: Application to an HIV/AIDS model

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Abstract

An existing infectious model describing the interaction of HIV virus and the immune system of the human body is utilized to determine the optimal methodology for administering anti-viral medication therapies to fight HIV infection. This work investigates the fundamental role of chemotherapy treatment in controlling the virus reproduction. We work in the nonlinear optimal control framework. The existence and the uniqueness results of the solution are discussed. A characterization of the optimal control via adjoint variables is established. We obtain an optimality system that we seek to solve numerically by a competitive Gauss–Seidel like implicit difference method.

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1. Introduction

In recent years, several studies have been devoted to understand the spread of infectious diseases [2,3,5,12]. The acquired immunodeficiency syndrome (AIDS) emerged in 1981 and has become an important sexuality transmitted disease throughout the world. Consequently, many mathematical models have been developed to describe the relationships between the Human Immunodeficiency Virus (HIV), etiological agent for AIDS, and $CD4^+T$ cells which are the target for the virus [1,4,6,13]. These models are utilized to explore optimal chemotherapy treatment to avoid an excessive use of drugs [14–17,19]. Indeed, when these drugs are administered in high dose they are toxic to the human body and cause damages. For the purposes of this investigation, we will expound on the model of Gumel et al. [11] given, for all $t > t_0$, by

$$\frac{dT_4(t)}{dt} = \varrho s + rT_4(t)V(t) - \gamma_1 T_4(t) - k_v T_a(t)V(t), \quad (1)$$

$$\frac{dT_i(t)}{dt} = k_v T_a(t)V(t) + k_v r T_4(t)V(t) - \gamma_2 T_i(t) - k_c k_v T_a(t)V(t) - k_c k_v r T_4(t)V(t), \quad (2)$$

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$$\frac{dV(t)}{dt} = N(1 - L)T_i(t) - \gamma_3 V(t) - k_t T_r(t)V(t), \quad (3)$$

$$T_a(t) = \alpha T_4(t); \quad 0 < \alpha < 1. \quad (4)$$

$$T_r(t) = (1 - \alpha)T_4(t) \quad (5)$$

and satisfying $T_4(t_0) = T_4^0$, $T_i(t_0) = T_i^0$ and $V(t_0) = V^0$ where T_4 indicates the abundance of healthy $CD4^+$ cells, T_i represents the abundance of infected $CD4^+$ cells and V designates the abundance of free viruses. Activated and resting $CD4^+$ cells are respectively denoted T_a and T_r .

The first term in Eq. (1) describes the efficiency of thymic output (where s is the rate of supply of $CD4^+$ cells from precursors and ϱ is the value of functioning thymus). The second term in this equation represents the maximum proliferation of $CD4^+$ T cells due to primary HIV infection at a rate r , so that the T_4 cells never grow larger than a value T_4^{\max} . The third term translates the death of uninfected T cells at a constant rate γ_1 . The fourth term models the infection of the activated cells T_a leading to HIV integration at a rate k_v .

The first term in Eq. (2) encompasses the production of pre-existing activated $CD4^+$ T cells. The second term indicates the infection of newly-activated $CD4^+$ T cells. The third term models the natural death of infected $CD4^+$ T cells. The fourth and the last terms explain the anti-HIV CTL action and the viral lysis at a constant rate k_c .

In Eq. (3) the first term quantifies the production of HIV from infected $CD4^+$ T cells at a rate N , except for those infected latently (L). The second term transmits the death of free virus particles at a rate γ_3 . The third term models the viral entry into quiescent resting $CD4^+$ T cells T_r and their thymic precursors at a constant rate k_t .

In this paper, we are concerned with the problem of adopting the best strategy of treatment; more exactly we seek to search a maximum count of healthy cells with a minimum dose of the administered drugs. To introduce a control to the above mentioned model, we analyse the interactions of healthy $CD4^+$ T cells, infected $CD4^+$ T cells and free virus: two major categories of anti-retroviral drugs to combat HIV are reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). RTIs prevent new HIV infection by disrupting the conversion of viral RNA into DNA inside of T cells. PIs reduce the number of viruses particles produced by an actively-infected T cells [17,7].

Hence, if we denote $u_1(t)$ the RTI control variable and $u_2(t)$ the PI control variable equations (1)–(3) can be re-written, to accommodate control actions or chemotherapy treatment, as follows:

$$\frac{dT_4(t)}{dt} = \varrho s + rT_4(t)V(t) - \gamma_1 T_4(t) - k_v(1 - u_1(t))T_a(t)V(t), \quad (6)$$

$$\begin{aligned} \frac{dT_i(t)}{dt} &= k_v(1 - u_1(t))T_a(t)V(t) + k_v(1 - u_1(t))rT_4(t)V(t) - \gamma_2 T_i(t) \\ &\quad - k_c k_v T_a(t)V(t) - k_c k_v r T_4(t)V(t), \end{aligned} \quad (7)$$

$$\frac{dV(t)}{dt} = N(1 - L)(1 - u_2(t))T_i(t) - \gamma_3 V(t) - k_t T_r(t)V(t), \quad (8)$$

with given initial values for T_4 , T_i and V at t_0 respectively by T_4^0 , T_i^0 and V^0 .

Using $T_a = \alpha T_4$ and $T_r = (1 - \alpha)T_4$, the system (6)–(8) may be written as

$$\frac{dT_4(t)}{dt} = \varrho s + rT_4(t)V(t) - \gamma_1 T_4(t) - \alpha k_v(1 - u_1(t))T_4(t)V(t), \quad (9)$$

$$\begin{aligned} \frac{dT_i(t)}{dt} &= \alpha k_v(1 - u_1(t))T_4(t)V(t) + r k_v(1 - u_1(t))T_4(t)V(t) - \gamma_2 T_i(t) \\ &\quad - \alpha k_c k_v T_4(t)V(t) - r k_c k_v T_4(t)V(t), \end{aligned} \quad (10)$$

$$\frac{dV(t)}{dt} = N(1 - L)(1 - u_2(t))T_i(t) - \gamma_3 V(t) - (1 - \alpha)k_t T_4(t)V(t). \quad (11)$$

Define the objective functional

$$J(u_1, u_2) = \int_{t_0}^{t_f} \{T_4(t) - [A_1(u_1(t))^2 + A_2(u_2(t))^2]\} dt.$$

In words, we are maximizing the benefit based on the healthy T cells count and minimizing the cost based on the percentage effect chemotherapy given (i.e. u_1 and u_2). The parameters $A_1 \geq 0, A_2 \geq 0$ represent the weights on the benefit and cost.

The goal is to seek an 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 U is the control set defined by

$$U = \{u = (u_1, u_2) : u_i \text{ measurable, } 0 \leq u_i(t) \leq 1, t \in [t_0, t_f] \text{ for } i = 1, 2\}.$$

The basic framework of this problem is to prove the existence and the uniqueness of the optimal control and to characterize it.

To illustrate this study, numerical simulations are given using a Gauss–Seidel like first order implicit finite-difference method developed by [11].

Notation: $(\cdot, \cdot)_{\mathbb{R}^n}$ indicates the usual product scalar in \mathbb{R}^n for all $n \in \mathbb{N}$.

2. Existence of an optimal control pair

We show the existence of the solution through a classical result well known: according to [10], the solution exists if the following hypotheses are met:

- (H_1) The set of controls and corresponding state variables is non-empty.
- (H_2) The admissible control set U is closed and convex.
- (H_3) Each right hand side of Eqs. (9)–(11) is continuous, is bounded above by a sum of the bounded control and state, and can be written as a linear function of u with coefficients depending on time and state.
- (H_4) There exist constants $c_1, c_2 > 0$ and $\beta > 1$ such that the integrand $L(y, u, t)$ of the objective functional J is concave and satisfies

$$L(y, u, t) \leq c_2 - c_1(|u_1(t)|^2 + |u_2(t)|^2)^{\beta/2}.$$

Theorem 2.1. *Given the objective functional $J(u_1, u_2) = \int_{t_0}^{t_f} \{T_4(t) - [A_1(u_1(t))^2 + A_2(u_2(t))^2]\} dt$ where $U = \{u = (u_1, u_2) : u_i \text{ measurable, } 0 \leq u_i(t) \leq 1, t \in [t_0, t_f] \text{ for } i = 1, 2\}$ subject to Eqs. (9)–(11) with $T_4(0) = T_4^0, T_i(0) = T_i^0$ and $V(t_0) = V^0$, then there exists an optimal control $u^* = (u_1^*, u_2^*)$ such that $\max_{u \in U} J(u_1, u_2) = J(u_1^*, u_2^*)$.*

Proof

- (H_1) Since the system Eqs. (9)–(11) has bounded coefficients and any solutions are bounded on the finite time interval, we can use a result from [18] to obtain the existence of the solution of the system Eqs. (9)–(11).
- (H_2) It suffices to remark that $U = U_1 \times U_2$, where U_1 and U_2 are closed and convex sets defined by

$$U_1 = U_2 = \{u \text{ measurable; } u(t) \in [0, 1] \forall t \in [t_0, t_f]\}.$$
- (H_3) By definition, each right hand side of system (9)–(11) is continuous and can be written as a linear function of u with coefficients depending on time and state. Furthermore, The fact that all variables T_4, T_i, V , and u are bounded on $[t_0, t_f]$ implies the rest of the hypothesis.
- (H_4) It is easy to see that $(-L(y, u, t))$ is convex in U and so the integrand $L(y, u, t)$ is concave in U . Also, it suffices to choose $c_1 = \inf(A_1, A_2), c_2 = T_4^{\max}$ and $\beta = 2$ since we have

$$\begin{aligned} L(y, u, t) &= T_4(t) - [A_1(u_1(t))^2 + A_2(u_2(t))^2] \\ &\leq T_4^{\max} - \inf(A_1, A_2)(|u_1(t)|^2 + |u_2(t)|^2). \quad \square \end{aligned}$$

3. Characterization of the optimal control pair

Here, we discuss the theorem that relates to the characterization of the optimal control. This results depends on Pontryagin's Maximum Principle which gives necessary conditions for the optimal control [8]: at first, we rewrite the system (9)–(11) as follows:

$$\begin{cases} \frac{dy(t)}{dt} = A(y, u, t); & \forall t > t_0, \forall u \in U, \\ y(t_0) = y_0, \end{cases} \quad (12)$$

where $y(t)$ and $A(y, u, t)$ are vectors in \mathbb{R}^3 determined by

$$y(t) = \begin{pmatrix} T_4(t) \\ T_i(t) \\ V(t) \end{pmatrix}$$

and

$$A(y, u, t) = \begin{pmatrix} g_1(y, u, t) \\ g_2(y, u, t) \\ g_3(y, u, t) \end{pmatrix},$$

with $g_1(y, u, t)$, $g_2(y, u, t)$ and $g_3(y, u, t)$ are respectively the right hand side of Eqs. (9)–(11).

The Hamiltonian associated with our problem is

$$H(y, u, p, t) = L(y, u, t) + (p(t), A(y, u, t))_{\mathbb{R}^3}.$$

The adjoint vector $p(t)$ is defined by the adjoint equation

$$\frac{dp(t)}{dt} = -A_y^{\text{tr}} p(t) - L_y \quad (13)$$

and the final condition

$$p(t_f) = 0, \quad (14)$$

where A_y (resp. L_y) designates the derivative of the vector $A(y, u, t)$ (resp. of the integrand $L(y, u, t)$) with respect to y and A_y^{tr} is the transposed vector of A_y .

More exactly, the vectors A_y and L_y are defined by

$$A_y = \begin{pmatrix} \frac{\partial g_1}{\partial T_4} \\ \frac{\partial g_2}{\partial T_i} \\ \frac{\partial g_3}{\partial V} \end{pmatrix}$$

and

$$L_y = \begin{pmatrix} \frac{\partial L}{\partial T_4} \\ \frac{\partial L}{\partial T_i} \\ \frac{\partial L}{\partial V} \end{pmatrix}.$$

We obtain the optimality condition with the help of the Lagrangian, which is formed by adding a penalized term to the criterion. So, the Lagrangian $\mathcal{L}(y, u, p, t)$ is given by

$$\mathcal{L}(y, u, p, t) = H(y, u, p, t) + (w(t), Bu(t))_{\mathbb{R}^4}.$$

B is the operator defined from \mathbb{R}^2 to \mathbb{R}^4 by

$$Bu(t) = \begin{pmatrix} 1 - u_1(t) \\ u_1(t) \\ 1 - u_2(t) \\ u_2(t) \end{pmatrix},$$

$w(t)$ is the vector of \mathbb{R}^4 given by

$$w(t) = \begin{pmatrix} w_{11}(t) \\ w_{12}(t) \\ w_{21}(t) \\ w_{22}(t) \end{pmatrix},$$

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

$$w_{11}(t)(1 - u_1^*(t)) = w_{12}(t)u_1^*(t) = w_{21}(t)(1 - u_2^*(t)) = w_{22}(t)u_2^*(t) = 0. \tag{15}$$

According to Pontryagin’s Maximum Principle, if the control $u^*(t)$ and the corresponding state $y^*(t)$ are an optimal couple necessarily there exists an adjoint vector $p(t)$ defined by (13) and (14) such that the function $\mathcal{L}(y, \dots, p, t)$ reaches its maximum on the set U at the point u^* . It ensues the following result.

Theorem 3.1. *Given an optimal control pair $u^*(\cdot) = (u_1^*(\cdot), u_2^*(\cdot))$ and a solution $y^*(\cdot) = (T_4^*(\cdot), T_i^*(\cdot), V^*(\cdot))$ of the corresponding state system (9)–(11), there exist adjoint variables $\lambda_1(\cdot), \lambda_2(\cdot), \lambda_3(\cdot)$ satisfying*

$$\begin{aligned} \frac{d\lambda_1(t)}{dt} &= -1 + \lambda_1(t)[\gamma_1 + (\alpha k_v(1 - u_1^*(t)) - r)V^*(t)] + \lambda_2(t)[k_v(\alpha + r)(k_c - 1 + u_1^*(t))V^*(t)] \\ &\quad + \lambda_3(t)[k_t(1 - \alpha)V^*(t)], \\ \frac{d\lambda_2(t)}{dt} &= \lambda_2(t)\gamma_2 + \lambda_3(t)[N(L - 1)(1 - u_2^*(t))], \\ \frac{d\lambda_3(t)}{dt} &= \lambda_1(t)[(\alpha k_v(1 - u_1^*(t)) - r)T_4^*(t)] + \lambda_2(t)[(\alpha + r)(k_c k_v - k_v(1 - u_1^*(t)))T_4^*(t)] \\ &\quad + \lambda_3(t)[\gamma_3 + k_t(1 - \alpha)T_4^*(t)], \end{aligned}$$

with final conditions

$$\lambda_1(t_f) = \lambda_2(t_f) = \lambda_3(t_f) = 0.$$

Moreover

$$u_1^*(t) = \min(\max(0, R_1(t)), 1), \tag{16}$$

$$u_2^*(t) = \min(\max(0, R_2(t)), 1), \tag{17}$$

where

$$\begin{aligned} R_1(t) &= \frac{1}{2A_1}[\alpha k_v \lambda_1(t)T_4^*(t)V^*(t) - (\alpha + r)k_v \lambda_2(t)T_4^*(t)V^*(t)], \\ R_2(t) &= \frac{1}{2A_2}[N(L - 1)\lambda_3(t)T_i^*(t)]. \end{aligned}$$

Proof. In the precedent section, we proved the existence of an optimal couple $(y^*(\cdot), u^*(\cdot))$ for maximizing the functional J subject to Eqs. (9)–(11). So by direct application of Pontryagin’s Maximum Principle, it must exist

a vector $p(t) = \begin{pmatrix} \lambda_1(t) \\ \lambda_2(t) \\ \lambda_3(t) \end{pmatrix}$ checking (13) and (14).

That yields

$$\begin{aligned}\frac{d\lambda_1(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial T_4}, \frac{\partial g_2(y^*, u^*, t)}{\partial T_4}, \frac{\partial g_3(y^*, u^*, t)}{\partial T_4}\right) \begin{pmatrix} \lambda_1(t) \\ \lambda_2(t) \\ \lambda_3(t) \end{pmatrix} - \frac{\partial L(y^*, u^*, t)}{\partial T_4}, \\ \frac{d\lambda_2(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial T_i}, \frac{\partial g_2(y^*, u^*, t)}{\partial T_i}, \frac{\partial g_3(y^*, u^*, t)}{\partial T_i}\right) \begin{pmatrix} \lambda_1(t) \\ \lambda_2(t) \\ \lambda_3(t) \end{pmatrix} - \frac{\partial L(y^*, u^*, t)}{\partial T_i}, \\ \frac{d\lambda_3(t)}{dt} &= -\left(\frac{\partial g_1(y^*, u^*, t)}{\partial V}, \frac{\partial g_2(y^*, u^*, t)}{\partial V}, \frac{\partial g_3(y^*, u^*, t)}{\partial V}\right) \begin{pmatrix} \lambda_1(t) \\ \lambda_2(t) \\ \lambda_3(t) \end{pmatrix} - \frac{\partial L(y^*, u^*, t)}{\partial V}.\end{aligned}$$

A simple calculation leads to the three first equalities of the theorem.

Also, Pontryagin's Maximum Principle necessitates the following optimality conditions to have the couple (y^*, u^*) optimal:

$$\frac{\partial \mathcal{L}(y^*, u^*, p, t)}{\partial u_1} = 0, \quad \frac{\partial \mathcal{L}(y^*, u^*, p, t)}{\partial u_2} = 0.$$

It ensues from these equations

$$\begin{aligned}u_1^*(t) &= \frac{1}{2A_1} [\alpha \lambda_1(t) k_v T_4^*(t) V^*(t) - \lambda_2(t) k_v (\alpha + r) T_4^*(t) V^*(t) - \omega_{11}(t) + \omega_{12}(t)], \\ u_2^*(t) &= \frac{1}{2A_2} [\lambda_3(t) N(L-1) T_i^*(t) - \omega_{21}(t) + \omega_{22}(t)].\end{aligned}$$

According to (15), we distinguish three cases

(i) On the set $\{t; 0 < u_1^*(t) < 1\}$, $\omega_{11}(t) = \omega_{12}(t) = 0$. Then

$$u_1^*(t) = \frac{1}{2A_1} [\alpha \lambda_1(t) k_v T_4^*(t) V^*(t) - \lambda_2(t) k_v (\alpha + r) T_4^*(t) V^*(t)].$$

(ii) On the set $\{t; u_1^*(t) = 0\}$, $\omega_{11}(t) = 0$. In this case

$$0 = u_1^*(t) = \frac{1}{2A_1} [\alpha \lambda_1(t) k_v T_4^*(t) V^*(t) - \lambda_2(t) k_v (\alpha + r) T_4^*(t) V^*(t) + \omega_{12}(t)].$$

Or

$$-\frac{\omega_{12}(t)}{2A_1} = \frac{1}{2A_1} [\alpha \lambda_1(t) k_v T_4^*(t) V^*(t) - \lambda_2(t) k_v (\alpha + r) T_4^*(t) V^*(t)].$$

Since $\omega_{12}(t) \geq 0$, then $-\frac{\omega_{12}(t)}{2A_1} \leq 0$. Thus

$$0 = u_1^*(t) \geq \frac{1}{2A_1} [\alpha \lambda_1(t) k_v T_4^*(t) V^*(t) - \lambda_2(t) k_v (\alpha + r) T_4^*(t) V^*(t)].$$

(iii) On the set $\{t; u_1^*(t) = 1\}$, $\omega_{12}(t) = 0$. So

$$u_1^*(t) = \frac{1}{2A_1} [\alpha \lambda_1(t) k_v T_4^*(t) V^*(t) - \lambda_2(t) k_v (\alpha + r) T_4^*(t) V^*(t) - \omega_{11}(t)].$$

Since $\omega_{11}(t) \geq 0$, then $1 = u_1^*(t) \leq \frac{1}{2A_1} [\alpha \lambda_1(t) k_v T_4^*(t) V^*(t) - \lambda_2(t) k_v (\alpha + r) T_4^*(t) V^*(t)]$.

Combining all three cases in a compact form gives

$$u_1^*(t) = \min(\max(0, R_1(t)), 1).$$

Similarly, we conclude

$$u_2^*(t) = \min(\max(0, R_2(t)), 1). \quad \square$$

Remark 3.1. The optimality system is given by incorporating the optimal control pair in the state system coupled with the adjoint system. Thus, we have

$$\begin{cases} \frac{dy^*(t)}{dt} = A(y^*, u^*, t); & \forall t > t_0, \\ \frac{dp(t)}{dt} = -A_{y^*}^{tr} p(t) - L_{y^*}, \\ y^*(t_0) = y_0^*, \\ p(t_f) = 0. \end{cases} \tag{18}$$

We replace $u^* = (u_1^*, u_2^*)$ by its expression obtained in (16) and (17). The uniqueness of the solution of the optimality system is obtained by standard results. The reader can refer to [9,14] for more details on the proof.

4. Numerical illustration

4.1. The improved GSS1 method

The resolution of the optimality system is created improving the Gauss–Seidel-like implicit finite-difference method developed by [11] and denoted GSS1 method. It consists on discretizing the interval $[t_0, t_f]$ at the points $t_k = kl + t_0 (k = 0, 1, \dots, n)$, where l is the time step. Next, we define the state and adjoint variables $T_4(t), T_i(t), V(t), \lambda_1(t), \lambda_2(t), \lambda_3(t)$ and the controls $u_1(t), u_2(t)$ in terms of nodal points $T_4^k, T_i^k, V^k, \lambda_1^k, \lambda_2^k, \lambda_3^k, u_1^k, u_2^k$, with $T_4^0, T_i^0, V^0, \lambda_1^0, \lambda_2^0, \lambda_3^0, u_1^0, u_2^0$ as the state and adjoint variables and the controls at initial time t_0 . $T_4^n, T_i^n, V^n, \lambda_1^n, \lambda_2^n, \lambda_3^n, u_1^n, u_2^n$ as the state and adjoint variables and the controls at final time t_f . As it is well known, the approximation of the time derivative by its first-order *forward*-difference is given, for the first state variable T_4 , by

$$\frac{dT_4(t)}{dt} = \lim_{l \rightarrow 0} \frac{T_4(t+l) - T_4(t)}{l}.$$

We use the scheme developed by Gumel et al. [11] to adapt it to our case as following:

$$\frac{T_4^{k+1} - T_4^k}{l} = \varrho s + rT_4^{k+1}V^k - \gamma_1 T_4^{k+1} - \alpha k_v(1 - u_1^k)T_4^{k+1}V^k. \tag{19}$$

Similarly, we have

$$\frac{T_i^{k+1} - T_i^k}{l} = \alpha k_v(1 - u_1^k)T_4^{k+1}V^k + rk_v(1 - u_1^k)T_4^{k+1}V^k - \gamma_2 T_i^{k+1} - \alpha k_c k_v T_4^{k+1}V^k - rk_c k_v T_4^{k+1}V^k, \tag{20}$$

$$\frac{V^{k+1} - V^k}{l} = N(1 - L)(1 - u_2^k)T_i^{k+1} - \gamma_3 V^{k+1} - (1 - \alpha)k_t T_4^{k+1}V^{k+1}. \tag{21}$$

By using a similar technique, we approximate the time derivative of the adjoint variables by their first-order *backward*-difference and we use the appropriated scheme as follows:

$$\begin{aligned} \frac{\lambda_1^{n-k} - \lambda_1^{n-k-1}}{l} &= -1 + \lambda_1^{n-k-1}[\gamma_1 + (\alpha k_v(1 - u_1^k) - r)V^{k+1}] + \lambda_2^{n-k}[k_v(\alpha + r)(k_c - 1 + u_1^k)V^{k+1}] \\ &\quad + \lambda_3^{n-k}[k_t(1 - \alpha)V^{k+1}], \end{aligned} \tag{22}$$

$$\frac{\lambda_2^{n-k} - \lambda_2^{n-k-1}}{l} = \lambda_2^{n-k-1}\gamma_2 + \lambda_3^{n-k}[N(L - 1)(1 - u_2^k)], \tag{23}$$

$$\begin{aligned} \frac{\lambda_3^{n-k} - \lambda_3^{n-k-1}}{l} &= \lambda_1^{n-k-1}[(\alpha k_v(1 - u_1^k) - r)T_4^{k+1}] + \lambda_2^{n-k-1}[(\alpha + r)(k_c k_v - k_v(1 - u_1^k))T_4^{k+1}] \\ &\quad + \lambda_3^{n-k-1}[\gamma_3 + k_t(1 - \alpha)T_4^{k+1}]. \end{aligned} \tag{24}$$

Hence, we can establish an algorithm to solve the optimality system and then to compute the optimal control pair utilizing the improved GSS1 method (19)–(24) that we denote by IGSS1 method.

Algorithm

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step 1 :  $T_4(0) \leftarrow T_4^0, T_i(0) \leftarrow T_i^0, V(0) \leftarrow V^0, \lambda_1(t_n) \leftarrow 0, \lambda_2(t_n) \leftarrow 0, \lambda_3(t_n) \leftarrow 0, u_1(0) \leftarrow 0,$ 
 $u_2(0) \leftarrow 0.$ 

step 2 : for  $k = 1, \dots, n$  do
    
$$T_4^k \leftarrow \frac{T_4^{k-1} + l\rho s}{1 + l(\gamma_1 + (\alpha k_v(1 - u_1^{k-1}) - r))V^{k-1}}$$


$$T_i^k \leftarrow \frac{T_i^{k-1} + l k_v(\alpha + r)(1 - u_1^{k-1} - k_c)T_4^k V^{k-1}}{1 + l\gamma_2}$$


$$V^k \leftarrow \frac{V^{k-1} + lN(1-L)(1 - u_2^{k-1})T_i^k}{1 + l(\gamma_3 + (1 - \alpha)k_t T_4^k)}$$


$$\lambda_1^{n-k} \leftarrow \frac{\lambda_1^{n-k+1} + l(1 - \lambda_2^{n-k+1}(\alpha + r)k_v(k_c - 1 + u_1^{k-1}) - \lambda_3^{n-k+1}k_t(1 - \alpha))V^k}{1 + l(\gamma_1 + \alpha k_v(1 - u_1^{k-1}) - r)V^k}$$


$$\lambda_2^{n-k} \leftarrow \frac{\lambda_2^{n-k+1} + lN(1-L)(1 - u_2^{k-1})\lambda_3^{n-k+1}}{1 + l\gamma_2}$$


$$\lambda_3^{n-k} \leftarrow \frac{\lambda_3^{n-k+1} - l(\lambda_1^{n-k}\alpha k_v(1 - u_1^{k-1}) - \lambda_2^{n-k}k_v(\alpha + r)(k_c - 1 + u_1^{k-1}))T_4^k}{1 + l(\gamma_3 + (1 - \alpha)k_t T_4^k)}$$


$$R_1^k \leftarrow \frac{k_v(\alpha\lambda_1^{n-k} - (\alpha + r)\lambda_2^{n-k})T_4^k V^k}{2A_1}, R_2^k \leftarrow \frac{N(L-1)\lambda_3^{n-k}T_i^k}{2A_2}$$


$$u_1^k \leftarrow \min(\max(0, R_1^k), 1), u_2^k \leftarrow \min(\max(0, R_2^k), 1)$$

end for

step 3 : for  $k = 1, \dots, n$  write
 $T_4^*(t_k) = T_4^k, u_1^*(t_k) = u_1^k, u_2^*(t_k) = u_2^k.$ 
end for
    
```

4.2. Numerical results

Utilizing the same data than Gumel et al. [11] for numerical experiments, we approach this part to compare the disease progression before and after the treatment chemotherapy is introduced. So, for the following parameters and initial values: $s = 10, l = 1, r = 0.00003, k_v = 1, N = 1000, k_c = 0, \gamma_1 = \gamma_2 = 0.01, \gamma_3 = 0.2, L = 0.1, k_t = 0.8, \varrho = 1, \alpha = 0.02, T_4^0 = 1000, T_i^0 = 0$ and $V^0 = 0.001$ we obtain the table below. Let’s note that the fact to have $k_c = 0$ supposes that the CTL action, which plays an important role in suppressing viremia, is absent. This permits a best illustration of the chemotherapy role in the reduction viral population and the improvement of the immune response.

For more clearness, it is better to present these comparative results through graphs.

Time (days)	T_4 population in absence of treatment	T_4 population during treatment	Viral load V in absence of treatment	Viral load V during treatment
0	1000	1000	0.001	0.001
2	1000	1000	0.5	0.0227
4	789	999.5	307	0.5299
6	1	999.5	526,953	0.5196
10	0	999.6	2,589,467	0.4993
50	0	999.7	4,511,557	0.3353

When the virus attacks the human body, it kills the healthy $CD4^+$ cells and consequently the number of uninfected T cells reduces (Fig. 1). The virus V does not cease to proliferate and so its abundance increases (Fig. 3). But if we introduce the treatment, the situation changes. After few days, the effect of chemotherapy

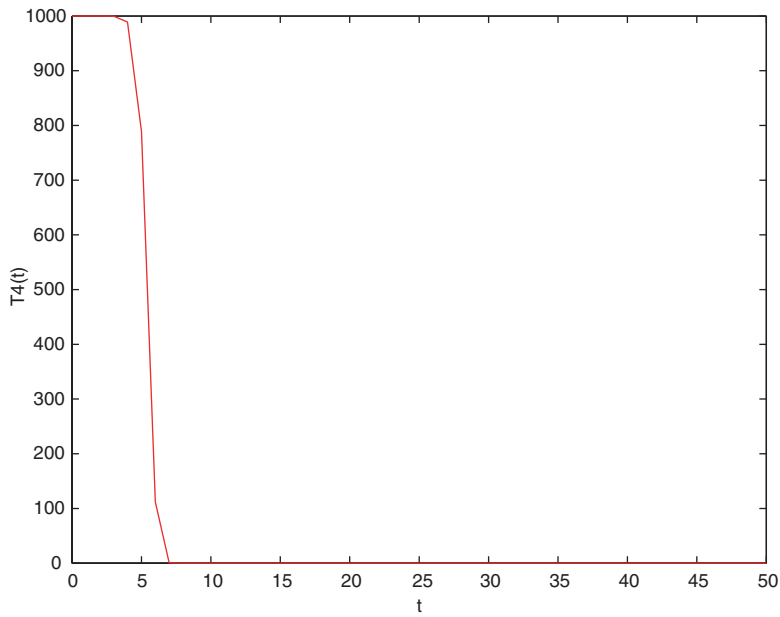


Fig. 1. Uninfected T cells in absence of treatment.

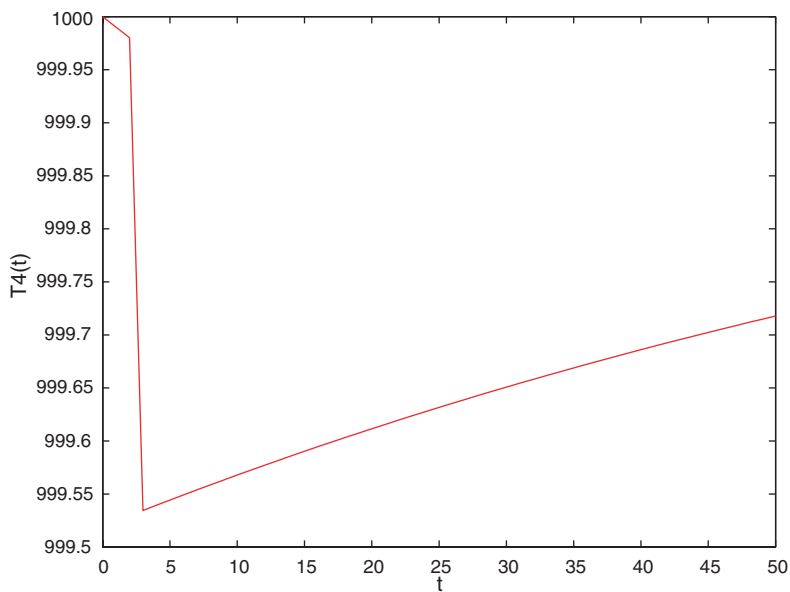


Fig. 2. Uninfected T cells in presence of treatment.

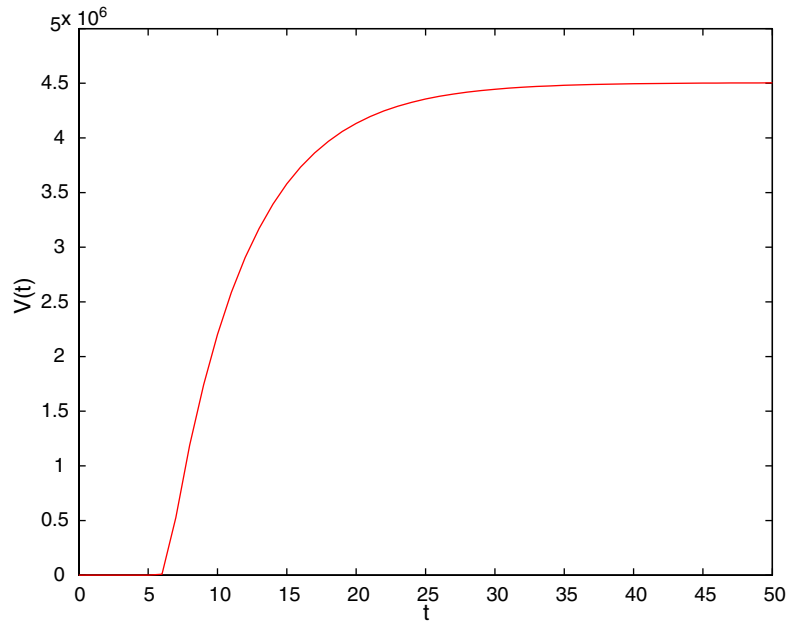


Fig. 3. Virus population in absence of treatment.

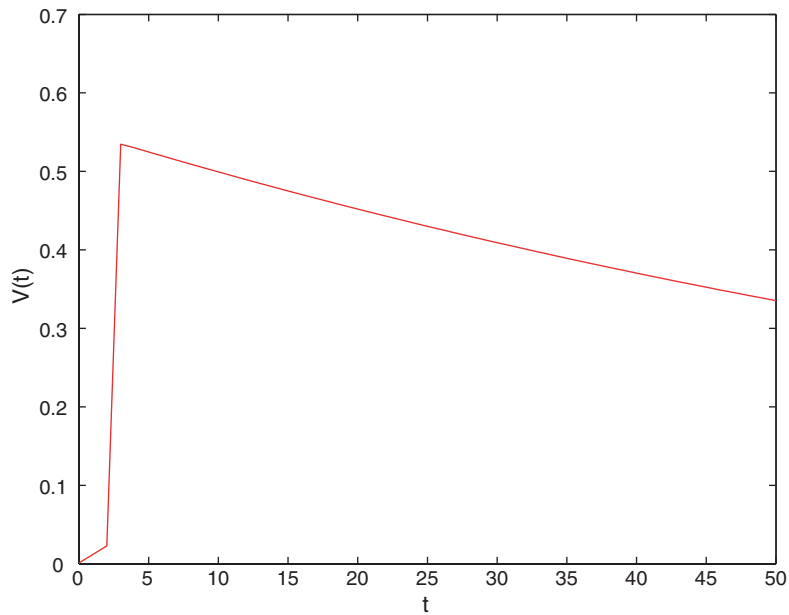


Fig. 4. Virus population in presence of treatment.

begins to appear; which explains the growth of uninfected T cells and the diminishing of virus V (Figs. 2 and 4). The optimal controls for drug administration are represented through Figs. 5 and 6 respectively by $U1$ and $U2$.

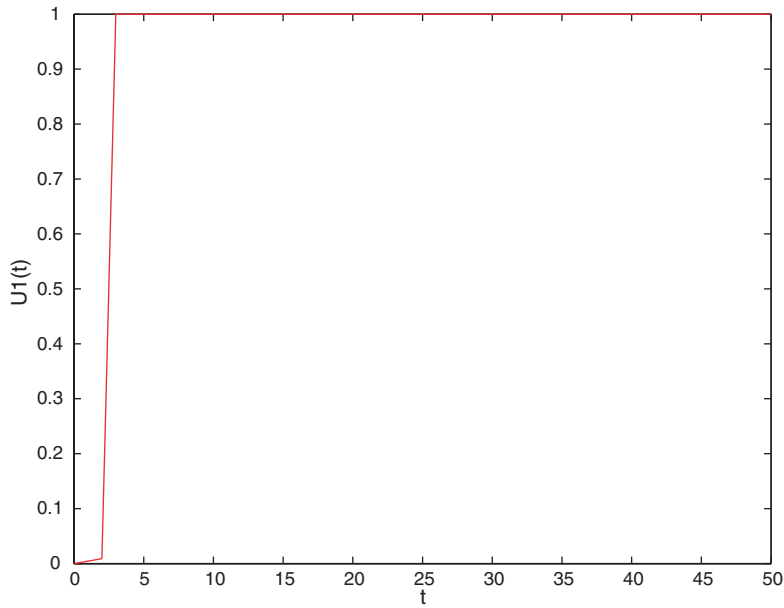


Fig. 5. First optimal control.

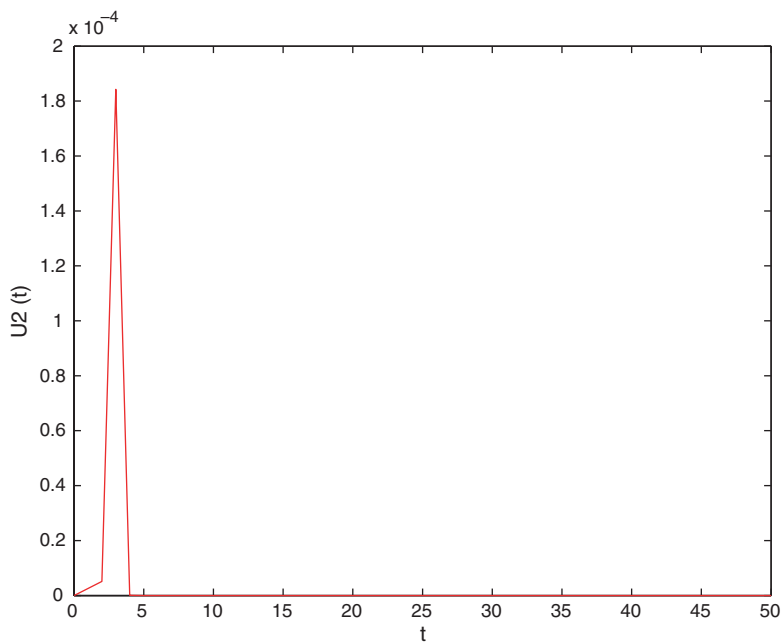


Fig. 6. Second optimal control.

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