

Optimal Control in Chemotherapy of a Viral Infection

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Abstract

In this study we develop some results concerning the optimal chemotherapy in case of HIV (human immunodeficiency virus). Generally, in viral infection, the drug strategy affects either the virus infectivity or reduce the virion production. The mathematical model proposed here, deals with the first situation, and represents an optimal control problem, with the state equation given by an ODE and the objective function based on a combination of maximizing benefit relied on T cells count (the white cells that coordinate activities of the immune system) and minimizing the systemic cost of chemotherapy. We demonstrate the existence of an optimal control and introduce the first order necessary optimality conditions in order to derive an algorithm to approximate the optimal chemotherapy strategy. Conclusive numerical simulations are presented.

Key word: Population dynamics, Optimal control involving ODEs, Optimality conditions, Numerical analysis for ODEs, Numerical algorithm, Matlab.

1 Introduction

One of the consequences of infection by HIV is the destruction of $CD4^+T$ cells, the cells commonly known as T cells or T4 cells. Due to the main importance of this cells, their depletion inflicts widespread negative effects on the functioning of the immune system. That's why the decline in the number of $CD4^+T$ cells in peripheral blood is used in medical clinics as an indicator of the disease stage.

Since the early 1980's there has been an extraordinary effort made in the mathematical modeling of HIV, the virus which is responsible for AIDS (Acquired Immune Deficiency Syndrome). Both stochastic and deterministic models have been developed to describe the interaction between the immune system

and HIV. Stochastic models, such the ones presented in [15], [16], [17], can be used to evaluate the early events in the infection, when there are few infected cells and a small number of viruses. The models developed in [13], [18], [19], [22], emphasize on the effect of variability among viral strains and try to explain better the rate of HIV quasispecies evolution and disease progression. In [14], the authors introduced a model which incorporates many important features of HIV dynamics and successfully reproduces all the tree-phase pattern observed in HIV infection: early infection, clinically asymptomatic stage or long latency period and symptomatic HIV infection. Accurate deterministic models may be found in [6], [9], [10], [11], [12], [20]. These type of models examine the changes in mean cell numbers and are more applicable to later stages of the process in which population sizes are large. Usually, the dynamics of the $CD4^+T$ cell and virus populations are taken account. In some of this models, other immune system populations such as B cells or $CD8^+T$ cells have been included.

In this paper, the immune system is modelled in terms of the population of $CD4^+T$ cells. Its dynamics in contact with HIV is described by the following initial value problem (see [2]):

$$\begin{cases} T'(t) = \frac{s}{1+V(t)} - \mu_1 T(t) + rT(t) \left(1 - \frac{T(t) + T_i(t)}{T_{\max}}\right) - k_1 V(t)T(t), \\ T_i'(t) = k_1 V(t)T(t) - \mu_2 T_i(t), \\ V'(t) = -k_1 V(t)T(t) - \mu_3 V(t) + N\mu_2 T_i(t), \\ T(0) = T_0, \quad T_i(0) = T_{i0}, \quad V(0) = V_0, \end{cases} \quad t \in (0, t_f], \quad (t_f > 0) \quad (1.1)$$

where $T(t)$ is the concentration of uninfected $CD4^+T$ cells, $T_i(t)$ represents the concentration of infected $CD4^+T$ cells and $V(t)$ corresponds to the free infectious virus particles, at moment t . $s, k_1, r, N, \mu_1, \mu_2, \mu_3, T_{\max}$ are positive constants and T_0, T_{i0}, V_0 , are the initial positive concentrations of $CD4^+T$ cells, infected $CD4^+T$ cells, and virus cells, respectively.

In the first equation, the term $\frac{s}{1+V(t)}$ represents the source of new T cells from the thymus. Since it has been shown that virus can infect the thymocytes (the precursors of T cells), the use of a function depending on viral load, to describe the decreasing source, is founded. T cells have a finite life-span and die at a rate of μ_1 per cell. The production rate of T cells is represented by the logistic term $r \left(1 - \frac{T(t) + T_i(t)}{T_{\max}}\right)$, so that the T cells never grow larger than T_{\max} . r denotes the natural growth rate of $CD4^+T$ cells.

The term $k_1 VT$ in the first equation in (1.1) together with $+k_1 VT$ in the second equation in (1.1) model the infection of T cells due to the viral concentration V ; the term $k_1 VT$ in the third equation in (1.1) simulates the binding of viruses to uninfected T cells, thus leading to infection.

The second equation in (1.1) governs the infected $CD4^+T$ population. The infected cells produce virus and die at rate μ_2 . The third equation in (1.1) models the free virus population. The evolution of viruses production during the decay of infected T cells is described by the term $N\mu_2T_i(t)$ and $-\mu_3V(t)$ accounts for natural viral loss.

In the absence of virion, the T cell population has the steady state value

$$T_0 = \frac{T_{\max}}{2} \left(1 - \frac{\mu_1}{r} + \sqrt{\left(1 - \frac{\mu_1}{r}\right)^2 + \frac{4s}{rT_{\max}}} \right),$$

so, an adequate initial conditions for (1.1) are $T(0) = T_0$, $T_i(0) = 0$, and $V(0) = V_0$ for infection by free virus or $T(0) = T_0$, $T_i(0) = T_{i0}$, $V(0) = V_0$ in case of a multiple infection both from infected cells and virus.

A more complex model governing the interaction of the immune system with human immunodeficiency virus can be found in [12], where the infected $CD4^+T$ population properties of being latently infected and actively infected are taken into account. However, as we shall show, our model can account for many of the characteristics of HIV infection seen clinically: the early infection, the long latency period, low level of virus in the body, and the depletion of $CD4^+T$ cells.

For general models describing interacting biological population species we refer to [7], while for the control problems related to such systems see [1], [3], and [4].

Our work is dedicated to the question of optimizing treatment scheduling, i.e. when and how treatment should be initiated assuming that treatment can be used only for a finite period of time due to both the adverse effects induced by the medications and the resistance developed by the virus at the prescribed drugs.

In the present, different chemotherapy are continually being tested, and once the National and International Public Health Agencies approved, these enter under intense study to establish an optimal methodology for administering the treatment. Generally, in viral infection, the drug strategy affects either the virus infectivity or reduce the virion production. Unfortunately, in case of HIV infection, even if it is a viral infection, anti-HIV chemotherapy drugs are virostatic rather than virotoxic, so the infected individuals must remain on drug therapy for long period of time, without the benefit of a complete recovery and despite of all the side effects inflicted by drugs and the emergence of anti-HIV chemotherapy drug-resistant viruses. Presently, the most widely used medications for chemotherapy of HIV infection are AZT, DDI, DDC and D4T, and all of them are developed to reduce the virus infectivity. That is why we focused to this type of strategy, and multiplying the k_1VT term in all three equations in (1.1) by a chemotherapy function $u(t)$, we consider the following problem of maximizing the number of uninfected T cells, while simultaneously minimizing the undesirable effects of the chemotherapy to the human body:

$$\text{Maximize } \int_0^{t_f} \left(aT(t) - \frac{1}{2} (1 - u(t))^2 \right) dt, \quad (OC)$$

where the set of controls K is given by

$$K = \left\{ u \in L^2(0, t_f); 0 \leq u(t) \leq 1 \text{ a.e. } t \in (0, t_f) \right\},$$

for $(T(t), T_i(t), V(t))$ subject to state equation

$$\begin{cases} T'(t) = \frac{s}{1+V(t)} - \mu_1 T(t) + rT(t) \left(1 - \frac{T(t) + T_i(t)}{T_{\max}} \right) - k_1 u(t) V(t) T(t), \\ T'_i(t) = k_1 u(t) V(t) T(t) - \mu_2 T_i(t), \\ V'(t) = -k_1 u(t) V(t) T(t) - \mu_3 V(t) + N\mu_2 T_i(t), \\ T(0) = T_0, T_i(0) = T_{i0}, V(0) = V_0. \end{cases} \quad t \in (0, t_f], (t_f > 0) \quad (SE)$$

The case when $u(t) = 0$ corresponds to maximal use of chemotherapy. The treatment is absent for $u(t) = 1$.

A greater or lower value for $a > 0$, corresponds to a lower or greater importance given to the minimizing the negative effects that occur during the treatment.

It is easy to prove that for any $u \in K$, problem (SE) admits a unique solution, denoted by $(T^u(t), T_i^u(t), V^u(t))$.

There are additional parameter restrictions that we shall impose to ensure that this model gives realistic population dynamics. Such conditions were proposed in [21] and assure the positivity of T , T_i and V , for $t \in [0, t_f]$, in case of positive initial data. Thus, in the sequel, we assume that

$$T(t) \geq 0, T_i(t) \geq 0, V(t) \geq 0, \forall t \in [0, t_f], \text{ for } T_0 \geq 0, T_{i0} \geq 0, V_0 \geq 0.$$

The outline of this paper is as follows: In section 2 we demonstrate the existence of an optimal control for (OC). Section 3 is dedicated to the necessary optimality conditions for (OC). The description of the numerical algorithm applied to the model under study, together with results of the numerical simulations are presented in section 4 and 5. Some concluding remarks are drawn in the last section.

2 Existence of an optimal control

Theorem 1. *Problem (OC) admits at least one optimal control.*

Proof. Define

$$\Phi(u) = \int_0^{t_f} \left(aT(t) - \frac{1}{2}(1 - u(t))^2 \right) dt, \quad u \in K \quad (2.1)$$

and let

$$d = \sup_{u \in K} \Phi(u).$$

We have that

$$(T_i + V)'(t) = -\mu_2 T_i(t) - \mu_3 V(t) + N\mu_2 T_i(t) \leq N\mu_2(T_i + V)(t) \text{ a.e. } t \in [0, t_f],$$

which implies

$$T_i(t), V(t) \leq e^{N\mu_2 t_f}(T_{i0} + V_0) = M_1 \in \mathbb{R}_+ \text{ a.e. } t \in [0, t_f]. \quad (2.2)$$

We have also that

$$T'(t) \leq \frac{s}{1 + V(t)} + rT(t) \leq s + rT(t) \text{ a.e. } t \in [0, t_f],$$

which leads to

$$T(t) \leq T_0 e^{rt_f} - \frac{s}{r}(1 - e^{rt}) \leq M_2 \in \mathbb{R}_+ \text{ a.e. } t \in [0, t_f]. \quad (2.3)$$

Therefore,

$$0 \leq \Phi(u) \leq \int_0^{t_f} aT(t) dt \leq \int_0^{t_f} aM_2 dt = at_f M_2 = M \in \mathbb{R}_+ \text{ a.e. } t \in [0, t_f].$$

In conclusion, $d \in [0, \infty)$.

For any $n \in \mathbb{N}$, there exists $u_n \in K$ such that

$$d - \frac{1}{n} < \Phi(u_n) \leq d. \quad (2.4)$$

We know that K is a closed and bounded subset of $L^2(0, t_f)$. Thus, it follows that exists a subsequence $\{u_{n_k}\}_{k \in \mathbb{N}^*}$ such that

$$u_{n_k} \rightharpoonup u^* \text{ weakly in } L^2(0, t_f). \quad (2.5)$$

But K is a closed convex subset of $L^2(0, t_f)$, and hence it is weakly closed. So, we obtain that $u^* \in K$.

From relations (2.2) and (2.3), we notice that the sets $\{T^{u_{n_k}}\}$, $\{T_i^{u_{n_k}}\}$, $\{V^{u_{n_k}}\}$ verify the conditions of Arzelà's theorem. According to this theorem, there is a subsequence of $\{u_{n_k}\}_{k \in \mathbb{N}^*}$, denoted by $\{u_{n_r}\}_{r \in \mathbb{N}^*}$, such that

$$\begin{aligned} T^{u_{n_r}} &\rightarrow T^{u^*} \text{ in } C(0, t_f), \\ T_i^{u_{n_r}} &\rightarrow T_i^{u^*} \text{ in } C(0, t_f), \\ V^{u_{n_r}} &\rightarrow V^{u^*} \text{ in } C(0, t_f), \end{aligned}$$

and let $n \rightarrow \infty$ in (2.4), we get

$$d = \int_0^{t_f} \left(aT^{u^*}(t) - \frac{1}{2}(1 - u^*(t))^2 \right) dt,$$

i.e. $(u^*, T^{u^*}, T_i^{u^*}, V^{u^*})$ is an optimal pair for (OC). \square

3 The optimality conditions

Theorem 2. Let (u^*, T^*, T_i^*, V^*) be an optimal pair for (OC). If p is the solution to

$$\left\{ \begin{array}{l} p'_1(t) = \left[\mu_1 - r \left(1 - \frac{T^*(t) + T_i^*(t)}{T_{\max}} \right) + \frac{rT^*(t)}{T_{\max}} + k_1 u^*(t) V^*(t) \right] p_1(t) - \\ \quad - k_1 u^*(t) V^*(t) p_2(t) + k_1 u^*(t) V^*(t) p_3(t) - a, \\ p'_2(t) = \frac{rT^*(t)}{T_{\max}} p_1(t) + \mu_2 p_2(t) - N \mu_2 p_3(t), \\ p'_3(t) = \left[\frac{s}{(1 + V^*(t))^2} + k_1 u^*(t) T^*(t) \right] p_1(t) - k_1 u^*(t) T^*(t) p_2(t) + \\ \quad + [k_1 u^*(t) T^*(t) + \mu_3] p_3(t) \\ p_1(t_f) = 0, \quad p_2(t_f) = 0, \quad p_3(t_f) = 0. \end{array} \right. \quad t \in [0, t_f], \quad (AE)$$

then

$$u^*(t) = \begin{cases} 0 & \text{if } 1 - u^*(t) - k_1 V^*(t) T^*(t) p_1(t) + k_1 V^*(t) T^*(t) p_2(t) - \\ & - k_1 V^*(t) T^*(t) p_3(t) < 0 \\ 1 & \text{if } 1 - u^*(t) - k_1 V^*(t) T^*(t) p_1(t) + k_1 V^*(t) T^*(t) p_2(t) - \\ & - k_1 V^*(t) T^*(t) p_3(t) > 0 \end{cases} \quad (3.1)$$

Proof. Consider $V = \{v \in L^2(0, t_f; \mathbb{R}); u^* + \lambda v \in K, \forall \lambda > 0 \text{ sufficiently small}\}$.

Let $(u^* + \lambda v, T^* + \lambda z_1, T_i^* + \lambda z_2, V^* + \lambda z_3)$ be an "increment" of the optimal pair (u^*, T^*, T_i^*, V^*) . Subtracting the corresponding equations from (SE) we obtain

$$\left\{ \begin{array}{l} z'_1 = \left[-\mu_1 + r \left(1 - \frac{T^* + T_i^*}{T_{\max}} \right) - \frac{rT^*}{T_{\max}} - k_1 u^* V^* \right] z_1 - \frac{rT^*}{T_{\max}} z_2 - \\ - \left[\frac{s}{(1 + V^*)^2} + k_1 u^* T^* \right] z_3 - k_1 v V^* T^*, \\ z'_2 = k_1 u^* V^* z_1 - \mu_2 z_2 + k_1 u^* T^* z_3 + k_1 v V^* T^*, \\ z'_3 = -k_1 u^* V^* z_1 + N \mu_2 z_2 - (k_1 u^* T^* + \mu_3) z_3 - k_1 v V^* T^*, \\ z_1(0) = 0, \quad z_2(0) = 0, \quad z_3(0) = 0, \end{array} \right. \quad t \in (0, t_f], \quad (3.2)$$

for any $v \in V$.

Using the same notation as in (2.1), we have

$$[\Phi(u^* + \lambda v) - \Phi(u^*)] / \lambda \leq 0.$$

Let $\lambda \rightarrow 0$ to obtain

$$\int_0^{t_f} [az_1 + (1 - u^*)v] dt \leq 0, \quad \forall v \in V. \quad (3.3)$$

Next, we introduce the adjoint system

$$\left\{ \begin{array}{l} p'_1 = \left[\mu_1 - r \left(1 - \frac{T^* + T_i^*}{T_{\max}} \right) + \frac{rT^*}{T_{\max}} + k_1 u^* V^* \right] p_1 - k_1 u^* V^* p_2 + \\ + k_1 u^* V^* p_3 - a, \\ p'_2 = \frac{rT^*}{T_{\max}} p_1 + \mu_2 p_2 - N \mu_2 p_3, \\ p'_3 = \left(\frac{s}{(1 + V^*)^2} + k_1 u^* T^* \right) p_1 - k_1 u^* T^* p_2 + (k_1 u^* T^* + \mu_3) p_3, \\ p_1(t_f) = 0, \quad p_2(t_f) = 0, \quad p_3(t_f) = 0. \end{array} \right. \quad t \in [0, t_f], \quad (3.4)$$

The existence and the uniqueness of the Carathéodory solution $p = (p_1, p_2, p_3)$ is straightforward.

Multiplying the equations from (3.2) by p_1 , p_2 and p_3 and integrating by parts on $[0, t_f]$, we obtain

$$\begin{aligned}
-\int_0^{t_f} z_1(t)p_1'(t)dt &= \int_0^{t_f} \left[\left(-\mu_1 + r \left(1 - \frac{T^* + T_i^*}{T_{\max}} \right) - \frac{rT^*}{T_{\max}} - k_1 u^* V^* \right) z_1 p_1 - \right. \\
&\quad \left. - \frac{rT^*}{T_{\max}} z_2 p_1 - \left(\frac{s}{(1+V^*)^2} + k_1 u^* T^* \right) z_3 p_1 - k_1 v V^* T^* p_1 \right] dt, \\
-\int_0^{t_f} z_2(t)p_2'(t)dt &= \int_0^{t_f} [k_1 u^* V^* z_1 p_2 - \mu_2 z_2 p_2 + k_1 u^* T^* z_3 p_2 + k_1 v V^* T^* p_2] dt, \\
-\int_0^{t_f} z_3(t)p_3'(t)dt &= \int_0^{t_f} [k_1 u^* V^* z_1 p_3 + N\mu_2 z_2 p_3 - (k_1 u^* T^* + \mu_3) z_3 p_3 - \\
&\quad - k_1 v V^* T^* p_3] dt.
\end{aligned}$$

By adding all the three equations from above and using the adjoint state equations (3.4), we get

$$\int_0^{t_f} v \left(k_1 V^* T^* p_2 - k_1 V^* T^* p_3 - k_1 V^* T^* p_1 \right) dt = \int_0^{t_f} a z_1 dt$$

for any $v \in V$. From (3.3), we finally find the following statement

$$\int_0^{t_f} v(t) \left[1 - u^* - k_1 V^* T^* p_1 + k_1 V^* T^* p_2 - k_1 V^* T^* p_3 \right] dt \leq 0 \quad (3.5)$$

for any $v \in V$. This is equivalent to

$$1 - u^* - k_1 V^* T^* p_1 + k_1 V^* T^* p_2 - k_1 V^* T^* p_3 \in N_K(u^*),$$

where $N_K(u^*)$ is the normal cone at K at $u^* \in K$. Taking into account the structure of $N_K(u^*)$, we may conclude that

$$u^*(t) = \begin{cases} 0 & \text{if } 1 - u^* - k_1 V^* T^* p_1 + k_1 V^* T^* p_2 - k_1 V^* T^* p_3 < 0 \\ 1 & \text{if } 1 - u^* - k_1 V^* T^* p_1 + k_1 V^* T^* p_2 - k_1 V^* T^* p_3 > 0 \end{cases}$$

a.e. $t \in [0, t_f]$. \square

4 A Numerical Algorithm

In this section, we present a projected gradient method for the optimal chemotherapy strategy, based on the mathematical results from section 3. Formula (3.1) asserts that u^* is a bang-bang control. Taking into account the control restriction and using a Rosen algorithm (see [5]), we derive the following algorithm for problem (OC).

Algorithm ALG-R

S0: Choose $u^{(0)} \in K$; set $j := 0$;

S1: Compute $Y^{(j)} = (T^{(j)}, T_i^{(j)}, V^{(j)})$ from (SE), i.e.

$$\left\{ \begin{array}{l} T^{(j)'}(t) = \frac{s}{1 + V^{(j)}(t)} - \mu_1 T^{(j)}(t) + r T^{(j)}(t) \left(1 - \frac{T^{(j)}(t) + T_i^{(j)}(t)}{T_{\max}} \right) - \\ \quad - k_1 u^{(j)}(t) V^{(j)}(t) T^{(j)}(t), \\ T_i^{(j)'}(t) = k_1 u^{(j)}(t) V^{(j)}(t) T^{(j)}(t) - \mu_2 T_i^{(j)}(t), \\ V^{(j)'}(t) = -k_1 u^{(j)}(t) V^{(j)}(t) T^{(j)}(t) - \mu_3 V^{(j)}(t) + N \mu_2 T_i^{(j)}(t), \\ T^{(j)}(0) = T_0, \quad T_i^{(j)}(0) = T_{i0}, \quad V^{(j)}(0) = V_0. \end{array} \right. \quad t \in (0, t_f]$$

S2: Compute $p^{(j)} = (p_1^{(j)}, p_2^{(j)}, p_3^{(j)})$, from (AE), i.e.

$$\left\{ \begin{array}{l} p_1^{(j)'}(t) = \left[\mu_1 - r \left(1 - \frac{T^{(j)}(t) + T_i^{(j)}(t)}{T_{\max}} \right) + \frac{r T^{(j)}(t)}{T_{\max}} + k_1 u^{(j)}(t) V^{(j)}(t) \right] p_1^{(j)}(t) - \\ \quad - k_1 u^{(j)}(t) V^{(j)}(t) p_2^{(j)}(t) + k_1 u^{(j)}(t) V^{(j)}(t) p_3^{(j)}(t) - a, \\ p_2^{(j)'}(t) = \frac{r T^{(j)}(t)}{T_{\max}} p_1^{(j)}(t) + \mu_2 p_2^{(j)}(t) - N \mu_2 p_3^{(j)}(t), \\ p_3^{(j)'}(t) = \left[\frac{s}{(1 + V^{(j)}(t))^2} + k_1 u^{(j)}(t) T^{(j)}(t) \right] p_1^{(j)}(t) - k_1 u^{(j)}(t) T^{(j)}(t) p_2^{(j)}(t) + \\ \quad + [k_1 u^{(j)}(t) T^{(j)}(t) + \mu_3] p_3^{(j)}(t), \\ p_1^{(j)}(t_f) = 0, \quad p_2^{(j)}(t_f) = 0, \quad p_3^{(j)}(t_f) = 0. \end{array} \right. \quad t \in [0, t_f),$$

S3: Compute $v^{(j)}$ according to the formula (3.1) in Theorem 2 :

$$v^{(j)}(t) = \begin{cases} 0 & \text{if } 1 - u^{(j)}(t) - k_1 V^{(j)}(t) T^{(j)}(t) p_1^{(j)}(t) + k_1 V^{(j)}(t) T^{(j)}(t) p_2^{(j)}(t) - \\ & - k_1 V^{(j)}(t) T^{(j)}(t) p_3^{(j)}(t) < 0 \\ 1 & \text{if } 1 - u^{(j)}(t) - k_1 V^{(j)}(t) T^{(j)}(t) p_1^{(j)}(t) + k_1 V^{(j)}(t) T^{(j)}(t) p_2^{(j)}(t) - \\ & - k_1 V^{(j)}(t) T^{(j)}(t) p_3^{(j)}(t) > 0. \end{cases}$$

S4: Compute the new control $u^{(j+1)}$

S4.1: Compute $\lambda_j \in [0, 1]$ the solution of the maximization problem

$$\max \left\{ \Phi \left(\lambda u^{(j)} + (1 - \lambda) v^{(j)} \right); \lambda \in [0, 1] \right\},$$

where Φ is the cost functional

$$\Phi(u) = \int_0^{t_f} \left(aT(t) - \frac{1}{2}(1 - u(t))^2 \right) dt.$$

S4.2 Set $u^{(j+1)} = \lambda_j u^{(j)} + (1 - \lambda_j) v^{(j)}$.

S5: The stopping criterion

if $|\Phi(u^{(j+1)}) - \Phi(u^{(j)})| < \epsilon$ then **STOP**

else $j := j + 1$; go to **S1**.

In order to compute a suboptimal bang-bang control, then the step **S4** of the algorithm ALG-R should be modified, since a convex combination of two bang-bang controls taking only values 0 and 1 is not a bang-bang control that admits only these two values. So, we introduce a net of switching points, the only points where a bang-bang function changes its value. To keep $u^{(j+1)}$ in the class of bang-bang controls, we shall use in step **S4** convex combinations of the switching points of $u^{(j)}$ and $v^{(j)}$. This idea was introduced, for the first time, in [8].

In step **S5**, $\epsilon > 0$ is a prescribed precision.

5 Numerical Simulations

First we introduce the parameters and constants used in our experiments.

μ_1 = death rate of uninfected $CD4^+T$ cell population	$0.02 d^{-1}$
μ_2 = death rate of infected $CD4^+T$ cell population	$0.15 d^{-1}$
μ_3 = death rate of free virus	$19 d^{-1}$
k_1 = rate $CD4^+T$ cells becomes infected by free virus	$2.4 \times 10^{-5} mm^3 d^{-1}$
r = rate of growth for the $CD4^+T$ cell population	$3 \times 10^{-3} d^{-1}$
N = number of free virus produced by T_i cells	1200
T_{\max} = maximum $CD4^+T$ cell population level	$1.5 \times 10^3 mm^3$
s = source term for uninfected $CD4^+T$ cells	$10 d^{-1} mm^3$,

The choice of these values was made according to [12], with some modification required by this particular model in respect with the clinically data regarding HIV infection.

The computer program which implement Algorithm ALG-R was created in MATLAB. The discretization is carried out by a Runge-Kutta method. The state system (SE) was solved by a time-ascending algorithm while the adjoint equation (AE) was in need of a time-descending one. A grid with equidistant nodes was used to cover the time interval.

Next, in order to find the optimal solution for (OC), we need initial values for T cells, infected T cells, and the virus population V . Thus, we solved the model (1.1) without chemotherapy treatment and without infection, so $V_0 = 0$ and $T_{i0} = 0$. We obtained, for any positive $T_0 \leq T_{\max}$ and with the parameters presented above, that after a period of time, the number of $CD4^+T$ cells is stabilized around 1000mm^3 . This value corresponds to the natural average number of T cells according to [11].

Supposing that the organism is infected only with virus, and taking $V_0 = 1\text{mm}^3$ as in [6], we determined the immunological response and HIV dynamics, on the first 1000 days after infection. This evolution is presented in Fig.1.

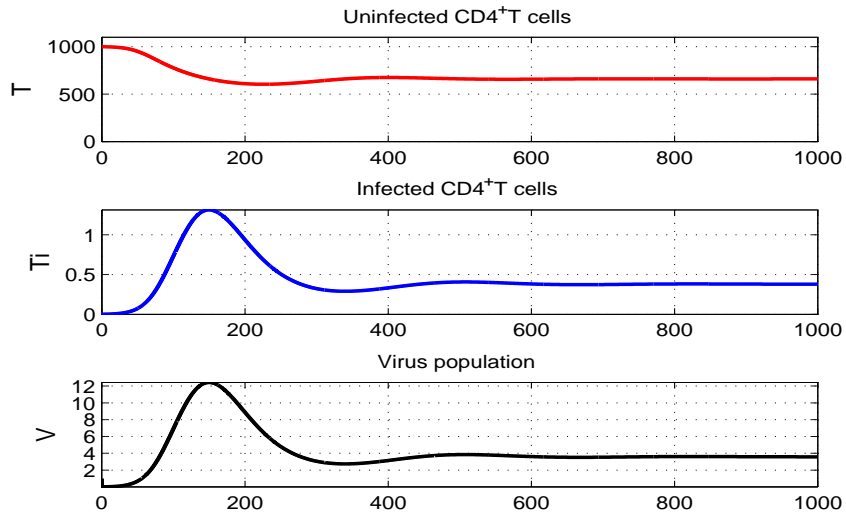


Figure 1: The evolution of the immune system dynamics in contact with HIV without any medical treatment.

We also obtained the starting values needed for different treatment initial conditions. These may be found in the table 1.

Table 1: A summary of the cell populations at different moments of time following the infection.

Days after infection	T cells	infected T cells	The virus population
50	$T = 819.677\text{mm}^3$	$T_i = 0.072\text{mm}^3$	$V = 0.68\text{mm}^3$
100	$T = 777.211\text{mm}^3$	$T_i = 0.729\text{mm}^3$	$V = 6.897\text{mm}^3$
200	$T = 610.266\text{mm}^3$	$T_i = 0.938\text{mm}^3$	$V = 8.89\text{mm}^3$
300	$T = 635.627\text{mm}^3$	$T_i = 0.323\text{mm}^3$	$V = 3.059\text{mm}^3$
1000	$T = 660.298\text{mm}^3$	$T_i = 0.378\text{mm}^3$	$V = 3.58\text{mm}^3$

A particular debate exists in scientific community regarding the level of infectivity in the early infection. We expect that a healthy organism which counts on 1000mm^3 of $CD4^+T$ cells, once infected, inflicts a powerful immunological response in comparison with other organisms where the level of T cells is lower. So, once again, we solved the system (1.1), for different values of T_0 and $T_i = 0$ and $V_0 = 1\text{mm}^3$. The results are illustrated in Fig.2 and are detailed in table 2.

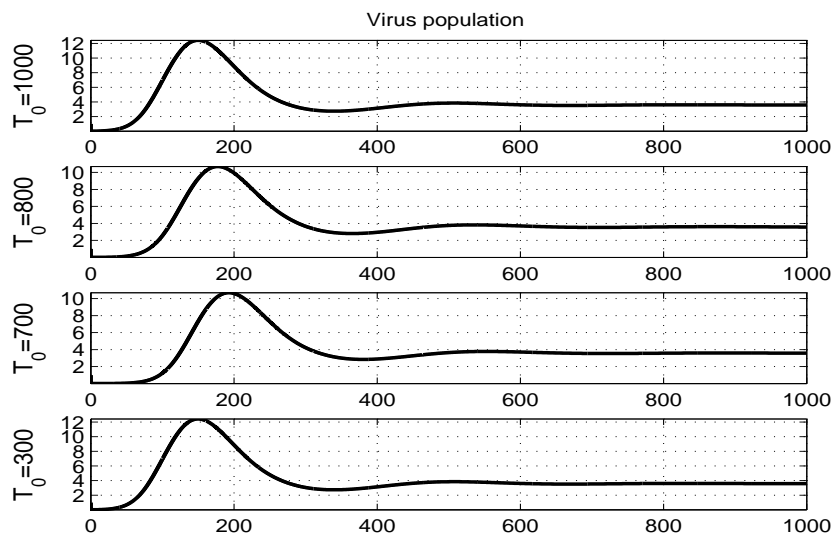


Figure 2: The evolution of the virus population in absence of treatment for various initial conditions.

We may noticed that the organism with the number of T cell between 700mm^3 and 800mm^3 has the lowest degree of infectivity, and the virus population reaches the maximum later than in all other cases.

In the sequel, we focus on the optimal control problem (OC). As we previous told, our model incorporates a drug strategy which affects the virus infectivity.

Table 2: The maximum number of virus cells.

T_0 cell counts	V_{\max}
1000	12.429mm ³
800	10.688mm ³
700	10.698mm ³
300	11.4736mm ³

Unfortunately, in our present day and in the case of HIV infection, the medication induces powerful side effects and has positive influence only for short periods of time due to the high adaptability of the virus. That is why we choose a limited treatment window for our numerical simulations.

We vary initiation of treatment beginning with 50 days, 100 days, 200 days, 300 days and 1000 days after the onset of infection and the treatment last 100 days. The numerical results are depicted in Fig.3, Fig.4, Fig.5, Fig.6, and Fig.7.

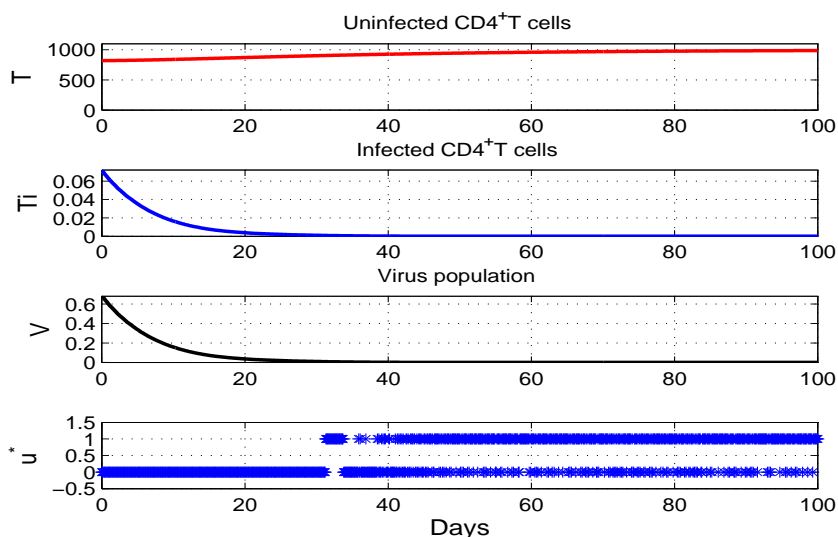


Figure 3: The evolution of the immune system dynamics in contact with HIV during the optimal chemotherapy strategy. Here we initiate treatment after 50 days from infection. $T_0 = 819.677\text{mm}^3$, $T_{i0} = 0.072\text{mm}^3$, $V_0 = 0.68\text{mm}^3$.

Table 3 is a summary of these results. In every case, the optimal control is of bang-bang type which takes only values 0 and 1, since we replaced the convex combination $\lambda u^{(j)} + (1 - \lambda) v^{(j)}$ from step **S4** of Algorithm ALG-R with a convex combination of the switching points of $u^{(j)}$ and $v^{(j)}$. Thus, we obtain a system of switching points for the new bang-bang control.

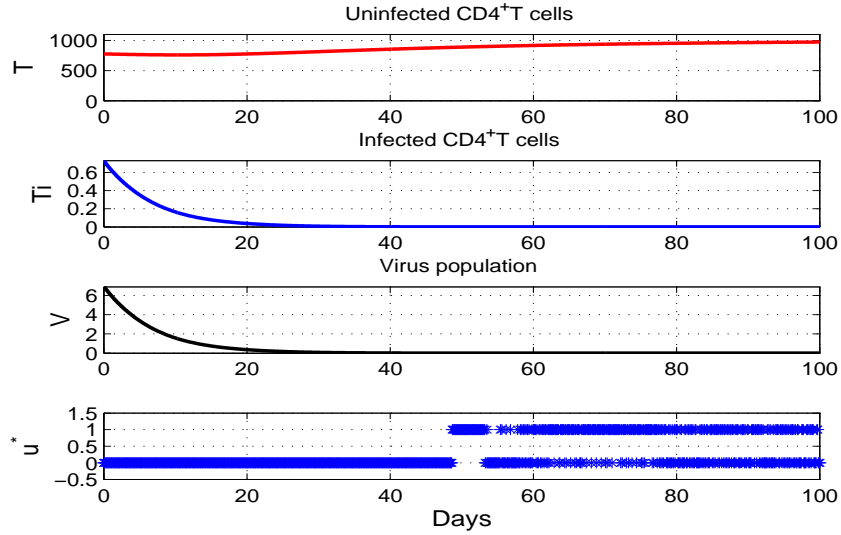


Figure 4: The evolution of the immune system dynamics in contact with HIV during the optimal chemotherapy strategy. Here we initiate treatment after 100 days from infection. $T_0 = 777.211\text{mm}^3$, $T_{i0} = 0.729\text{mm}^3$, $V_0 = 6.897\text{mm}^3$.

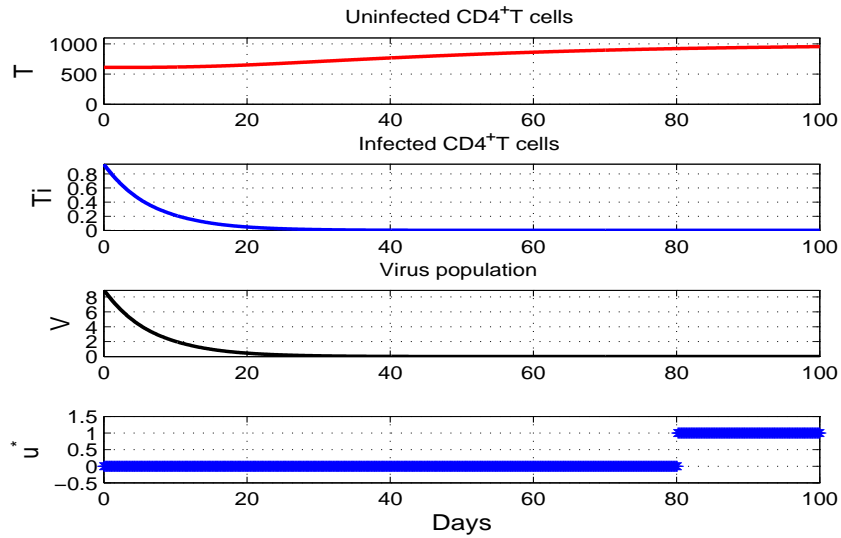


Figure 5: The evolution of the immune system dynamics in contact with HIV during the optimal chemotherapy strategy. Here we initiate treatment after 200 days from infection. $T_0 = 610.266\text{mm}^3$, $T_{i0} = 0.938\text{mm}^3$, $V_0 = 8.89\text{mm}^3$.

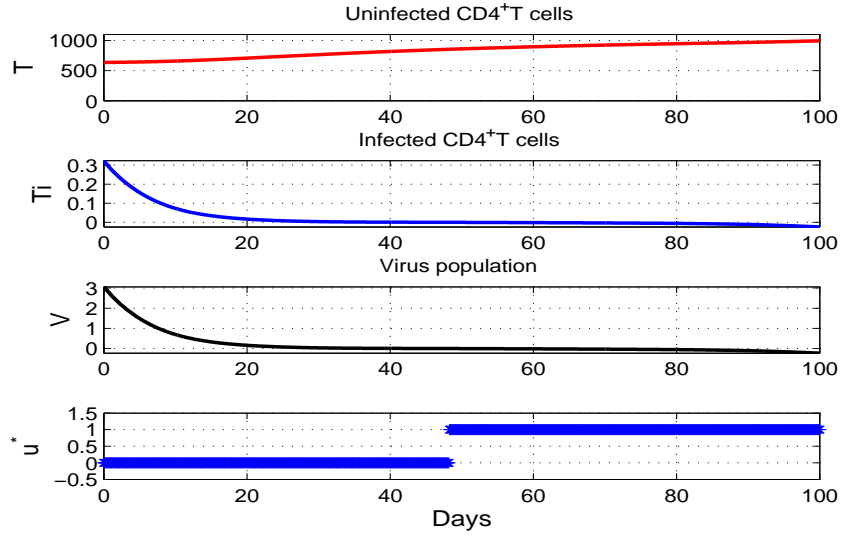


Figure 6: The evolution of the immune system dynamics in contact with HIV during the optimal chemotherapy strategy. Here we initiate treatment after 300 days from infection. $T_0 = 635.627\text{mm}^3$, $T_{i0} = 0.323\text{mm}^3$, $V_0 = 3.059\text{mm}^3$.

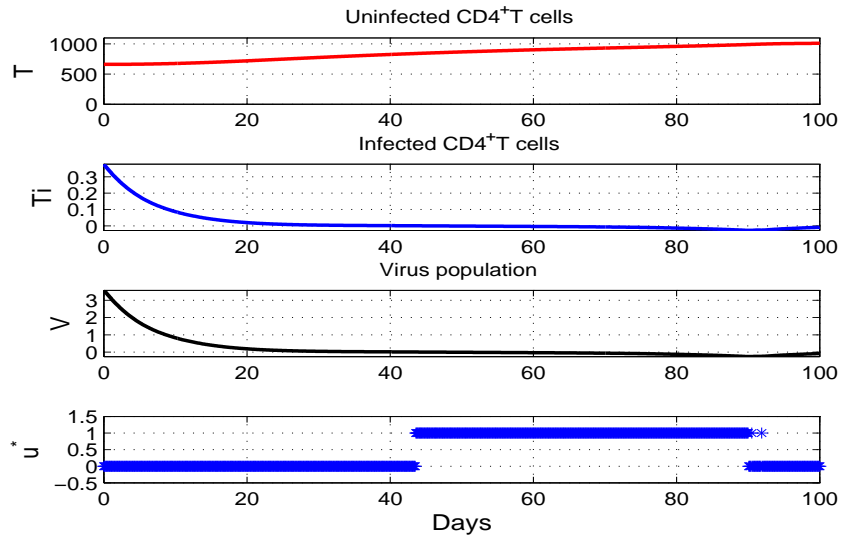


Figure 7: The evolution of the immune system dynamics in contact with HIV during the optimal chemotherapy strategy. Here we initiate treatment after 1000 days from infection. $T_0 = 660.298\text{mm}^3$, $T_{i0} = 0.378\text{mm}^3$, $V_0 = 3.58\text{mm}^3$.

Days after infection	T_0 cells counts	Objected function Φ
50	$T_0 = 819.677\text{mm}^3$	$\Phi(u^*) = 92922.9$
100	$T_0 = 777.211\text{mm}^3$	$\Phi(u^*) = 87379.9$
200	$T_0 = 610.266\text{mm}^3$	$\Phi(u^*) = 79593.77$
300	$T_0 = 635.627\text{mm}^3$	$\Phi(u^*) = 83509.9$
1000	$T_0 = 660.298\text{mm}^3$	$\Phi(u^*) = 84748.49$

Table 3: The values of the objective function at the optimal control u^* .

These simulations underline that treatment must be started immediately regardless the time elapsed since infection. We also notice the cases when the objective function values are larger - i.e. when T cell counts are higher. So, for the patients who are in the early stage of infection (less than 250 days after infection), the greatest effect does occur when treatment is initiated earlier.

Regarding the question of optimizing treatment scheduling, i.e. when the treatment should be initiated, whatever the stage of infection would be, the results from the table 3 are conclusive. When comparing the objective function values in case of treatment started after 200 days, 300 days or 1000 days following the infection (early stage of infection, early beginnings of long latency period or during the clinically asymptomatic stage) we remark that the best result is obtained in the last situation. However, we don't have enough information to tell precisely when is the optimal moment for an infected patient to start the treatment. To get closer to that, we need to improve the current model in order to simulate accurately the third stage of infection, when the number of $CD4^+T$ cells dramatically drops.

In the end, we point out that all the results presented here were obtained for $a = 1$. Modifying the value of a , we give a lower or greater importance to the minimizing the negative effects that occur during the treatment. In fig.8, we present the numerical results concerning the optimal therapy started after 300 days from the initial infection using several values for a .

6 Conclusions

In this paper, we studied an optimal control problem, with the state equation describing the interaction of the immune system with HIV and the objective function based on a contribution of maximizing benefit relied on T cells count and minimizing the side effects of the chemotherapy. We proved the existence of an optimal control and provided the necessary optimality conditions. A numerical algorithm was introduced and several numerical results were obtained.

Exploring initiation of treatment, table 3 compares the values of the objective function. We find out that the greatest effect of treatment does occur when it is initiated earliest. This optimal moment corresponds to the highest number of $CD4^+T$ cells.

The mathematical model described here simulates accurately the first two

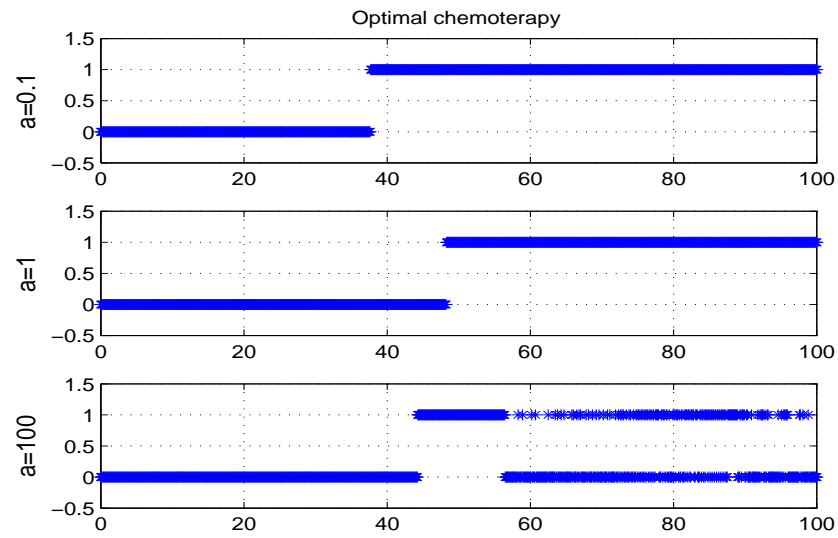


Figure 8: The treatment evolution initiated after 300 days from infection, for different values of a .

stages of HIV infection. This suggests that even models as simple as this may have great value in attaining and understanding of HIV's role in vivo infection.

Further studies need to be done to incorporate a more accurate model of the immune system and other things as multiple drug treatments together with the resistance effects.

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