Proceeding Series of the Brazilian Society of Computational and Applied Mathematics

An Optimal Control Strategy for HIV Treatment

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Abstract. Considering a simple model that describes the spread of HIV in the human body, this work proposes a strategy to minimize the side effects of medication by introducing control variables that represent the evolution of the medication levels with time. The strategy corresponds to an optimization problem with respect to a prescribed performance function. For a given performance function, an optimal medication strategy is obtained by means of Pontryagin's maximum principle. To solve the set of nonlinear ordinary differential equations that describe the dynamics of susceptible, infected, active cells and HIV, we make use of finite difference method.

Keywords. HIV, Mathematical Modelling, Optimal Control, Pontryagin's Maximum Principle.

1 Introduction

HIV infection is currently characterized by the count of CD4+ T cells, by the amount of viral particles in the blood (viral load) and also by the clinical symptoms. Not all patients develop every stage of the disease, and the time elapsed between the infection and the

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manifestation of different clinical symptoms is highly variable, even though the causes of such a variation remain partly unknown. To reproduce, HIV joins the membrane of the *T4* cell, which is vital to the immune response. The virus releases its *RNA* and an enzyme, which produces the *DNA* of the virus. Then, the *DNA* of the virus enters the nucleus and joins to the *DNA* of the cell, taking full control. The result of this union is the pro-viral *DNA*, that produces the messenger *RNA*, which contains the genetic code of the virus. The messenger *RNA* then reaches the cytoplasm and produces virions, which leave the host cell as newly formed *HIV's*. Thus, when joined to a T4 cell, a single virus produces many potential threats to other cells.

By making quantification possible, the analysis of viral load in HIV infection has facilitated the management of the disease. It turns out that an exponential decrease in viral levels in plasma can be attained by the reverse transcriptase inhibitors and protease that are included in Anti-retroviral Therapy (ART).

When HIV invades the human body, they attack the CD4+ T cells in their way. When attacked, these *auxiliary* cells signal the presence of an invader to other immune cells (CD8+ T cells). The CD8+ T cells then respond to this signal and become Cytotoxic T Lymphocytes (CTL) by attempting to destroy the infected cells [2,7,10,12]. This process, which is not exploited in typical HIV models, plays an important role in the proposed approach. Indeed, a novel feature of the present work is the introduction of a variable to represent the CD8+ T cells. Such a variable is extremely important to the model, since it enables the decision maker to evaluate the interaction between the CD8+ T cells, CTL and the other variables in the model, such as the virus load [1].

This work proposes a simple mathematical model to describe the dynamics of the HIV in the human immune system. The proposed model is a new approach of the work developed in [6] and modified existing models in the literature [4,8,9,11] with the introduction of a new variable to provide a more detailed description of the defense of the immune system, the number of unactivated CD8+ T defense cells, which can become activated (i.e. HIV-specific, or CTL) after being warned by some CD4+ T cell. So the proposed model keeps track of both the unactivated CD8+ T cells and the activated cells, thus taking into account the dynamics of the activation process.

Even though ART has produced undisputed advances in the treatment of HIV infection, it has been argued that the inhibitors that comprise ART may cause adverse effects, see for example [3, 13, 14]. Hence, one can argue that a compromise should be reached between the benefits obtained from ART and the adverse effects that it may cause. The ideal treatment should keep the benefits to a maximum degree while also minimizing the adverse effects. It is the development of such a treatment that we address in this paper, making use of the optimal control theory framework. We propose a dynamic model to represent the dynamics of the HIV infection, which takes into account the effects of the ART therapy and introduces control parameters that determine the intensity of the medication. An optimal control problem is then proposed to determine the optimal medication levels in such a way as to maximize the benefits of the therapy, while keeping the medication to a minimum efficient level.

DOI: 10.5540/03.2016.004.01.0031

2 Modelling

Based on the above discussions, a simplified model regarding to the HIV infection was presented in [1]. The model is the following set of ordinary differential equations:

$$\begin{cases} \dot{x} &= \lambda_x - \mu_x x - \beta_v x v - u_1 x \\ \dot{x_p} &= u_1 x - \mu_x x_p \\ \dot{y} &= \beta_v x v - \mu_y y - p_y y z_a - u_2 y \\ \dot{y_b} &= u_2 y - \mu_y y_b \\ \dot{v} &= k_v \mu_y y - \mu_v v - p_v v z_a \\ \dot{z} &= \lambda_z - \mu_z z - \beta_z z v \\ \dot{z_a} &= \beta_z z v - \mu_z z_a. \end{cases} \tag{1}$$

System (1) is described briefly here. For more details, we refer to [1]. In virus replication, free viruses (v) and uninfected CD4 + T cells (x) produce infected cells (y) at rate β_v. Uninfected and defense CD8 + T cells (z) are assumed to be generated at constant rates λ_x and λ_z, respectively. Uninfected, infected and defenses cells and the free virus decline at rates μ_x, μ_y, μ_z and μ_v, respectively. Infected cells produce new virus particles at rate $k_v\,\mu_y$. One can observe the introduction of two variables z and z_a to represent respectively the defense cells (CD8 + T) and the HIV activated defense cells (CTL). Defense cells z are activated for HIV at rate β_z and the activated cells z_a eliminate infected cells y and free viruses v at rates p_y and p_v, respectively. The model also includes the effects of cocktail drugs typically used in infected patients by means of the control variables u_1 e u_2. The variable u_1 represents the effects of the inhibitors, which protect the uninfected cells x, preventing their change into infected cells y. To account for that, we introduced the state variable x_p to represent the cells that are protected by the action of the inhibitors. The variable u_2 represents the effects of the inhibitors that block the infected cells, preventing the spread of the virus in the body. To account for this effect, we introduced the state variable y_b to represent the cells that were blocked by the inhibitors. We assume that $x_p(0) = y_b(0) = 0$. For this model the basic reproduction number of the virus before the treatment is given by:

$$R_0 = \frac{\lambda_x \beta_v k_v}{\mu_x \mu_v}. \tag{2}$$

If constant medication dosages are applied, such a number is changed to:

$$R_c = \frac{\mu_x}{\mu_x + u_1} \cdot \frac{\mu_y}{\mu_y + u_2} \cdot R_0; \tag{3}$$

it is worth reinforcing that, for the expression above to hold, the control parameters u_1 and u_2 have to be kept constant with respect to time. Note that if $R_0 < 1$, there will be no infection (virus extinction). In contrast, if $R_0 > 1$, infection is verified (HIV propagation). Observe that if $u_1 = u_2 = 0$ (no treatment), then $R_0 = R_c$.

To solve the system of equations described in this section we will make use of the Finite Difference Method.

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3 Optimal Control Problem

In order to minimize the side effects of drug treatments, we propose a cost functional devised in such a way that the decision maker is provided with an optimal strategy for the medication levels $u_1(t) \geq 0$ and $u_2(t) \geq 0$, with $t \geq 0$, which are the control parameters and, for that reason, are allowed to vary over time. The optimal strategy obtained from Problem (4) is designed to minimize the side effects, by lowering the medication dosages as much as possible, while also minimizing the virus in the system dynamics described by Eq. (1).

$$\begin{aligned} &\text{Minimize} \quad \mathrm{J} = \tfrac{1}{2}\int_0^{\mathrm{T}} \left(\mathrm{c_1 u_1^2} + \mathrm{c_2 u_2^2} + \mathrm{c_3 v^2}\right) \mathrm{dt}, \\ &\text{subject to (1)}, \end{aligned} \tag{4}$$

where T is the period of HIV treatment.

To solve Eq. (4), one can apply Pontryagin's Maximum Principle [5], which results in the following co-state equations:

$$\left\{\begin{array}{rcll} \frac{dw_1}{dt} & = & -\frac{\partial H}{\partial x} = & \mu_x w_1 + \beta_v v w_1 + u_1 w_1 - u_1 w_2 - \beta_v v w_3 \\ \frac{dw_2}{dt} & = & -\frac{\partial H}{\partial x_p} = & -c_1 x_p + \mu_x w_2 \\ \frac{dw_3}{dt} & = & -\frac{\partial H}{\partial y} = & \mu_y w_3 + p_y z_a w_3 + u_2 w_3 - u_2 w_4 - k_v \mu_y w_5 \\ \frac{dw_4}{dt} & = & -\frac{\partial H}{\partial y_b} = & \mu_y w_4 \\ \frac{dw_5}{dt} & = & -\frac{\partial H}{\partial v} = & \beta_v x w_1 - \beta_v x w_3 + \mu_v w_5 + p_v z_a w_5 + \beta_z z w_6 - \beta_z z w_7 \\ \frac{dw_6}{dt} & = & -\frac{\partial H}{\partial z} = & \mu_z w_6 + \beta_z v w_6 - \beta_z v w_7 \\ \frac{dw_7}{dt} & = & -\frac{\partial H}{\partial z_a} = & p_y y w_3 + p_v v w_5 + \mu_z w_7, \end{array}\right. \tag{5}$$

where $w_i(T) = 0, \quad i = 1, \ldots, 7$ and H is the Hamiltonian, which can be obtained by defining an appropriate expanded problem based on Problem (4); for more details on this procedure we refer to [5]. Applying optimal control theory, we obtain:

$$\begin{aligned} u_1^* &= max\left\{0\,,\, \tfrac{(w_2 - w_1)x}{c_2}\right\} \\ u_2^* &= max\left\{0\,,\, \tfrac{(w_4 - w_3)y}{c_3}\right\}. \end{aligned} \tag{6}$$

Hence the optimal control for the problem is characterized by Eq. (6). It is worth mentioned that, even though (6) provides an analytic solution to the problem, it cannot be directly obtained, for it holds only for the optimal trajectory, which results from the application of the optimal control, not known a priori. It can, however, be obtained by a standard gradient descent algorithm, which generates a sequence of increasingly accurate approximations to the optimal control strategy. This sequence converges to the solution of the system, described by Eq. (6). The optimal solution was found iteratively by means of a gradient algorithm [5].

DOI: 10.5540/03.2016.004.01.0031

4 Numerical Experiment

For the numerical experiment we have used the dataset described in Tables 1 and 2. We let the system evolve without control for one year to simulate the infection period prior to diagnosis and we define a one-year treatment period. The results can be observed in Figure 1 with $c_1 = c_2 = c_3 = 1$.

Table 1: Initial Conditions

State Variables	Variable	Value
CD4+ T cells in body (susceptible)	x	$10^3\ mm^{-3}$
CD4 + T cells infected by HIV	y	$0\ mm^{-3}$
Free HIV in the body	v	$10^{-3}\ mm^{-3}$
Defense cells CD8+ T HIV specific	z	$500\ mm^{-3}$
Activated defense cells	z_a	$0\ mm^{-3}$

Table 2: Parameters

Parameters and Constants	Variable	Value
Mortality of susceptible cells	μ_x	$0.02\,day^{-1}$
Mortality of infected cells	μ_y	$0.24\,day^{-1}$
Mortality of the virus	μ_v	$2.4\,day^{-1}$
Mortality of defense cells	μ_z	$0.04\,day^{-1}$
Average number of free virus from infected cells	k_v	360
Activation of immunologic response rate	β_z	$5 \cdot 10^{-6}\,mm^3 day^{-1}$
Virus infection rate	β_v	$2.4 \cdot 10^{-5}\,mm^3 day^{-1}$
Infected cells destruction rate	p_y	$0.02\,mm^3 day^{-1}$
Virus destruction rate	p_v	$0.02\,mm^3 day^{-1}$
Susceptible cells supply rate	λ_x	$20\,day^{-1} mm^{-3}$
Defense cells supply rate	λ_z	$20\,day^{-1} mm^{-3}$

The model adequately describes the behavior of the HIV in the human body. Early in the treatment, there is a reduction of the target cells (susceptible), given that these cells become protected with treatment. The same can be observed with the infected cells, that decrease while the blocked cells increase over the same period. It is also observed that the number of free viruses decays rather quickly while keeping very close to zero (trivial equilibrium). Observe that the medication levels considerably decreased as the side effects are confronted with the viral load. the optimal control prescribes high dosages in the early stages, to control the spread of the disease and comparably low dosages in the following stages, in order to keep the disease under control.

5 Conclusions

This paper presented a simple model of the immune response to HIV. The model includes an optimal control strategy to minimize the side effects of treatment. We proposed an

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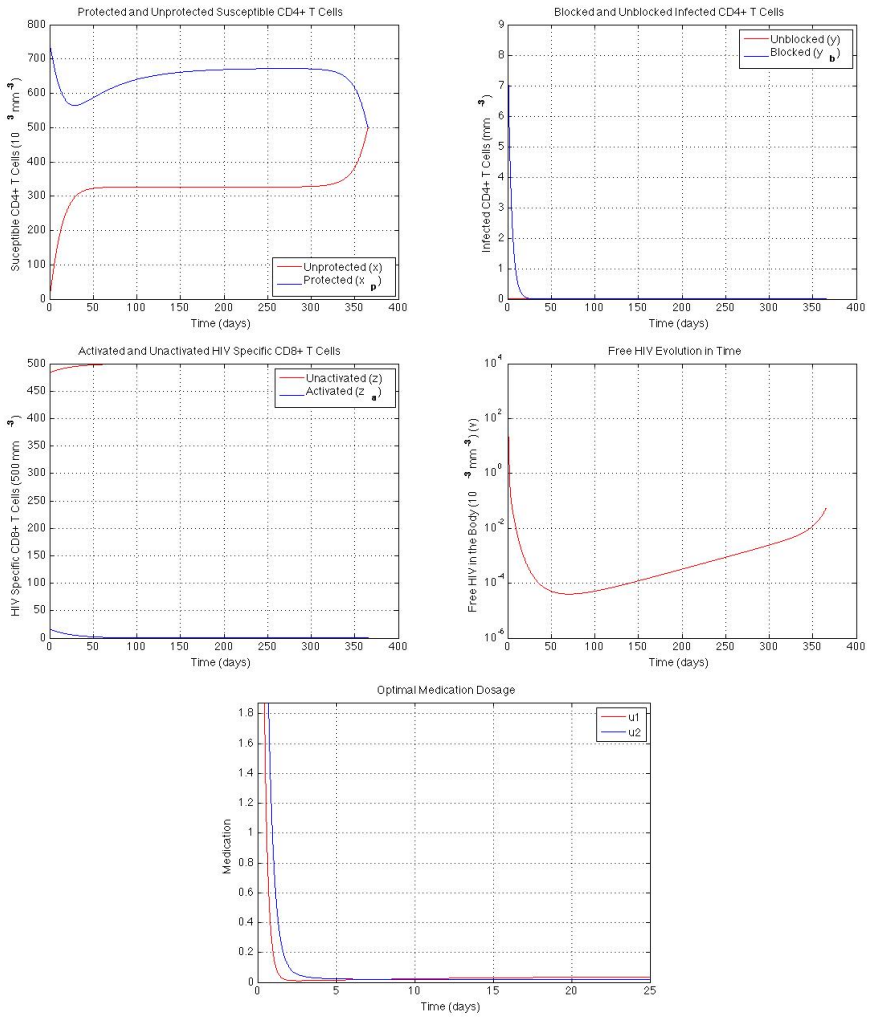

Figure 1: Numerical Simulation.

performance index to include the side effects as well as the viral load resulting from a treatment. The results opens the possibility of developing and solving more complex models, possibly taking into account other effects of the treatment.

Acknowledgments

The authors would like to thank The Carlos Chagas Filho Foundation for Research Support of the State of Rio de Janeiro, FAPERJ, for supporting the research by means of grants E-26/110.379/2012 and E-26/110.087/2014. This work was partially supported by the Coordination for the Improvement of Higher Education Personnel of Brazil - CAPES, under grant No. BEX2025/14-0, and by the National Council for Scientific and Technological Development - CNPq, under grant No.302716/2011-4.

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DOI: 10.5540/03.2016.004.01.0031