A model for interactions between immune cells during HIV treatment

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Abstract

In this work we analyze the capacity of the human body to combat HIV. The model here treated takes into consideration four types of defense of an organism infected by HIV: susceptible defense cells, the infected immune cells, killer T cells, and the HIV specific killer T cells. This model therefore analyzes the interactions between the responses of killer T cells and HIV infections, evidencing how the immune system is attacked and how it defends. An optimal control problem is proposed to derive an optimal sequence of dosages in the standard drug treatment, in such a way as to minimize the side effects.

Keywords: HIV, Mathematical Modelling, Optimal Control

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1. Introduction

Mathematical models are essential tools in decision making problems that arise in a wide range of areas. In particular, they provide the means for understanding population dynamics (e.g., Levin et al., 1997), which can be used as an abstraction to model epidemiological problems. According Heesterbeek et al. (2015) "*many factors, including increasing antimicrobial resistance, human connectivity, population growth, urbanization, environmental and land use change, as well as changing human behavior, present global challenges for prevention and control. Faced with this complexity, mathematical models offer valuable tools for understanding epidemiological patterns and for developing and evaluating evidence for decision-making in global health*". More specifically, Heesterbeek et al. (2015) provide an overview of the role of mathematical modeling in our understanding of the HIV epidemic, and in the decision making process that followed. Such a role is also discussed in the excellent work of Perelson and Ribeiro (2013), which discusses the importance of modeling to uncover important characteristics of HIV infection.

In the early 1990s, researchers started using fishing models to describe the dynamics *in vivo* of viral infections and immune responses; as one could expect, the human immunodeficiency virus (HIV) attracted particular interest (Nowak and Bangham, 1996; Perelson and Nelson, 1999; Nowak and May, 2000). At the time, researchers were focused on understanding both the viral dynamics and the mechanisms of the virus to deceive the immune system surveillance. They also sought to estimate basic viral parameters and to model the response of the HIV infection to drug treatments. Wodarz

et al. (2014) investigated the fundamental structure of the infection term, i.e. the overall rate at which target cells in a population become infected in the presence of the virus. In a related line of research, Wodarz and Levy (2011) accounted for the fact that multiple copies of the virus can infect the same cell, and addressed the so-called co-infection problem.

A specific part of the immune system is formed by killer T cells or cytotoxic T lymphocytes (CTL). These cells are very important in the fight against viral infections (e.g., Gulzar and Copeland, 2004; Kamata et al., 2015). Indeed, control models that account for the effects of drug treatment often seek to keep these cells healthy and active in the fight against the infection (e.g., Arruda et al., 2015). For a thorough discussion on the models of the dynamics of HIV infections, we refer to (Perelson and Ribeiro, 2013).

Recently, Arruda et al. (2015) proposed a model to describe the dynamics of HIV in human body with the introduction of a new variable dubbed *activated* or *HIV-specific* defense cell. That allows one to keep track of both *activated* and *non-activated* CTL cells, providing a better understanding of the infection. In their model, they employed free HIV viruses in the body as activators of the immune cells which, upon activation, become specific to the virus and dedicated to destroy it.

This paper improves the formulation in (Arruda et al., 2015) by introducing a change in the activation mechanism whereby the CTL cells are activated by the interaction with an infected cell. Such a change makes the model more realistic, given that this is how the activation actually takes place in the human body (Gulzar and Copeland, 2004). In addition, the proposed model also incorporates the innovation in (Arruda et al., 2015), namely that the

model keeps track of both the activated defense cells, providing an improved comprehension of the infection dynamics. An interesting byproduct of this modification is that it provides a better understanding about the resumption of the disease should the treatment be interrupted. In that case, the infection generally returns with renewed force (e.g., Kilby et al., 2000; Abbas and Mellors, 2002; Pinkevych et al., 2015), demanding additional medical attention and causing an increased damage to the patient's health. Another contribution of this paper is that the model applies normalized dosages of medication, to take into account the fact that dosages must be limited to prevent the possibility of overdose.

The proposed model aims to calibrate the dosage of the reverse transcriptase and protease inhibitors in standard Anti-retroviral Therapy (ART), which are capable of producing an exponential decrease in viral levels, see for example (Eisele and Siliciano, 2012; Finzi et al., 1999). The role of optimal control theory in such calibration has long been recognized (e.g., Adams et al., 2004; Joly and Pinto, 2006). Indeed, an optimal control approach is proposed here to derive optimal dosages in such a way as to guarantee an effective treatment while also minimizing the side effects. Another novelty of the model is that it applies normalized dosages of medication, to take into account the fact that the dosages must be limited to avoid damage to the patient's health. That makes the model more realistic, avoiding excessive dosages at the beginning of the treatment, which could be prescribed for a rapid response to the infection if overdose was not an issue.

This paper is organized as follows. Section 2 introduces the model and describes the dynamic of the infection under controlled medication. It also

derives the equilibrium points for the system under nil or constant control. In Section 3, we derive an optimal control formulation to procure an optimal medication dosage, taking into account both the benefits and the side effects of continued treatment. Next, Section 4 presents some numerical experiments aimed at providing an insight into the effect of the cost parameters in the optimal control values and the system dynamics. Finally, section 5 concludes the paper.

2. The Model

When HIV invades the human body, the target is the defense or T CD4+ cells present in the body. These cells, considered as "auxiliary", indicate the presence of an invader to other immune cells (B and T CD8 +). The T CD8+ cells respond to this signal by seeking the destruction of the infected cells, and by responding they become specific for HIV. In this work we propose a new mathematical model for studying the dynamics of HIV in the human immune system, based on several existing models in the literature (Grégio et al., 2009; Wodarz, 2007; Shu et al., 2014; Sánchez-Taltavull et al., 2016; Arruda et al., 2015; Yan et al., 2016).

This model is given by the ordinary differential equations system reproduced below, where the time index is dropped from the state and control

variables for the sake of simplicity:

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

In the above equations, the variable x represents susceptible cells, i.e., cells that the HIV can connect to, the variable x_p represents susceptible cells protected by reverse transcriptase inhibitors, protease and input; the variable y represents those cells already connected to the HIV (infected), whereas the variable y_b represents infected cells that are blocked by protease inhibitors. We use v to represent the free virus present in the body, and employ the variable z to describe the population of killer T cells (CTL) of the immune response. Finally, the variable z_a represents the population of CTL cells activated to fight the infected cells, which is responding with antibodies (De Boer, 2002). The model accounts for the fact that when the treatment is interrupted, the blocked cells lose their protection and resume the production of the virus. As previously discussed, in the absence of protected and blocked cells, the infection generally returns with renewed force (e.g., Kilby et al., 2000). From the model in (1) we see that the treatment works by turning susceptible cells x, which can be contaminated by the virus, into protected cells x_p that cannot. In addition, it also transforms infected cells y, which release virus, into blocked cells y_b that do not. Hence, in the absence of

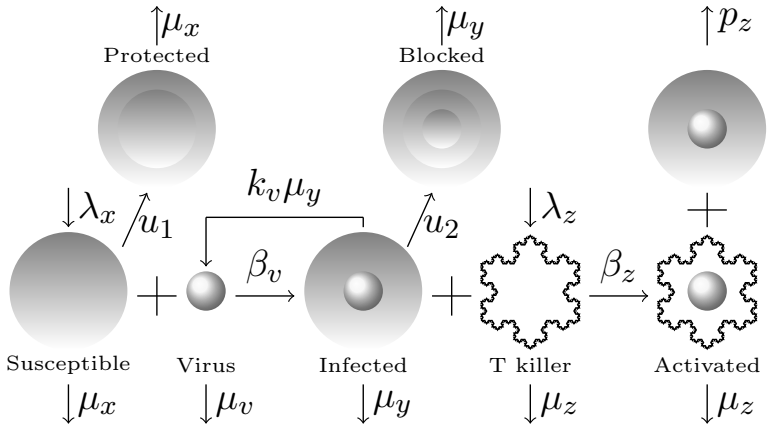

Figure 1: System Dynamics.

protected and blocked cells the infection of susceptible cells and the release of free viruses return to their pre-treatment behavior, and the equilibrium point to be reached will be that of the system under no treatment.

To set up the initial condition, we consider the time instant of the first contact of the virus with the body, i.e. the trivial equilibrium point of the system without the virus, and introduce a tiny amount v_0 of viruses: $x(0) = \lambda_x/\mu_x,\ x_p(0) = 0,\ y(0) = 0,\ y_b(0) = 0,\ v(0) = v_0,\ z(0) = \lambda_z/\mu_z,\ z_a(0) = 0.$

In Eq. (1) u_1 and u_2 are the control variables, which represent the dosages of the reverse transcriptase and the protease inhibitor, respectively. We assume that the dosages are normalized between 0 and 1, with the latter value representing the maximum dosage that does no harm to the patient. Note that x_p and y_b vanish when $u_1 = u_2 = 0$, for the patient is subject to no treatment. In that case, the system dynamics mechanism depicted in Fig. 1 implies that the contact of the virus v with susceptible cells x produces infected cells y, which in turn produce more virus v, and so on. Observe also

that the infected cells y activate the killer cells z, which then become z_a and start eliminating infected cells y. We stress that z and z_a are the natural immune responses of the patient, which do not depend upon the treatment to be generated.

The parameters employed in the system of equations in (1) are described in Table 1. Their values were obtained from the specialized literature (Nowak and Bangham, 1996; Nowak and May, 2000; Mclean, 2013; Perelson and Ribeiro, 2013). We consider that the susceptible cells are produced at a constant rate λ_x, and decay at a constant rate μ_x. Given the time scale - we wish to simulate the system's dynamics until the system reaches an equilibrium point - these constant rates are a satisfactory approximation well-documented in the literature, see for example (Nowak and Bangham, 1996; Nowak and May, 2000; Mclean, 2013; Perelson and Ribeiro, 2013). We also assume that the susceptible cells are infected with the virus at a rate β_v. Hence, the variable x migrates to the compartment of the variable y at a rate β_v. The variable y decays at a rate μ_y and is terminated at a rate p_y, which is the rate at which the HIV activated CTL cells z_a eliminate the infection. The free virus v is produced at a rate k_v, for we assume that the virus is released in the body upon the death of an infected cell, and it decays at rate μ_v. The CTL cells are produced at a constant rate λ_z, and decay at an also constant rate μ_z. Note that β_z is the cell activation rate, the rate at which CTL cells z interact with infected cells and become activated CTL cells z_a. Finally the activated CTL cells decay at the same rate of their non activated counterpart.

The control variable u_1 represents permissible dosages of reverse tran-

scriptase inhibitors, integrase and input. These protect the target cells x, preventing the infection, i.e. preventing them from becoming infected cells y. To keep track of the effect of the medicine, our model introduces the variable x_p to represent the cells that are protected by the action of these inhibitors. It is this variable that allows us to estimate the effect of interrupting the treatment at any point in time, which is not possible in other models in the literature.

On the other hand, the control variable u_2 simulates permissible dosages of the protease inhibitor, which blocks the infected cells y, preventing them from releasing the virus in the body. Once again, this variable enables us to estimate the effect of interrupting the treatment, for it provides an estimate of the amount of virus released in the body at the precise moment when the treatment is interrupted.

The values used in numerical simulations (see Tables 1 and 2), can be found at literature (Mclean, 2013; Wodarz, 2007; Perelson and Nelson, 1999).

2.1. Equilibrium Points

The equilibria of the dynamic system (1) are given by the relationship:

$$\begin{aligned} P &= (\bar{x}, \bar{x}_p, \bar{y}, \bar{y}_b, \bar{v}, \bar{z}, \bar{z}_a) \qquad (2)\\ &= \left(\frac{\lambda_x}{\mu_x + u_1 + \beta_v \bar{v}}, \frac{\lambda_x \mu_x}{u_1(\mu_x + u_1 + \beta_v \bar{v})}, \frac{\mu_v\, \bar{v}}{k_v \mu_y}, \frac{\mu_v \bar{v}}{k_v u_2}, \bar{v}, \frac{k_v \lambda_z \mu_y}{\beta_z \mu_v \bar{v} + k_v\, \mu_y\, \mu_z}, \right.\\ &\quad \left. \frac{\lambda_z \beta_z \mu_v \bar{v}}{\mu_z(\beta_z\, \mu_v \bar{v} + k_v\, \mu_y\, \mu_z)} \right), \end{aligned}$$

where:

$$\bar{y} = 0 \quad or \quad a\,\bar{y}^2 + b\bar{y} + c = 0, \qquad (3)$$

Table 1: Parameters Dataset.

Mortality of susceptible cells	μ_x	$0.02\,day^{-1}$
Mortality of infected cells	μ_y	$0.24\,day^{-1}$
Virus mortality	μ_v	$2.4\,day^{-1}$
Mortality of CTL cells	μ_z	$0.04\,day^{-1}$
Average number of free virus released from an infected cell	k_v	360
Immune response activation rate	β_z	$5 \cdot 10^{-6}\,mm^3 day^{-1}$
Virus infection rate	β_v	$2.4 \cdot 10^{-5}\,mm^3 day^{-1}$
Rate of destruction of infected cells	p_y	$0.02\,mm^3 day^{-1}$
Supply rate of susceptible cells	λ_x	$20\,day^{-1} mm^{-3}$
Supply rate of CTL cells	λ_z	$20\,day^{-1} mm^{-3}$
Control by inhibitors of reverse transcriptase, integrase and input	u_1	$[0, 1]$
Control over protease inhibitors	u_2	$[0, 1]$

with,

$$
\begin{aligned}
a &= \beta_v\,\beta_z\,\mu_v^2\,(\mu_y\,\mu_z + \lambda_z\,p_y + \mu_z\,u_2),\\
b &= \mu_v(\beta_v k_v \mu_y^2\,\mu_z^2 + \beta_z\mu_v\mu_x\mu_y\mu_z + \beta_z\lambda_z\mu_v\mu_x p_y + \beta_z\mu_v\mu_x\mu_z u_2 + \beta_z\mu_v\mu_y\mu_z u_1\\
&\quad + \beta_z\lambda_z\mu_v p_y u_1 + \beta_z\mu_v\mu_z u_1 u_2 + \beta_v k_v\mu_y\mu_z^2 u_2 - \beta_v\beta_z k_v\lambda_x\mu_y\mu_z),\\
c &= k_v\mu_v\mu_x\mu_y^2\mu_z^2 + k_v\mu_v\mu_y^2\mu_z^2 u_1 - \beta_v k_v^2\lambda_x\mu_y^2\mu_z^2 + k_v\mu_v\mu_x\mu_y\mu_z^2 u_2 + k_v\mu_v\mu_y\mu_z^2 u_1 u_2.
\end{aligned}
$$

For an uninfected individual we have $\bar{v} = 0$. Substituting this value in the expression (2), we have the trivial equilibrium point:

$$
P_o = (\bar{x}, \bar{x}_p, \bar{y}, \bar{y}_b, \bar{v}, \bar{z}, \bar{z}_a) = \left(\frac{\lambda_x}{\mu_x + u_1}, \frac{\lambda_x\mu_x}{u_1(\mu_x + u_1)}, 0, 0, 0, \frac{\lambda_z}{\mu_z}, 0\right). \qquad (4)
$$

Table 2: Initial conditions.

Susceptible cells	x	$10^3\ mm^{-3}$
Protected cells	x_p	$0\ mm^{-3}$
HIV infected cells	y	$0\ mm^{-3}$
Blocked cells	y_b	$0\ mm^{-3}$
Free HIV in the body	v	$10^{-3}\ mm^{-3}$
HIV activated CTL cells	z	$500\ mm^{-3}$
Activated immune cells	z_a	$0\ mm^{-3}$

Conversely, for an infected individual we have $\bar{v} \neq 0$. In that case one is forced to solve the quadratic equation in (3). We recall that an equilibrium point is stable if the sign of the real part of the eigenvalues of the Jacobian matrix at this point is negative, as stated in the Hartman-Grobman Theorem (Kreyszig, 1978). It is easy to see that the condition for the stability of the trivial equilibrium point is:

$$\frac{k_v \beta_v \lambda_x \mu_y}{(\mu_x + u_1)(\mu_y + u_2)\mu_v} < 1. \tag{5}$$

Consequently, we conclude that the basic reproduction number is given by:

$$R_0 = \frac{k_v \beta_v \lambda_x \mu_y}{(\mu_x + u_1)(\mu_y + u_2)\mu_v}. \tag{6}$$

Hence, if (5) holds true, the trivial equilibrium P_o in (4) is stable. In that case, the infection does not spread in the organism of the contaminated individual.

3. Optimal Control Formulation

To apply the model, we obtain the initial conditions by running the uncontrolled model from Eq. (1) for a period of 365 days. That simulates an individual that has been diagnosed one year after the infection.

We point out that u_1 and u_2 are dynamic variables in continuous time, which prescribe the maximum medication dosages administered without injury to the patient at each time $t \in [0, T]$, where T is the total length of the planned treatment. Thus, $u_1(t)$ represents the dosage of inhibitors of reverse transcriptase, integrase and input at time $t \in [0, T]$; whereas $u_2(t)$ indicates the dosage of the protease inhibitor at time $t \in [0, T]$. To simplify the treatment, doctors can apply a sub-optimal treatment, with regular dosages of medication corresponding to the combined medication prescribed by continuous variables u_1 and u_2 for each regular interval. For example, if the treatment is prescribed daily for a period of 365 days, the sub-optimal treatment would be comprised of a discrete sequence of dosages $\bar{u_1}_k,\ k \in \{1, \ldots, 365\}$ and $\bar{u_2}_k,\ k \in \{1, \ldots, 365\}$, such that

$$\begin{aligned} \bar{u_1}_{k+1} &= \int_k^{k+1} u_1(s)ds,\ k = 0, \ldots, 364, \\ \bar{u_2}_{k+1} &= \int_k^{k+1} u_2(s)ds,\ k = 0, \ldots, 364. \end{aligned} \tag{7}$$

Alternatively, doctors could prescribe average values of the sequences $\bar{u_1}$ and $\bar{u_2}$ over predetermined intervals, such as monthly intervals for example, re-evaluating the treatment between successive intervals.

Observe that, if the dosages u_1 and u_2 were to be kept constant, one could replace μ_x for $(\mu_x + u_1)$ and μ_y for $(\mu_y + u_2)$ in terms involving u_1 and u_2, and

all the results regarding the equilibrium points and their stability obtained in the foregoing section would be retrieved here. In that case, the number of primary virus replication after treatment (control), represented by R_c, is given by:

$$R_c = \frac{\mu_x}{\mu_x + u_1} \frac{\mu_y}{\mu_y + u_2} R_0. \tag{8}$$

Note that the terms multiplying R_0 in the above equation arise due to the (now constant) control variables $u_1(t) = u_1,\ \forall t \in \mathbb{R}$, and $u_2(t) = u_2,\ \forall t \in \mathbb{R}$. Note also that, if $u_1 = u_2 = 0$ (no treatment), then $R_c = R_0$, where R_0 was defined in (6).

In the remainder of this paper, we analyze the system's dynamics with $u_1 : t \to \mathbb{R}_+$ and $u_2 : t \to \mathbb{R}_+$ varying over time, and strive to obtain an optimal treatment, prescribing the values of these variables at each time in such a way that an optimal compromise between the efficiency of the treatment and its side effects is obtained.

The system is now optimized with respect to control parameters u_1 and u_2. To reach a compromise between medication and side effects, we introduce an optimal control problem aimed at maximizing the number of protected cells while also mitigating the side effects. The optimal control problem is defined as follows:

$$\begin{aligned} &Maximize \quad J = \tfrac{1}{2} \int_0^T \left(c_1 x_p^2 - c_2 (1 - v_1)^2 - c_3 (1 - v_2)^2 \right) dt, \\ &\quad Subject\ to\ (1). \end{aligned} \tag{9}$$

Note that we have used $u_1 = (1 - v_1)$ and $u_2 = (1 - v_2)$ arbitrarily limiting

the maximum dosage between 0 and 1.

In the expression above, c_1, c_2 and c_3 are non-negative scalars. The functional J in (9) can be interpreted as follows: we seek to maximize the protected cells (x_p) while also trying to minimize the drug administrations (u_1 and u_2). We are assuming that the higher u_1 and u_2, the higher the side effects.

To find the optimal control variables u_1^* and u_2^* that solve Problem (9), we make use of Pontryagin's maximum principle (Kirk, 1970; Lewis and Syrmos, 1995; Pontryagin et al., 1961), and derive the Hamiltonian of our optimal control problem, which is given by:

$$H = \tfrac{1}{2}\left[c_1 x_p^2 - c_2(1-v_1)^2 - c_3(1-v_2)^2\right] +$$

$$+w_1\left[\lambda_x - \mu_x x - \beta_v x v - (1-v_1)x\right] +$$

$$+w_2\left[(1-v_1)x - \mu_x x_p\right] + w_3\left[\beta_v x v - \mu_y y - p_y y z_a - (1-v_2)y\right] +$$

$$+w_4\left[(1-v_2)y - \mu_y y_b\right] +$$

$$+w_5\left[k_v \mu_y y - \mu_v v\right] + w_6\left[\lambda_z - \mu_z z - \beta_z z y\right] +$$

$$w_7\left[\beta_z z y - \mu_z z_a\right] + \eta_1 v_1 + \eta_2 v_2,$$

where $w_j,\ j = 1, \ldots, 7$, are the co-state variables, that determine the adjoint systems. It is well known that the optimal solution must satisfy both the original and the adjoint system of equations. The variables η_1 and η_2 are

penalty multipliers (slack variables), added to the model to ensure that the constraints $v_1 \geq 0$ and $v_2 \geq 0$ are satisfied. For the optimal values $v_1^* = 1 - u_1^*$ and $v_2^* = 1 - u_2^*$, it holds that $\eta_1 u_1^* = 0$ and $\eta_2 u_2^* = 0$. For the latter equality to hold, v_1 and v_2 must either be nil or positive. Both cases are considered below.

(i) Considering the set: $\{t \mid v_1 > 0 \text{ and } v_2 > 0\}$

It follows from Pontryagin's maximum principle that the optimal control variables $v_1^* = 1 - u_1^*$ and $v_2^* = 1 - u_2^*$ must satisfy:

$$\frac{\partial H}{\partial v_1^*} = \frac{\partial H}{\partial v_2^*} = 0.$$

Then,

$$\begin{cases} \frac{\partial H}{\partial v_1^*} &= c_2 - c_2 v_1^* + x w_1 - x w_2 + \eta_1 = 0 \\ \frac{\partial H}{\partial v_2^*} &= c_3 - c_3 v_2^* + y w_3 - y w_4 + \eta_2 = 0. \end{cases}$$

Thus, isolating u_1^* and u_2^*, we obtain,

$$\begin{cases} v_1^* = \frac{(w_1 - w_2)x + c_2 + \eta_1}{c_2} \\ v_2^* = \frac{(w_3 - w_4)y + c_3 + \eta_2}{c_3} \end{cases}. \tag{10}$$

As in this case we necessarily have $\eta_1 = \eta_2 = 0$, since $\eta_1 v_1^* = \eta_2 v_2^* = 0$, the optimal control can be expressed as:

$$\begin{cases} v_1^* = \frac{(w_1 - w_2)x + c_2}{c_2} \\ v_2^* = \frac{(w_3 - w_4)y + c_3}{c_3} \end{cases}. \tag{11}$$

(ii) Considering the set: $\{t \mid v_1 = 0 \text{ and } v_2 = 0\}$

It follows from Eq. (10), that

$$\begin{cases} 0 = \frac{(w_1 - w_2)x + c_2 + \eta_1}{c_2} \\ 0 = \frac{(w_3 - w_4)y + c_3 + \eta_2}{c_3} \ . \end{cases} \tag{12}$$

Since, by definition, $\eta_1 \geq 0$ and $\eta_2 \geq 0$, it follows from Eq. (12) that

$$\begin{cases} -\eta_1 &= (w_2 - w_1)x + c_2 \leq 0 \\ -\eta_2 &= (w_4 - w_3)y + c_3 \leq 0 \ . \end{cases} \tag{13}$$

Therefore, to ensure that u_1^* and u_2^* do not take negative values, we summarize the results obtained in (11) and (13) by:

$$\begin{aligned} v_1^* &= \max\left\{0 \ , \frac{(w_1 - w_2)x + c_2}{c_2}\right\} \\ v_2^* &= \max\left\{0 \ , \frac{(w_3 - w_4)y + c_3}{c_3}\right\} . \end{aligned} \tag{14}$$

Hence, the optimal control for Problem (9) is characterized by (14).

3.1. The Co-State Equations

The necessary conditions of the Pontryagin's maximum principle (Kirk, 1970) also establish that the adjoint variables satisfy:

$$
\begin{cases}
\frac{dw_1}{dt} = -\frac{\partial H}{\partial x} = & \mu_x w_1 + \beta_v v w_1 + v_1 w_1 - v_1 w_2 - \beta_v v w_3 \\
\frac{dw_2}{dt} = -\frac{\partial H}{\partial x_p} = & -c_1 x_p + \mu_x w_2 \\
\frac{dw_3}{dt} = -\frac{\partial H}{\partial y} = & \mu_y w_3 + p_y z_a w_3 + v_2 w_3 - v_2 w_4 - k_v \mu_y w_5 + \beta_z z w6 - \beta_z z w_7 \\
\frac{dw_4}{dt} = -\frac{\partial H}{\partial y_b} = & \mu_y w_4 \\
\frac{dw_5}{dt} = -\frac{\partial H}{\partial v} = & \beta_v x w_1 - \beta_v x w_3 + \mu_v w_5 + p_v z_a w_5 \\
\frac{dw_6}{dt} = -\frac{\partial H}{\partial z} = & \mu_z w_6 + \beta_z y w_6 - \beta_z y w_7 \\
\frac{dw_7}{dt} = -\frac{\partial H}{\partial z_a} = & p_y y w_3 + \mu_z w_7.
\end{cases}
\tag{15}
$$

Finally, we analyze the conditions of transversality. In our case, there is no final value for the state variables. Therefore, the transversal conditions to the adjoint variables are given by

$$w_i(T) = 0, \quad i = 1, \ldots, 7.$$

Observe that the optimal control values in (14) depend directly on the co-state variables and, through these variables, on the dynamics described in (1). Hence, they cannot be analytically determined. Consequently, to solve Problem (9), one searches for optimal control values v_1^* and v_2^* that simultaneously solve the initial value problem and the final value problem in Eq. (15). In this paper, we find the optimal control trajectories iteratively, employing a classical specialized gradient algorithm (Kirk, 1970) and solve the differential equation systems by means of finite difference methods.

4. Numerical simulations

The optimal control problem in Eq. (9) was solved for a one year treatment period. The initial condition for the state variables was obtained by running the uncontrolled system for one year. The last value of each variable (after 365 days) was taken as the initial value for the same variable in the controlled problem. In this work, we first consider Case 1, with $c_1 = 10^{-6}$, $c_2 = 1$ and $c_3 = 1$, which will be used as our benchmark for model evaluation. Note that, under such parameters, the objective function in (9) evaluates the number of protected cells versus the side effects attained from the medication. The small value of c_1 is due to the large number of immune cells, which render the first term in Eq. (9) quite significant. The optimal trajectories of the system for the selected parameters are depicted in Figure 2.

Note in that in the beginning of treatment we have a substantial decrease in the unprotected CD4+ T cells, with an increase in the number of protected cells. That is because the treatment makes most of these cells become protected cells. Note that the HIV-specific CD8+ T cells are rapidly activated to fight the virus. With regards to the infected cells, blocked and unblocked, they rapidly vanish. Note that the number of remaining viruses rapidly decays to zero, its trivial equilibrium point. It is also noteworthy that the optimal dosage of the transcriptase inhibitor is higher than that of the integrase inhibitor.

As discussed in Section 3, the parameters c_2 and c_3 refer to the side effects of the transcriptase and protease inhibitors, represented equation (9) by their dosages u_1 and u_2, respectively. Naturally, the side effects will depend upon the drugs employed and may vary over time as these drugs evolve and are

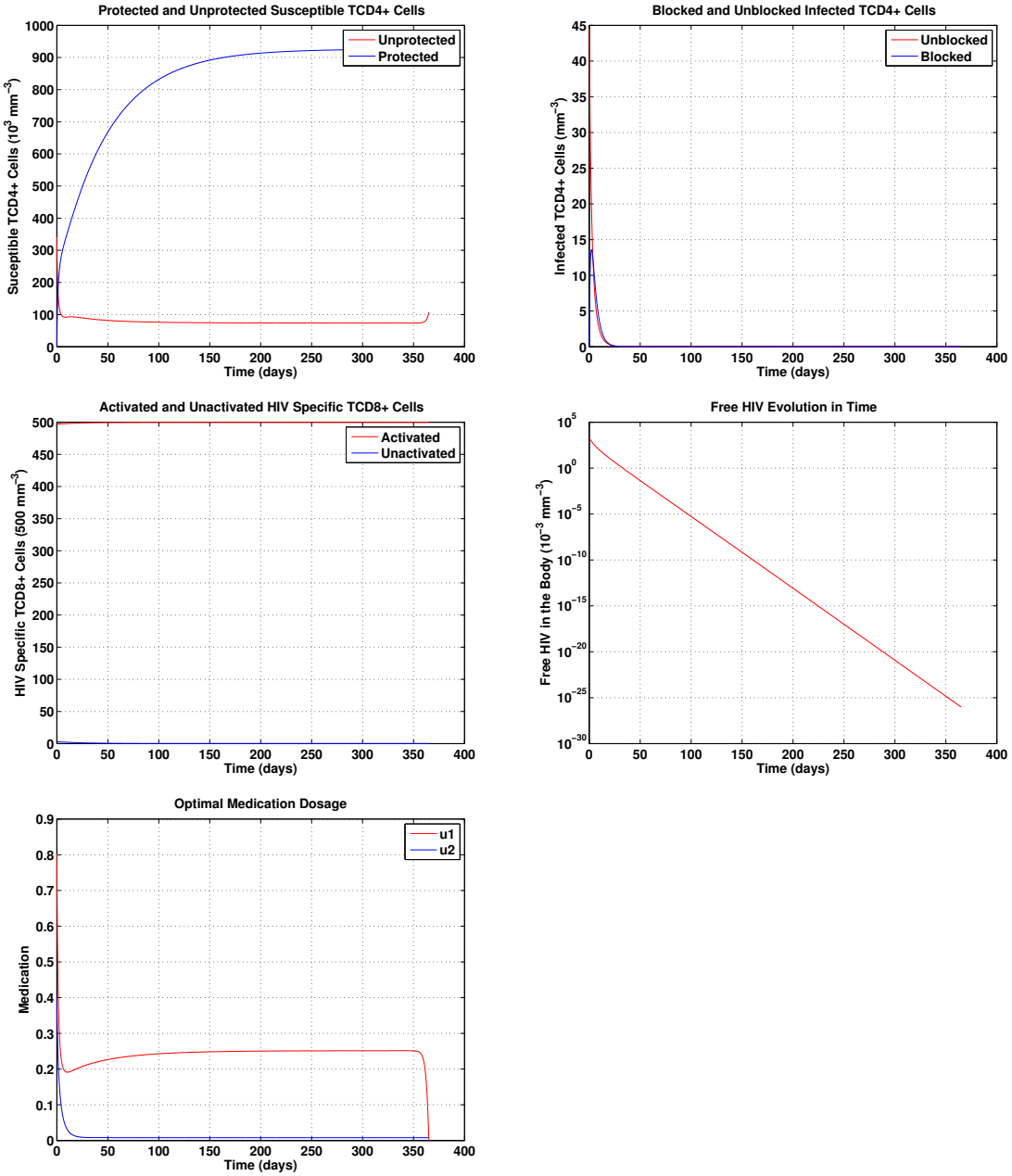

Figure 2: Optimal Trajectories for Case 1: $c_1 = 10^{-6},\ c_2 = c_3 = 1$.

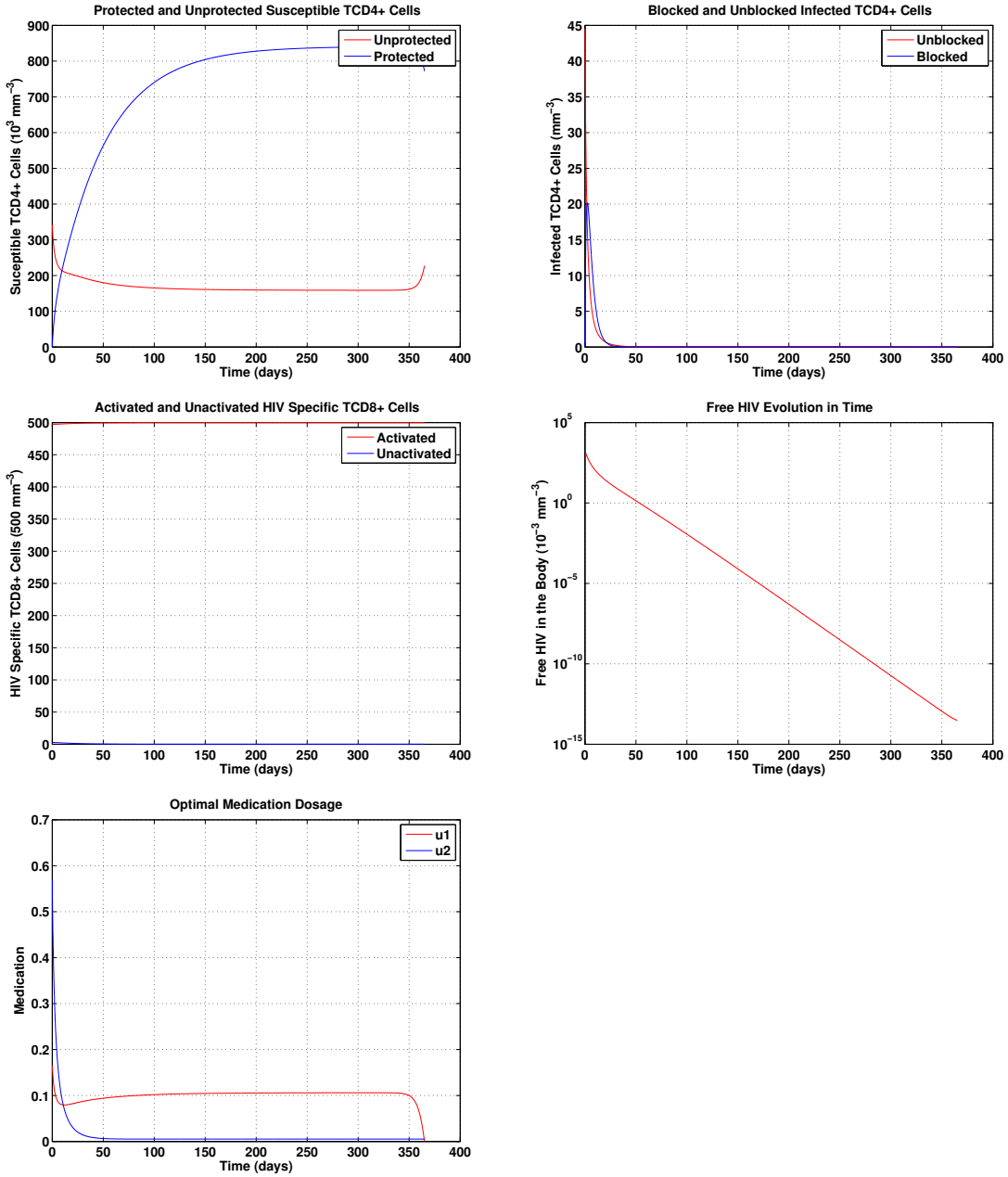

Figure 3: Optimal Trajectories for Case 2: $c_1 = 10^{-6},\ c_2 = 10, c_3 = 1$.

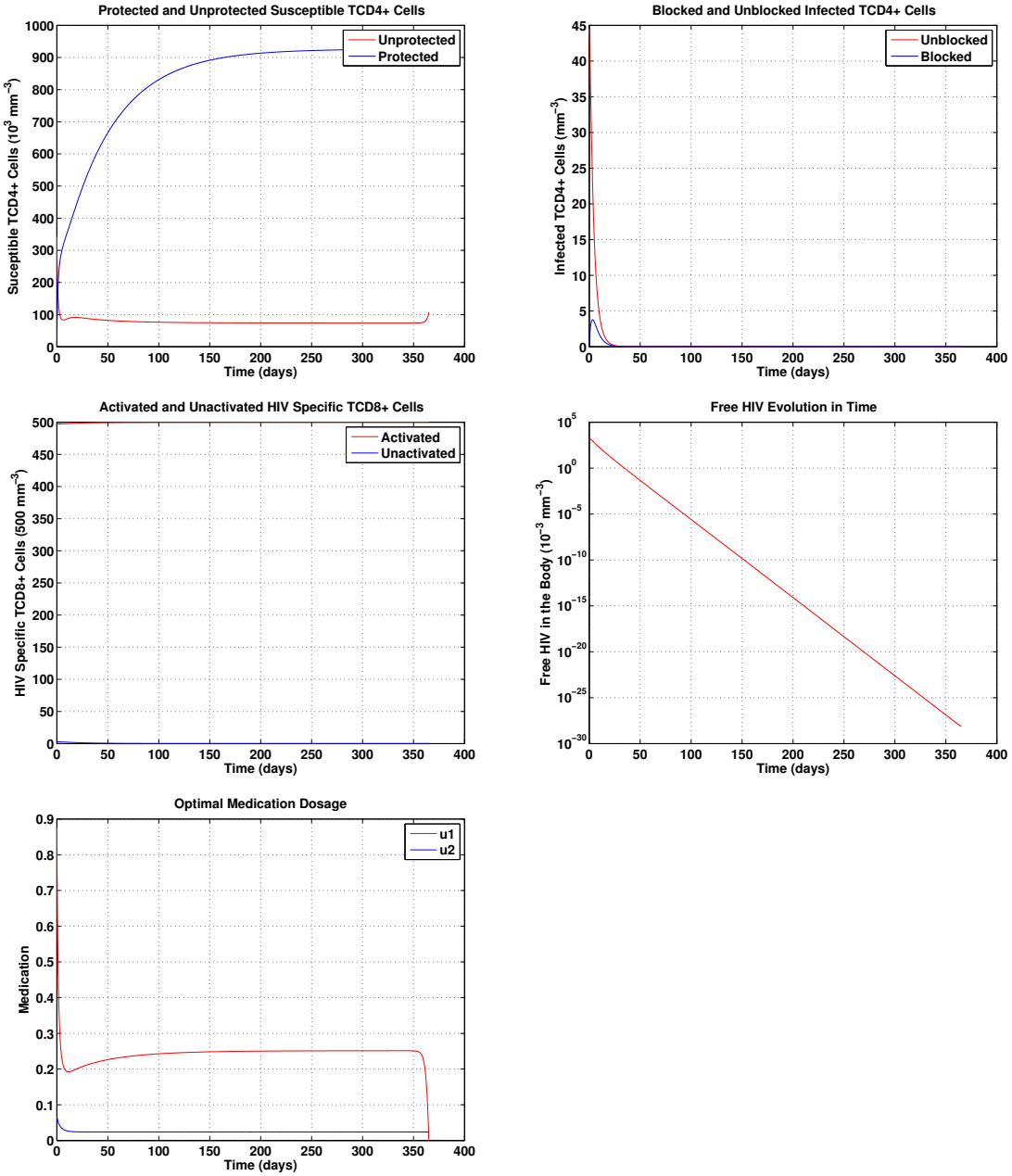

Figure 4: Optimal Trajectories for Case 3: $c_1 = 10^{-6},\ c_2 = 1, c_3 = 10$.

modified. Hence, in the next couple of experiments we will explore two possible scenarios: one in which u_1 is associated with more side effects than u_2 and another in which the opposite holds. While the experiments are by no means extensive, they provide an insight into what happens with the optimal dosages should one treatment present more side effects than the other. In particular, our experiments show the case when the side effects of one drug are tenfold those of the other.

To verify the effects of the variations in the controlled system dynamics, we consider Case 2, with $c_1 = 10^{-6}$, $c_2 = 10$ and $c_3 = 1$, depicted at Figure 3. In this case, we assume that the reverse transcriptase inhibitor presents more side effects than the protease inhibitor, thus causing an augmented value of c_2 with respect to Case 1. It can be noted that, with the increase of c_2 there is a different balance between protected cells and unprotected cells compared with Case 1. The evolution of the virus shows that, in this case, it reaches extinction more slowly than in Case 1. The same applies to the infected cells and blocked cells . Apparently, the changes do not cause significant changes in the values of z and z_a . With regards to the control variables, i.e. the medication levels, the levels of u_1 are reduced in this example.

For Case 3, we set $c_1 = 10^{-6}$, $c_2 = 1$ and $c_3 = 10$, and the results are depicted in Figure 4. In that case we assume that u_2 produces more side effects than u_1. It can be noted that the viruses get extinct at same rate than in Case 1 . The medication levels are similar to those in Case 1 with a not so significant increase of u_2.

5. Concluding Remarks

This paper introduces a model of HIV dynamics that explicitly describes the protected CD4+ T cells and the HIV-specific CD8+ T cells. This allows us to explicitly understand and quantify the effects of medication, providing a better understanding the system's dynamics, and a prompt evaluation of the consequences of an interruption in the treatment. The model takes into account the Anti-retroviral Therapy (ART), which has produced significant advances in the treatment of HIV infection, but also introduces side effects, which should be avoided whenever possible. To take account of the side effects and produce a desirable compromise between treatment effectiveness and side effects, we propose an optimal control approach which prescribes an optimal treatment aimed at maximizing the benefits of the treatment, while also minimizing the side effects. To make the results meaningful, we limit the dosage in a normalized interval to account for the fact that the dosages must be limited in order to avoid harmful effects to the patients. Numerical examples were presented which provide insight into the behavior of the system under different compromises between medication effectiveness and side effects.

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