Optimal Chemotherapeutic Strategy for HIV Infections – State Constrained Case

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***Abstract*—This study investigates a mathematical model of HIV infections in terms of a set of ordinary differential equations (ODEs) which describes the interactions between the $CD4^+T$ cells in the human immune systems and the viruses. In this work, we propose a modification of the model proposed by [5] by imposing a state constraint in the dynamics. The aim is to obtain a new optimal chemotherapeutic strategy where the state constraints play a crucial role. We treat our problem numerically and compare results with existing literature.**

I. Introduction

More than 30 years after the first detection of the *Acquired Immune Deficiency Syndrome* (AIDS) and its etiological agent the *Human Immunodeficiency Virus* (HIV) in the early 1980s, the global health of the whole populations in the world is still under a great threat due to a mysterious and difficult unknown mechanism of HIV infections in the human body. Of the 34.3 million people worldwide living with HIV infections today, more than 24 million are in the developing world. A proper treatment or complete cure from AIDS is yet far away from the reality and even an *anti-HIV vaccine* is still a *dream* to the biologists and physicists [1], [2].

Chemotherapy has been the only way of treatment for HIV positive patients. It aims at killing or halting the virus pathogen thus helping the body to fight against infections [8]. Several (more that 30 varieties of single and/or combined) antiretroviral drugs for the chemotherapy treatments have been approved by the US Food and Drug Administration (FDA) since 1987s aiming at reducing the viral population and improving the immune response. All these drugs cannot cure the diseases completely; rather they can improve the lives of HIV positive patients for a certain period depending on the optimal chemotherapeutic drug dosage strategies. This brings new hope to the treatment of the HIV infection in absence of the HIV vaccine. In this work we explore new strategies for such treatments using optimal control techniques as explained next.

II. Mathematical Model

Several mathematical models describing the *cell-virus* interactions have been developed just in the past few years and even these are constantly being updated to improve the modeling aspects. We refer readers to ([3], [5], [6], [7], [8], [9], [10] and references therein) for more details about the background and analysis of different models as well as the propagation of diseases. The mathematical model of HIV we consider here is a set of ordinary differential equations (ODEs) describing the interactions between the $CD4^+T$ cells in the human immune systems and the viruses.

A. Existing Model

The mathematical model we focus on represents the dynamics of the *cell-virus interactions*. Here a crucial role is played by $CD4^+T$ lymphocytes, commonly referred to as *helper-T-cells*. These cells are the main target of the virus and the command system in the defense against it. A command from these cells activates $CD8^+T$ cells, shortly called *killer-T-cells*, which then fight the virus by killing its main source of reproduction. An infected $CD4^+T$ cell can produce around 500 new viruses before its death and thus becomes a much more important target to destroy then the virus itself [9]. When a free HIV virus enters the body and attacks the *uninfected* $CD4^+T$ cells, the cells become infected and go through a *neutral stage* before becoming *actively infected* for a certain period. The cells in this *latent/interim stage*, which cannot infect other cells are called the *latently infected*. Thus the $CD4^+T$ cells are classified into three classes: *active/uninfected* $CD4^+T$ cells, whose concentration is represented by a variable $T_A(t)$, and the other two types of infected $CD4^+T$ cells are *latently infected* and *actively infected* cells with their concentrations represented by $T_L(t)$ and $T_I(t)$ respectively. The concentration of the free infectious virus is represented by $V(t)$.

When modeling the chemotherapy treatment in a time interval $[t_s, t_f]$, the rate of chemotherapy at each instant t is denoted by u. So $0 \leq u(t) \leq 1$. Taking into account the chemotherapy the dynamics of the four populations can be modeled as in [5] by the following system of ordinary differential equations:

$$\frac{dT_A}{dt} = \frac{s}{1+V(t)} - \mu_{T_A} T_A(t) + rT_A(t)\Big(1 - \frac{T_A(t)+T_L(t)+T_I(t)}{T_{\max}}\Big) - \mu_i V(t) T_A(t) \tag{1}$$

$$\frac{dT_L}{dt} = \mu_i V(t) T_A(t) - \mu_{T_L} T_L(t) - \mu_c T_L(t) \tag{2}$$

TABLE I
PARAMETERS AND CONSTANTS USED IN HIV MODEL.

Parameters/ Constants	Definitions of the parameters and constants	Values
μ_{T_A}	natural death rate of uninfected T cell	$0.02\ d^{-1}$
μ_{T_L}	natural death rate of latently infected T cell	$0.02\ d^{-1}$
μ_{T_I}	natural death rate of actively infected T cell	$0.24\ d^{-1}$
μ_V	natural death rate of free virus population	$2.4\ d^{-1}$
μ_i	rate T cells become infected by free virus	$2.4 \times 10^{-5}\ d^{-1}$
μ_c	rate T_L cells convert to actively infected	$3 \times 10^{-3}\ d^{-1}$
r	growth rate for the T cell population	$0.03\ d^{-1}$
N	number of free virus produced by T_I cell	1200
$T_{\max}$	maximum T cell population level	$1.5 \times 10^3\ mm^{-3}$
s	source term for uninfected T cells where s is the parameter in the term $\frac{s}{1+V}$	$10\ d^{-1}\ mm^{-3}$

$$\frac{dT_I}{dt} = \mu_c T_L(t) - \mu_{T_I} T_I(t) \tag{3}$$

$$\frac{dV}{dt} = (1-u(t))N\mu_{T_I} T_I(t) - \mu_i V(t) T_A(t) - \mu_V V(t), \tag{4}$$

with the initial conditions

$$T_A(0) = T_{A0},\ T_L(0) = T_{L0},\ T_I(0) = T_{I0},\ V(0) = V_0 \tag{5}$$

for the case of infections by both free virus and infected cells.

Here the control u, the rate of chemotherapy, is assumed to be a *measurable function* defined on the fixed interval $[t_s, t_f]$, with the restriction that $0 \le u(t) \le 1,\ \forall t \in [t_s, t_f]$.

The aim is to find the control strategy so that the amount of uninfected cells T_A at the end of treatment is maximized while minimizing the side effects of the treatment. Thus the objective functional is chosen to be

$$\text{Minimize}\quad J(u) = \int_{t_s}^{t_f} \Big(-T_A(t) + \frac{1}{2} B u^2(t) \Big) dt \tag{6}$$

where $B > 0$ denotes a weight parameter. The details, explanations and analysis of the model can be found in [5]. We provide the definitions of the parameters and their clinically approved values in Table I.

B. Extended Model

The existing HIV models including [5] have been treated in absence of state constraints. Our intention here is to find a new solution of the model in [5] imposing some state constraints in the data. We see that the $CD4^+T$ cells count is very crucial for the treatments of HIV infections. The number of $CD4^+T$ cells $200/mm^3$ indicates the severity of the disease [4]. Our idea behind imposing the state constraints is to guarantee that the uninfected $CD4^+T$ cells count T_A should not go below a certain lower bound, for example $200/mm^3$, during the entire treatment. If the T_A cells count goes below the certain level, the concerned person is assumed to be seriously infected by the HIV resulting in an AIDS patient. We modify the model proposed by [5] imposing a state constraint on the uninfected $CD4^+T$ cell populations $T_A(t)$ in addition to the dynamics (1)–(4):

$$T_A(t) \ge \tilde{T} \tag{7}$$

where $\tilde{T}$ is a lower bound belonging to $\mathbb{R}$.

III. RESULT DISCUSSION AND CONCLUSION

We solve our proposed model numerically. All our dynamics have been written in '*MATLAB*' codes and solved by the '*General Pseudospectral Optimization Software (GPOPS)*'. For the convenient of comparing the results, we run the program taking both '*without state constraint*' and '*with state constraint*' into account, but the same cost as in (6). All initial values and the parameters presented in the Table I are considered same as in [5]. We initiate a chemotherapeutic schedules for a 200 days schemes. We obtain the optimal chemotherapy schedules without state constraint for $T_A(0) = 900$, $T_L(0) = 0.05$, $T_I(0) = 0.5$, $V(0) = 0.001$ and $B = 30$ and the objective functional for the cost in (6) is $-1.9764466394E+05$. In the state constrained case, we obtain the optimal chemotherapy schedules for $T_A(0) = 900$, $T_L(0) = 0.05$, $T_I(0) = 0.5$, $V(0) = 0.001$, $B = 30$ and $\tilde{T} = 200$ and the objective functional for the cost in (6) is $-1.9764466848E+05$ which is less than the other case. We omit the graphical representation here due to the page restriction.

The results we present here are preliminary ones. After analyzing these preliminary results obtained from the objective functional (6) in two different cases, it can be concluded that imposing state constraint on the uninfected $CD4^+T$ cells has less significant impact than our expectation because of the increasing behavior of the uninfected $CD4^+T$ cell trajectory. In spite of that, we see from the cost that our state constrained model gives better result compared to that of without state constraint. Finally this preliminary study suggests that our model is less appropriate to illustrate the impact of state constraints more effectively. We hope to study the impact of state constraints using a related model.

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