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An optimal strategy for HIV multitherapy

Yinggao Zhou [a,*], Yiting Liang [a], Jianhong Wu [b]

[a] School of Mathematics and Statistics, Central South University, Changsha, Hunan 410083, PR China

[b] MITACS Centre for Disease Modeling, Department of Mathematics and Statistics, York University, 4700 Keele Street, Toronto, ON, Canada M3J 1P3

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ABSTRACT

The purpose of the paper is to use numerical analysis and optimization tools to suggest improved therapies to try and cure HIV infection. A HIV model of an ordinary differential equation, which includes immune response, neutralizing antibodies and multi-drug effects, is improved. For a fixed time, two drugs treatment strategies are explored based on Pontryagin's Maximum Principle. Four types of treatments are used, and existence and uniqueness results for the optimal control fair are established. The optimality system is derived and then solved numerically using Gradient Projection Method. On the basis of weight factors for controls, we find a well treatment strategy with steady lower dosage of RTIs and PIs during the main part of treatment, almost unchanged higher population of uninfected $CD4^+T$ cells and few increase of active virus throughout the duration.

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1. Introduction

Mathematical models are often used to study disease spread and have become essential tools to make assumptions, suggest new experiments or help one explaining easily complex processes. Many important papers investigate dynamic models of host–drug–virus interactions [1,2]. Most of the models are deterministic prey–predator systems of nonlinear differential equations. Sometimes stochastic terms are included to address the random behavior of features of the disease process. Typically, dynamic changes are modeled considering cell numbers progression of $CD4^+T$ cells, infected cells and virus population under drugs effects [2–7]. At the same time, optimal control has received much attention. The main idea is to use optimization techniques and theories to propose an alternative treatment based on administrating continually adjustable antiviral drug doses once a proper model is obtained. We refer to [4–7] for studies of the HIV model based on optimal control that maximizes/minimizes a prescribed objective function.

In 2011, an optimal control problem including immune response and multi-drug effects for HIV multitherapy enhancement

$$\min J = \frac{c}{2}V^2(t_f) + \int_{t_0}^{t_f}\left[\frac{c}{2}V^2 + \frac{b}{2}\dot{V}^2 + \frac{\varepsilon}{2}(u_1^2 + u_2^2)\right]dt \tag{1}$$

s.t.

$$\dot{T} = rT\left(1 - \frac{T+L+I}{T_m}\right) - \mu_T T - (1-u_1)k_1VT + s_1, \tag{2}$$

* Corresponding author. Tel.: +86 73182255383.
E-mail addresses: ygzhou@csu.edu.cn, ygzhou@mail.csu.edu.cn (Y. Zhou), liang_yiting@sina.cn (Y. Liang), wujh@mathstat.yorku.ca (J. Wu).

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$$\dot{L} = \omega(1-u_1)k_1VT - \mu_T L - k_2 I, \tag{3}$$

$$\dot{I} = (1-\omega)(1-u_1)k_1VT + k_2 I - \mu_I I - k_3 IE, \tag{4}$$

$$\dot{V} = a(1-u_2)I - k_1VT - \mu_V V, \tag{5}$$

$$\dot{E} = k_4 ITE - \mu_E E + s_2, \tag{6}$$

$$T(t_0), L(t_0), I(t_0), V(t_0), E(t_0) \geq 0, \quad 0 \leq u_1,\ u_2 \leq 1$$

was studied by Orellana [5]. For a fixed time, a two drugs treatment strategy was obtained based on Pontryagin's Minimum Principle. Basically, the method studied can be considered as an optimal control one where drug doses are regarded as control inputs. The quadratic objective function considered takes into account three contributions: the viral load, the transient evolution of infection and the quantities of drug used. Simulations were carried out using an indirect optimization method. At each step the differential system was solved using the Runge–Kutta five order scheme. Results highlighted that a progressive reduction of Reverse Transcriptase Inhibitor (RTI) drug dose on the one hand along with on the other hand a progressive increase of Protease Inhibitor (PI) one was needed for optimality.

Orellana [5] takes the Cytotoxic T Lymphocytes (CTL) into account, however, ignores the neutralizing antibodies. The antibodies can combine with the virus such that the virus cannot get into target cells, yet HIV-1 can mutate very quickly, so the antibodies' periods of validity is short. The antibodies can protect a host against the infection by HIV-1. The antibodies can be induced several weeks after infection [8,9]. The facts imply that the neutralizing antibodies may be important in the early stage of the infection. Because the concentration of antibodies is secreted by effector B cells, we add a term $B(t)$, which represents the concentration of effector B cells, to the control system. Because the differentiation and proliferation of B-cells to effector B-cells need the help of $CD4^+T$-cells, we assume the generation rate is k_5VT, where k_5 is a positive constant. Since HIV-1 mutates very fast, the average term of validity of effector B-cells is shorter than normal, therefore we multiply the death rate, μ_B, by a positive constant β, which is bigger than 1. And so, the term $B(t)$ should satisfy the following equation.

$$\dot{B} = k_5VT - \beta\mu_B B. \tag{7}$$

Owing to the assumption that the antibodies' concentration is proportional to effector B cells' concentration, the neutralizing rate should be expressed by qBV and the Eq. (5) should be modified to the following equation.

$$\dot{V} = a(1-u_2)I - k_1VI - \mu_V V - qBV. \tag{8}$$

Further more, due to the fact that latently infected cells could be aroused while the actively infected cells' concentration is quite low [10], we advise the arousing rate is not proportional to $I(t)$, but to its own concentration. As a result, Eqs. (3) and (4) should be modified to the following two equations respectively.

$$\dot{L} = \omega(1-u_1)k_1VT - \mu_T L - k_2 L, \tag{9}$$

$$\dot{I} = (1-\omega)(1-u_1)k_1VT + k_2 L - \mu_I I - k_3 IE. \tag{10}$$

In this paper, a new HIV treatment system is established as the following system (11).

$$\begin{cases} \dot{T} = rT\left(1 - \dfrac{T+L+I}{T_m}\right) - \mu_T T - (1-u_1)k_1VT + s_1, \\ \dot{L} = \omega(1-u_1)k_1VT - \mu_T L - k_2 L, \\ \dot{I} = (1-\omega)(1-u_1)k_1VT + k_2 L - \mu_I I - k_3 IE, \\ \dot{V} = a(1-u_2)I - k_1VT - \mu_V V - qBV, \\ \dot{E} = k_4 ITE - \mu_E E + s_2, \\ \dot{B} = k_5VT - \beta\mu_B B, \\ T(t_0), L(t_0), I(t_0), V(t_0), E(t_0), B(t_0) \geq 0, \\ 0 \leq u_1 \leq b_1, \qquad 0 \leq u_2 \leq b_2, \qquad 0 \leq b_1, b_2 \leq 1 \end{cases} \tag{11}$$

where T, L, I, V, E, B denote the concentration of uninfected $CD4^+T$ cells, latently infected T cells, actively infected cells, infectious viruses, cytotoxic lymphocytes effector and B cells respectively. Drugs efficiency is represented by the controls u_1 and u_2 which accounts respectively for reverse transcriptase and protease inhibitors actions.

It is worth pointing out that our model could be valid in a well mixed sample of blood, but by no means in all the body.

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