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Optimal control of an age-structured model of HIV infection

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ABSTRACT

The optimal treatment strategies with an age-structured model of HIV infection are investigated. The age-structured model allows for variations in the virion production rate and the death rate of infected T cells as a function of age, which is the length of time since infection. The optimal therapy protocol is derived by formulating and analyzing an optimal control problem and the existence of solutions to the optimal control problem is established. The optimal treatment strategy is obtained by solving the corresponding optimality system numerically. It is demonstrated by numerical simulations that the dynamic treatment strategy delays the time to reach the peak viral load and reduces the viral load. Moreover, we propose that optimal therapy protocols should be changed according to different viral production rates and death rates of infected T cells.

1. Introduction

The human immunodeficiency virus (HIV) causes acquired immune deficiency syndrome (AIDS). The viral infection is characterized by a severe impairment of the immune system and related opportunistic infections. The main target cell of HIV is the CD4+ T helper cell. Several drugs that substantially decrease morbidity and mortality in HIV-infected patients have been developed in the last few years. Despite this progress, there is still no treatment protocol that results in clearance of the HIV from patients. In addition, many complications can arise from long-term drug use. For example, drug-resistant strains of HIV can appear, resulting in the resurgence of viral loads after their long-term suppression from treatment [17,21]. There are also a number of harmful side effects from such drug use. Moreover, high drug costs and complicated drug regimens make effective Highly Active Anti-Retroviral Therapy (HAART) use burdensome for some patients and impossible for others.

A number of researchers have searched for optimal treatment strategies that can decrease virus mutations, pharmaceutical side effects, and complex and expensive medication burdens. The optimal control problems of HIV infection have been examined by using different types of models and objective functionals [1,2,9,14]. These authors suggested the continuous optimal treatment schedules that can be found by solving the corresponding optimality systems. B.M. Adams et al. considered two different kinds of treatment as control functions. One prevents HIV from infecting cells by blocking the integration of the HIV viral code into the host cell genome and the other prevents infected cells from replication of infectious virus particles [1,2]. L.M. Wein, et al. used a control theoretic approach for multi-drug therapies with models allowing mutations [27]. An approximating method was employed because of the high dimensionality of the control problem. Feedback control problems have been explored [3,5,7,23]. In [7], several methods of the stable control of the HIV population were considered by using an external feedback control term that was analogous to the introduction of a therapeutic drug regimen. The optimal

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feedback control problems and the state estimator problems based on the state dependent Riccati equation (SDRE) approach for HIV infection were considered in [5].

More recently, substantial progress has been made with on–off treatments, which are also known as structured treatment interruption (STI). STI has received considerable attention because it may reduce the risk of HIV mutating to strains resistant to current medication regimens. The STI approach may also reduce the possible long-term toxicity of drugs [1,2,6,15,28]. A concise summary of clinical STI studies, including protocols and results, is presented in [4]. Some researchers have used a fixed length, prescribed interruption schedule, whereas others have used viral loads and T-cell measurements from patients to determine the interruption period [15,22]. There is currently no general agreement on which treatment strategies or interruption schemes are optimal. One way to consider the optimal STI is to use a mathematical model for HIV infection in conjunction with control theory. The authors in [1,2] introduced a method called the direct search approach; this method uses ideas from dynamic programming to obtain an optimal STI treatment.

To date, many mathematical models have been developed to describe the interaction of CD4+ T cells and HIV in the immune system [8,16,19,24]. Some models of HIV infection have used optimal control theory, generally focusing on a system of ordinary differential equations. However, to our knowledge, optimal control theory based on age-structured models has not been considered in the identification of an optimal methodology for administering HIV treatment. The proposed age-structured model in [18] allows for variations in the death rate of infected CD4+ T cells and the production rate of viral particles. We use this model as constraint equations in the optimal control problem.

The remainder of this paper proceeds as follows. In Section 2, we describe the age-structured HIV model suggested by Nelson et al. [18]. In Section 3, we present the formulation of the optimal control problem and the corresponding optimality system. We provide a proof of the existence of an optimal control function. We then derive an optimality system that characterizes the optimal control. In Section 4, we present the numerical results of the continuous optimal therapy by solving the optimality system. We briefly summarize our efforts and findings in Section 5.

2. Age-structured model

The age-structured model of HIV infection has three state variables: $T(t)$, which represents the number of uninfected CD4+ T cells at time t; $T^*(a,t)$, which represents the number of infected CD4+ T cells structured by the age, a, of their infection at time t; and $V(t)$, which represents the number of virus particles at time t. A system of two ordinary differential equations and one first order hyperbolic equation describing the HIV dynamics is given by

$$\begin{aligned}
&\frac{dT}{dt} = s - dT(t) - (1-\epsilon(t))kV(t)T(t),\\
&\frac{\partial T^*}{\partial t} + \frac{\partial T^*}{\partial a}\frac{da}{dt} = -\delta(a)T^*(a,t),\\
&\frac{dV}{dt} = \int_0^\infty P(a)T^*(a,t)da - cV(t).
\end{aligned} \tag{2.1}$$

In this model, we assume that uninfected T cells are produced at a constant rate, s, and die at a rate, d, per cell. The term kVT represents the infection process wherein infected cells, T^*, are produced by encounters between uninfected target cells, T, and virus particles, V, with an infection rate constant k. The death rate, $\delta(a)$, and the virion production rate, $P(a)$, of T^* are assumed to be functions of the age of cellular infection, a, and virions, V, are assumed to be cleared at a constant rate, c. We also assume $\frac{da}{dt} = 1$, which means scales for the age infection a and time t are the same. Since a first order hyperbolic equation is contained in the model, boundary and initial conditions must be introduced that the infected CD4+ T cells of age zero are created by infection; that is,

$$T^*(0,t) = (1-\epsilon(t))kV(t)T(t).$$

We may also impose the specific initial conditions $T(0) = T_0, T^*(a,0) = T_0^*(a)$, and $V(0) = V_0$. The control term $\epsilon(t)$ represents the effectiveness of the reverse transcriptase inhibitors (RTI), which block new infection. Thus the infection rate, k, is reduced to $(1-\epsilon(t))k$, where $0 \leqslant \epsilon_{min} \leqslant \epsilon(t) \leqslant \epsilon_{max} < 1$. Here ϵ_{min} and ϵ_{max} represent minimal and maximal drug efficacy, respectively.

Remark 2.1. With the above boundary and initial conditions and a smooth enough control function, we note that there exists a unique solution to the system (2.1) which remains bounded and non-negative for $t > 0$ (see [18,26]).

The mathematical model (2.1) contains several constant parameters and function parameters that must be assigned for numerical simulations. The descriptions and numerical values for the parameters are summarized in Table 1, which are principally extracted from the paper authored by Nelson et al. [18]. Since the age of every cell is considered, in general, each cell will have a different viral production and infected-cell death rate. To represent these rates, we need explicit functional forms of the viral production kernel, $P(a)$, and the death rate of the infected cells, $\delta(a)$. According to prior research [12,18], the viral production kernel can be defined as follows:

$$P(a) = \begin{cases} P_{max}(1 - \exp^{-\beta(a-d_1)}) & \text{if } a \geqslant d_1,\\ 0 & \text{otherwise,} \end{cases} \tag{2.2}$$