



A control systems analysis of HIV prevention model using impulsive input



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ABSTRACT

We investigate a control systems analysis on HIV infection dynamics with regard to enhancement of the immune response. The HIV dynamic model is modified to include the pharmacokinetics and pharmacodynamics of antiretroviral HIV drugs, and the intake of drug is considered as impulsive control input. As it is administrated at discrete time instants, we assume that this yields an impulsive control problem for a nonlinear continuous-time system. Based on this new model, we study clinical experiments about antiretroviral treatments via numerical simulation and analyse the experimental results. It is noted that this modeling approach can help to provide a theoretical explanation of the clinical results. The analysis result in the paper could imply that the protocol of the experiment might enhance the immune response against HIV.

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1. Introduction

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). After HIV infection, CD4 T-cells are infected by the virus. An infected CD4 T-cell does not perform its role in the human immune system and makes multiple HIV copies. With a low level of CD4 T-cell count, the human immune system cannot work properly.

HIV/AIDS is still a prevalent and lethal infectious disease worldwide. In 2009 the estimated number of HIV-infected people was 33.3 million and 1.8 million people died of AIDS [1]. Several studies have reported model-based approaches to understand the HIV/AIDS infection process. Some examples of HIV dynamic models are found in [2,3] and control theoretic studies of the authors, based on the HIV models in [3], are reported in [4,5].

In this paper we research a control scheme using a model-based approach to enhance the human immune response in HIV infection dynamics.¹ The control method is applied to the HIV model in [3],

together with the pharmacological dynamics in [7,8], on the basis of the immune boosting process analysed by the authors in [5].

The research in this paper is supported by the experimental data recently published in [9,10]. Although our research can be applicable to analyse the data of [10], we focus on the experimental result of [9]. Note that we do not analyse the properties of the controlled system formally, which will be done elsewhere, but focus on the conceptual method of the controller design, as well as on the application to the HIV infection dynamics.

This paper contains two major contributions. First, it presents a model modification based on an existing HIV model, considering pharmacological dynamics. The modification introduces dynamic equations describing the pharmacokinetics and pharmacodynamics of antiretroviral drugs. In addition we assume that the controlled drug intake can be considered as impulsive control input for the mathematical model, although in general the drugs are taken orally as extended-release formulation (see [11] for more details). Impulsive control gives a sudden change of the state variable at discrete instants (see [12] for rigorous definition of impulsive control). The modified model is able to accurately describe the effect on HIV patients of a drug regimen. This model helps to study HIV infection dynamics with a realistic regimen of HIV therapy.

Second, the experimental results in [9] can be explained by the immune system analysis on the modified HIV model in the paper.

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¹ A preliminary version of this paper has been published in [6].

The clinical work of [9] leads to the application of a mathematical approach to the HIV dynamics. Based on the modified HIV model we obtain an insight into the result of [9], providing an interpretation of the experiment. By analysing the simulation study it is implied that the protocol of the experiment might enhance the immune response against HIV.

The paper is organised as follows. The proposed modeling method is presented in Section 2. Particularly Section 2.1 gives a brief description of the experiments in [9]. Then in Section 2.2 we recall some of the analysis of [5] for the HIV dynamic model of [3] and we modify the model to study numerical realisation of the experiments in [9]. Then Section 3 reports the numerical results with the modified HIV infection model. Finally we discuss the results and conclude the paper in Section 4.

2. Methods

2.1. A summary of the experiments in Grant et al. [9]

Antiretroviral chemoprophylaxis prior to exposure to HIV is regarded as a promising approach for the prevention of HIV infection [13,14]. In [13] it has been shown that the side effect of daily preexposure with tenofovir disoproxil fumarate (TDF) is acceptable while in [14] it has been shown that HIV infection rates of women is decreased up to 39% using a tenofovir 1% vaginal gel. For men and transgender women who have sex with men the current use of preexposure prophylaxis is not common, however most of these people are willing to consider such use if evidence of safety and efficacy were provided [15,16].

We now briefly discuss the experiments of [9]. To evaluate the clinical effect of preexposure chemoprophylaxis, experiments have been designed and conducted in [9]. The experiments assigned 2499 HIV-negative subjects randomly to take a combination of two antiretroviral drugs, i.e. emtricitabine and tenofovir disoproxil fumarate (FTC-TDF), or placebo once a day.

The subjects were observed for 3324 person-years (median, 1.2 years; maximum, 2.8 years). For the studied subjects 10 were revealed to have been infected with HIV at enrollment and 100 became infected with HIV during the follow-up, among which 36 and 64 were in the FTC-TDF and the placebo groups, respectively, implying a 44% reduction in the HIV incidence.

Thus the experimental result concludes that oral FTC-TDF could provide protection against the acquisition of HIV infection. For a complete description of the experiment and the data see [9] and the Supplementary Appendix available at NEJM.org.

Following the pioneering work in [9], over the past few years there have been considerable advances in the issues of the suppression of HIV transmission by using antiretroviral drug [17] with new scientific findings including the results in [18–20]. In [18] it has been shown that, compared to the delayed initiation of anti-HIV therapy, the early initiation reduces the rate of HIV transmission in couples. Particularly the protection against HIV infection in heterosexual men and women has been studied in [20] with daily intake of FTC-TDF, while in [19] it has been concluded that both TDF and FTC-TDF can prevent HIV infection in heterosexual subjects.

2.2. Modeling of HIV dynamics with impulsive control input

In this subsection we consider the HIV infection model of [3] and modify this model including the pharmacokinetics and pharmacodynamics of the FTC-TDF as considered in [9].

2.2.1. HIV infection model with CTL response

The model of [3,21] is given by

$$\dot{x} = \lambda - dx - (1 - \eta)\beta xy, \quad (1)$$

Table 1
HIV model parameters and values [3]

Parameters	Value	Parameters	Value
λ	1	d	0.1
β	1	a	0.2
p_1	1	p_2	1
c_1	0.03	c_2	0.06
q	0.5	b_1	0.1
b_2	0.01	h	0.1

$$\dot{y} = (1 - \eta)\beta xy - ay - p_1 z_1 y - p_2 z_2 y, \quad (2)$$

$$\dot{z}_1 = c_1 z_1 y - b_1 z_1, \quad (3)$$

$$\dot{w} = c_2 xyw - c_2 qw - b_2 w, \quad (4)$$

$$\dot{z}_2 = c_2 qw - h z_2, \quad (5)$$

where the states are the populations of specific cells in a unit volume of blood. x , y , z_1 , w , and z_2 describe the concentrations of uninfected CD4 T-cells, infected CD4 T-cells, helper-independent CTLs, CTL precursors, and helper-dependent CTLs, respectively.

The quantity η varies between 0 and 1 and describes the control input affecting the parameter β . From a control perspective it represents the efficacy of the drug of the anti-retroviral therapy. If $\eta = 1$ a patient receives the maximal effect of drug (i.e. 100% block of HIV infection process), while $\eta = 0$ means no effect. The remaining parameters λ , d , β , a , p_1 , p_2 , c_1 , c_2 , q , b_1 , b_2 , and h are positive constants. For a detailed explanation of the model see [3].

2.2.2. Analysis of the model

Now we show that the Wodarz model ((1)–(5)) displays 5 equilibrium points [3,6], including a HIV-free equilibrium, a LTNP equilibrium, and other which the virus dominates. The basin of attraction of the third equilibrium is estimated. This lower order model of the HIV-dynamics is shown to be maximally nonlinear in the sense that the largest possible linearization by a state feedback has dimension 2. The three important equilibria are given in what follows.

Point A:

$$x^{(A)} = \frac{\lambda}{d}, \quad y^{(A)} = 0, \quad z_1^{(A)} = 0, \quad w^{(A)} = 0, \quad z_2^{(A)} = 0.$$

Point B:

$$x^{(B)} = \frac{\lambda c_1}{dc_1 + b_1(1 - \eta)\beta}, \quad y^{(B)} = \frac{b_1}{c_1}, \quad z_1^{(B)} = \frac{(1 - \eta)\beta x^{(B)} - a}{p_1},$$

$$w^{(B)} = 0, \quad z_2^{(B)} = 0.$$

Point C:

$$y^{(C)} = \frac{\theta(\eta) - \sqrt{\theta(\eta)^2 - 4(1 - \eta)\beta c_2 q d b_2}}{2(1 - \eta)\beta c_2 q},$$

$$x^{(C)} = \frac{\lambda}{d + (1 - \eta)\beta y^{(C)}}, \quad z_1^{(C)} = 0, \quad w^{(C)} = \frac{h z_2^{(C)}}{c_2 q y^{(C)}},$$

$$z_2^{(C)} = \frac{y^{(C)}(c_2(1 - \eta)\beta q - c_2 a) + b_2(1 - \eta)\beta}{c_2 p_2 y^{(C)}},$$

where $\theta(\eta) = c_2(\lambda - dq) - b_2(1 - \eta)\beta$.

The values of the model parameters suggested in [3] for the HIV model are summarised in Table 1. Note that these parameters in [3] are normalised, with which the HIV model can show bistability phenomenon.

With this parameter set and $\eta = 0$ (i.e., no drug treatment), Point A, B and C are $x_A = (10, 0, 0, 0, 0)$, $x_B = (0.2913, 3.3333, 0.0913, 0, 0)$, and $x_C = (8.2255, 0.0216, 0, 1240, 8.0255)$, respectively. In [3], the model ((1)–(5)), with the parameter set of Table 1, has been shown to be bistable when the drug treatment is stopped.

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