Analysis of the HIV Eradication Phenomenon at the Early Stage of Infection with an Extracellular Deterministic Model*

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***Abstract*— We investigate the phenomenon of HIV eradication at the early stage of the infection and evaluate the chance of the eradication with a mathematical model. We employ an extracellular deterministic model of the HIV infection dynamics and modify the model to include the pharmacokinetics and pharmacodynamics of antiretroviral HIV drugs. In addition we consider clinical experiments for the prevention of HIV infection using pre-exposure chemoprophylaxis treatment. Exploiting the mathematical model we implement the experiment numerically. The study in this paper is supported by the clinical results and provides a theoretical explanation for the results. The result suggests that the protocol of the experiment eradicates the virus in HIV infected patients.**

I. Introduction

The human immunodeficiency virus (HIV) is the virus causing acquired immune deficiency syndrome (AIDS). After HIV infection the virus infects CD4 T-cells. An infected CD4 T-cell produces multiple HIV copies. Thus the infection decreases the count of healthy CD4 T-cell. The low level of healthy CD4 T-cell count affects the human immune system.

In this paper the HIV eradication phenomenon is analysed using a model-based approach, and we consider the clinical experimental results published in [1]. The main purpose of the experiments in [1] is to evaluate the clinical effect of pre-exposure to antiretroviral chemoprophylaxis for the prevention of HIV infection. The experiments randomly assigned 2499 HIV negative subjects to take a placebo or a combination of two HIV drugs, emtricitabine and tenofovir disoproxil fumarate (FTC-TDF), once a day. The subjects were observed for 3324 person-years (median, 1.2 years; maximum, 2.8 years). During the follow up, 36 subjects in the FTC-TDF group have been infected with HIV, while 64 subjects in the placebo group have been infected. This implies a 44% reduction effect in the HIV incidence, thus it is concluded that the FTC-TDF can provide protection against the HIV infection. For a complete description of the experiments, see [1].

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These experimental results can be understood by means of an extracellular deterministic HIV model which is completed by the pharmacological dynamics described in [2], [3]. With this modified model, the virus eradication is obtained for the case of pre-exposure chemoprophylaxis HIV treatment. The results in this paper are supported by the experimental data in [1].

The main contribution of this paper is as follows. The model of the HIV dynamics including pharmacological dynamics is shown to be sufficiently realistic to be consistent with the experimental results in [1]. The analysis of the mathematical model is consistent with the protocol of the experiment which displays the eradication of the virus under the specific conditions of the protocol.

Compared to [4], the mathematical model considered in this paper does not include any term related to the cellular immune response because we focus on the virus eradication phenomenon at the early stage of the HIV infection. In addition the HIV model in this paper does not contain any dynamics of cellular reservoirs of HIV, by which the virus cannot be eradicated at the later stage of HIV infection. Note that the considered experiment has been designed for pre-exposure prophylaxis for HIV, which corresponds to the treatment immediately before (or after) the contact with HIV.

The paper is organised as follows. In Section II we recall the 3-dimensional HIV dynamic model of [5], [6] and we modify the model for the pharmacological dynamics to study numerical realisation of the experiments in [1]. Section III reports the numerical results with the modified HIV infection model. Finally we discuss the results and conclude the paper in Section IV.

II. Modeling of HIV Dynamics with Pharmacological Dynamics

In this section we consider the HIV infection model of [5], [6] and modify this model including the pharmacokinetics and pharmacodynamics of the FTC-TDF considered in [1].

A. 3-dimensional HIV Infection Model

The basic model in [5], [6] is given by

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta x v, \\ \dot{y} &= \beta x v - a y, \\ \dot{v} &= k y - c v, \end{aligned} \tag{1}$$

where the states are the populations of specific cells in a unit volume of blood. In particular x, y, and v describe the

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TABLE I
HIV MODEL PARAMETERS AND VALUES ESTIMATED IN [7].

Parameters	Median Value	Parameters	Median Value
λ	5.36 (mm^{-3} day^{-1})	d	0.012 (day^{-1})
β	8.38×10^{-8} (ml day^{-1})	a	0.041 (day^{-1})
k	6.85 (mm^3 ml^{-1} day^{-1})	c	0.280 (day^{-1})

concentrations of uninfected CD4 T-cells (CD4/mm^3), infected CD4 T-cells (CD4/mm^3), and virion (RNA copies/ml), respectively.

To describe the control effect of drug on the parameter β we introduce the control input η which varies between 0 and 1. β is thus rewritten as

$$\beta = (1 - \eta)\bar{\beta}. \tag{2}$$

From a biomedical control perspective this input η represents the efficacy of the antiretroviral drugs in the category of reverse transcriptase inhibitors (RTIs), which we consider in this paper. For example, if $\eta = 1$ a patient receives the ideal effect of drug (i.e. 100% block of the HIV infection process), while $\eta = 0$ implies no effect of the drug. η is studied and modelled in Subsection II-B to describe the drug effect of FTC-TDF. For a detailed explanation of the model see [5], [6].

1) Model parameter values: The parameters of the HIV model (1), i.e. λ, d, β, a, k, and c are positive constants. These parameters have been estimated in [7] based on clinical data and their median values are given in Table I.

Note that in [7] the parameter estimation has been performed for HIV patients during the antiretroviral drug treatment. Table I shows the estimated β with full medication condition, instead of $\bar{\beta}$. In [8] the parameter estimation has been performed for six volunteer patients based on the pre-treatment clinical data and the post-treatment clinical data. From the evaluation in [8] with pre-treatment clinical data set the median value of $\bar{\beta}$ is 9.34×10^{-7} (ml day^{-1}).

In addition Table I shows the estimated value of λ for HIV infected patients. It is known that the CD4 T-cell count for healthy individuals is normally around 1000/mm^3 [5]. Thus, in this paper we assume that the median value of λ for HIV-free person is 12 (= $1000 \times d$).

B. Model Extension with Pharmacological Concepts

Most of the existing control methods for the HIV treatment, for example as suggested in [9]–[12], cannot be applied easily to HIV infected patients because the control input considered in mathematical models is the efficiency of the drug, instead of the amount of drug. The drug efficiency varies between 0 (i.e. no medication) and 1 (i.e. full medication), not precisely described in terms of drug dose.

In this subsection the relation between the drug dosage and the control input is studied for the model (1), particularly with additional pharmacokinetic and pharmacodynamic terms. Note that in [4] a preliminary extension of the HIV model has been reported, similarly to this section, for the HIV model with immune system in [12], [13]. The extended model has the amount of drug as control inputs and thus is more significant in practical terms.

The process of drug administration consists of two phases [2]. First, the pharmacokinetic phase is related to the drug level-time profile resulting from the drug dosage, intake frequency, and administration route. Second, the pharmacodynamic phase is related to the magnitude of the realised drug effects resulting from the drug concentration at the sites of action.

1) Pharmacokinetic model: Generally medicines are prescribed to be taken in a constant dosage at constant time intervals. In this study the drug is assumed to be absorbed completely and instantaneously. Also we assume that the drug distributes in a one-compartmental human body, and that it is eliminated from the human body by first-order kinetics. The rate of drug elimination is modelled by

$$\dot{\sigma} = -k\sigma, \tag{3}$$

where σ is the intracellular amount of drug in the human body at time t and k is the constant elimination rate of the first order. Note that k is related to the intracellular half-life of the drug $t_{\frac{1}{2}}$, i.e. $t_{\frac{1}{2}} = \log 2/k$. The intake of the HIV drug is considered as an impulsive input.

2) Pharmacodynamic model: Numerous pharmacodynamic models have been investigated for fitting response-concentration curves empirically [3]. A class of these models can be described by the equation

$$\eta(t) = \eta_{max}\frac{C(t)^\gamma}{C(t)^\gamma + 1/Q}, \tag{4}$$

where $\eta(t)$ is the drug efficiency response at drug plasma concentration $C(t)$ and η_{max} is the maximum response. γ and Q are constants.

As in [3] we consider $Q = 1/C_{50}$, where C_{50} is the plasma concentration of drug which reduces the drug effect by 50% of η_{max}. Based on [14]–[16] it is assumed that $\gamma = 1$, due to the fact that the FTC-TDF is a combination of emtricitabine and tenofovir, two nucleoside reverse transcriptase inhibitors (NRTIs).

In the pharmacokinetic model of Subsection II-B.1 we consider the human body as one-compartment. Then at time t the amount of drug in the human body is the product of the plasma concentration $C(t)$, the apparent volume of distribution V_d, and the mass of the human body M. Hence $\sigma(t) = C(t)V_dM$, $\sigma_{50} = C_{50}V_dM$, and

$$\eta(t) = \eta_{max}\frac{\sigma(t)}{\sigma(t) + \sigma_{50}}. \tag{5}$$

For a full explanation of the pharmacological modelling, see [8].

3) Pharmacological model parameters: We consider the HIV drug FTC-TDF as in [1]. One FTC-TDF tablet is a combination of FTC (200 mg) and TDF (300 mg). To describe the

effect of FTC-TDF we employ two pharmacological models for FTC and TDF, respectively.

In this subsection we suggest the pharmacological parameters $k_F = 0.0178\,(/h)$ (i.e., 0.4266 (/day)), $k_T = 0.0042\,(/h)$ (i.e., 0.1014 (/day)), $\sigma_{50,F} = 0.0069\ (mg/l)$, and $\sigma_{50,T} = 0.3674\ (mg/l)$ where the subscripts F and T stand for FTC and TDF, respectively. For the evaluation process of these parameters see [4].

As in [8] the average weight of a subject is assumed to be $70\ kg$. Then $\sigma_{50,F}$ is obtained as 0.6762 ($= 0.0069 \times 1.4 \times 70$), and $\sigma_{50,T}$ as 20.5744 ($= 0.3674 \times 0.8 \times 70$).

C. Integrated Model with Impulsive Input

The model (1) and (2) is integrated with the pharmacological system for FTC and TDF (i.e. (3) and (5)), namely

$$\begin{aligned} \dot{x} &= \lambda - dx - (1-\eta_F)(1-\eta_T)\bar{\beta}xv, \\ \dot{y} &= (1-\eta_F)(1-\eta_T)\bar{\beta}xv - ay, \\ \dot{v} &= ky - cv, \\ \dot{\sigma}_F &= -k_F\sigma_F, \\ \dot{\sigma}_T &= -k_T\sigma_T, \end{aligned} \tag{6}$$

where

$$\eta_F = \eta_{max,F}\frac{\sigma_F}{\sigma_F + \sigma_{50,F}}, \qquad \eta_T = \eta_{max,T}\frac{\sigma_T}{\sigma_T + \sigma_{50,T}}.$$

Note that it is assumed that the antiretroviral effects of both drugs are independent of each other.

Let $X(t) := [x(t),\, y(t),\, v(t),\, \sigma_F(t),\, \sigma_T(t)]^T$ and represent model (6) by the equation

$$\dot{X} = F(X). \tag{7}$$

We now realise the experiment of [1] numerically with the model (7). To this end impulsive inputs to the model are introduced for FTC-TDF intake and exposure to HIV during the experiment. These can be approximately considered as impulsive changes of states σ_F, σ_T, and v, respectively. Although the HIV drugs are usually delivered as extended-release formulation [17], we assume that the drug intake is an impulsive control input for the HIV model: it is administrated at discrete time instants. Note that it is still more realistic than the continuous variation of drug efficiency.

While an impulsive input can be modelled by a Dirac delta function on $\dot{X}$ as in [18], we employ a hybrid system description as in [19]. Then the system can be described by a discontinuity in X, namely

$$\begin{aligned} \dot{X}(t) &= F(X(t)), && \text{if } \ t \notin S_d \cup S_v, \\ X^+ &= X + V_d, && \text{if } \ t \in S_d, \\ X^+ &= X + V_v, && \text{if } \ t \in S_v, \end{aligned} \tag{8}$$

where V_v and V_d are the vectors corresponding to the magnitude of change for the state v and for the states σ_F and σ_T, respectively. S_v is the set of time instants at which the impulsive changes occur for the state v, while S_d is the set of time instants at which the impulsive changes occur for the states σ_F and σ_T.

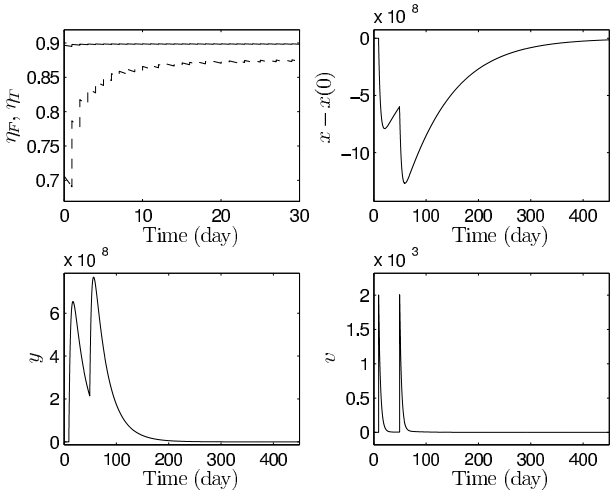

Fig. 1. Numerical simulation of the experiment in [1] via the model (7) with $\eta_{max,F} = 0.9$ and $\eta_{max,T} = 0.9$. We set $M_v = 0.002$ and $S_v = \{10, 50\}$ for the implementation of the impulsive virus infusion. In the upper left graph the solid line and the dotted line indicate the time histories of η_F and η_T, respectively.

For the impulsive changes of σ_F and σ_T we additionally introduce 'oral bioavailability' into V_d, a pharmacokinetic parameter describing the available fraction of an administered drug that reaches the system, namely

$$V_d = [0, 0, 0, 200(mg) \times B_F, 300(mg) \times B_T]^T, \tag{9}$$

where B_F and B_T are the bioavailability of FTC and TDF, respectively. The median of B_F is 0.92 and the median of B_T is 0.25 [20]. In addition we assume that once some fraction of the oral dose of FTC-TDF reaches the system, it is fully converted to the activated form intracellularly.

According to the protocol of the experiment in [1], select $S_d = \{1, 2, 3, \cdots, T_d\}$, with $T_d = 450$ (day). The contacts with HIV are assumed to occur at the time instants of the set S_v. The values of M_v in $V_v = [0,\ 0,\ M_v,\ 0,\ 0]^T$ are discussed in the next section.

III. Numerical Simulations

In this section the initial state $X(0)$ is taken as $[1000,\ 0,\ 0,\ 0,\ 0]^T$, the status of a HIV-negative subject. Note that the CD4 T-cell count for healthy individuals is generally around 1000 /mm^3 [5].

We assume $M_v = 0.002$ and $S_v = \{10, 50\}$, implying that the contacts with HIV occur at Day 10 and Day 50, the time instants defined by the set S_v, and a small amount of the virus is infused into the human body: for the total volume of human blood 5,000 (ml), the value $M_v = 0.002$ corresponds to 10 virion particles. To follow the experimental protocol we set $\max(S_v) < T_d$ so that the virus contacts occur only during the drug prescription.

Since it is ideally assumed that drug-resistant species of HIV do not exist for the two NRTIs (FTC and TDF) in the

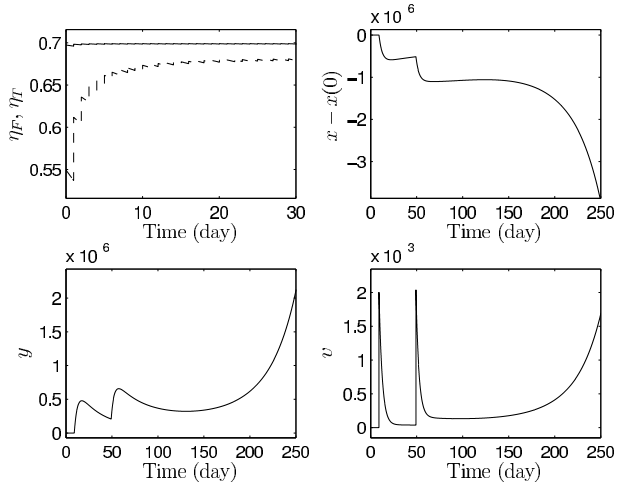

Fig. 2. Numerical realisation of the experiment in [1] via the model (7) with $\eta_{max,F} = 0.7$ and $\eta_{max,T} = 0.7$.

subject, one can set $\eta_{max,F} = 1$ and $\eta_{max,T} = 1$, see [14]–[16]. However anti-retroviral HIV treatment often fails due to the emergence of resistant virus [6] and sometimes this emergence is due to pre-existence of drug resistant virus [21].

While the case $\eta_{max,F} = 1$ and $\eta_{max,T} = 1$ might be reasonable because the two NRTIs are highly effective anti-HIV drugs [14]–[16], the emergence of resistant virus results in the reduction of drug efficiency. Thus, to describe the effect of resistant virus on the drug treatment, variation of the parameters $\eta_{max,F}$ and $\eta_{max,T}$ are considered and in this subsection we discuss three different scenarios with different parameter values for $\eta_{max,F}$ and $\eta_{max,T}$.

In the first case it is assumed that $\eta_{max,F} = 0.9$ and $\eta_{max,T} = 0.9$. Fig. 1 shows the results of the numerical simulation of the experimental protocol in [1]. The hybrid system (8) is used and the parameter values k_F, k_T, $\sigma_{50,F}$, and $\sigma_{50,T}$ are obtained from Subsection II-B. In the upper left graph of Fig. 1, the solid line and the dotted line indicate the time histories of η_F and η_T, respectively. Note the different time scales. For this simulation, the y and v states converge to zero.

For the second simulation of this subsection one sets $\eta_{max,F} = 0.7$ and $\eta_{max,T} = 0.7$. Fig. 2 shows the simulation results. Note the different time scales to Fig. 1. In this simulation HIV eradication is not achieved.

IV. Conclusion

In this paper the phenomenon of HIV eradication has been considered at the early stage of the infection using a model-based approach. The clinical experimental results in [1] have been considered. To implement the experiments the 3-dimensional HIV dynamic model in [5], [6] has been modified to include the pharmacological dynamics of HIV drugs. A simulation of the experiments has been implemented.

By the computer simulations of the modified model we have studied and analysed the experimental results and we have provided insights to understand the implications of the experiments. The analysis has shown that the protocol of the experiment might lead to the virus extinction at the early stage of the HIV infection.

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