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A piecewise model of virus-immune system with two thresholds

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ABSTRACT

The combined antiretroviral therapy with interleukin (IL)-2 treatment may not be enough to preclude exceptionally high growth of HIV virus nor rebuilt the HIV-specific CD4 or CD8 T-cell proliferative immune response for management of HIV infected patients. Whether extra inclusion of immune therapy can induce the HIV-specific immune response and control HIV replication remains challenging. Here a piecewise virus-immune model with two thresholds is proposed to represent the HIV-1 RNA and effector cell-guided therapy strategies. We first analyze the dynamics of the virus-immune system with effector cell-guided immune therapy only and prove that there exists a critical level of the intensity of immune therapy determining whether the HIV-1 RAN virus loads can be controlled below a relative low level. Our analysis of the global dynamics of the proposed model shows that the pseudo-equilibrium can be globally stable or locally bistable with order 1 periodic solution or bistable with the virus-free periodic solution under various appropriate conditions. This indicates that HIV viral loads can either be eradicated or stabilize at a previously given level or go to infinity (corresponding to the effector cells oscillating), depending on the threshold levels and the initial HIV virus loads and effector cell counts. Comparing with the single threshold therapy strategy we obtain that with two thresholds therapy strategies either virus can be eradicated or the controllable region, where HIV viral loads can be maintained below a certain value, can be enlarged.

1. Introduction

Lifelong highly active antiretroviral therapy (HAART) continues to be associated with many problems such as adherence difficulties and evolution of drug resistance [1–4]. Structured therapy interruptions (STIs) have been suggested as being capable of achieving sustained specific immunity for early therapy in HIV infection. As an alternative strategy, STI is a good choice for some chronically infected individuals who may need to take drugs throughout their lives, and it is beneficial for the patients' immune reconstruction during the period when they are not taking the drugs [5].

Recently, to compare STI strategies with the continuous antiretroviral therapy, several clinical studies have been done with conflicting results [5–12]. In particular, Ruiz et al. [12] designed an experiment to evaluate the safety of CD4 cell counts and plasma HIV-1 RNA-guided structured treatment interruptions (STIs) aiming to maintain CD4 T cell counts higher than 350 cells/μl and plasma HIV-1 RNA less than 100,000 copies/μl. Although many mathematical models have been formulated to model continuous therapy [13–15], few attempts have been made to model structured treatment interruptions. In 2012, Tang et al. [16] proposed a piecewise system to describe the CD4 cell-guided STIs, to quantitatively explore STI strategies and to investigate the virus dynamics under these strategies. This system has offered explanations for some controversial conclusions from different clinical studies. In 2015, by considering combined antiretroviral therapy with interleukin (IL)-2 treatment, we proposed a piecewise virus-immune dynamic model with HIV-1 RNA-guided therapy [17]. This model is given as follows:

$$\begin{cases} \left.\begin{aligned} x' &= rx - pxy, \\ y' &= \frac{cxy}{1+\omega x} - qxy - \delta y, \end{aligned}\right\} x < V_s, \\ \left.\begin{aligned} x' &= rx - pxy - \epsilon_1 x, \\ y' &= \frac{cxy}{1+\omega x} - qxy - \delta y + \epsilon_2 y, \end{aligned}\right\} x > V_s, \end{cases} \tag{1}$$

where x and y represent the HIV virus loads and the density of effector cells, respectively. V_s is the critical value of HIV virus loads determining whether the therapy is carried out or not. Here ϵ_1 represents the rate of elimination of HIV virus due to antiretroviral therapy and ϵ_2 denotes the growth rate of the effector cells due to interleukin (IL)-2 treatment. r denotes the growth rate of HIV virus which incorporates both multiplication and death of HIV

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virus, δ is the death rate of the effector cells, p denotes the rate of binding of the effector cells to the HIV viruses. When interacting with the HIV virus, the effector cells usually have a limited ability to repeatedly kill the virus because the virus can also inhibit the activity of immune cells. Here q represents the rate of inactivation of the effector cells. $cx/(1+\omega x)$ denotes the rate at which effector cells accumulate due to the immune response.

In the paper [17], we concluded that proper combinations of threshold and initial HIV virus loads and effector cell counts can successfully preclude exceptionally high growth of HIV virus and, in particular, maximize the controllable region. However, whatever the threshold is, depending on the initial conditions of patients' HIV virus can not be eradicated but even increase to infinity, which means that the combined antiretroviral therapy with interleukin (IL)-2 treatment may not be enough to rebuild the HIV-specific CD4 or CD8 T-cell proliferative immune response for management of HIV infected patients. In [18], the authors developed a clinic experiment studying combined antiretroviral therapy and interleukin (IL)-2 treatment with immune therapy. The patients were divided into four groups, in which the group C simultaneously received antiretroviral therapy, interleukin (IL)-2 treatment and immune therapy with HIV vaccine was injected once every 3 months. They showed that interleukin (IL)-2 treatment and immune therapy can induce the HIV-specific immune response. How the impulsive immune therapy affects the dynamics of virus-immune system with HIV-1 RNA-guided therapy and whether the inclusion of impulsive immune therapy can maintain the virus below a certain level, remain unclear. Addressing these issues through a mathematical modeling framework falls within the scope of this study.

More precisely, the purpose of this study is to propose a mathematical model to describe the combined antiretroviral therapy and interleukin (IL)-2 treatment with immune therapy. We address such challenging questions as whether the comprehensive therapy under the HIV-1 RNA and effector cell-guided structured treatment can successfully inhibit replication of HIV virus and rebuild the HIV-specific CD4 or CD8 T-cell proliferative immune response, and whether the therapy can control HIV-1 RNA below a certain level and maintain the density of effector cells above a certain level. The rest parts of this paper is organized as follows. In Section 2, we formulate a piecewise virus-immune model with two thresholds and introduce the relative definitions. The dynamics of the proposed model with either only the effector cell or the HIV-1 RNA-guided therapy is discussed in Section 3. Then, in Section 4, we investigate the global dynamics of the proposed model. Finally, we conclude the paper with some remarks.

2. Model formulation and preliminaries

In this paper, we formulate the model that incorporate both the antiretroviral therapy and interleukin (IL)-2 treatment under the assumption that whenever the virus load exceeds the critical level (i.e. V_s), antiretroviral drugs are applied to inhibit the growth of the virus, and simultaneously interleukin (IL)-2 treatment is used [17]. The immune therapy mainly aims at rebuilding the HIV-special T cell immune response and guaranteeing the density of effector cells is enough to control the growth of HIV virus. Thus, there can be a critical value of the density of effector cells, denoted by T_s, determining whether the immune therapy is carried out. In particular, the immune therapy isn't carried out when the density of the effector cells is above the level T_s and one dose of HIV vaccine is injected immediately once the density of the effector cells declines to the level T_s. Let ρ represent the intensity of the immune therapy every time with $\rho \geq 1$. Therefore, based on model (1), we have proposed the following formulation:

$$\begin{cases} \left.\begin{cases} x' = rx - pxy, \\ y' = \frac{cxy}{1+\omega x} - qxy - \delta y, \end{cases}\right\} y > T_s, \\ \left.\begin{cases} x(t^+) = x(t), \\ y(t^+) = \rho y(t), \end{cases}\right\} y = T_s, \end{cases} \Bigg\} x < V_s, \quad \begin{cases} \left.\begin{cases} x' = rx - pxy - \epsilon_1 x, \\ y' = \frac{cxy}{1+\omega x} - qxy - \delta y + \epsilon_2 y, \end{cases}\right\} y > T_s, \\ \left.\begin{cases} x(t^+) = x(t), \\ y(t^+) = \rho y(t), \end{cases}\right\} y = T_s, \end{cases} \Bigg\} x > V_s. \tag{2}$$

Before going further discussing the dynamics of system (2), we now introduce some technical definitions.

Let $R^2_+ = \{X = (x, y) | x \geq 0, y \geq 0\}$. A generic planar Filippov system is defined as follows [19–26]:

$$\dot{X} = \begin{cases} F_{D_1}(X), & X \in D_1, \\ F_{D_2}(X), & X \in D_2, \end{cases} \tag{3}$$

where $D_1 = \{X \in R^2_+ | H(X) < 0\}$ and $D_2 = \{X \in R^2_+ |\ H(X) > 0\}$ with $H(X)$ as a smooth scale function.

Definition 1. A point X^* is called a regular equilibrium of system (3) if $F_{D_1}(X^*) = 0,\ H(X^*) < 0$ or $F_{D_2}(X^*) = 0,\ H(X^*) > 0$ while it is called a virtual equilibrium of system (3) if $F_{D_1}(X^*) = 0,\ H(X^*) > 0$ or $F_{D_2}(X^*) = 0,\ H(X^*) < 0$.

Definition 2. A point X^* is called a pseudo-equilibrium if it is an equilibrium of the sliding mode of system (3), i.e. $\lambda F_{D_1}(X^*) + (1-\lambda)F_{D_2}(X^*) = 0, H(X^*) = 0$ with $0 < \lambda < 1$ and

$$\lambda = \frac{\langle H_X(X^*), F_{D_2}(X^*)\rangle}{\langle H_X(X^*), F_{D_2}(X^*) - F_{D_1}(X^*)\rangle}.$$

A generalized planar impulsive semi-dynamic system can be defined as follows [27–33]:

$$\begin{cases} \frac{dx}{dt} = P(x, y),\ \frac{dy}{dt} = Q(x, y), if\ \phi(x, y) \neq 0, \\ \triangle x = a(x, y),\ \triangle y = b(x, y), if\ \phi(x, y) = 0, \end{cases} \tag{4}$$

where $(x, y) \in R^2_+$, $\triangle x = x^+ - x$ and $\triangle y = y^+ - y$. P, Q, a, b are continuous functions from R^2_+ into R_+. The impulsive function $I : R^2_+ \to R^2_+$ is defined as follows:

$$I(x, y) = (I_1(x, y), I_2(x, y)) = (x + a(x, y), y + b(x, y)),$$

and $Z^+ = (x^+, y^+)$ is called an impulsive point of $Z = (x, y)$.

Let (R^2_+, π) be a planar semi-dynamic system. For any $Z \in R^2_+$, the positive orbit of Z is given by $C^+(z) = \{\pi(Z, t) | t \in R_+\}$ which is denoted by $\pi^+(Z)$. And we define $F(Z, t) = \{Z' | \pi(Z', t) = Z\}$ for $t \geq 0$ and $Z \in R^2_+$.

Definition 3. A planar impulsive semi-dynamic system $(R^2_+, \pi; M, I)$ consists of a continuous semi-dynamic system (R^2_+, π) together with a nonempty closed subset M of R^2_+ and a continuous function $I : M \to R^2_+$ such that for every $Z \in M$, there exists a $\epsilon_Z > 0$ such that

$$F(Z, (0, \epsilon_Z)) \cap M = \emptyset \quad \text{and} \quad \pi(Z, (0, \epsilon_Z)) \cap M = \emptyset.$$

Definition 4. A trajectory $\pi^+(Z)$ of $(R^2_+, \pi; M, I)$ is said to be order k periodic if there exist nonnegative integers m and k such that k is the smallest integer for which $I^m(Z) = I^{m+k}(Z)$ with $Z \in M$.

Definition 5. The Lambert W function [34] is defined to be a multivalued inverse of the function $z \mapsto ze^z$ satisfying

$$\text{LambertW}(z)\exp(\text{LambertW}(z)) = z.$$

And we denote it as W for simplicity. Note that the function $z\exp(z)$ has the positive derivative $(z+1)\exp(z)$ when $z > -1$. Define the inverse function of $z\exp(z)$ restricted on the interval