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Analysis of an HIV infection model with treatments and delayed immune response

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ABSTRACT

In this paper, we establish and investigate an HIV infection model with treatments and delayed immune response and study its dynamical behaviors. By identifying a critical parameter, we show that if the effectiveness of RT inhibitor and protease inhibitor satisfy some conditions, the uninfected steady state is a unique equilibrium in the feasible region, and the point is globally asymptotically stable. However, if the treatment is not effective enough, then the equilibrium becomes unstable and HIV infection persists. In this case, the other two steady states can be either stable or unstable. By theoretical analyzing, we obtain the results that time delay can affect the stability of the immune-exhausted equilibrium and the infected equilibrium under some conditions. Finally, numerical simulations are carried out to illustrate the main mathematical conclusions.

1. Introduction

Mathematical modeling has been proven to be valuable in understanding the dynamics of HIV infection. It is well known that HIV mainly targets a host's $CD4^+$T cells, the main driver of the immune response. Chronic HIV infection causes gradual depletion of the $CD4^+$T cell pool, and thus progressively compromises the host's immune response to opportunistic infections, leading to Acquired Immunodeficiency Syndrome (AIDS) as demonstrated [1]. The basic model describing the interactions between a replicating virus population and a specific antiviral CTL response takes into account four variables: uninfected $CD4^+$T cell x, infected $CD4^+$T cell y, virus v and CTL z. It is given by the following set of differential equations as demonstrated [2]:

$$\begin{cases} \dot{x} = s - dx - kxv \\ \dot{y} = kxv - \beta y - pyz \\ \dot{v} = N\beta y - av \\ \dot{z} = cy - bz, \end{cases} \tag{1.1}$$

In (1.1), the parameters $s, d, k, \beta, p, N, a, c, b$ are positive. Uninfected $CD4^+$T cells are produced at a rate s, dies at a rate dx, and become infected at a rate kxv. Infected $CD4^+$T cells die at a rate βy, and are lysed by CTL at a rate pyz. On average, each productively infected cell produces N virions during its lifetime. Free virus particles decay at a rate av. The CTL population expands at a rate cy and decays at a rate bz.

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This model only considers the source of uninfected CD4$^+$T cells but ignores proliferation of the target cells. Therefore, a reasonable model for the population dynamics of target cells should take logistic proliferation term $rx(1-\frac{x}{x_{max}})$ into consideration as demonstrated [3,4]. From (1.1), we can see that the production of CTL depends only on the population of infected cells y. Motivated by the work, in this paper, we assume that the production of CTL also depends on the population of CTL cells, i.e. $\dot{z} = cyz - bz$. In fact, the models considered as demonstrated [5,6] are all with bilinear CTL proliferation rate. In fact, time delays cannot be ignored in models for immune response, and time delays will describe the period that antigenic stimulations generating CTL need, as demonstrated [6–8]. Furthermore, delay-differential equations will exhibit much more complicated dynamics than the ordinary differential equations since a time delay could cause a stable equilibrium to become unstable one, and cause the populations to fluctuate. The CTL response with time may depends on the population of antigen and CTL at some previous time.

The best current therapy for HIV-infected patients involves inhibiting either reverse transcriptase (RT) or HIV protease, or the combination of the two as demonstrated [9]. If RT is inhibited, HIV can enter a T cell but may not successfully infect it, i.e. only a portion of T cells are infected. If HIV protease is inhibited, some of the virus produced by infected T cells will be noninfectious. Above all, we can obtain the following model:

$$\begin{cases} \dot{x} = s - dx + rx\left(1 - \dfrac{x}{x_{max}}\right) - kxv_i \\ \dot{y} = \sigma_1 kxv_i - \beta y - pyz \\ \dot{v}_i = \sigma_2 N\beta y - av_i \\ \dot{v}_n = (1-\sigma_2)N\beta y - av_n \\ \dot{z} = cy(t-\tau)z(t-\tau) - bz, \end{cases} \tag{1.2}$$

where v_i and v_n are the concentrations of infectious virus and noninfectious virus, and only infectious virus infect the T cells. We have $v = v_i + v_n$. The parameters σ_1, σ_2 satisfy $0 \le \sigma_1 \le 1$, $0 \le \sigma_2 \le 1$ and $(1-\sigma_1)$, $(1-\sigma_2)$ are the effectiveness of the RT treatment and the protease treatment, respectively. Note that v_n does not appear in the first four equations. Therefore, we can consider the following subsystem of (1.2) and we replace v_i with v.

$$\begin{cases} \dot{x} = s - dx + rx\left(1 - \dfrac{x}{x_{max}}\right) - kxv \\ \dot{y} = \sigma_1 kxv - \beta y - pyz \\ \dot{v} = \sigma_2 N\beta y - av \\ \dot{z} = cy(t-\tau)z(t-\tau) - bz, \end{cases} \tag{1.3}$$

The initial conditions for system (1.3) have the following forms:

$$\begin{cases} x(\theta) = \varphi_1(\theta), y(\theta) = \varphi_2(\theta), v(\theta) = \varphi_3(\theta), z(\theta) = \varphi_4(\theta), \\ \varphi_1(\theta) \ge 0, \varphi_2(\theta) \ge 0, \varphi_3(\theta) \ge 0, \varphi_4(\theta) \ge 0, \theta \in [-\tau, 0], \\ \varphi_1(0) > 0, \varphi_2(0) > 0, \varphi_3(0) > 0, \varphi_4(0) > 0 \end{cases} \tag{1.4}$$

where $(\varphi_1(\theta), \varphi_2(\theta), \varphi_3(\theta), \varphi_4(\theta)) \in C([-\tau, 0], R^4_{+0})$, the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into R^4_{+0}, where $R^4_{+0} = \{(x_1, x_2, x_3, x_4) : x_i \ge 0, i = 1, 2, 3, 4\}$.

It is well known by the fundamental theory of functional differential equation as demonstrated [10] that system (1.3) has a unique solution $(x(t), y(t), v(t), z(t))$ satisfying the initial condition (1.4). It is easy to show that all solutions of system (1.3) with initial conditions (1.4) are defined on $[0, +\infty)$ and remain positive for all $t \ge 0$.

2. Preliminaries

In the absence of HIV infection, the CD4$^+$T cell dynamics can be described by

$$\dot{x} = s - dx + rx\left(1 - \frac{x}{x_{max}}\right)$$

It can be shown that in this case the CD4$^+$T cell concentration regulates at the level x_0, where

$$x_0 = \frac{x_{max}}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{x_{max}}}\right]$$

It follows from the first equation of system (1.3) that if $x(0) < x_0$, then $x(t) < x_0$ for all $t > 0$. Furthermore, the first two equations of system (1.3) give

$$\dot{x} + \frac{1}{\sigma_1}\dot{y} = s - dx + rx\left(1 - \frac{x}{x_{max}}\right) - \frac{\beta}{\sigma_1}y - \frac{p}{\sigma_1}yz \le s + \frac{rx_{max}}{4} - \mu\left(x + \frac{1}{\sigma_1}y\right)$$

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