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# Global threshold dynamics in a five-dimensional virus model with cell-mediated, humoral immune responses and distributed delays

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ABSTRACT

In this paper, we investigate the dynamics of a five-dimensional virus model with immune responses and an intracellular delay which describes the interactions of the HIV virus, CD4 cells and CTLs within host, which is an improvement of some existing models by incorporating (i) two distributed kernels reflecting the variance of time for virus to invade into cells and the variance of time for invaded virions to reproduce within cells; (ii) a nonlinear incidence function $f$ for virus infections, and (iii) antibody responses, which are implemented by the functioning of immunocompetent B lymphocytes, play a critical role in preventing and modulating infections. By constructing Lyapunov functionals and subtle estimates of the derivatives of these Lyapunov functionals, we show that the global dynamics of the model is determined by the reproductive numbers for viral infection $\mathfrak{R}_0$, for CTL immune response $\mathfrak{R}_1$, for antibody immune response $\mathfrak{R}_2$, for CTL immune competition $\mathfrak{R}_3$ and for antibody immune competition $\mathfrak{R}_4$. The global stability of the model precludes the existence of Hopf bifurcation and other complex dynamical behaviors in long time. Numerical simulations are also performed in order to illustrate the dynamical behavior.



## 1. Introduction

Over recent years, many authors have formulated and studied mathematical models which describe the dynamics of virus population in vivo and these provide insights in our understanding of HIV-1 (human immunodeficiency virus 1) and other viruses, such as HBV (hepatitis B virus) and HCV (hepatitis C virus) (see [11,12,16,17,22,23] and the references therein). Mathematical analysis for these models is necessary to obtain an integrated view for the virus dynamics in vivo. In particular, the global stability of a steady state for these models will give us a detailed information and enhances our understanding about the virus dynamics.

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During viral infections, it is well-known and pointed out by the work of [45] that antigen-specific immune response after viral infection is universal and necessary for identifying and killing pathogens and infected cells. Antibodies, cytokines, natural killer cells, and T cells are essential components of a normal immune response to a virus. In particular, cytotoxic T lymphocytes (CTLs) play a key role in antiviral defense by attacking virus-infected cell, and it is also believed that they are the main host immune factor that limits the extent of virus replication in vivo and thus determines virus load [43].

However, in the real virus dynamics, infection processes are not instantaneous. For example, during HIV infection, the intracellular phase is about 0.9 days, but the average half-life of plasma virus is only around 6 h [34]. Time delays are usually introduced for the purpose of accurate representations of intracellular phase of the viral life-cycle, defined as the time between infection of a cell and production of new virus particles (see, e.g. [6,11,21,23,30,38,41,44,45]). Thus, delays should be incorporated into the infection equation and/or the virus production equation of a model to account for effect of intracellular delay which leads to mathematical models by delay differential equation (DDE). Many authors have studied the mathematical modeling of viral dynamics with CTL immune response in the literature, which are given by systems of ordinary differential equation (ODE) and DDE (see, e.g. [2,3,8,9] and the references therein). It has been found in [5,40,46] that when a time delay was incorporated into HIV infection models with immune response, very complicated dynamics may occur including stable periodic solutions and chaos.

Arguing that constant delays are not biologically realistic, in [25,29,36], the authors provocated the use of distributed intracellular delays represented by general kernel functions. Nakata [29] investigated the stability of an HIV-1 infection model with immunity mediated and two finite distributed intracellular delays incorporated. Wang et al. [36] and Li and Shu [24] investigated the global stability of an HIV-1 infection model with infinite distributed intracellular delays by constructing Lyapunov functionals.

To investigate effects among incorporating distributed delay into the cell infection equation and another virus production equation and nonlinear incidence rate and a nonlinear removal rate for the infected cells, Yuan and Zou [43] proposed and developed the following mathematical model:

$$\begin{cases} x'(t) = \mu - kx(t) - \alpha x(t) f(v(t)), \\ y'(t) = \alpha \int_0^\infty G_1(\tau) x(t-\tau) f(v(t-\tau)) \mathrm{d}\tau - ry(t) - \beta y(t) h(z(t)), \\ v'(t) = Nr \int_0^\infty G_2(\tau) y(t-\tau) \mathrm{d}\tau - dv(t), \\ z'(t) = \lambda y(t) - qz(t), \quad t > 0, \end{cases} \tag{1.1}$$

where $x(t),\ y(t),\ v(t)$ and $z(t)$ represent the concentration of uninfected target cells, productively infected cells, free virus in the serum, and the abundance of virus-specific CTLs, respectively. Uninfected target cells are produced at a constant rate $\mu$ and die at a per capita rate $k$. Infected cells are produced from uninfected cells and virus at rate $\alpha \int_0^\infty G_1(\tau) x(t-\tau) f(v(t-\tau)) \mathrm{d}\tau$, where $\alpha$ is a constant characterizing the infection rate. The infected cells are assumed to die at a rate $r$ (say, via lysis) due to the action of virus, each releasing $N$ new virus particles as the lysis of infected cells occurs. The rate of CTL proliferation is given by $\lambda$ and decay at rate $qz(t)$ in the absence of stimulation by the infected cells. Infected cells are killed via mass action kinetics by CTLs, which is described by $\beta y(t) h(z(t))$. $\beta$ accounts for the strength of the lytic component. Virus particles are cleared from the system at rate $d$. As pointed in [43], the function $f(\xi)$ denotes the force of infection by virus at density $\xi$, which is locally Lipschitz on $[0,\infty)$ satisfying

$$(\mathbf{A}_1):\ f(0) = 0, \quad f'(\xi) \text{ exists and satisfies } f'(\xi) \geqslant 0 \quad \text{and} \quad \left(\frac{f(\xi)}{\xi}\right)' \leqslant 0 \text{ in } (0,\infty).$$

A class of the function $f$ that satisfies $(\mathbf{A}_1)$ include both bilinear incidence $f(\xi) = \xi$, saturated incidence $f(\xi) = \frac{\xi}{1+\alpha\xi}$ and Beddington–DeAngelis functional response $f(\xi) = \frac{\xi}{1+a\xi+b\xi}$, which have been widely used in the literature of viral dynamics [12,13,17,23,24,31,32,38].

Distributed intracellular delays used here are represented by general kernel functions $G_i(\tau) = f_i(\tau) e^{-m_i\tau},\ i = 1,2$. Here the factor $e^{-m_1\tau}$ accounts for the loss of uninfected cells during time interval $[t-\tau, t]$ due to viral infection, and the factor $e^{-m_2\tau}$ accounts for the infected cell loss during the delay period. Probability distribution functions $f_1(\tau)$ and $f_2(\tau)$ are assumed to satisfy $f_i(\tau) \geqslant 0$ and $\int_0^\infty f_i(\tau) d\tau = 1$ for $i = 1,2$. $G_1(\tau)$ is the probability that target cells contacted by the virus particles at time $t-\tau$ survived $\tau$ time units and become infected at time $t$ and $G_2(\tau)$ is the probability that a cell infected at time $t-\tau$ starts to yield new infectious virus at time $t$ [43]. Assume that the kernel functions $G_i(\tau),\ i = 1,2$ satisfy

$$(\mathbf{A}_2):\ G_i(\tau) > 0, \text{ for } \tau > 0, \quad \text{and} \quad 0 < a_i := \int_0^\infty G_i(\xi) \mathrm{d}\xi \leqslant 1, \quad i = 1,2.$$

On the other hand, although the pathogenesis of chronic virus infection is not well understood, there is a consensus that infection damage is immune-mediated [42]. It is also pointed out in [42] that antibody responses, which are implemented by the functioning of immunocompetent B lymphocytes, play a critical role in preventing and modulating infections. More generally, viral infection models have a general immune response, which can have both lytic and non-lytic effector mechanisms. Thus, it is realistic to consider two independent branches of the immune system: one is a lytic branch (such as CTL response), and the other is non-lytic branch (such as antibody response), and assume both branches are stimulated by antigens and suppress the viral population, they are in competition with each other. Therefore, Wodarz [37] presented a mathematical model to study the highly complex and non-linear interaction between replicating viruses, uninfected cells,