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Global dynamics of a diffusive and delayed viral infection model with cellular infection and nonlinear infection rate☆

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ABSTRACT

A diffusive and delayed viral dynamics model which incorporates cell-to-cell transmission, cell-mediated immune responses and general nonlinear incidence is investigated. By constructing Lyapunov functionals, it is shown that the global threshold dynamics of the model is fully determined by the basic reproduction numbers of the virus and the immune response, R_0 and R_1. The result implies that both the basic reproduction number of the virus and the immune response might be underevaluated without considering either the virus-to-cell transmission or cell-to-cell transmission. The main results obtained in this paper extend some known results.

1. Introduction

Over the past few decades, there has been a great effort in the mathematical model of within-host virus dynamics models. These models have been used to describe the dynamics inside the host of various infectious diseases such as HIV, HCV, HBV, HTLV, as well as the malaria parasite. Since samples cannot always be taken frequently from patients, or detection techniques of the virus may not be accurate, testing specific hypotheses based on clinical data is a challengeable task. This justifies the central role played by mathematical models in this area. The basic virus dynamics model takes the following form [1,2]:

$$\begin{cases} u'(t) = \lambda - du(t) - \beta u(t)v(t), \\ w'(t) = \beta u(t)v(t) - \delta w(t), \\ v'(t) = pw(t) - cv(t). \end{cases} \tag{1.1}$$

Here u, w and v denote the concentrations of uninfected cells, infected cells and virus particles at time t, respectively. The uninfected cells are produced at a constant rate λ and are infected by free virions at a rate βuv. Parameters d, δ and c represent the death rates of uninfected cells, infected cells and free virus, respectively. The free virions are produced from the infected cells at a rate pw. By constructing Lyapunov functions, Korobeiniklv [3] established the global stability of system (1.1).

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A key assumption in system (1.1) is that cells and viruses are well mixed, and ignores the mobility of viruses. To study the influences of spatial structures of virus dynamics, Wang et al. [4] proposed the following delayed and diffusive system by assuming the motion of virus follows the Fickian diffusion [5]

$$\begin{cases} \dfrac{\partial u(x,t)}{\partial t} = \lambda - du(x,t) - \beta u(x,t)v(x,t), \\ \dfrac{\partial w(x,t)}{\partial t} = \beta u(x,t-\tau)v(x,t-\tau) - \delta w(x,t), \\ \dfrac{\partial v(x,t)}{\partial t} = D\triangle v(x,t) + pw(x,t) - cv(x,t), \end{cases} \tag{1.2}$$

where $u(x,t)$, $w(x,t)$ and $v(x,t)$ represent the densities of uninfected cells, infected cells and free virus at position x and at time t, respectively. $\tau \geq 0$ accounts for the time between viral entry into a target cell and the production of new viral particles. $\triangle$ is the Laplacian operator and D is the diffusion coefficient.

As mentioned in [6] that cytotoxic T lymphocytes (CTL) cells play a key role in antiviral defense by attacking virus-infected cell in most virus infections. Thus, Nowak and Bangham [6] incorporated immune response into system (1.1). After that many literatures have been done with immune response [7–9] and references therein. Notice that the above mentioned studies only focus on virus-to-cell spread in the bloodstream even though some literatures reveal that cell-to-cell (infected source cell and a susceptible target cell) transmission is vital to spread of virus in vivo [10–13]. Indeed, direct cell-to-cell transmission mode has been reported for many infections, such as HIV, HCV, HTLV, murine leukemia virus (MLV), Alphaherpesviruses and so on [14–16]. An understanding of viral cell-to-cell spreading will enhance our ability to intervene in the efficient spreading of viral infections. Recently, Lai et al. [16] proposed a time delayed viral infection model that incorporates cell-to-cell transmission mechanism and they investigated the global stability of equilibria by constructing Lyapunov functionals. Wang et al. [17] extended and studied a viral infection model with cell-to-cell transmission and cell-mediated immune responses. Though Yang et al. [18] considered a diffusive virus dynamics model with cell-to-cell transmission, time delay and immune response have not been taken into account. For more information on dealing with target cell dynamics and cell-to-cell transmission one can refer [19–30]. However, there is no investigation for delayed and diffusive virus dynamics model with cell-to-cell transmission and cell-mediated immune response in the above mentioned literatures. Inspired by the aforementioned studies, in this paper we propose the following model:

$$\begin{cases} \dfrac{\partial u(x,t)}{\partial t} = \lambda - du(x,t) - \beta_1 u(x,t)f(v(x,t)) - \beta_2 u(x,t)g(w(x,t)), \\ \dfrac{\partial w(x,t)}{\partial t} = \beta_1 u(x,t-\tau_1)f(v(x,t-\tau_1)) + \beta_2 u(x,t-\tau_1)g(w(x,t-\tau_1)) - \delta w(x,t) - rw(x,t)z(x,t), \\ \dfrac{\partial v(x,t)}{\partial t} = D\triangle v(x,t) + pw(x,t-\tau_2) - cv(x,t), \\ \dfrac{\partial z(x,t)}{\partial t} = kw(x,t)z(x,t) - qz(x,t), \end{cases} \tag{1.3}$$

where $z(x,t)$ denotes the concentration of CTL cells at position x and time t. Infected cells are killed at rate $rw(x,t)z(x,t)$. CTL cells are proliferated at rate $kw(x,t)z(x,t)$ and die at rate $qz(x,t)$. Generally, we have $d < \delta$. τ_1 represents the latent delay, i.e. the time period from being infected to becoming productive infected cells. Initially, the newly released virions are immature, subsequently, they undergo a proteolytic maturation step to become infectious particles. The delay τ_2 represents the time necessary for the newly produced virions to become mature. Here, the incidences are assumed to be the nonlinear responses to the concentrations of virus particles and infected cells, taking the forms $\beta_1 u(x,t)f(v(x,t))$ and $\beta_2 u(x,t)g(w(x,t))$, where $f(v)$ and $g(w)$ denote the force of infection by virus particles and infected cells satisfy the following properties [31]:

$$f(0) = g(0) = 0, \qquad f'(v) > 0, \qquad g'(w) > 0, \qquad f''(v) \leq 0, \qquad g''(w) \leq 0. \tag{1.4}$$

Based on condition (1.4), it follows from the Mean Value Theorem that

$$f'(v)v \leq f(v) \leq f'(0)v, \qquad g'(w)w \leq g(w) \leq g'(0)w, \quad \text{for } w,\ v \geq 0. \tag{1.5}$$

Epidemiologically, condition (1.4) indicates that: (i) the disease cannot spread if there is no infection; (ii) the incidences $\beta_1 uf(v)$ and $\beta_2 ug(w)$ become faster as the densities of the virus particles and infected cells increase; (iii) the per capita infection rates by virus particles and infected cells will slow down due to certain inhibition effect since (1.5) implies that $(\frac{f(v)}{v})' \leq 0$ and $(\frac{g(w)}{w})' \leq 0$.

Obviously, the incidence rate with condition (1.4) contains the bilinear and the saturation incidences. In this paper, we consider system (1.3) with initial conditions as follows

$$\begin{aligned} u(x,s) &= \phi_1(x,s) \geq 0, \qquad w(x,s) = \phi_2(x,s) \geq 0, \\ v(x,s) &= \phi_3(x,s) \geq 0, \qquad z(x,s) = \phi_4(x,s) \geq 0, \quad (x,s) \in \bar{\Omega} \times [-\tau, 0], \end{aligned} \tag{1.6}$$