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Global stability of humoral immunity virus dynamics models with nonlinear infection rate and removal

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ABSTRACT

In this paper, we investigate the dynamical behavior of two nonlinear models for viral infection with humoral immune response. The first model contains four compartments; uninfected target cells, actively infected cells, free virus particles and B cells. The intrinsic growth rate of uninfected cells, incidence rate of infection, removal rate of infected cells, production rate of viruses, neutralization rate of viruses, activation rate of B cells and removal rate of B cells are given by more general nonlinear functions. The second model is a modification of the first one by including an eclipse stage of infected cells. We assume that the latent-to-active conversion rate is also given by a more general nonlinear function. For each model we derive two threshold parameters and establish a set of conditions on the general functions which are sufficient to determine the global dynamics of the models. By using suitable Lyapunov functions and LaSalle's invariance principle, we prove the global asymptotic stability of the all equilibria of the models. We perform some numerical simulations for the models with specific forms of the general functions and show that the numerical results are consistent with the theoretical results.

1. Introduction

Mathematical modeling and analysis of virus dynamics can be helpful to develop treatment strategies for infections and to provide insights on evaluating effective antiviral drug therapies to clear viruses from the human body. Several authors have devoted their efforts in studying the global stability of mathematical models which describe the dynamics of virus population in *vivo*, such as human immunodeficiency virus (HIV) [1–16], hepatitis B virus (HBV) [17–19], hepatitis C virus (HCV) [20] and human T cell leukemia virus (HTLV) [21]. The immune response plays a significant role in controlling the virus propagation. Therefore, several mathematical models have been proposed to describe the virus dynamics with cellular immunity (see e.g. [1,3,11,22]) or with humoral immunity [23–28]. The humoral immunity can be more effective than cellular

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in some viral infections [29]. Murase et al. [23] discussed a model with humoral immunity by assuming that the incidence rate of infection is given by bilinear. In reality, bilinear incidence rate is not accurate to describe the viral dynamics during the full course of infection. Recently, Wang et al. [28] have proposed the following model:

$$\dot{x} = s - dx - \psi(x, v)v, \tag{1}$$

$$\dot{y} = \psi(x, v)v - ay, \tag{2}$$

$$\dot{v} = ky - cv - qzv, \tag{3}$$

$$\dot{z} = rzv - \mu z, \tag{4}$$

where x, y, v and z denote the concentrations of the uninfected target cells, infected cells, free virus particles and B cells, respectively. Parameters s, k and r represent, the production rate of new healthy cells, the generation rate constant of free viruses produced from infected cells and the proliferation rate constant of the B cells, respectively. Parameters d, a, c and μ are the natural death rate constants of the uninfected cells, infected cells, free virus particles and B cells, respectively. $\psi(x, v)v$, represents the incidence rate of infection, where ψ is a general function. q is neutralization rate constant. All the parameters given in model (1)–(4) are positive.

Recently, some incidence rate forms have been included in viral infection models as $\psi(x, v)$ [30–34] and $C(x)\psi(v)$ [35], $\beta x\psi(v)$ [3], where C and ψ are general nonlinear functions. However, in [3,30–35], the humoral immune response was neglected. In model (1)–(4), the removal rates of the four compartments and the production rate of viruses are given by linear functions. Moreover, the activation rate of the B cells and the neutralization rate of viruses are given by specific forms. However, all of these rates may be different under different situations and different infections.

In this paper we aim to propose and analyze two general nonlinear viral infection models with humoral immune response which contains most of the above mentioned models as special cases. In the second model, we include the latently infected cells into the model, which is due to the delay between the moment when the virus contacts the uninfected cell and the moment when the infected cell becomes active to produce infectious viruses. For both models we derive two threshold parameters, the basic infection reproduction number and the humoral immune response activation number. We establish a set of conditions which are sufficient for the global stability of all equilibria of the models.

2. Nonlinear humoral immunity viral infection model

In this section, we propose a viral infection model with humoral immune response. We assume that the dynamics of the uninfected cells in the absence of infection is given by:

$$\dot{x} = n(x),$$

where $n(x)$ represents the intrinsic growth rate of uninfected cells accounting for both production and natural mortality. In the literature of virus dynamics, the following form of the growth rate $n(x) = s - dx$, has been widely used (see e.g. [4,8,22,30,34]). Another form of the function $n(x)$ which has been used in several works (see e.g. [2,13,36,37]) and contains a mitosis term is given by $n(x) = s - dx + \varsigma x\left(1 - \frac{x}{x_{\max}}\right)$, where $\varsigma > 0$ is the maximum proliferation rate of uninfected cells and $x_{\max} > 0$ is the maximum level of uninfected cell concentration in the body. However, in [2,13,36,37], the humoral immune response has been neglected.

We assume that the contacts between the viruses and uninfected target cells are given by an incidence function $\psi(x, v)$. This form of incident rate is general to encompass several forms of commonly used incidence rates such as bilinear incidence βxv [4,38], saturated incidence $\frac{\beta xv}{1+\alpha v}$ [39], Beddington–DeAngelis incidence $\frac{\beta xv}{1+\gamma x+\alpha v}$ [9,10,40], Crowley–Martin incidence $\frac{\beta xv}{(1+\gamma x)(1+\alpha v)}$ [41], Hill-type incidence $\frac{\beta x^m v}{\gamma^m+x^m}$ [7], and nonlinear incidence rate of the form $\psi(x, v)v$ [28], where β, m, α and γ are positive constants.