Chaos, Solitons and Fractals 110 (2018) 280–291

Contents lists available at ScienceDirect

Chaos, Solitons and Fractals

Nonlinear Science, and Nonequilibrium and Complex Phenomena

journal homepage: www.elsevier.com/locate/chaos

Dynamical analysis of a delayed reaction-diffusion virus infection model with logistic growth and humoral immune impairment

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ARTICLE INFO

Article history:
Received 15 February 2017
Revised 28 January 2018
Accepted 1 March 2018

Keywords:
Delayed virus infection model
Diffusion
Humoral immune impairment
Stability
Hopf bifurcation

ABSTRACT

In this paper, the dynamical analysis of a delayed reaction-diffusion virus infection model with logistic growth and chemotaxis for the uninfected target cells and humoral immune impairment is studied. By analyzing corresponding characteristic equations, the local stability of the infection-free equilibrium is established. The stability properties and Turing instability of the antibody-free equilibrium and antibody-present infection equilibrium have been extensively discussed. The existence of Hopf bifurcation with antibody response delay as a bifurcation parameter at the antibody-present infection equilibrium is established. The numerical simulations are carried out in order to illustrate the dynamical behavior of the model.

1. Introduction

Mathematical models can provide insights into the dynamics of viral load in vivo. A proper model has proven to be valuable on the development of a better understanding of the disease. There has been much interest in mathematical modeling of viral dynamics within-host. Recently, many virus dynamics models with specific immune response which plays a significant role in controlling the virus propagation were studied [1–10]. A specific immunity is composed of humoral immunity and cellular immunity, which is mainly expressed by B cells and T cells separately. Models with cellular immunity were studied more times [1–6,9]. But the humoral immunity is more effective than cellular in some infection processes [11]. Wang [7] constructed a mathematical model discussing the basic dynamical model with humoral immunity between uninfected cells $T(t)$, infected cells $I(t)$, virus $V(t)$ and B cells $B(t)$. The model is described by the following differential equation

$$\begin{cases} \dfrac{dT(t)}{dt} = A - dT(t) - \beta T(t)V(t), \\ \dfrac{dI(t)}{dt} = \beta T(t)V(t) - aI(t), \\ \dfrac{dV(t)}{dt} = kI(t) - uV(t) - qB(t)V(t), \\ \dfrac{dB(t)}{dt} = gB(t)V(t) - cB(t), \end{cases} \tag{1}$$

In principle, uninfected cells are produced from precursors in the bone marrow and thymus in the body, and could multiply through mitosis when stimulated by antigen or mitogen. The proliferation rate of uninfected cells slows with the increase of the concentration of the uninfected cells. Adding logistic growth term in virus infection models has improved the understanding of the latent stage of infection.

However, there are numerous experimental results suggesting that the virus generates mutants which escape from specific immune responses [12,13]. Many models are constructed under the assumption that the presence of the antigen can stimulate immunity and ignore the immune impairment. In certain circumstances, some pathogens can also suppress immune response or even destroy immunity especially when the load of pathogens is too high. Some researchers have studied the dynamics of virus infection models with impair immunity (see [2,6]).

To study the influences of spatial structures on virus dynamics, Wang [16] proposed an HBV model with spatial dependence and assumed that the motion of virus follows the Fickian diffusion. However, the mobility of susceptible cells, infected cells and immune cells are further neglected under normal conditions but viruses move freely in body in [16–23]. From a biological perspective, cells are distributed in space and typically interact with the physical environment and other organisms in their spatial neighborhood [24]. There is a tendency that the uninfected cells would keep away from infected cells. In the same manner, the infected cells would get closer to the uninfected cells. During the process of viral infection, cytotoxic T lymphocyte (CTL) cells which attack in-

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https://doi.org/10.1016/j.chaos.2018.03.006
0960-0779/

fected cells, and antibody cells which attack virus. The target cells, infected cells, virus and immune cells were assumed to follow the Fickian diffusion with the constant diffusion rate D_1, D_2, D_3 and D_4. The fluxes of the target cells, infected cells, virus and immune cells are related to their concentration gradient and go from regions of high concentration to regions of low concentration.

Mathematical modelling of chemotaxis (the movement of cells or organisms in response to chemical gradients) has applied not only in medicine but also in mathematics. In medicine, chemoattraction is defined as a directed movement of organisms up a concentration gradients of chemotactic agents. On the contrary, chemorepulsion represents a directed movement of organisms down a concentration gradient of chemotactic agents (see [25,26]). However, from mathematical point, chemotaxis plays an important role in the directed movements of organisms towards or away from the chemotactic agents (see [27]). Here we also use a spatial chemotaxis term $\chi\nabla(T\nabla I)$ to describe this interesting phenomenon [23].

For a full understanding of the dynamical behavior, in this paper, we propose a delayed reaction-diffusion virus infection model with logistic growth and humoral immune impairment given by

$$\begin{cases} \dfrac{\partial T(t,x)}{\partial t} = D_1\Delta T(t,x) - \chi\nabla(T(t,x)\nabla I(t,x)) + A - dT(t,x) \\ \qquad\qquad +rT(t,x)(1-\dfrac{T(t,x)}{k}) - \beta T(t,x)V(t,x), \\ \dfrac{\partial I(t,x)}{\partial t} = D_2\Delta I(t,x) + \beta T(t,x)V(t,x) - aI(t,x), \\ \dfrac{\partial V(t,x)}{\partial t} = D_3\Delta V(t,x) + pI(t,x) - uV(t,x) - qB(t,x)V(t,x), \\ \dfrac{\partial B(t,x)}{\partial t} = D_4\Delta B(t,x) + gB(t-\tau,x)V(t-\tau,x) \\ \qquad\qquad -cB(t,x) - mB(t,x)V(t,x), \end{cases} \tag{2}$$

where $t\in[0,\infty)$ and $x\in[0,\pi]$, with the homogeneous Neumann boundary conditions

$$\frac{\partial T(t,x)}{\partial x} = \frac{\partial I(t,x)}{\partial x} = \frac{\partial V(t,x)}{\partial x} = \frac{\partial B(t,x)}{\partial x} = 0 \text{ as } x = 0,\ \pi,\ t \geq 0, \tag{3}$$

and the initial conditions

$$\begin{aligned} &T(\theta,x) = \phi_1(\theta,x) \geq 0,\ I(\theta,x) = \phi_2(\theta,x) \geq 0, \\ &V(\theta,x) = \phi_3(\theta,x) \geq 0,\ B(\theta,x) = \phi_4(\theta,x) \geq 0, \end{aligned} \quad x\in[0,\pi],\ \theta\in[-\tau,0], \tag{4}$$

where $\phi_i(\theta,x)(i=1,2,3,4)$ is Hölder continuous in $[-\tau,0]\times[0,\pi]$, which accounts for spatial dependence of the initial value of the target cells, infected cells, virus and immune cells at x, respectively. $\Delta = \frac{\partial^2}{\partial x^2}$ is the Laplacian operator, $\nabla = \frac{\partial}{\partial x}$ is the gradient operator, D_1, D_2, D_3 and D_4 are the rates at which the uninfected cells, the infected cells, the virus and the B cells diffuse. We choose the closed interval $[0,\pi]$ as the spatial domain mainly for simplicity of notations in computing the normal forms and for convenience of carrying out demonstrating numeric results. Generally, closed interval $[a, b]$ can be transformed to $[0,\pi]$ by a translation and rescaling. According to the fundamental theory of partial functional differential equations [28], the model (2) has a unique solution ($T(t, x)$, $I(t, x)$, $V(t, x)$, $B(t, x)$) satisfying Neumann boundary conditions (3) and initial conditions (4). The boundary conditions (3) imply that the target cells, infected cells, virus and immune cells do not move across the boundary.

Our purpose in this paper is to investigate the dynamical properties of model (2). Particularly, we will investigate the stability of equilibria and the existence of Hopf bifurcation of the model.

The organization of this paper is as follows. In the next section, the basic properties, such as the positivity and boundedness of solutions, the threshold values and the existence of equilibria are discussed. In Section 3, the criteria on the local asymptotic stability of the infection-free equilibrium and antibody-free infection equilibrium are stated and proved. In Section 4, the sufficient conditions for the local asymptotic stability of the antibody-present infection equilibrium in case of delay $\tau = 0$ are established. When delay $\tau > 0$, the Hopf bifurcation at the antibody-present infection equilibrium is discussed, and the existence criterion is established. In Section 5, the numerical examples are presented to illustrate main theoretical results. Lastly, a conclusion is given in Section 6.

2. Basic properties

In model (2)–(4), the parameters d, a, u and c represent the death rate of the uninfected cells, the infected cells, the virus and the B cells, respectively; β is the infection rate; A, p and g are birth rate of the uninfected cells, the virus and the B cells, respectively; q is the B cells neutralize rate; r is the maximum proliferation rate of uninfected cells; k is the maximum level of uninfected cell concentration in the body; τ denotes immune response delay which is suggested between antigenic stimulation and generating B cells; an immune impairment term is $mB(t)V(t)$. During the course of viral infection, the modulation of infected cells is a key aspect in viral pathogenesis. It contributes to viral evasion from immunity because the dysfunction of target cells engenders some impairment effects for CTL inducement [14]. Iwami et al. [15] discovered the existence of so-called Risky threshold and Immunodeficiency threshold on the impairment rate. This implies that immune system may activate when the birth rate of immune cells exceeds the impairment rate; otherwise, the immune system always collapses. So, we always assume $g > m$ in this paper.

Denote $\mathcal{C} = C([-\tau,0]\times[0,\pi], R^4)$, $\mathcal{X} = \{\phi\in C^2([0,\pi], R^4) : \frac{d\phi(x)}{dx} = 0 \text{ for } x = 0,\pi\}$ and $\mathbb{N}_0 = \{0,1,2,\cdots\}$. For any continuous function $\omega : [-\tau, b)\times[0,\pi]\to R^4$ for $b > 0$, we define $\omega_t\in\mathcal{C}$ by $\omega_t(s,x) = \omega(t+s,x)$ for $s\in[-\tau,0]$ and $x\in[0,\pi]$. It is easy to prove that function $h(t) = \omega_t$ is a continuous function from $[0, b)$ to $\mathcal{C}$.

Theorem 1. *For any given initial function $\phi\in\mathcal{C}$, model (2) has a unique nonnegative solution $x(t,x) = (T(t,x), I(t,x), V(t,x), B(t,x))$ satisfying Neumann boundary conditions (3) and initial conditions (4). Furthermore, when $\chi = 0$ (that is in the absence of chemotactic effects), $D_1 = D_2$ and $D_3 = D_4$, then this solution is defined for all $t\geq 0$ and is also bounded.*

Proof. We define $F = (F_1, F_2, F_3, F_4) : \mathcal{C}\to R^4$ by for any $\phi = (\phi_1,\phi_2,\phi_3,\phi_4)^T\in\mathcal{C}$

$$\begin{aligned} F_1(\phi) &= A - d\phi_1(0,x) + r\phi_1(0,x)\left(1-\frac{\phi_1(0,x)}{k}\right) \\ &\quad - \beta\phi_1(0,x)\phi_3(0,x), \\ F_2(\phi) &= \beta\phi_1(0,x)\phi_3(0,x) - a\phi_2(0,x), \\ F_3(\phi) &= p\phi_2(0,x) - u\phi_3(0,x) - q\phi_3(0,x)\phi_4(0,x), \\ F_4(\phi) &= g\phi_3(-\tau,x)\phi_4(-\tau,x) - c\phi_4(0,x) - m\phi_3(0,x)\phi_4(0,x). \end{aligned}$$

Then, model (2)–(4) can be rewritten as the following abstract functional differential equation

$$\frac{d\omega(t)}{dt} = D\omega + F(\omega_t),\ \omega(0) = \phi\in\mathcal{C}, \tag{5}$$

where $\omega = (T,I,V,B)^T$, $\phi = (\phi_1,\phi_2,\phi_3,\phi_4)^T$ and $D\omega = (D_1\Delta T - \chi\nabla(T\nabla I), D_2\Delta I, D_3\Delta V, D_4\Delta B)^T$. It is clear that F is locally Lipschitz in $\mathcal{C}$. By [28–30], we deduce that model (5) admits a unique local solution $\omega_t = (T(t,x), I(t,x), V(t,x), B(t,x))$ defined on $[0, T_{\max})$, where $T_{\max} > 0$ is a constant. From [29], we further can obtain that ω_t is also nonnegative for $t\in[0, T_{\max})$.