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Dynamics of virus infection models with density-dependent diffusion☆

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ABSTRACT

Density-dependent diffusion plays an important role in the process of viral infection. In this paper, we construct mathematical models to investigate the dynamics of the viruses and their control. Single strain and multi-strain viral infections are both considered in this work. Using the method proposed by Pao and Ruan (2013), we prove the well-posedness of the models. By constructing appropriate Lyapunov functions, we proved the global asymptotical stabilities of the models. For the multi-strain model, we show that when the basic reproduction number for each strain is greater than one, all viral strains coexist. Since the effect of different treatments may result in competitive exclusion, it is essential to employ the treatment with combined therapy. We find with surprise that the density-dependent diffusion of the virus does not influence the global stabilities of the model with homogeneous Neumann boundary conditions.

1. Introduction

In the literature, mathematical models have been introduced to investigate the evolution of viruses. By evaluating such models, an insight into the dynamics of viral load in vivo is obtained and, based on such insights, appropriate clinical treatment strategy may be developed. For example, Wei et al. established a mathematical model to investigate the dynamics of human immunodeficiency virus [2]. Nowak et al. constructed a mathematical model to describe the dynamics of hepatitis B virus (HBV) infection and estimated the turnover rates of infected cells and free virus [3]. The infection with HBV causes a variety of health problems. In particular, persistent infection of the disease may lead to cirrhosis and primary hepatocellular carcinoma [4,5].

Song and Neumann [6] designed a system to model viral infection dynamics using saturated infection rate. The authors proved the global stability of the periodic solution. Wang and Wang [7] established a HBV model with viral diffusion with the assumption that the motion of virus follows the Fickian diffusion, i.e., the viral flux is proportional to the concentration gradient with negative proportionality constant [8]. The authors did not take the mobility of susceptible cells and infected cells into account. Based on the fact that the size of free viral particles is much smaller than the size of a liver and the fact that it usually takes at least 10 years for an individual to be chronically infected with HBV, Wang and Wang [7] made the

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assumption that the domain of free viral particles was an infinite spatial domain $(-\infty, \infty)$. Wang et al. [9] introduced time delay between the infection of a cell and its production of new viral particles to a viral model and investigated its effects on the viral infection process. Xu and Ma [10], by integrating saturation response into a viral model, investigated the viral dynamics and proved the global stability of the infected steady state by the method of upper and lower solutions. Wang et al. [11] gave the global stability of the infected steady state by constructing Lyapunov functions. Hattaf and Yousfi [12] studied the global stability for reaction–diffusion equations in biology. McCluskey and Yang [13] designed a mathematical model with diffusion, time delay and a general incidence function to study virus dynamics and interactions among uninfected cells, infected cells and free virus. The authors performed a thorough study on the threshold dynamics of the model by constructing Lyapunov functionals. Virus infection dynamic models with absorption effect and chemotaxis have been investigated in the literature with interesting results obtained [14–16].

The classical Fickian diffusion equation, which assumes that random walkers (individuals) in a system do not interact, has been applied to the study of real-world dispersal problems. However, in some scenario, there exist interactions between random walkers, which may change the diffusivity, and as such should be described as density-dependent diffusion [17]. Pao et al. [1,18–21] performed a thorough study on a class of quasilinear parabolic and elliptic systems, in which mixed quasimonotone reaction functions are used. The authors presented the well-posedness of the systems and studied their dynamics. Chen [22] discussed the dynamics of prey–predator n-species models with density dependent diffusion.

Virus dynamics with multi-strains has been investigated in the literature. With the aim of revealing the combined effects of competitive exclusion and coexistence of pathogens, a variety of viral models have been constructed and investigated. For example, Bremerman and Thieme performed a thorough study on an SIR multi-strain model and proved its competitive exclusion [23]. Andreasen and Pugliese studied the coexistence of two competing infectious diseases and considered the effects of host density on the transmission rate of virus [24]. Andreasen et al. established a disease model with a finite number of viral strains to consider the immunity structure of the host population [25]. Feng et al. constructed an SIR model to investigate the transmission of vector-borne disease with two viral strains [26]. Martcheva and Pilyugin designed a model to study multidisease dynamics and proved the existence of bistability and bifurcation [27]. Castillo-Chavez et al. established a mathematical model to investigate the transmission of sexually transmitted disease with two competing viral strains and performed a thorough study on the stability of the equilibria [28]. Iggidr et al. performed global analysis on new Malaria intrahost models with n viral strains and age structures [29]. Leenheer and Pilyugin designed a within-host multi-virus model with viral mutation [30]. By constructing Lyapunov function, the authors proved the global stability of the steady state. Dai and Zou designed a within-host age-structured disease model with two viral strains [31]. The authors considered the effects of viral mutation between strains on the propagation of virus and studied the global stability of the coexisting equilibrium.

Motivated by the above discussion, in this work, we construct mathematical models to investigate the dynamics of viral infection process in which density-dependent diffusion is involved.

Here, we assume that Ω is a bounded domain in R^n with smooth boundary $\partial\Omega$. At position $x \in \Omega$ and $t < \infty$, the production rate of uninfected susceptible host cells $u(x, t)$ is s, and their death rate is $du(x, t)$. A susceptible cell may be infected at rate $\frac{\beta uv}{1+\alpha v}$ [6], where positive constant α is the saturation reaction parameter, β is a constant determined by the process of infection. The production rate of infected host cells $w(x, t)$ is $\frac{\beta u(x,t)v(x,t)}{1+\alpha v(x,t)}$, and their death rate is $aw(x, t)$. Infected cells produce free viruses $v(x, t)$ at rate $kw(x, t)$ and these free viruses are removed at rate $mv(x, t)$.

The interaction among uninfected cells, infected cells and free viruses is described by the following PDEs.

$$\begin{cases} \dfrac{\partial u}{\partial t} = \nabla \cdot (D_u(u)\nabla u) + s - du(x, t) - \dfrac{\beta u(x, t)v(x, t)}{1 + \alpha v(x, t)}, \\ \dfrac{\partial w}{\partial t} = \nabla \cdot (D_w(w)\nabla w) + \dfrac{\beta u(x, t)v(x, t)}{1 + \alpha v(x, t)} - aw(x, t), \\ \dfrac{\partial v}{\partial t} = \nabla \cdot (D_v(v)\nabla v) + kw(x, t) - mv(x, t), \end{cases} \tag{1.1}$$

where $(t, x) \in (0, T] \times \Omega$ for any $T < \infty$. The initial condition of the model is given by

$$u(x, 0) = \phi_1(x) \geq 0, \qquad w(x, 0) = \phi_2(x) \geq 0, \qquad v(x, 0) = \phi_3(x) \geq 0, \tag{1.2}$$

and the homogeneous Neumann boundary condition is

$$D_u(u)\frac{\partial u}{\partial n} = 0, \qquad D_w(w)\frac{\partial w}{\partial n} = 0, \qquad D_v(v)\frac{\partial v}{\partial n} = 0, \tag{1.3}$$

where $(t, x) \in (0, T] \times \partial\Omega$ for any $T < \infty$. Here, we use $\frac{\partial}{\partial n}$ to denote the outward normal derivative on $\partial\Omega$.

The boundary condition in (1.3) restrains the viruses from migrating beyond the boundary $\partial\Omega$. We assume nonnegative $\phi_i(x)$, $i = 1, 2, 3$ are Hölder continuous, and satisfy $\frac{\partial\phi_i}{\partial n} = 0$, $i = 1, 2, 3$ on $\partial\Omega$. $D_u(u) = u^m$, $D_w(w) = w^m$, $D_v(v) = v^m$, $m > 0$ are density-dependent diffusion coefficients.

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