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Hepatitis C virus infection is blocked by HMGB1: A new nonlocal and time-delayed reaction–diffusion model☆

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ABSTRACT

This paper is devoted to developing a nonlocal and time-delayed reaction–diffusion model which makes contributions to understanding the mechanism of block effect on HCV by high-mobility group box 1 (HMGB1). Then basic reproduction number $\mathcal{R}_0$ is established. The existence of HMGB1 can make $\mathcal{R}_0 < 1$, that is, can induce the extinction of virus. Further, threshold dynamics are investigated in terms of $\mathcal{R}_0$ in a bounded spatial domain. From the biological perspective, threshold-type result can predict whether the disease will die out or persist. To investigate the invasion speed of the infectious disease, the existence of traveling waves is investigated in an unbounded spatial domain. Our results imply that the nonlocal time delay cannot change threshold dynamics, while it can slow down the wave speed of virus.

1. Introduction and model derivation

Viruses are considered to spread in infected hosts through a complicated process, which involves entry of virus into the cell, reverse transcription of virus RNA to DNA, and integration of viral DNA into the host-cell genome [9]. After then, new virions are released to infect other uninfected cells. Following one or two days of virus replication, infected cells die due to apoptosis mediated by the action of caspase-3 [9]. Spatial structure plays a significant role in describing the dynamical behavior of viral infection dynamics. To study the evolutionary competition between lytic and budding, Komarova [25] developed a diffusive viral infection dynamical model. In the subsequent papers, some further studies have been performed on the viral infection models (e.g., [20,32,48,49,56,57,63,65–67] and the references therein).

The spreading speed which is one of the most important problems in spatially dynamical models is usually used to describe the invasion speed of species. For cooperative systems, the spreading speed equals the minimum wave speed (e.g., [26,52]). For some non-cooperative systems, the spreading speed also equals the minimum wave speed (e.g., [53]). However, for some epidemic mathematical models and viral infection dynamical models, it seems to be very difficult to show the similar conclusion. Particularly, for diffusive viral infection dynamical models, Lai and Zou [32] numerically show that the spreading speed of virus may be larger than its minimal wave speed (see, also [56]). In this case, it is extremely difficult to compute the spreading speed of virus in mathematics. Nevertheless, one can study travelling wave solutions and compute its corresponding minimum wave speed, which is a significant step towards the spreading speed.

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Hepatitis C virus (HCV) has spread quickly to most regions around the world since its discovery (e.g., [23,42] and the references therein). A recent study published in [24] reveals that HCV spreads much slower than previously thought. Biologically, HCV infection can be blocked by HMGB1 released from virus-infected cells. By monitoring the effects of TLR4 knockdown and over-expression on HCV infection, Jung et al. [24] show that secreted HMGB1 can trigger the production of antiviral proteins through TLR4-mediated interferon responses, which can prevent the replication and generation of new viruses. Mathematical models have given insights to HCV infection (e.g., [8,12,35] and the references therein). In order to provide insight into the blocking effect on HCV infection by HMGB1, Wang and Ma [58] firstly proposed the following HCV infection dynamical model

$$\begin{cases} \dfrac{\partial U(x,t)}{\partial t} = D_0\Delta U + \xi(x) - \dfrac{\beta(x)U(x,t)\omega(x,t)}{1+a(x)\omega(x,t)+b(x)U(x,t)} - d_U U(x,t), \\ \dfrac{\partial V(x,t)}{\partial t} = D_0\Delta V + \dfrac{\beta(x)U(x,t)\omega(x,t)}{1+a(x)\omega(x,t)+b(x)U(x,t)} - d_V V(x,t) - \alpha_1(x)V(x,t), \\ \dfrac{\partial M(x,t)}{\partial t} = D_1\Delta M + \alpha_2(x)V(x,t) - d_M M(x,t), \\ \dfrac{\partial \omega(x,t)}{\partial t} = \nabla\cdot\Big(D_\omega(M)\nabla\omega\Big) + \dfrac{k(x)V(x,t)}{1+\gamma(x)M(x,t)} - d_\omega\omega(x,t). \end{cases} \tag{1.1}$$

In model (1.1), $U(x, t)$, $V(x, t)$, $M(x, t)$, and $\omega(x, t)$ represent the concentration of uninfected cells, infected cells, HMGB1, and virus at time t and location x, respectively. Uninfected cell production rate $\xi(x)$, infection rate of virus $\beta(x)$, measure of virus interference during infection $a(x)$, the speed of the infection rate approaches its saturation value $b(x)$, the loss rate of infected cells to produce HMGB1 $\alpha_1(x)$, the production rate of HMGB1 protein $\alpha_2(x)$, virus production rate $k(x)$, and $\gamma(x)$ (production of free virus is dependent on the presence of HMGB1) are spatially dependent. For mathematical considerations, these functions are positive and continuous on $\overline{\Omega}$, assuming

$$\overline{\xi} = \max_{x\in\overline{\Omega}}\xi(x) > 0, \quad \overline{\beta} = \max_{x\in\overline{\Omega}}\beta(x) > 0, \quad \overline{k} = \max_{x\in\overline{\Omega}}k(x) > 0,$$
$$\overline{\alpha}_2 = \max_{x\in\overline{\Omega}}\alpha_2(x) > 0, \quad \underline{\alpha}_1 = \min_{x\in\overline{\Omega}}\alpha_1(x) > 0, \quad \underline{a} = \min_{x\in\overline{\Omega}}a(x) > 0,$$

where $\overline{\Omega}$ is the closure of Ω. The death rate of $U(x, t)$, $V(x, t)$, $M(x, t)$, and $\omega(x, t)$ are d_U, d_V, d_M and d_ω, respective.

In model (1.1), uninfected cells, infected cells and HMGB1 can move according to the Fickian diffusion with the diffusion rate D_0, D_0 and D_1, respectively,

$$\overrightarrow{J}_U = -D_0\nabla U, \quad \overrightarrow{J}_V = -D_0\nabla V, \quad \overrightarrow{J}_M = -D_1\nabla M.$$

In addition, Jung et al. [24] has revealed that high concentration of HMGB1 can block the spread of virus. Hence, the flux of virus has the following form

$$\overrightarrow{J}_\omega = D_\omega(M)(-\nabla\omega).$$

Here, $D_\omega(M)$ is a decreasing function of the concentration of HMGB1 satisfying $D_\omega(0) = D_2$. That is, if there is no HMGB1, the diffusion of virus only depends on their concentration gradient with the diffusion rate D_2.

In model (1.1), threshold dynamics, travelling wave solutions and spreading speed for model (1.1) are investigated in [58]. Further, Wang and Ma [58] also shows that high concentration of HMGB1 can block the spread of virus [24].

In more realistic viral infection dynamical models, any time delays should be spatially inhomogeneous. This is due to the fact that any given individuals may not necessarily have been at the same location at previous time (e.g., [16,18]). Britton [5] and [6] firstly attempted to investigate travelling wave solutions for partial differential equation models with nonlocal time delays. In the subsequent papers, many methods have been established to show the travelling waves. The first method is to use the perturbation theory coupled with the Fredholm alterative [3,17]. The second method is to employ the geometric singular perturbation theory [2,4,15,39]. The third method is to employ monotone iteration to establish a new monotone iteration scheme [28,29,59]. Based on some nonlinear perturbation analysis and the Fredholm theory, Faria et al. [14] established a new method to obtain the existence of travelling wave solutions (see, also [36]). In addition, Schauder fixed point theorem was employed to establish traveling waves with the help of suitable upper and lower solutions (e.g., [10,33,50,51,59,62] and the references therein).

When studying the spread of virus, the mobility of the cells in the latent period will cause nonlocal infection. This is due to the fact that infected cells to their present position may be caused by virus from all possible positions. In order to derive the nonlocal time delay mathematical model, from [19], we easily get

$$\frac{\partial Y(t,a_1,x)}{\partial t} + \frac{\partial Y(t,a_1,x)}{\partial a_1} = D_0\Delta Y(t,a_1,x) - d_V(x)Y(t,a_1,x) - \alpha(x,a_1)Y(t,a_1,x),$$

where $Y(t, a_1, x)$ is the density of cells with infection age a_1 at time t and habitat x.