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Research paper

Dynamics of an HBV/HCV infection model with intracellular delay and cell proliferation

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ABSTRACT

A new mathematical model of hepatitis B/C virus (HBV/HCV) infection which incorporates the proliferation of healthy hepatocyte cells and the latent period of infected hepatocyte cells is proposed and studied. The dynamics is analyzed via Pontryagin's method and a newly proposed alternative geometric stability switch criterion. Sharp conditions ensuring stability of the infection persistent equilibrium are derived by applying Pontryagin's method. Using the intracellular delay as the bifurcation parameter and applying an alternative geometric stability switch criterion, we show that the HBV/HCV infection model undergoes stability switches. Furthermore, numerical simulations illustrate that the intracellular delay can induce complex dynamics such as persistence bubbles and chaos.

1. Introduction

Mathematical modeling of viral infection has played an important role in understanding the effect of free virus in vivo on target cells and the mechanism of viral infection. A classical viral infection model describing the interactions among healthy cells, infected cells and free virus was proposed in [30,31]. It is assumed that in the basic model, the infected cells can produce virus without going through a latent stage. However, Ho et al. found that, following the infection of virus, within a cell the provirus may remain latent and may not produce virus for months or even years [14]. Therefore, the latent stage to infected cells should be incorporated into the viral infection modeling. Typically, there are two ways to include the latency into viral infection models. One is to assume that the progress of infected cells from latent stage to active stage is subject to exponential distribution, which results in a system of ordinary differential equations, see for example [8,16,34]. The other assumes that the infected cells initially enter the latent stage lasting a certain period of time, which is referred to as an intracellular delay, and then become actively infected. This process can then be modeled by a system of delay differential equations [5,7,11,12,15,19–23,25,26,28,29,33,35].

For hepatitis B and C viruses, healthy hepatocyte cells possess the ability of proliferation [27], the growth of healthy hepatocyte cells is thus density-dependent. In the literature, the logistic growth of healthy hepatocyte cells has been adopted for models of HBV/HCV infection [3,4,7,13,24]. For more generic assumption on the growth of target cells, we refer the reader to [23,33].

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On the basis of the basic viral infection model, incorporating the intracellular delay and the logistic growth for cell proliferation, we obtain the following model of HBV/HCV infection

$$\begin{cases} \dfrac{dT(t)}{dt} = rT(t)\left(1-\dfrac{T(t)}{K}\right) - \mu_1 T(t) - \beta T(t)V(t), \\ \dfrac{dT_1(t)}{dt} = \beta T(t)V(t) - \beta e^{-\mu_1\tau}T(t-\tau)V(t-\tau) - \mu_1 T_1(t), \\ \dfrac{dT^*(t)}{dt} = \beta e^{-\mu_1\tau}T(t-\tau)V(t-\tau) - \mu_2 T^*(t), \\ \dfrac{dV(t)}{dt} = k\mu_2 T^*(t) - \gamma V(t). \end{cases} \tag{1.1}$$

Here, $T(t)$ represents the number of healthy hepatocyte cells at time t, $T_1(t)$ represents the number of cells that have been infected but are not yet producing virions (latently infected cells) at time t, $T^*(t)$ represents the number of infected cells actively producing virions (actively infected cells) at time t, and $V(t)$ denotes the number of free virions at time t. The positive parameter r is the maximal proliferation rate per healthy hepatocyte, and K is the carrying capacity, μ_1 is the death rate of healthy hepatocyte cells. It is assumed that healthy hepatocyte cells are infected at a rate βTV, actively infected cells die at a rate $\mu_2 T^*$ ($\mu_2 \geq \mu_1$), free virions are produced by the actively infected cells at a rate $k\mu_2 T^*$ and are removed at a rate γV. The latently infected hepatocyte cells are transferred from latent to active at the rate $\beta e^{-\mu_1\tau}T(t-\tau)V(t-\tau)$, where $e^{-\mu_1\tau}$ represents the proportion of latently infected cells becoming actively infected after τ period of time.

Note that the variable T_1 only appears in the second equation of (1.1), we then only need to consider a subsystem of (1.1)

$$\begin{cases} \dfrac{dT(t)}{dt} = rT(t)\left(1-\dfrac{T(t)}{K}\right) - \mu_1 T(t) - \beta T(t)V(t), \\ \dfrac{dT^*(t)}{dt} = \beta e^{-\mu_1\tau}T(t-\tau)V(t-\tau) - \mu_2 T^*(t), \\ \dfrac{dV(t)}{dt} = k\mu_2 T^*(t) - \gamma V(t). \end{cases} \tag{1.2}$$

We should point out that though Model (1.2) seems to be a special case of the model considered in [21] with $\lambda = 0$, the analysis carried in [21] does not apply to Model (1.2) since the feasible region Γ mentioned in [21] would thus contain only one single point if $\lambda = 0$ is assumed.

Clinical data indicates that the viral production and clearance are on much faster time-scale than the infection process [32]. Since our focus lies in the impacts of the intracellular delay on viral dynamics, it is reasonable to apply the quasi-steady state approach [6] and the singular perturbation theory [9] to System (1.2). That is, we can substitute $V = k\mu_2 T^*/\gamma$ into the first two equations of (1.2) to get

$$\begin{cases} \dfrac{dT(t)}{dt} = rT(t)\left(1-\dfrac{T(t)}{K}\right) - \mu_1 T(t) - \dfrac{\beta k\mu_2}{\gamma}T(t)T^*(t), \\ \dfrac{dT^*(t)}{dt} = \dfrac{\beta k\mu_2}{\gamma}e^{-\mu_1\tau}T(t-\tau)T^*(t-\tau) - \mu_2 T^*(t). \end{cases} \tag{1.3}$$

For (1.3), making the scaling

$$T = \frac{K(r-\mu_1)}{r}x, \qquad T^* = \frac{K(r-\mu_1)}{r}y, \quad t = \frac{\bar{t}}{\mu_2},$$

and denoting

$$\bar{r} = \frac{r-\mu_1}{\mu_2}, \qquad \bar{\beta} = \frac{\beta k K(r-\mu_1)}{r\gamma}, \quad \bar{\mu} = \frac{\mu_1}{\mu_2}, \quad \bar{\tau} = \mu_2\tau,$$

then dropping the bars, we obtain

$$\begin{cases} \dfrac{dx(t)}{dt} = rx(t)(1-x(t)) - \beta x(t)y(t), \\ \dfrac{dy(t)}{dt} = \beta e^{-\mu\tau}x(t-\tau)y(t-\tau) - y(t). \end{cases} \tag{1.4}$$

The rest of this paper is organized as follows. In Section 2, we establish the global dynamics for the infection free equilibrium. In Section 3, we investigate stability of the infection persistent equilibrium. We then examine the stability switching pattern and bifurcation structure in Section 4. A brief summary and discussion is presented in Section 5.