Stability analysis of a model for HBV infection with cure of infected cells and intracellular delay

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ABSTRACT

A viral infection model of HBV infection of hepatocytes with "cure" of infected cells and intracellular delay is studied. The delay corresponds to the time necessary for a newly produced virion to become infectious particles. We prove that the stability is completely determined by the basic reproductive number $R_0(\tau)$. If $R_0(\tau) \leq 1$, the infection-free steady state is globally asymptotically stable. If $R_0(\tau) > 1$ then infection-free steady state becomes unstable and a unique infected steady state exists and is locally asymptotically stable. On the other hand, we derive sufficient conditions for the global asymptotic stability of the infected steady state. Numerical simulations are presented to illustrate the results.

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1. Introduction

The basic model of virus dynamics was proposed by Nowak and Bangham to study HIV infection [1,2], and later adapted to HBV [3,4] and HCV [5] infection. The basic model can be formulated as a system of three differential equations:

$$\frac{d}{dt}x(t) = \lambda - \mu x(t) - \beta x(t) v(t),$$

$$\frac{d}{dt}y(t) = \beta x(t) v(t) - \alpha y(t), \tag{1}$$

$$\frac{d}{dt}v(t) = \sigma y(t) - \gamma v(t).$$

Here, $x(t), y(t)$ and $v(t)$ denote the concentration of uninfected hepatocytes, actively infected hepatocytes, and free virions, respectively. Uninfected hepatocytes are assumed to be produced at the constant rate λ. Uninfected hepatocytes are assumed to die at the rate of $\mu x(t)$, and become infected at the rate of $\beta x(t) v(t)$, where β is the infection rate constant characteristic of the infection efficiency. The death rate of infected hepatocytes is $\alpha y(t)$. Free virions are assumed to be produced from infected hepatocytes at the rate of $\sigma y(t)$ and $\gamma v(t)$ is the clearance rate of viral particles.

In a recent model for HBV dynamics, Lewin et al. [6] have introduced a reversion rate constant to the uninfected state into basic model [3] to reflect a non-cytolytic mechanism, cytokine-induced "curing" of infected cells [7]. In other words, infected hepatocytes may also revert to the uninfected state by loss of all cccDNA from their nucleus [7]. This model is described by the following system of non-linear differential equations:

$$\frac{d}{dt}x(t) = \lambda - \mu x(t) - \beta x(t)v(t) + \delta y(t),$$
$$\frac{d}{dt}y(t) = \beta x(t)v(t) - (\alpha + \delta)y(t), \tag{2}$$
$$\frac{d}{dt}v(t) = \sigma y(t) - \gamma v(t).$$

The term $\delta y(t)$ into first equation of (2), corresponding to the rate at which uninfected hepatocytes are created through "cure".

In this paper, we incorporate a delay into HBV infection model (2). That is, we propose the following model:

$$\frac{d}{dt}x(t) = \lambda - \mu x(t) - \beta x(t)v(t) + \delta y(t),$$
$$\frac{d}{dt}y(t) = \beta x(t)v(t) - (\alpha + \delta)y(t), \tag{3}$$
$$\frac{d}{dt}v(t) = \sigma y(t - \tau)e^{-\varrho\tau} - \gamma v(t).$$

The assumptions are the following. It is assumed that on average each actively infected hepatocytes produces σ/α viral particles during its lifetime. Initially, the newly released virions are immature, subsequently, they undergo a proteolytic maturation step to become infectious particles. The delay τ represents the time necessary for the newly produced virions to become mature and then infectious particles. The probability of survival of immature virions is given by $e^{-\varrho\tau}$ and the average life time of an immature virus is given by $1/\varrho$.

The paper is organized as follows. In the next section, basic mathematical properties of the model are studied. Local stability of the steady states are studied in Section 3. The global asymptotic stability of the infection-free steady state is established in Section 4. Sufficient conditions for global asymptotic stability of the infected steady state are obtained in Section 4. In Section 5, we apply our results to delay virus dynamics model without cure rate.

2. Basic properties

Let $\mathcal{C}([-\tau, 0], \mathcal{R}_+^3)$ be the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathcal{R}_+^3$, where

$$\mathcal{R}_+^3 = \left\{ (x, y, v) \in \mathcal{R}^3 : x \geqslant 0, \ y \geqslant 0, \ v \geqslant 0 \right\}.$$

It is biologically reasonable to consider the following initial conditions for (3):

$$x(\phi) = \varphi_1(\phi), \quad y(\phi) = \varphi_2(\phi), \quad v(\phi) = \varphi_3(\phi), \quad \phi \in [-\tau, 0], \tag{4}$$

where $\varphi = (\varphi_1(0), \varphi_2(0), \varphi_3(0)) \in \mathcal{C}$. From the fundamental theory of functional differential equations [11], it is easy to see that the solution $(x(t), y(t), v(t))$ of system (3) with the initial condition (4) exists for all $t \geqslant 0$ and is unique.

For model (3) to be mathematically tractable and biologically meaningful, it is important to prove that all the state variables (Uninfected cells, infected cells, and viral particles) are nonnegative for all time. We prove that all solutions of system (3) with positive initial data will remain positive for all time $t \geqslant 0$.

Theorem 2.1. *Let the initial data be $x(\phi) = x_0(\phi) \geqslant 0$, $y(\phi) = y_0(\phi) \geqslant 0$, $v(\phi) = v_0(\phi) \geqslant 0$ for all $\phi \in [-\tau, 0)$, with $x_0(0) > 0$, $y_0(0) > 0$ and $v_0(0) > 0$. Then solutions $x(t), y(t)$ and $v(t)$ of system (3) are positive for all $t \geqslant 0$.*

Proof. Let $t_1 = \sup\{t \geqslant 0 : x > 0, y > 0, v > 0 \in [0, t]\}$. Clearly $t_1 > 0$, and if $0 \leqslant t \leqslant t_1$ then one of $x(t_1), y(t_1), v(t_1)$ must be zero. It follows from the first equation of the system (3) that

$$\frac{d}{dt}x(t) = \lambda - \mu x(t) - \beta x(t)v(t) + \delta y(t) \geqslant \lambda - (\mu + \beta v(t))x(t)$$

which can be re-written as,

$$\frac{d}{dt}\left[x(t)\exp\left[\mu t + \int_0^t \beta v(\phi)d\phi \right] \right] \geqslant \lambda \exp\left[\mu t + \int_0^t \beta v(\phi)d\phi \right].$$

Hence,

$$x(t_1)\exp\left[\mu t_1 + \int_0^{t_1} \beta v(\phi)d\phi \right] - x(0) \geqslant \int_0^{t_1} \lambda \exp\left[\mu u + \int_0^u \beta v(\phi)d\phi \right]du,$$

so that,

$$x(t_1) \geqslant x(0)\exp\left[-\mu t_1 - \int_0^{t_1} \beta v(\phi)d\phi \right] + \exp\left[-\mu t_1 - \int_0^{t_1} \beta v(\phi)d\phi \right]\int_0^{t_1} \lambda \exp\left[\mu u + \int_0^u \beta v(\phi)d\phi \right]du > 0. \tag{5}$$