Dynamical Analysis of a Delayed Hepatitis B Virus Model with Immune Responses

KEJUN ZHUANG
Anhui University of Finance and Economics
School of Statistics and Applied Mathematics
Caoshan Road 962, 233030 Bengbu
CHINA
zhkj123@163.com

Abstract: In this paper, a novel hepatitis B virus infection model with time delay and CTL immune responses is proposed. The threshold parameters are derived and existence of equilibria is discussed. Then, the uniform boundedness and nonnegativeness of solutions are obtained. By analyzing the transcendental characteristic equations, asymptotic stabilities of nonnegative equilibria are investigated. In particular, the occurrence of Hopf bifurcation phenomena is considered by regarding time delay as a bifurcation parameter. Finally, some numerical simulations are given to confirm the theoretical findings.

Key–Words: HBV infection, CTL immune responses, stability, Hopf bifurcation

1 Introduction

Hepatitis B virus (HBV) infection is the most common chronic viral infection in the world. An estimated 2 billion people have been infected, and more than 350 million are chronic carriers of the virus [1]. HBV is transmitted through contact with infected blood or semen. In the 2010 Global Burden of Disease Study, HBV infection ranked in the top health priorities in the world, and was the tenth leading cause of death [2]. These data have led WHO to include viral hepatitis in its major public health priorities.

However, the mathematical models may help to understand the HBV infection process and study the anti–HBV infection treatment [3]. Based on the pioneering model of virus dynamics proposed by Nowak and Bangham to study HIV infection [4, 5, 6], a large number of mathematical models have been introduced. These models can also be adapted to HBV and HCV infection.

The basic model describing the interaction between the susceptible host cells (hepatocytes, x), infected host cells (y), and free virus particles (v), is formulated by the following ordinary differential equations:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = s - dx - \beta xv, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \beta xv - ay, \\ \frac{\mathrm{d}v}{\mathrm{d}t} = ky - uv, \end{cases} \tag{1}$$

where hepatocytes are produced at a rate s, die at a rate dx, and become infected at a rate βxv; infected hepatocytes are produced at a rate βxv and die at a rate ay; free viruses are produced from infected cells at a rate ky and are removed at a rate uv. It is assumed that parameters s, d, β, a, k, u are all positive constants. Based on system (1), many modified models have been established. For example, Wang et al. [7] studied the global stability of an improved HBV model with standard incidence function and cytokine–mediated 'cure', Huang et al. [8, 9] considered the global properties for delayed or undelayed HBV models with Beddington–DeAngelis functional response, Zhuang et al. [10] discussed the local and global Hopf bifurcations for an improved HIV model with time delay and cure rate.

In view of the responses of the immune system, Nowak and Bangham [4] constructed the new model as follows:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = s - dx - \beta xv, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \beta xv - ay - pyz, \\ \frac{\mathrm{d}v}{\mathrm{d}t} = ky - uv, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = cyz - \mu z, \end{cases} \tag{2}$$

where z denotes the cytotoxic–T–lymphocyte (CTL) cells. Many researches have shown that although protection against infection is multifactorial phenomenon depending on both the innate and adaptive immune mechanisms, CTL cells play an important role in the control of HBV infection, see [11, 12].

Furthermore, time delay can not be ignored in models for immune responses. There is always a lag

between the time target cells are contacted by the virus particles and the time the contacted cells become actively infected [13, 14, 15]. As a consequence, the CTL cells produced at time t may depend on the number of CTL cells and infected target cells at time $t-\tau$, for a time delay $\tau > 0$. Accordingly, the CTL responses in (2) can be more realistically modeled by $cy(t-\tau)z(t-\tau)$. Therefore, Canabarro et al. [16] proposed the following delayed differential equations model

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = s - dx - \beta xv, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \beta xv - ay - p, \\ \frac{\mathrm{d}v}{\mathrm{d}t} = ky - \beta xv - uv, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = cy(t-\tau)z(t-\tau) - \mu z, \end{cases} \tag{3}$$

They only numerically investigated the solutions of delayed system (5). The stability and periodicity of solutions were founded by numerical simulations.

Thus, in this paper, we consider the more general model as follows:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = s - dx - \beta xv + qyz, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \beta xv - ay - (p+q)yz, \\ \frac{\mathrm{d}v}{\mathrm{d}t} = ky - uv, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = cy(t-\tau)z(t-\tau) - \mu z, \end{cases} \tag{4}$$

where the bilinear term qyz represents that the CTL cells cure the infected hepatocytes by a nonanalytic effector mechanism [17, 18]. In system (4) all parameters are positive constants.

For system (4), Xie et al. [15], Bai and Zhou [19] studied the dynamical behaviors in the absence of v when $q = 0$, respectively. Tian and Xu [20] studied the global stability and Hopf bifurcation when $q = 0$ with saturation incidence. Wang et al. [21] also studied the global stability of the model with Beddington–DeAngelis incidence rate when $q = 0$ and $\tau = 0$.

The aim of this paper is to investigate the stability of nonnegative equilibrium and existence of Hopf bifurcation phenomena. The paper is organized as follows. In Section 2, basic mathematical properties of the model are studied. Asymptotic stabilities of infection–free equilibrium and immune–free equilibrium are studied in Sections 3 and 4, respectively. The stability of immune–present equilibrium and existence of Hopf bifurcation are established in Section 5. In Section 6, we give a numerical example to verify the theoretical results. Finally, conclusions and discussions are drawn.

2 Preliminaries

Let $X = C([-\tau, 0]; R)$ be the Banach space of continuous mapping from $[-\tau, 0]$ to R equipped with the sup–norm. The initial conditions are given by

$$\begin{cases} x(\theta) \geq 0, y(\theta) \geq 0, v(\theta) \geq 0, z(\theta) \geq 0, \theta \in [-\tau, 0] \\ x(0) > 0, y(0) > 0, v(0) > 0, z(0) > 0. \end{cases} \tag{5}$$

By the standard theory of functional differential equations [22, 23], we can obtain that there exists a unique solution $(x(t), y(t), v(t), z(t))$ of system (4) satisfying the above initial conditions.

2.1 Positiveness and Boundedness of Solutions

Proposition 1 *Let $(x(t), y(t), v(t), z(t))$ be any solution of (4) with the initial conditions (5). Then $(x(t), y(t), v(t), z(t))$ are positive and ultimately bounded.*

Proof: From (4), we have

$$\begin{aligned} x(t) &= x(0)e^{-\int_0^t (d+\beta v(\zeta))\mathrm{d}\zeta} \\ &\quad + \int_0^t (s + qy(\eta)z(\eta))e^{-\int_\eta^t (d+\beta v(\zeta))\mathrm{d}\zeta}\mathrm{d}\eta, \\ y(t) &= y(0)e^{-\int_0^t (a+qz(\zeta))\mathrm{d}\zeta} \\ &\quad + \int_0^t \beta x(\eta)v(\eta)e^{-\int_\eta^t (a+qz(\zeta))\mathrm{d}\zeta}\mathrm{d}\eta, \\ v(t) &= v(0)e^{-ut} + \int_0^t ky(\eta)e^{-u(t-\eta)}\mathrm{d}\eta, \\ z(t) &= z(0)e^{-bt} + \int_0^t cy(\eta-\tau)z(\eta-\tau)e^{bt}\mathrm{d}\eta. \end{aligned}$$

It is obvious that $x(t)$ is positive on the existence interval. Then, we can prove the positiveness of $y(t)$. On one hand, let $t_1 > 0$ be the first time such that $y(t_1) = 0$. By the third equation of (4), we have $v(t_1) = v(0)e^{-ut_1} + \int_0^{t_1} ky(\eta)e^{-u(t_1-\eta)}\mathrm{d}\eta > 0$. On the other hand, from the second equation of (4), we have $\dot{y}(t_1) = \beta x(t_1)v(t_1) > 0$ and $y(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$, where ε is an arbitrarily small positive constant. This leads to a contradiction. It follows that $y(t) > 0$ and $v(t) > 0$. Similarly, we can also prove that $z(t) > 0$.

Next, we shall check the ultimate boundedness of solution. From the first two equations of (4), we have

$$\begin{aligned} \frac{\mathrm{d}(x+y)}{\mathrm{d}t} &= s - dx - ay - pyz \\ &\leq s - dx - ay \leq s - \sigma(x+y), \end{aligned}$$

where $\sigma = \min\{a, d\}$. Thus, we have

$$\limsup_{t\to\infty}(x(t) + y(t)) \leq s/\sigma,$$

$x(t)$ and $y(t)$ are ultimately bounded.

Let

$$N(t) = x(t) + y(t) + \frac{a}{2k}v(t) + \frac{p}{c}z(t+\tau)$$

and denote $\delta = \min\{d, \frac{a}{2}, u, \mu\}$. Then we have

$$\begin{aligned}\dot{N}(t) &= s - dx(t) - \frac{a}{2}y(t) - \frac{au}{2k}v(t) \\ &\quad -\frac{p\mu}{c}z(t+\tau) \\ &\leq s - \delta(x(t) + y(t) + \frac{a}{2k}v(t) + \frac{p}{c}z(t+\tau)) \\ &= s - \delta N.\end{aligned}$$

Therefore, $\limsup_{t\to\infty} N(t) \leq \frac{s}{\delta}$. Hence, $(x(t), y(t), v(t), z(t))$ are ultimately bounded and the proof is complete. □

2.2 Existence of Nonnegative Equilibria

Let the right sides of (4) be zero, we can find that system (4) has three nonnegative equilibria with the help of Mathematica. They are infection–free equilibrium $E_0 = (\frac{s}{d}, 0, 0, 0)$, immune–free equilibrium

$$E_1 = \left(\frac{au}{k\beta}, \frac{ks\beta - adu}{ak\beta}, \frac{ks\beta - adu}{au\beta}, 0\right)$$

and immune–present equilibrium $E_2 = (x_0, y_0, v_0, z_0)$, where

$$\begin{aligned}x_0 &= \frac{cpsu + cqsu - aqu\mu}{cdpu + cdqu + kp\beta\mu}, \\ y_0 &= \frac{\mu}{s}, \quad v_0 = \frac{k\mu}{cu}, \\ z_0 &= \frac{cks\beta - acdu - ak\beta\mu}{cdpu + cdqu + kp\beta\mu}.\end{aligned}$$

Note that $R_0 = ks\beta/(adu)$ is the basic reproductive ratio of virus, which describes the number of cells one cell generates on average over the course of its infectious period.

3 Stability of Infection–free Equilibrium

Assume $R_0 < 1$ so that E_0 is the unique equilibrium. Linearizing (4) around E_0, we obtain the linear system

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = -dx - \frac{\beta s}{d}v, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = -ay + \frac{\beta s}{d}v, \\ \frac{\mathrm{d}v}{\mathrm{d}t} = ky - uv, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = -\mu z. \end{cases}$$

The characteristic equation is

$$(\lambda+d)(\lambda+\mu)\left(\lambda^2 + (a+\mu)\lambda + \frac{adu - k\beta s}{d}\right) = 0.$$

Due to Routh–Hurwitz criterion, all the characteristic roots have negative real parts if and only if $R_0 < 1$. Thus the immune–free equilibrium is locally asymptotically stable when $R_0 < 1$ and unstable when $R_0 > 1$.

Theorem 2 *If $R_0 < 1$, then the immune–free equilibrium E_0 is globally asymptotically stable. If $R_0 > 1$, then E_0 is unstable.*

Proof: Let $x(t), y(t), v(t), z(t)$ be any positive solution of system (4) with initial conditions (5).

Define

$$\begin{aligned}V(t) &= \frac{1}{2}\left(x(t) - \frac{s}{d}\right)^2 + \frac{s}{d}y(t) + \frac{s}{cd}(p+q)z(t) \\ &\quad + mv(t) + \frac{s}{d}(p+q)\int_{t-\tau}^{t} y(\theta)z(\theta)\mathrm{d}\theta,\end{aligned}$$

where $m \in \left[\frac{\beta s^2}{d^2 u}, \frac{as}{dk}\right]$. Calculating the derivative of $V(t)$ along positive solutions of system (4), we derive that

$$\begin{aligned}\frac{\mathrm{d}V(t)}{\mathrm{d}t} &= -(d + \beta v(t))\left(x(t) - \frac{s}{d}\right)^2 \\ &\quad + qy(t)z(t)\left(x(t) - \frac{s}{d}\right) - y(t)\left(\frac{as}{d} - km\right) \\ &\quad - v(t)\left(mu - \frac{\beta s^2}{d^2}\right) - \frac{s}{cd}(p+q)\mu z(t).\end{aligned}$$

Combining the proof of Proposition 1, it follows that $V'(t) \leq 0$. It is obvious that $V'(t) = 0$ if and only if $x = \frac{s}{d}, y = v = z = 0$. By LaSalle's invariance principle, the global asymptotic stability of E_0 follows. This completes the proof. □

4 Stability of Immune–free Equilibrium

It is well known that the stability of the equilibrium of delay differential equation depends on the distribution of the zeros of characteristic equation. In the following, we shall use the main results in Ruan and Wei [24], which is a generalization of the lemma in Cook and Grossman [25], to analyze the distribution of characteristic roots. We first state the useful lemma as follows.

Lemma 3 *Consider the following exponential polynomial:*

$$\begin{aligned} & P(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2}, \ldots, e^{-\lambda\tau_m}) \\ = \; & \lambda^n + p_1^{(0)}\lambda^{n-1} + p_2^{(0)}\lambda^{n-2} + \ldots + p_n^{(0)} \\ & + [p_1^{(1)}\lambda^{n-1} + p_2^{(1)}\lambda^{n-2} + \ldots + p_n^{(1)}]e^{-\lambda\tau_1} \\ & + \ldots \\ & + [p_1^{(m)}\lambda^{n-1} + p_2^{(m)}\lambda^{n-2} + \ldots + p_n^{(m)}]e^{-\lambda\tau_m}, \end{aligned}$$

where $\tau_i \geq 0 (i = 1, 2, \ldots, m)$ *and* $p_j^{(i)} (i = 0, 1, \ldots, m; j = 1, 2, \ldots, n)$ *are constants. As* $(\tau_1, \tau_2, \ldots, \tau_m)$ *vary, the sum of the orders of the zeros of* $P(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2}, \ldots, e^{-\lambda\tau_m})$ *in the open right half plane can change only if a zero appears on or crosses the imaginary axis.*

Theorem 4 *Assume that* $cs > a\mu$. *If* $1 < R_0 < 1 + \frac{a\mu}{cs-a\mu}$, *then the immune–free equilibrium* E_1 *is asymptotically stable. If* $R_0 > 1 + \frac{a\mu}{cs-a\mu}$, *then* E_1 *is unstable.*

Proof: Consider the linearized system of (4) at E_1:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = -\frac{ks\beta}{au}x(t) - \frac{au}{k}v(t) + \frac{q(ks\beta-adu)}{ak\beta}z(t), \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \frac{ks\beta-adu}{au}x(t) - ay(t) + \frac{au}{k}v(t) \\ \qquad - \frac{(p+q)(ks\beta-adu)}{ak\beta}z(t), \\ \frac{\mathrm{d}v}{\mathrm{d}t} = ky(t) - uv(t), \\ \frac{\mathrm{d}z}{\mathrm{d}t} = \frac{c(ks\beta-adu)}{ak\beta}z(t-\tau) - \mu z(t). \end{cases}$$

Then the characteristic equation is

$$\begin{aligned} & \left(\lambda + \mu - \tfrac{c(ks\beta-adu)}{ak\beta}e^{-\lambda\tau}\right)\left[\lambda^3 + \left(a + u + \tfrac{ks\beta}{au}\right)\lambda^2\right. \\ & \left. + (a+u)\tfrac{ks\beta}{au}\lambda + ks\beta - adu\right] = 0. \end{aligned} \tag{6}$$

Notice that $1 < R_0 < 1 + \frac{a\mu}{cs-a\mu}$, it is easy to verify $\mu - \frac{c(ks\beta-adu)}{ak\beta} > 0$ and $(a+u)^2\frac{ks\beta}{au} + (a+u)\frac{k^2s^2\beta^2}{a^2u^2} > ks\beta - adu$. According to Routh–Hurwitz criterion, E_1 is asymptotically stable when $\tau = 0$.

When $\tau \neq 0$, we only need to discuss the following equation

$$\lambda + \mu - \frac{c(ks\beta - adu)}{ak\beta}e^{-\lambda\tau} = 0. \tag{7}$$

Let $\lambda = i\omega(\omega > 0)$ be the root of (7). Substituting it into (7), we have

$$\omega^2 = \left(\frac{c(ks\beta - adu)}{ak\beta} + \mu\right)\frac{cks\beta - acdu - ak\mu\beta}{ak\beta}.$$

If $1 < R_0 < 1 + \frac{a\mu}{cs-a\mu}$, then $\omega^2 < 0$, which means characteristic equation (6) has no purely imaginary root and all the roots have negative real parts. Hence, the immune–free equilibrium E_1 is asymptotically stable.

If $R_0 > 1 + \frac{a\mu}{cs-a\mu}$, then $\omega^2 > 0$. Substituting $\lambda = i\omega$ into (7) and separating real and imaginary parts, we get

$$\begin{cases} \sin\omega\tau = -\frac{\omega}{A} < 0, \\ \cos\omega\tau = \frac{\mu}{A} > 0, \end{cases}$$

where $A = \frac{c(ks\beta-adu)}{ak\beta} > 0$ when $R_0 > 1$. Then equation (7) has a pair of purely imaginary roots $\pm i\omega_1$ with $\tau = \tau^{(l)}, l = 0, 1, 2, \cdots$, where

$$\omega_1 = \sqrt{\frac{c^2(ks\beta - adu)^2}{a^2k^2\beta^2} - \mu^2},$$

and

$$\tau^{(l)} = \frac{1}{\omega_1}\left\{\arcsin\frac{\omega_1}{A} + 2l\pi\right\}, \; l = 0, 1, 2, \cdots.$$

Differentiating both sides of (7) with respect to τ, we have

$$\left.\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right|_{\lambda=i\omega_1} = -\frac{i\omega_1 A}{\cos\omega_1\tau^{(l)} + i\sin\omega_1\tau_l + A\tau^{(l)}},$$

and

$$\begin{aligned} & \mathrm{Re}\left[\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right]_{\lambda=i\omega_1} \\ = \; & \frac{\omega_1^2}{(\cos\omega_1\tau^{(l)} + A\tau^{(l)})^2 + (\sin\omega_1\tau^{(l)})^2} \\ > \; & 0. \end{aligned}$$

From above analysis, we can conclude that the immune–free equilibrium E_1 is stable when $1 < R_0 < 1 + \frac{a\mu}{cs-a\mu}$ and unstable when $R_0 > 1 + \frac{a\mu}{cs-a\mu}$. Moreover, Hopf bifurcation will occur when time delay is slightly larger than $\tau^{(0)}$ and small–amplitude periodic solutions will bifurcate from the equilibrium E_1. The proof is then complete. □

5 Stability of Positive Equilibrium and Existence of Hopf Bifurcation

Assume $R_0 > 1 + \frac{a\mu}{cs-a\mu}$ and $cs > a\mu$ so that the positive immune–present equilibrium E_2 exists. In this section, we shall take the CTL–response delay τ as a bifurcation parameter and show that the immune–present equilibrium E_2 will lose its linear stability and a Hopf bifurcation occurs when the time delay τ passes through a critical value.

Linearizing system (4) at $E_2 = (x_0, y_0, v_0, z_0)$, we obtain

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = -(d+\beta v_0)x(t) + qz_0y(t) - \beta x_0 v(t) \\ \qquad +qy_0z(t), \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \beta v_0 x(t) - (a+(p+q)z_0)y(t)y(t) \\ \qquad +\beta x_0 v(t) - (p+q)y_0 z(t), \\ \frac{\mathrm{d}v}{\mathrm{d}t} = ky(t) - uv(t), \\ \frac{\mathrm{d}z}{\mathrm{d}t} = cz_0y(t-\tau) + cy_0z(t-\tau) - \mu z(t). \end{cases}$$

The characteristic equation is

$$\begin{aligned} &\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 - e^{-\lambda\tau}(b_1\lambda^3 \\ &+b_2\lambda^2 + b_3\lambda + b_4) = 0, \end{aligned} \tag{8}$$

whose coefficients are

$$\begin{aligned} a_1 &= a + d + u + \beta v_0 + (p+q)z_0 + \mu, \\ a_2 &= ad + au + du + a\beta v_0 + \beta u v_0 - k\beta x_0 \\ &\quad +(p+q)dz_0 + (p+q)uz_0 + \beta p v_0 z_0 \\ &\quad +(a+d+u)\mu + \mu\beta v_0 + (p+q)\mu z_0, \\ a_3 &= adu + a\beta u v_0 - \beta dk x_0 + (p+q)duz_0 \\ &\quad +\beta p u v_0 z_0 + (ad + au + du)\mu + (a+u)\beta\mu v_0 \\ &\quad -\beta k\mu x_0 + (p+q)d\mu z_0 + (p+q)u\mu z_0 \\ &\quad +\beta p\mu v_0 z_0, \\ a_4 &= \mu(adu + dpuz_0 + dquz_0 + auv_0\beta - dk\beta x_0 \\ &\quad +puv_0z_0), \\ b_1 &= cy_0, \\ b_2 &= (a+d+u)\mu + \beta v_0, \\ b_3 &= \mu(ad + au + du + a\beta v_0 + \beta u v_0 - k\beta x_0), \\ b_4 &= \mu(adu + au\beta v_0 - dk\beta x_0). \end{aligned}$$

When $\tau = 0$, equation (8) becomes

$$\lambda^4 + (a_1 - b_1)\lambda^3 + (a_2 - b_2)\lambda^2 + (a_3 - b_3)\lambda + a_4 - b_4 = 0.$$

Through trivial computation, we can obtain

$$\begin{aligned} D_1 &= a_1 - b_1 > 0, \\ D_2 &= (a_1 - b_1)(a_2 - b_2) - (a_3 - b_3) > 0, \\ D_3 &= (a_1 - b_1)[(a_2 - b_2)(a_3 - b_3) \\ &\quad -(a_1 - b_1)(a_4 - b_4)] - (a_3 - b_3)^2 > 0, \\ D_4 &= (a_4 - b_4)D_3 > 0. \end{aligned}$$

Routh–Hurwitz criterion implies that all roots of (8) have negative real parts if and only if $R_0 > 1 + \frac{a\mu}{cs - a\mu}$ and $cs > a\mu$ with $\tau = 0$.

Proposition 5 *Assume that $R_0 > 1 + \frac{a\mu}{cs-a\mu}$ and $cs > a\mu$. Then, at $\tau = 0$, the immune–present equilibrium E_2 is locally asymptotically stable.*

When $\tau \neq 0$, let $\lambda = i\omega$ $(\omega > 0)$ be a purely imaginary root of (8). Substituting it into (8), we can get

$$\begin{aligned} &\omega^4 - ia_1\omega^3 - a_2\omega^2 + ia_3\omega + a_4 - (\cos\omega\tau \\ &-i\sin\omega\tau)(-ib_1\omega^3 - b_2\omega^2 + ib_3\omega + b_4) = 0. \end{aligned}$$

Separating the real and imaginary parts leads to

$$\begin{cases} \omega^4 - a_2\omega^2 + a_4 = (b_4 - b_2\omega^2)\cos\omega\tau \\ \qquad\qquad +(b_3\omega - b_1\omega^3)\sin\omega\tau \\ -a_1\omega^3 + a_3\omega = (b_3\omega - b_1\omega^3)\cos\omega\tau \\ \qquad\qquad -(b_4 - b_2\omega^2)\sin\omega\tau. \end{cases} \tag{9}$$

Squaring and adding both equations of (9), we have

$$\sigma^4 + c_1\sigma^3 + c_2\sigma^2 + c_3\sigma + c_4 = 0, \tag{10}$$

where

$$\begin{aligned} \sigma &= \omega^2, \\ c_1 &= a_1^2 - b_1^2 - 2a_2, \\ c_2 &= a_2^2 + 2a_4 - 2a_1a_3 - b_2^2 + 2b_1b_3, \\ c_3 &= a_3^2 - 2a_2a_4 + 2b_2b_4 - b_3^2, \\ c_4 &= a_4^2 - b_4^2. \end{aligned}$$

If equation (10) has positive real root, then characteristic equation (8) has purely imaginary roots. For convenience, we make the following assumption:

(H_1) Equation (10) has at least one positive real root.

Let $\sigma = \sigma_0$ be the positive root of (10). Then characteristic equation (8) has a pair of purely imaginary roots $\lambda = \pm i\omega_0$, where $\omega_0 = \sigma_0^2$. Solving the linear algebraic equations (9), we obtain

$$\begin{cases} \cos\omega\tau = -\frac{B}{(b_4 - b_2\omega^2)^2 + (b_3\omega - b_1\omega^3)^2}, \\ \sin\omega\tau = -\frac{C}{(b_4 - b_2\omega^2)^2 + (b_3\omega - b_1\omega^3)^2}, \end{cases}$$

where

$$\begin{aligned} B &= (b_2 - a_1b_1)\omega^6 + (a_3b_1 + a_1b_3 - b_4 - a_2b_2)\omega^4 \\ &\quad +(a_2b_4 + a_4b_2 - a_3b_3)\omega^2 - a_4b_4, \\ C &= b_1\omega^7 + (a_1b_2 - b_3 - a_2b_1)\omega^5 + (a_2b_3 + a_4b_1 \\ &\quad -a_3b_2 - a_1b_4)\omega^3 + (a_3b_4 - a_4b_3)\omega. \end{aligned}$$

We can find that there always exists $\tau_0 > 0$ such that all roots of (8) have negative real parts when $\tau \in [0, \tau_0)$ and equation (8) has a pair of purely imaginary roots $\lambda = \pm\omega_0$ when $\tau = \tau_0$.

Next, we shall verify the transversality condition at $\tau = \tau_0$ to explore the existence of Hopf bifurcation. By the continuous dependence of characteristic roots

on parameter τ, we can differentiate both sides of (8) with respect to τ:

$$\left[\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right]^{-1} = -\frac{\tau}{\lambda} - \frac{(4\lambda^3+3a_1\lambda^2+2a_2\lambda+a_3)e^{\lambda\tau}}{\lambda(b_1\lambda^3+b_2\lambda^2+b_3\lambda+b_4)} + \frac{3b_1\lambda^2+2b_2\lambda+b_3}{\lambda(b_1\lambda^3+b_2\lambda^2+b_3\lambda+b_4)}$$

and

$$\begin{aligned}
&\mathrm{Re}\left[\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right]^{-1}_{\tau=\tau_0} \\
=\ & \frac{1}{\omega_0\Lambda}\Big[(3a_1\omega_0^2-a_3)(b_1\omega_0^3\cos\omega_0\tau_0 \\
& -b_3\omega_0\cos\omega_0\tau_0+b_4\sin\omega_0\tau_0 \\
& -b_4\omega_0^2\sin\omega_0\tau_0)+(4\omega_0^3-2a_2\omega_0) \\
& (b_4\cos\omega_0\tau_0-b_2\omega_0^2\cos\omega_0\tau_0 \\
& -b_1\omega_0^3\sin\omega_0\tau_0+b_3\omega_0\sin\omega_0\tau_0) \\
& +(b_3-3b_1\omega_0^2)(b_1\omega_0^3-b_3\omega_0) \\
& +2b_2\omega_0(b_4-b_2\omega_0^2)\Big] \\
=\ & \frac{1}{\omega_0\Lambda}\Big[4\omega_0^6+3(a_1^2-2a_2-b_1^2)\omega_0^4 \\
& +2(a_2^2-b_2^2+2a_4+2b_1b_3 \\
& -2a_1a_3)\omega_0^2+a_3^2-b_3^2+2b_2b_4 \\
& -2a_2a_4\Big],
\end{aligned}$$

where $\Lambda=(b_1\omega_0^3-b_3\omega_0)^2+(b_4-b_2\omega_0^2)^2>0$.

If the following assumption is satisfied:
(H_2) $4\omega_0^6+3(a_1^2-2a_2-b_1^2)\omega_0^4+2(a_2^2-b_2^2+2a_4+2b_1b_3-2a_1a_3)\omega_0^2+a_3^2-b_3^2+2b_2b_4-2a_2a_4>0$, then we have

$$\mathrm{sign}\left\{\mathrm{Re}\left[\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right]_{\tau=\tau_0}\right\}=\mathrm{sign}\left\{\mathrm{Re}\left[\frac{\mathrm{d}\lambda}{\mathrm{d}\tau}\right]^{-1}_{\tau=\tau_0}\right\}=1.$$

Due to Lemma 3, the real part of characteristic root of (8) becomes positive when $\tau>\tau_0$ and the equilibrium becomes unstable. Moreover, a Hopf bifurcation occurs when τ passes through the critical value τ_0 (see [26]).

The above analysis can be summarized into the following proposition.

Proposition 6 *Suppose that $R_0>1+\frac{a\mu}{cs-a\mu}$ and $cs>a\mu$. If conditions (H_1) and (H_2) are satisfied, then the immune–present equilibrium E_2 is asymptotically stable when $\tau<\tau_0$ and unstable when $\tau>\tau_0$. When $\tau=\tau_0$, Hopf bifurcation occurs, that is, a family of periodic solutions bifurcates from E_2 as τ passes through the critical value τ_0.*

6 Numerical Simulations

In this section, we give some numerical examples to support our theoretical analysis. Here, we solve the delay differential equation model numerically by dde23 in MATLAB, which employs the explicit Runge–Kutta method. We first fix the parameters $d=0.5$, $\beta=0.009$, $a=0.1$, $p=0.024$, $k=100$, $u=15$, $c=0.15$, $\mu=0.5$, $q=0.01$ and denote $R_1=1+\frac{a\mu}{cs-a\mu}$. Consider the following special system

$$\begin{cases}
\frac{\mathrm{d}x}{\mathrm{d}t}=s-0.5x-0.009xv+0.01yz,\\
\frac{\mathrm{d}y}{\mathrm{d}t}=0.009xv-0.1y-0.034yz,\\
\frac{\mathrm{d}v}{\mathrm{d}t}=100y-15v,\\
\frac{\mathrm{d}z}{\mathrm{d}t}=0.15y(t-\tau)z(t-\tau)-0.5z.
\end{cases}\tag{11}$$

Then we will vary birth rate of susceptible cells s. By taking $s=0.6$, then $R_0=0.72<1$ and system (11) has the unique equilibrium $E_0=(1.2,0,0,0)$. In this case, E_2 is globally asymptotically stable, see Figure 1.

When $s=1$, then

$$1<R_0=1.2<R_1=1.5$$

and system (11) has two nonnegative equilibria: infection–free equilibrium E_0 and immune–free equilibrium $E_1=(1.66667,1.66667,11.1111,0)$. In this case, E_0 is unstable and we can not simulate it. Equilibrium E_1 is asymptotically stable, see Figure 2.

When $s=1.5$, then

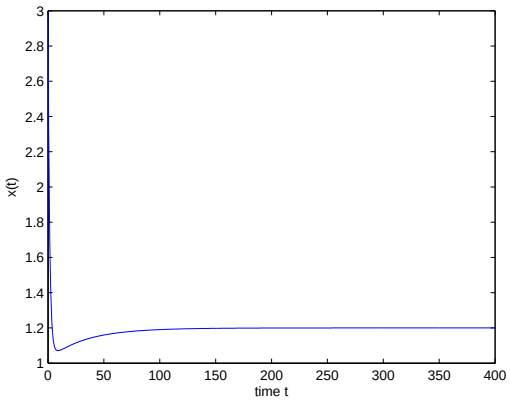
$$R_1=1.8>R_1=1.28571$$

and (11) has three nonnegative equilibria. For immune–present equilibrium

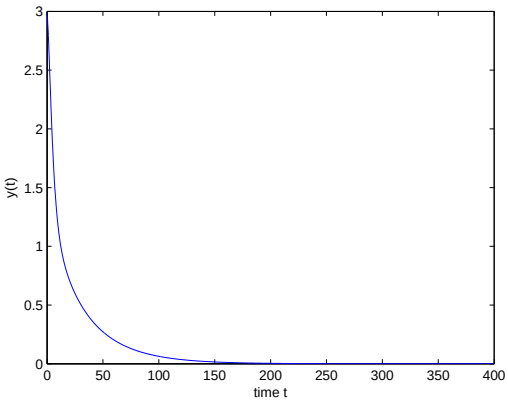
$$E_2=(2.18654,3.33333,22.2222,0.917431)$$

using the software Mathematica, we can easily verify the conditions in Proposition 6 and obtain the critical value $\tau_0=31.6281$. Therefore, the equilibrium E_2 is asymptotically stable when $\tau=10<\tau_0$ (see Figure 3) and unstable when $\tau=80>\tau_0$ (see Figure 4).

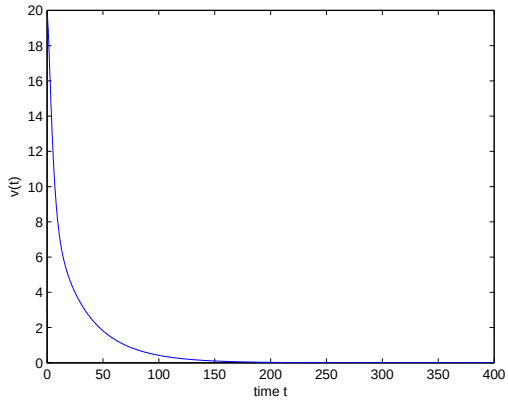
However, according to the previous theoretical analysis, the existence of Hopf bifurcation is only local, which means that periodic oscillations only exist in the small neighborhood of the critical value τ_0. Whether the oscillations exist for arbitrarily large time delay is the global bifurcation problem and it needs further investigation, see, for example [10]. Therefore, it is an interesting question on global continuation of the local Hopf bifurcation obtained in this paper. We leave this for future work.



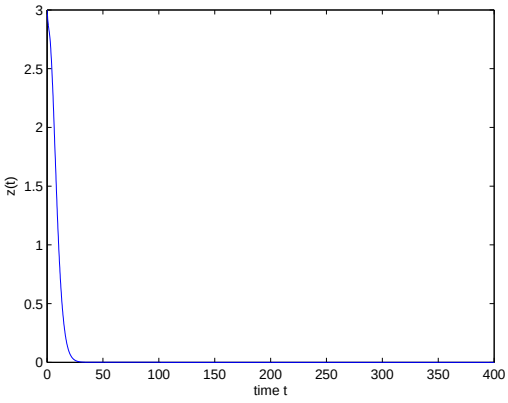
(a) $x-t$



(b) $y-t$



(c) $v-t$



(d) $z-t$

Figure 1: The infection–free equilibrium E_0 is globally asymptotically stable for $s = 0.6$ and $\tau = 2$ with initial value $(3, 3, 3, 3)$.

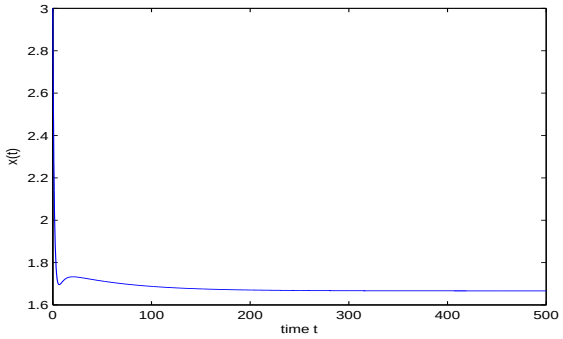
7 Conclusion

Incorporating the time delay and immune responses into viral infection models has been done by many researchers (see [15, 16, 19, 20]). However, it is still an interesting exercise to determine how the intercellular delay affects overall disease progression and, mathematically, how the delay affects the dynamics of systems [27].

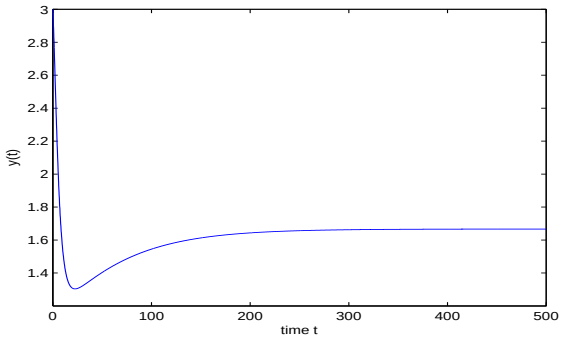
Taking account of the cure of infected cells by the CTL immune responses, our model is more general and the models in [15, 19] are only special cases of system (4) in the present paper.

In this paper, we first proved the positiveness and ultimately boundedness of solutions of the new model. By analyzing the corresponding transcendental characteristic equation and constructing appropriate Lyapunov function, we proved that the infection–free equilibrium is globally asymptotically stable when basic reproduction number $R_0 < 1$. Then, by stability analysis, we obtained the sufficient conditions for stability of two infected equilibria and existence of Hopf bifurcation. Thus, the positive immune–present equilibrium is stable when time delay is smaller than certain critical value τ_0. Numerical simulations confirmed our analysis. Biologically, it implies that time delay may cause the cell and virus populations to oscillate under certain conditions.

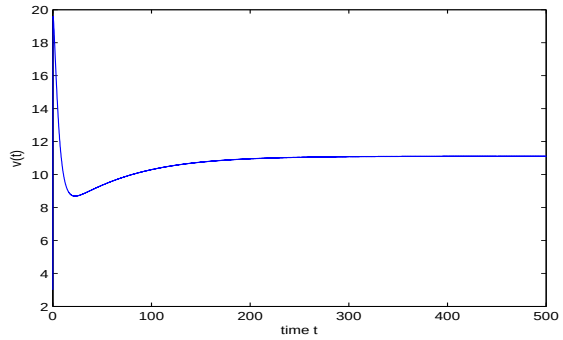
In fact, the actual incidence rate is probably not linear and it is more reasonable to assume that the infection of HBV is given by Beddington–DeAngelis functional response [8, 9, 21]. In addition, viruses can move freely in liver. It is more practical to consider the random mobility for viruses (see [28, 29]). Based on these factors, we will think over the diffusive and delayed HBV infection model with immune responses and Beddington–DeAngelis functional response in future.



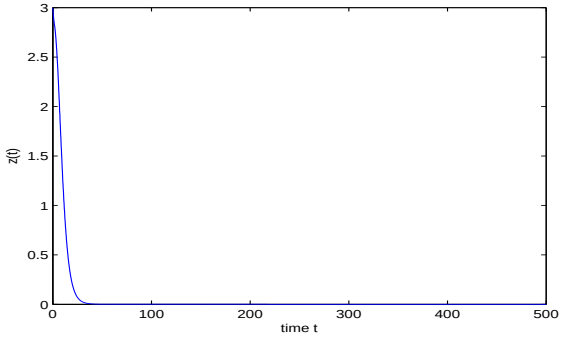
(a) $x-t$



(b) $y-t$

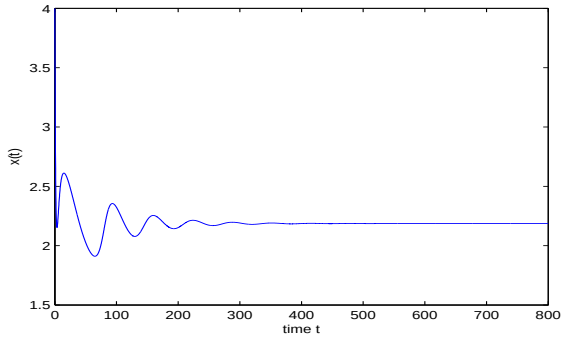


(c) $v-t$

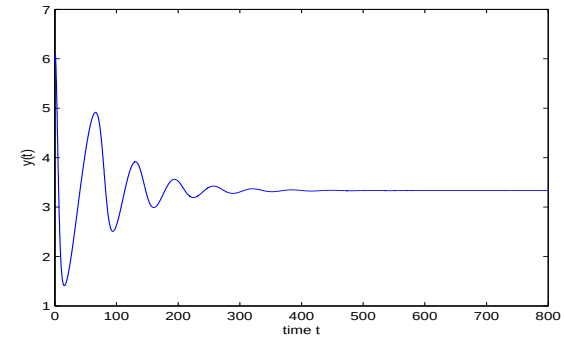


(d) $z-t$

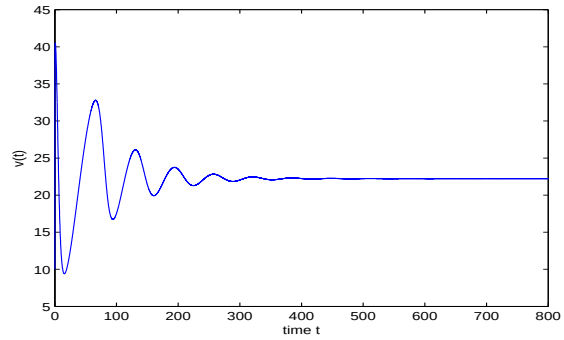
Figure 2: The immune–free equilibrium E_1 is asymptotically stable for $s=1$ and $\tau=2$ with initial value $(3,3,3,3)$.



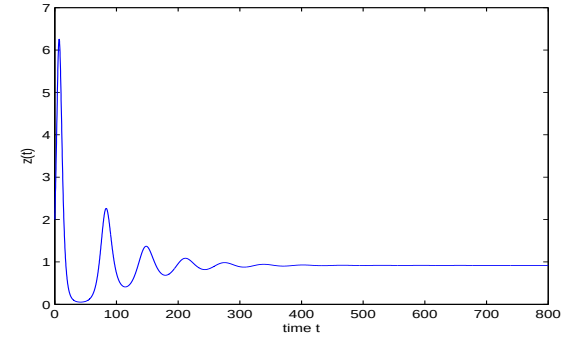
(a) $x-t$



(b) $y-t$

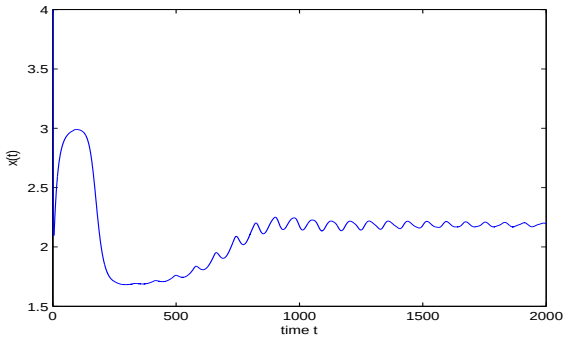


(c) $v-t$

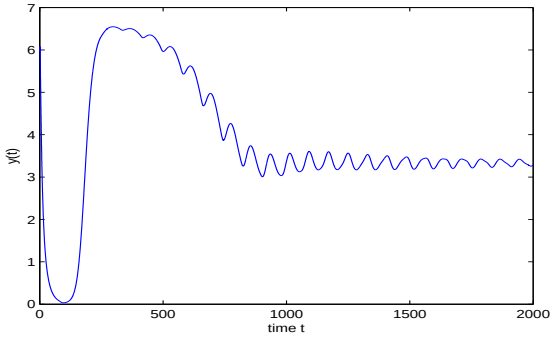


(d) $z-t$

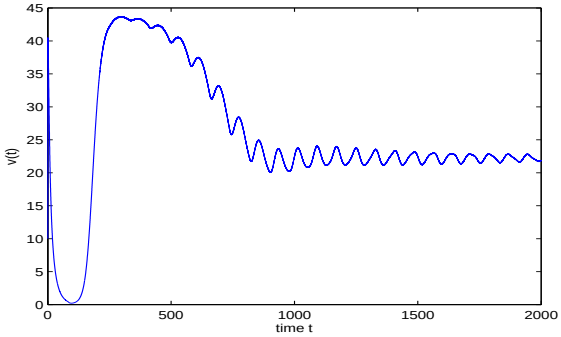
Figure 3: The immune–present equilibrium E_2 is asymptotically stable when $\tau=10<\tau_0$ and $s=1.5$ with initial value $(4,6,10,2)$.



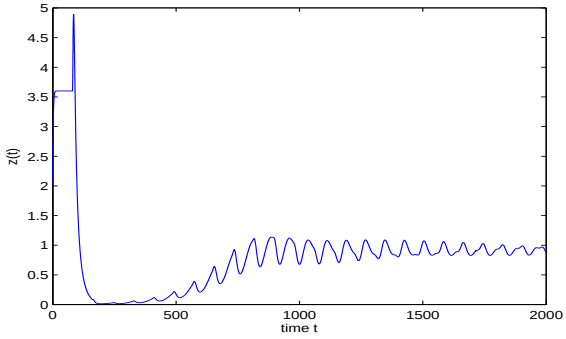
(a) $x-t$



(b) $y-t$



(c) $v-t$



(d) $z-t$

Figure 4: Small–amplitude periodic solution bifurcates from the immune-present equilibrium E_2 when $\tau = 80 > \tau_0$ and $s = 1.5$ with initial value $(4, 6, 10, 2)$.

Acknowledgements: The research was supported by the National Natural Science Foundation of China (grant No. 11301001). It was also supported by the Anhui Provincial Natural Science Foundation (grant No. 1508085QA13) and 1508085MA09, and Natural Science Foundation of Universities of Anhui Province (grant No. KJ2014A003, 2013SQRL030ZD).

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