GLOBAL STABILITY OF A DIFFUSIVE AND DELAYED HBV INFECTION MODEL WITH HBV DNA-CONTAINING CAPSIDS AND GENERAL INCIDENCE RATE

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ABSTRACT. The aim of this paper is to study the dynamics of a new chronic HBV infection model that includes spatial diffusion, three time delays and a general incidence function. First, we analyze the well-posedness of the initial value problem of the model in the bounded domain. Then, we define a threshold parameter $R_0$ called the basic reproduction number and show that our model admits two possible equilibria, namely the infection-free equilibrium $E_1$ as well as the chronic infection equilibrium $E_2$. Further, by constructing two appropriate Lyapunov functionals, we prove that $E_1$ is globally asymptotically stable when $R_0 < 1$, corresponding to the viruses are cleared and the disease dies out; if $R_0 > 1$, then $E_1$ becomes unstable and the equilibrium point $E_2$ appears and is globally asymptotically stable, which means that the viruses persist in the host and the infection becomes chronic. An application is provided to confirm the main theoretical results. Additionally, it is worth saying that, our results suggest theoretically useful method to control HBV infection and these results can be applied to a variety of possible incidence functions presented in a series of other papers.

1. Introduction. As one of the top three infectious diseases in China, Hepatitis B can result in acute or chronic liver diseases and put people at high risk of death from cirrhosis of the liver and liver cancer. Nowadays, it is a major global health problem and is carrying an enormous economic and social burdens. According to World Health Organization (WHO), roughly 0.24 billion people are chronically infected with hepatitis B. Besides, more than 0.78 million people die every year due to complications of hepatitis B, including fatty liver, liver cirrhosis and hepatocellular carcinoma (HCC) [1].

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Hepatitis B is liver infection caused by the hepatitis B virus (HBV), which is an enveloped hepatotropic virus containing a 3.2 kilobase (kb) relaxed circular partially double-stranded (ds) open DNA genome \([32, 41, 21]\). During the replication of HBV, DNA genome is transformed to covalently closed circular DNA (cccDNA) firstly \([19, 9]\). Whereafter, cccDNA can be transcribed into at least four major viral RNAs \([18, 30]\). One of them (pgRNA) and polymerase (P) are encapsidated into the viral nucleocapsid, which means the initiation of genome replication \([18, 17]\). Next, pgRNA convert to a double-stranded HBV DNA through the process of reverse transcription \([19, 26]\). Finally, a part of newly produced core particle is further packed by HBsAg to produce the complete virion \([31]\), another part of core particle is reused for the next cycle of the replication. The life cycle of HBV is schematically outlined in Fig. 1.

Figure 1. Schematic view of the replication process of HBV.

In the last decades, a number of dynamic models with respect to HBV infection have been introduced \([21, 8, 3, 34, 16, 4, 29]\), and these models have been proved to be of use in understanding pathogenesis and designing better treatments protocols. A basic HBV infection model, containing uninfected target cells (presumably hepatocytes, the same as below), infected cells and free viruses, has been analyzed quantificationally by Nowak et al. \([27]\). To accurately determine the dynamics of infection and clearance in three acutely infected chimpanzees, Murray et al. \([26]\) proposed the mathematical model with all intracellular components of HBV infection. In the literature \([25]\), Murray et al. researched a simplified version of the HBV infection model described in \([26]\) and found that the half-life of HBV virions is approximately 4 hours. These models however do not incorporate the uninfected cells and the intracellular HBV DNA-containing capsids simultaneously. For this purpose, Manna and Chakrabarty \([22]\) was the first to contain both uninfected cells and intracellular HBV DNA-containing capsids aside from infected cells and free viruses. The corresponding mathematical model is as follows:

\[
\begin{align*}
\frac{dH(t)}{dt} &= s - \mu H(t) - kH(t)V(t), \\
\frac{dI(t)}{dt} &= kH(t)V(t) - \delta I(t), \\
\frac{dD(t)}{dt} &= aI(t) - \beta D(t) - \delta D(t), \\
\frac{dV(t)}{dt} &= \beta D(t) - cV(t),
\end{align*}
\] (1)
in which state variables $H$, $I$, $D$ and $V$ are the concentrations of uninfected (susceptible) hepatocytes, infected hepatocytes, intracellular HBV DNA-containing capsids and free HBVs, respectively. In the first state equation in (1), healthy hepatocytes are created at a constant rate $s$, either from differentiation of progenitor cells or by direct proliferation of mature hepatocytes [29]. Furthermore, $\mu$ is the death rate of healthy hepatocytes and $k$ is a constant infection rate characterized by the infection efficiency. In the second state equation in (1), $\delta$ represents the natural death rate of infected hepatocytes. In the third state equation in (1), the parameter $a$ indicates the production rate of intracellular HBV DNA-containing capsids per infected hepatocyte, $\beta$ denotes the rate at which these capsids are transmitted to blood which then lead to the growth of free virions, and $\delta$ is per capita death rate for infected hepatocytes. The parameter $c$ that appears in the last state equation in (1) stands for the clearance rate of virions in plasma. It is assumed that all parameters in (1) are strictly positive and $\mu \leq \delta$ [22]. Fig. 2 expounds the connection between four compartments and model parameters.

Note that the forenamed model (1) assumed that the uninfected hepatocytes which are exposed to free HBVs immediately become infected and the maturation process of the capsids is instantaneous despite the fact that this two delays actually exist [21, 22, 36, 13]. To make model (1) much closer to reality, Manna and Chakrabarty [21] incorporated the eclipse phase and capsids maturation period, which are denoted as $\tau_1$ and $\tau_2$ respectively. More specifically, they assumed that the uninfected hepatocytes become actively infected at time $t$ but are infected by free HBVs at time $t - \tau_1$, and the infected cells create new intracellular HBV DNA-containing capsids at time $t$ but are penetrated by viruses at time $t - \tau_2$. Therefore, in the document [21], they considered the following refined model with two time delays:

\[
\begin{align*}
\frac{dH(t)}{dt} &= s - \mu H(t) - kH(t)V(t), \\
\frac{dI(t)}{dt} &= kH(t - \tau_1)V(t - \tau_1) - \delta I(t), \\
\frac{dD(t)}{dt} &= aI(t - \tau_2) - \beta D(t) - \delta D(t), \\
\frac{dV(t)}{dt} &= \beta D(t) - cV(t),
\end{align*}
\]

obtained the equilibrium solutions of system (2) and proved their global stability by constructing Liapunov functionals.
In model (2), the key assumptions are that cells and viruses are well mixed in space at all times, and the mobility of cells and viruses are ignored. Several models [37, 23, 11, 35, 40] have corrected this problem by including a spatial component and adding Fickian diffusion for the virus while assuming that hepatocytes cannot move under normal conditions. Another important feature is the fact that there is a lag between the maturation time of the intracellular HBV DNA-containing capsids and the time of the mature capsids producing free viruses, and some researchers have incorporated the exponentially decay functions during the delays into the viral dynamic models [13, 23, 11, 40, 12]. Besides, the viral infection rate in model (2) is assumed to be bilinear in the free viruses and uninfected cells, which is not very appropriate. As pointed out by Min et al. [24] and Chen et al. [2], the bilinear incidence rate is replaced by standard incidence in [2], by Holling type II functional response in [38], by Beddington-DeAngelis incidence in [5], by Crowley-Martin incidence in [20], by general functional response in [13]. Motivated by above three biological facts, we establish the following diffused HBV model with three time delays and a general incidence rate (excluding bilinear incidence and saturation incidence):

\[
\begin{align*}
\frac{dH}{dt} &= s - \mu H(x,t) - f(H(x,t), I(x,t), V(x,t))V(x,t), \\
\frac{dI}{dt} &= e^{-\alpha_1 s}f(H(x,t - \tau_1), I(x,t - \tau_1), V(x,t - \tau_1))V(x,t - \tau_1) - \delta I(x,t), \\
\frac{dD}{dt} &= a e^{-\alpha_2 s}I(x,t - \tau_2) - \beta D(x,t) - \delta D(x,t), \\
\frac{dV}{dt} &= d_v \Delta V + \beta e^{-\alpha_3 s}D(x,t - \tau_3) - cV(x,t) \\
\end{align*}
\]

for \( t > 0, \ x \in \Omega \), with initial conditions

\[
\begin{align*}
H(x, \theta) &= \varphi_1(x, \theta) \geq 0, \quad I(x, \theta) = \varphi_2(x, \theta) \geq 0, \quad D(x, \theta) = \varphi_3(x, \theta) \geq 0, \\
V(x, \theta) &= \varphi_4(x, \theta) \geq 0, \quad (x, \theta) \in \Omega \times [-\tau, 0], \\
\tau &= \max \{\tau_1, \tau_2, \tau_3\},
\end{align*}
\]

and homogeneous Neumann boundary conditions

\[
\frac{\partial V}{\partial \mathbf{n}} = 0, \quad \text{on} \quad \partial \Omega \times (0, +\infty),
\]

where \( \Omega \) is a connected, bounded open set in \( \mathbb{R}^n \) with smooth boundary \( \partial \Omega \) and \( \frac{\partial}{\partial \mathbf{n}} \) denotes the outward normal derivative on \( \partial \Omega \). The boundary conditions in (5) imply that the virus populations do not move across the boundary \( \partial \Omega \). In biological terms, \( H(x,t), I(x,t), D(x,t) \) and \( V(x,t) \) denote the densities of uninfected cells, infected cells, intracellular HBV DNA-containing capsids and free viruses at position \( x \) and time \( t \), respectively. The diffusion coefficient is indicated by \( d_v \) and \( \Delta = \frac{\partial^2}{\partial x^2} \) is the Laplacian operator. The third delay \( \tau_3 \) represents the time necessary for the newly produced HBV DNA-containing capsids to become free viruses and we assume the surviving rates for the infected cells from time \( t - \tau_1 \) to time \( t \), the immature capsids from time \( t - \tau_2 \) to time \( t \), as well as the immature free viruses from time \( t - \tau_3 \) to time \( t \) obey exponentially decay functions. The biological meanings of all other parameters are the same as those given in (2). As in [23, 11, 14], the general incidence function \( f(H, I, V) \) is assumed to be continuously differentiable in the interior of \( \mathbb{R}^3_+ \) and satisfies the following conditions:
Theorem 2.1. For each $C(\bar{\Omega})$ this solution remains bounded for all $t$.

Proof. For any $u = (\phi_1, \phi_2, \phi_3, \phi_4)^T \in \mathbb{C}$, we define $F = (F_1, F_2, F_3, F_4) : \mathbb{C} \to \mathbb{R}^4$ as follows:

$$F_1(\phi)(x) = s - \mu \phi_1(x, 0) - f(\phi_1(x, 0), \phi_2(x, 0), \phi_4(x, 0)) \phi_4(x, 0),$$
\[ F_2(\phi)(x) = e^{-\alpha_1 \tau_1} f (\phi_1(x, -\tau_1), \phi_2(x, -\tau_1), \phi_4(x, -\tau_1)) \phi_4(x, -\tau_1) - \delta \phi_2(x, 0), \]
\[ F_3(\phi)(x) = a e^{-\alpha_2 \tau_2} \phi_2(x, -\tau_2) - \beta \phi_3(x, 0) - \delta \phi_3(x, 0), \]
\[ F_4(\phi)(x) = \beta e^{-\alpha_3 \tau_3} \phi_3(x, -\tau_3) - c \phi_4(x, 0). \]

It is easy to see that \( F \) is locally Lipschitz in \( \mathbb{C} \). Then we reformulate model (3)-(5) as the following abstract functional differential equation:

\[
\dot{u}(t) = Au + F(u_t), \quad t \geq 0, \quad u_t \in \mathbb{C},
\]

where \( u = (H, I, D, V)^T, \varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4)^T \) and \( Au = (0, 0, 0, d_v \Delta V)^T \). According to standard existence theory [33, 6], it is not hard to deduce that there exists a unique local solution for model (6) on \([0, T_{\text{max}}] \), where \( T_{\text{max}} \) is the maximal existence time for solutions of model (6). In addition, the inequalities \( H(x, t) \geq 0, I(x, t) \geq 0, D(x, t) \geq 0 \) and \( V(x, t) \geq 0 \) are established because the sub-solution of each equation of model (3) are 0.

Next, we show that the solutions of (3)-(5) are bounded. Firstly, we define a new variable:

\[ G(x, t) = e^{-\alpha_1 \tau_1 - \alpha_2 \tau_2} H(x, t - \tau_1 - \tau_2) + e^{-\alpha_2 \tau_2} I(x, t - \tau_2) + \frac{\delta}{2a} D(x, t). \]

From the first three equations of (3), we get

\[
\frac{\partial G(x, t)}{\partial t} = se^{-\alpha_1 \tau_1 - \alpha_2 \tau_2} - \mu e^{-\alpha_1 \tau_1 - \alpha_2 \tau_2} H(x, t - \tau_1 - \tau_2) - \frac{\delta}{2a} e^{-\alpha_2 \tau_2} I(x, t - \tau_2)
\]

\[ \leq se^{-\alpha_1 \tau_1 - \alpha_2 \tau_2} - mG(x, t) \]

\[ \leq s - mG(x, t), \quad \text{since} \quad 0 < e^{-\alpha_1 \tau_1 - \alpha_2 \tau_2} \leq 1, \]

where \( m = \min \{ \mu, \frac{s}{2}, \beta + \delta \} \). Let \( M = \max \{ \frac{\alpha_1}{m}, \max_{x \in \Omega} \{ e^{-\alpha_1 \tau_1 - \alpha_2 \tau_2} \phi_1(x, -\tau_1), e^{-\alpha_2 \tau_2} \phi_2(x, -\tau_2) + \frac{\delta}{2a} \phi_3(x, 0) \} \} \), and thus \( G(x, t) \leq M \), which implies that \( G(x, t) \) is bounded and so are \( H, I \) and \( D \).

Then we can prove that \( V(x, t) \) is bounded. Using the boundedness of \( D \) and model (3)-(5), we obtain the following system

\[
\begin{aligned}
\frac{\partial V}{\partial t} - d_v \Delta V &\leq \beta M e^{-\alpha_3 \tau_3} - cV, \\
\frac{\partial V}{\partial n} &\bigg|_{x \in \partial \Omega} = 0, \\
V(x, 0) &= \varphi_4(x, 0) \geq 0.
\end{aligned}
\]

If \( \tilde{V}(t) \) is a solution to the ordinary differential equation

\[
\begin{aligned}
\frac{d \tilde{V}}{dt} &= \beta M e^{-\alpha_3 \tau_3} - cV, \\
\tilde{V}(0) &= \max_{x \in \Omega} \varphi_4(x, 0).
\end{aligned}
\]

Then for any \( t \in [0, T_{\text{max}}] \), we have \( \tilde{V}(t) \leq \max \{ \frac{\beta M e^{-\alpha_3 \tau_3}}{c}, \max_{x \in \Omega} \varphi_4(x, 0) \} \).

By the comparison principle [28], we get \( V(x, t) \leq \tilde{V}(t) \). Hence,

\[ V(x, t) \leq \max \left\{ \frac{\beta M e^{-\alpha_3 \tau_3}}{c}, \max_{x \in \Omega} \varphi_4(x, 0) \right\}, \quad \forall (x, t) \in \Omega \times [0, T_{\text{max}}]. \]

The above analysis supports the conclusion that \( H(x, t), I(x, t), D(x, t) \) and \( V(x, t) \) are bounded on \( \Omega \times [0, T_{\text{max}}] \). Therefore, we deduce that \( T_{\text{max}} = +\infty \) from the standard theory for semilinear parabolic systems [15]. This completes the proof. \( \square \)
2.2. Basic reproduction number and existence of positive equilibria. In this subsection, we show that model (3)-(5) has two possible equilibria. Moreover, existence of these equilibria is determined by a threshold parameter $R_0$, which is given by

$$
R_0 = \frac{\beta e^{-\alpha_3 \tau_3}}{c} \cdot \frac{ae^{-\alpha_2 \tau_2}}{\beta + \delta} \cdot \frac{f \left( \frac{s}{\mu}, 0, 0 \right) e^{-\alpha_1 \tau_1}}{\delta} = \frac{a\beta e^{-\alpha_1 \tau_1 - \alpha_2 \tau_2 - \alpha_3 \tau_3}}{c\delta (\beta + \delta)} f \left( \frac{s}{\mu}, 0, 0 \right). 
$$

Here, $R_0$ is called the basic reproduction number and describes the average number of new infected cells derived from one infected cell when the free HBVs have just entered the body.

In the expression (7), $\frac{s}{\mu}$ is the average survival time of an infectious cell. During this period a virus-producing cell generates $a$ intracellular HBV DNA-containing capsids per unit time. $\frac{\beta e^{-\alpha_3 \tau_3}}{c}$ gives the amount of free viruses produced from an intracellular HBV DNA-containing capsid during its survival period. $e^{-\alpha_1 \tau_1}, e^{-\alpha_2 \tau_2}$ and $e^{-\alpha_3 \tau_3}$ denote the probabilities of surviving the infected cells from time $t - \tau_1$ to time $t$, the immature capsids from time $t - \tau_2$ to time $t$, as well as the immature free viruses from time $t - \tau_3$ to time $t$, respectively. $\frac{1}{c}$ represents the average life expectancy of a virus and $f \left( \frac{s}{\mu}, 0, 0 \right)$ represents the value of the function $f$ at the beginning of the infection process. By multiplying the above quantities together, we get the expected number of newly infected cells generated by one infected cell, beginning of the infection process. By multiplying the above quantities together, we get the expected number of newly infected cells generated by one infected cell, that is $R_0$. Furthermore, it is important to note the following remark.

**Remark 1.** If no delays are considered ($\tau_1 = \tau_2 = \tau_3 = 0$) or the mortalities during the three delays are ignored ($\alpha_1 = \alpha_2 = \alpha_3 = 0$), our $R_0$ coincides with the basic reproduction number of model (2). Whereas, in presence of the three delays, $R_0$ is a decreasing function of the mortalities. This implies that, any one of the mortalities during the three delays can decrease $R_0$. Hence, ignoring the mortality during the delay in a viral model will overestimate $R_0$. In other words, our $R_0$ is biologically well defined.

To simplify the analysis, we show only the existence conditions of positive homogeneous equilibria of model (3)-(5) and have the following theorem:

**Theorem 2.2.** When $R_0 \leq 1$, the system (3)-(5) admits only an infection-free equilibrium $E_1 = \left( \frac{s}{\mu}, 0, 0, 0 \right)$. When $R_0 > 1$, there is an unique chronic infection equilibrium $E_2 = (H_2, I_2, D_2, V_2)$ with $H_2 \in \left( 0, \frac{s}{\mu} \right)$ and $I_2, D_2, V_2 > 0$, except for $E_1$.

**Proof.** Obviously, model (3)-(5) always has an infection-free equilibrium $E_1$, which represents the state that the cellular infection initiated by HBVs will ultimately die out. To find the positive equilibrium, we study the following system:

$$
\begin{align*}
    s - \mu H - f(H, I, V) V &= 0, \\
    e^{-\alpha_1 \tau_1} f(H, I, V) V - \delta I &= 0, \\
    a e^{-\alpha_2 \tau_2} I - \beta D - \delta D &= 0, \\
    \beta e^{-\alpha_3 \tau_3} D - cV &= 0. \\
\end{align*}
$$

A short calculation gives

$$
V = \frac{\beta e^{-\alpha_3 \tau_3}}{c} D, \quad D = \frac{a e^{-\alpha_2 \tau_2} I}{\beta + \delta} \quad \text{and} \quad s - \mu H - \delta e^{-\alpha_1 \tau_1} I = 0.
$$
This means that we can get the following equation:

\[
    f \left( H, \frac{s - \mu H}{\delta e^{\alpha_1}}, \frac{a\beta e^{-\alpha_1 t - \alpha_2 t_2 - \alpha_3 t_3} (s - \mu H)}{c\delta (\beta + \delta)} \right) = \frac{c\delta (\beta + \delta) e^{\alpha_1 t + \alpha_2 t_2 + \alpha_3 t_3}}{a\beta}.
\]

In order to guarantee \( I = \frac{s - \mu H}{\delta e^{\alpha_1}} \geq 0 \), we must have \( H \leq \frac{s}{\mu} \). Thus there is not equilibrium point if \( H > \frac{s}{\mu} \).

Now, we redefine the function \( g \) on interval \([0, \frac{s}{\mu}]\) as follows:

\[
    g(H) = f \left( H, \frac{s - \mu H}{\delta e^{\alpha_1}}, \frac{a\beta e^{-\alpha_1 t - \alpha_2 t_2 - \alpha_3 t_3} (s - \mu H)}{c\delta (\beta + \delta)} \right) - \frac{c\delta (\beta + \delta) e^{\alpha_1 t + \alpha_2 t_2 + \alpha_3 t_3}}{a\beta}.
\]

From (9), it is easy to show that

\[
    g(0) = -\frac{c\delta (\beta + \delta) e^{\alpha_1 t + \alpha_2 t_2 + \alpha_3 t_3}}{a\beta} < 0 \tag{10}
\]

and

\[
    g \left( \frac{s}{\mu} \right) = f \left( \frac{s}{\mu}, 0, 0 \right) - \frac{c\delta (\beta + \delta) e^{\alpha_1 t + \alpha_2 t_2 + \alpha_3 t_3}}{a\beta}
\]

\[
    = \frac{c\delta (\beta + \delta) e^{\alpha_1 t + \alpha_2 t_2 + \alpha_3 t_3}}{a\beta} (R_0 - 1) > 0, \quad \text{if} \quad R_0 > 1. \tag{11}
\]

Thus, when \( R_0 > 1 \), there exists at least one positive equilibrium point \( E_2 = (H_2, I_2, D_2, V_2) \in \mathbb{R}^4 > 0 \). Next, we show that \( E_2 \) is the unique chronic infection equilibrium of system (3)-(5). Using hypothesis (T1), we have

\[
    g'(H) = \frac{\partial f}{\partial H} - \frac{\mu}{\delta e^{\alpha_1}} \frac{\partial f}{\partial I} - \frac{a\beta \mu e^{-\alpha_1 t - \alpha_2 t_2 - \alpha_3 t_3} \partial f}{c\delta (\beta + \delta)} \frac{\partial f}{\partial V} > 0.
\]

This implies \( g \) is strictly increasing in the interior of the feasible region. Combining (10) and (11), it follows that if \( R_0 > 1 \), there exists a unique chronic infection equilibrium \( E_2 \) with \( H_2 \in \left( 0, \frac{s}{\mu} \right) \) and \( I_2, D_2, V_2 > 0 \). \( \square \)

3. **Stability of the infection-free equilibrium** \( E_1 \). The purpose of this section is to give a rigorous investigation for the local and global stability of the infection-free equilibrium \( E_1 \). First, we analyze the local asymptotic stability of \( E_1 \). To do so, we need to determine the characteristic equation about this point.

Let \( 0 = \eta_1 < \eta_2 < \cdots < \eta_n < \cdots \) be the eigenvalues of the operator \(-\Delta\) on \( \Omega \) with homogeneous Neumann boundary conditions, and denote the eigenfunction space corresponding to \( \eta_i \) in \( C^1(\Omega) \) by \( E(\eta_i) \) for \( i = 1, 2, \ldots \). Let \( X = [C^1(\Omega)]^4 \), \( \{\phi_{ij} : j = 1, \ldots, \dim E(\eta_i)\} \) be an orthonormal basis of \( E(\eta_i) \) and \( X_{ij} = \{c\phi_{ij} : c \in \mathbb{R}^4\} \). Then

\[
    X = \bigotimes_{i=1}^{\infty} X_i, \quad X_i = \bigotimes_{j=1}^{\dim E(\eta_i)} X_{ij}.
\]

Suppose \( E^* = (H^*, I^*, D^*, V^*) \) be any feasible steady state of system (3)-(5), \( E_1 \) or \( E_2 \), and consider the following change of variables:

\[
    Z_1(x, t) = H(x, t) - H^*, \quad Z_2(x, t) = I(x, t) - I^*.
\]
Then by substituting $Z_1(x,t), Z_2(x,t), Z_3(x,t)$ and $Z_4(x,t)$ into model (3) and linearizing, we obtain a new system of the form

\[
\frac{\partial Z_1}{\partial t} = -\left(\mu + \frac{\partial f}{\partial H} V^*\right) Z_1(x,t) - \frac{\partial f}{\partial I} V^* Z_2(x,t)
\]

\[
- \left(\frac{\partial f}{\partial V} V^* + f(H^*, I^*, V^*)\right) Z_2(x,t),
\]

\[
\frac{\partial Z_2}{\partial t} = \frac{\partial f}{\partial H} e^{-\alpha_1 \tau_1} V^* Z_1(x,t) - \frac{\partial f}{\partial I} e^{-\alpha_1 \tau_1} V^* Z_2(x,t) + e^{-\alpha_1 \tau_1} Z_4(x,t - \tau_1)
\]

\[
\cdot \left(\frac{\partial f}{\partial V} V^* + f(H^*, I^*, V^*)\right) - \delta Z_2(x,t),
\]

\[
\frac{\partial Z_3}{\partial t} = a e^{-\alpha_3 \tau_3} Z_2(x,t) - \beta Z_3(x,t) - \delta Z_3(x,t),
\]

\[
\frac{\partial Z_4}{\partial t} = d_0 \Delta Z_4 + \beta e^{-\alpha_3 \tau_3} Z_3(x,t - \tau_3) - c Z_4(x,t).
\]

This new system can be equivalently expressed by

\[
\frac{\partial Z}{\partial t} = Q \Delta Z + B Z(x,t) + C Z(x,t - \tau_1) + L Z(x,t - \tau_2) + N Z(x,t - \tau_3),
\]

where

\[
Q = \text{diag}(0, 0, 0, d_0), \quad B = \begin{pmatrix}
-\mu & \frac{\partial f}{\partial H} V^* & -\frac{\partial f}{\partial I} V^* & 0 \\
0 & 0 & -\delta & 0 \\
0 & 0 & -(\beta + \delta) & 0 \\
0 & 0 & 0 & -c
\end{pmatrix},
\]

\[
C = \begin{pmatrix}
\frac{\partial f}{\partial H} e^{-\alpha_1 \tau_1} V^* \\
\frac{\partial f}{\partial I} e^{-\alpha_1 \tau_1} V^* \\
\frac{\partial f}{\partial H} e^{-\alpha_1 \tau_1} V^* \\
\frac{\partial f}{\partial I} e^{-\alpha_1 \tau_1} V^* + f(H^*, I^*, V^*) e^{-\alpha_1 \tau_1}
\end{pmatrix}, \quad L = \begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}
\]

and

\[
N = \begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{pmatrix}.
\]

Thus, $\lambda$ is an eigenvalue if and only if the matrix $-\lambda I - Q \eta \delta + B + C e^{-\lambda \tau_1} + L e^{-\lambda \tau_2} + N e^{-\lambda \tau_3}$ has determinant zero for all $i \geq 1$, here $I$ denotes $4 \times 4$ identity matrix. In addition, we get the characteristic equation at equilibrium point $E^*$ as follow:

\[
\begin{vmatrix}
\lambda + \mu & \frac{\partial f}{\partial H} V^* \\
0 & -\mu e^{-\tau_1 \lambda_1} V^* - \alpha_1 \frac{\partial f}{\partial I} V^* + \delta & 0 & 0 \\
0 & 0 & 0 & -\frac{\partial f}{\partial I} V^* + f(H^*, I^*, V^*) e^{-\alpha_1 \tau_1} + \lambda + \beta + \delta - \mu
\end{vmatrix} = 0.
\]

The infection free equilibrium $E_1$ is locally asymptotically stable for any time delays $\tau_1, \tau_2, \tau_3 \geq 0$ if $R_0 < 1$ and unstable if $R_0 > 1$.
Proof. Let \((H^*, I^*, D^*, V^*) = \left( \frac{s}{\mu}, 0, 0, 0 \right)\) in (12). It follows that
\[
(\lambda + \mu) \left( \lambda^3 + (2\delta + \beta + d_v\eta_i + c)\lambda^2 + \left( (2\delta + \beta)(d_v\eta_i + c) + \delta\beta + \delta^2 \right)\lambda + (\delta^2 + \delta\beta)(d_v\eta_i + c) - a\beta f \left( \frac{s}{\mu}, 0, 0 \right) e^{-\left( \lambda + \alpha_1 \right)\tau_1 - \left( \lambda + \alpha_2 \right)\tau_2 - \left( \lambda + \alpha_3 \right)\tau_3} \right) = 0.
\]
(13)

Clearly, \(\lambda = -\mu < 0\) is a real root of Eq. (13) for any \(\eta_i\). Then the remaining eigenvalues are determined from the following transcendental equation

\[
\lambda^3 + q_2\lambda^2 + q_1\lambda + q_0 = 0,
\]
where
\[
q_2 = 2\delta + \beta + d_v\eta_i + c, \quad q_1 = (2\delta + \beta)(d_v\eta_i + c) + \delta(\beta + \delta),
\]
\[
q_0 = (\delta^2 + \delta\beta)(d_v\eta_i + c) - a\beta f \left( \frac{s}{\mu}, 0, 0 \right) e^{-\left( \lambda + \alpha_1 \right)\tau_1 - \left( \lambda + \alpha_2 \right)\tau_2 - \left( \lambda + \alpha_3 \right)\tau_3}.
\]
(15)

First we consider the case \(R_0 > 1\). In this case, it’s easy to show that (14) has a positive real root. Indeed, we put

\[
\sigma_1(\lambda) = \lambda^3 + q_2\lambda^2 + q_1\lambda + q_0,
\]
then we have \(\lim_{\lambda \to +\infty} \sigma_1(\lambda) = +\infty\). Since \(\eta_i = 0\) when \(i = 1\), we get \(\sigma_1(0) = c\delta(\beta + \delta)(1 - R_0) < 0\). Therefore, the infection-free equilibrium \(E_1\) is unstable for \(R_0 > 1\).

Now consider the case \(R_0 < 1\). If the condition \(\tau_1 = \tau_2 = \tau_3 = 0\) is also satisfied, the third equation of (15) will be rewritten as
\[
q_0 = (\delta^2 + \delta\beta)(d_v\eta_i + c) - a\beta f \left( \frac{s}{\mu}, 0, 0 \right) = (\delta^2 + \delta\beta) \left[ d_v\eta_i + c(1 - R_0) \right].
\]

It is clear that \(q_2, q_1, q_0 > 0\) due to all parameters of model (3) are positive and \(R_0 < 1\). Additionally,
\[
\begin{vmatrix}
q_2 & 1 \\
q_0 & q_1
\end{vmatrix} = (\beta + \delta)(4\delta d_v\eta_i + 4\delta c + 2\delta^2 + \beta\delta + \lambda^2 + \delta c R_0 + d_v^2 \eta_i^2 + 2d_v\eta_i c) + c(2\delta + c\delta + d_v\eta_i)(\beta^2 + \lambda^2 + d_v\eta_i \delta) + 2d_v\eta_i \delta c > 0.
\]

From the well-known Routh-Hurwitz criterion given in [7], we see that all roots of (14) have negative real parts. Hence, the equilibrium point \(E_1\) is locally asymptotically stable when \(\tau_1 = \tau_2 = \tau_3 = 0\).

Next, let us consider the distribution of the roots of (14) when \(\tau_1, \tau_2, \tau_3 > 0\). Considering the root of Eq. (14) as a purely imaginary number given by \(\lambda = i\omega (\omega > 0)\), plugging into Eq. (14), and separating the real and imaginary parts, we derive that
\[
\begin{cases}
-2(2\delta + \beta + d_v\eta_i + c)\omega^2 + (\beta + \delta)(\delta d_v\eta_i + c\delta) = c\delta(\beta + \delta)R_0 \cos(\omega \tau_1 + \tau_2 + \tau_3), \\
\omega^3 - \left( (d_v\eta_i + c)(\beta + \delta) + \delta(\beta + \delta) \right)\omega = c\delta(\beta + \delta)R_0 \sin(\omega \tau_1 + \tau_2 + \tau_3).
\end{cases}
\]
(16)
Squaring and adding the two equations of (16) gives
\[ \omega^6 + p_1 \omega^4 + p_2 \omega^2 + p_3 = 0, \]
here
\[ p_1 = (d_v \eta + c)^2 + (\beta + \delta)^2 + \delta^2 > 0, \]
\[ p_2 = 2(d_v \eta \delta + c\delta)^2 + 2\delta \beta (d_v \eta + c)^2 + (c\beta + \beta d_v \eta)^2 + (\delta^2 + \delta \beta)^2 > 0, \]
\[ p_3 = (\delta \beta d_v \eta + \delta^2 d_v \eta)^2 + 2c\delta^2 d_v \eta (\beta + \delta)^2 + \epsilon^2 \delta^2 (\beta + \delta)^2 (1 - R_0^2) > 0. \]
Letting \( \psi = \omega^2 \) yields
\[ \psi^3 + p_1 \psi^2 + p_2 \psi + p_3 = 0. \] (17)
Clearly, all real roots of (17) are negative provided \( R_0 < 1 \). Therefore, we conclude that \( E_1 \) is locally asymptotically stable for any time delay \( \tau_1, \tau_2, \tau_3 \geq 0 \) when \( R_0 < 1 \), completing the proof. \( \square \)

Theorem 3.1 only establishes local stability of infection-free equilibrium \( E_1 \). However, the global stability of equilibrium is very useful in researching the fundamental question of whether this equilibrium be induced ultimately. So, in the next content, we focus on the mathematical analysis of the global dynamics of \( E_1 \). Moreover, for the global stability of \( E_1 \), we have the following theorem:

**Theorem 3.2.** If \( R_0 < 1 \), then the infection-free equilibrium \( E_1 \) of model (3)-(5) is globally asymptotically stable.

**Proof.** Define the following Lyapunov functional:
\[
U = \int_\Omega \left\{ H(x,t) - H_1 - \int_{H_1}^{H(x,t)} \frac{f(H_1,0,0)}{f(\xi,0,0)} d\xi + e^{\alpha_1 \tau_1} I(x,t) + \frac{\delta}{a} e^{\alpha_1 \tau_1 + \alpha_2 \tau_2} D(x,t) \right. \\
+ \frac{\delta (\beta + \delta)}{a \beta} V(x,t) e^{\alpha_1 \tau_1 + \alpha_2 \tau_2 + \alpha_3 \tau_3} + \int_{t-\tau_1}^{t} f(H(x,\xi), I(x,\xi), V(x,\xi)) V(x,\xi) d\xi \right. \\
+ \delta e^{\alpha_1 \tau_1} \int_{t-\tau_2}^{t} I(x,\xi) d\xi + \frac{\delta (\beta + \delta)}{a} e^{\alpha_1 \tau_1 + \alpha_2 \tau_2} \int_{t-\tau_3}^{t} D(x,\xi) d\xi \left\} dx,
\] (18)
where \( H_1 = \frac{2}{p} \). Obviously, the summation of the first three terms in the right-hand side of \( U \) is a non-negative number. Indeed, if \( H(x,t) \geq H_1 \), then
\[
\int_{H_1}^{H(x,t)} \frac{f(H_1,0,0)}{f(\xi,0,0)} d\xi \leq \int_{H_1}^{H(x,t)} \frac{f(H_1,0,0)}{f(H_1,0,0)} d\xi = H(x,t) - H_1
\]
with the aid of hypothesis \( (T1) \). If \( H(x,t) < H_1 \) holds, apply similar reasoning to the above formula, we have the same conclusion that the functional \( U \) is non-negative.

For convenience, we will use the following notations: \( w = w(x,t) \) and \( w_{x_i} = w(x,t-\tau_i), i = 1, 2, 3 \) for any \( w \in \{ H, I, D, V \} \). Calculating the time derivative of \( U \) along solutions of system (3)-(5), we obtain
\[
\frac{dU}{dt} = \int_\Omega \left\{ -e^{\alpha_1 \tau_1 + \alpha_2 \tau_2 + \alpha_3 \tau_3} f(H,I,V) - f(H_{\tau_1}, I_{\tau_1}, V_{\tau_1}) V_{\tau_1} + \delta e^{\alpha_1 \tau_1} (I - I_{\tau_2}) \right. \\
+ \left. \frac{\delta (\beta + \delta)}{a} e^{\alpha_1 \tau_1 + \alpha_2 \tau_2} \partial V \right\} dx.
\]
According to the Divergence theorem and the homogeneous Neumann boundary condition (5), we have

$$\int_{\Omega} \Delta V \, dx = \int_{\partial \Omega} \frac{\partial V}{\partial n} \, dx = 0.$$ 

Besides, we use hypothesis (T1) again to note that since the function $f(H,I,V)$ is strictly monotonically increasing with respect to $H$, it follows that

$$\left(1 - \frac{H}{H_1}\right) \left(1 - \frac{f(H_1,0,0)}{f(H,0,0)}\right) \leq 0.$$ 

Thus, we have that if $R_0 < 1$, $\frac{dV}{dt} \leq 0$ for all $H, I, D, V \geq 0$. Furthermore, it is easy to see that for $\frac{dV}{dt} = 0$, then $V = 0$ and $H = \frac{z}{\mu}$ hold. When the conditions $V = 0$ and $H = \frac{z}{\mu}$ are satisfied, combined with system (3)-(5), we have $D = I = 0$.

That is to say, the largest compact invariant set in $\{(H, I, D, V) \in \mathbb{R}_+^4 : \frac{dV}{dt} = 0\}$ is the singleton $E_1$. From LaSalle invariance principle [39], we conclude that the infection-free equilibrium $E_1$ of system (3)-(5) is globally asymptotically stable when $R_0 < 1$. 

\[ \square \]

4. **Global stability of the chronic infection equilibrium $E_2$.** According to the above analysis, we know $E_1$ becomes unstable and the chronic infection equilibrium $E_2$ emerges when $R_0 > 1$. Thus, in this section, we discuss the global stability of $E_2$ by constructing a Lyapunov functional based on the Volterra function

$$R(z) = z - 1 - \ln z.$$ 

It is obvious that the function $R$ attains its strict global minimum at 1 and satisfies $R(1) = 0$. And in the next theorem, we will make use of the following further assumption about $f$:

(T2) \(1 - \frac{f(H,I,V)}{f(H,I_2,V_2)}\) \(\frac{f(H,I_2,V_2)}{f(H,I,V)} - \frac{V}{V_2}\) $\leq 0$, for all $H, I, V > 0$.

**Theorem 4.1.** If $R_0 > 1$ and (T2) hold, then the chronic infection equilibrium $E_2$ of model (3)-(5) is globally asymptotically stable.

**Proof.** Consider the following Lyapunov functional:

$$L(x, t) = \int_{\Omega} \left( L_1(x, t) + L_2(x, t) \right) \, dx,$$
where
\[ L_1(x, t) = H - H_2 - \int_{H_2}^{H} f(H, I_2, V_2) \, d\xi + e^{\alpha_1} R \left( \frac{I_2}{I_2} \right) + \delta e^{\alpha_1} \left( \frac{D_2}{D_2} \right) + \frac{\delta(\beta + \delta)}{\alpha} \left( \frac{V}{V_2} \right) V_2 e^{\alpha_1 + \alpha_2 + \alpha_3} \]
and
\[ L_2(x, t) = f(H, I_2, V_2) V_2 \int_{t-t}^{t} R \left( \frac{f(H, I_2, V_2)}{I_2} \right) d\xi + \delta e^{\alpha_1} \]
Clearly, \( L(x, t) \geq 0 \) with equality holds if and only if \( H = H_2, I = I_2, D = D_2 \) and \( V = V_2 \), showing that \( E_2 \) is the unique global minimum of Lyapunov functional.
Calculating the time derivative of \( L_1(x, t) \) and \( L_2(x, t) \) along solutions of model (3)-(5), we get
\[
\frac{\partial L_1}{\partial t} = \left( 1 - \frac{f(H, I_2, V_2)}{f(H, I_2, V_2)} \right) \frac{\partial H}{\partial t} + e^{\alpha_1} \left( 1 - \frac{I_2}{I_2} \right) \frac{\partial I}{\partial t} + \frac{\delta(\beta + \delta)}{\alpha} \left( \frac{V}{V_2} \right) V_2 e^{\alpha_1 + \alpha_2 + \alpha_3} \left( 1 - \frac{D_2}{D_2} \right) \frac{\partial D}{\partial t} + \frac{\delta(\beta + \delta)}{\alpha} \left( \frac{V}{V_2} \right) V_2 e^{\alpha_1 + \alpha_2 + \alpha_3} \left( 1 - \frac{V_2}{V_2} \right) d\xi \]
(19)
Here, the identities \( s = \mu H_2 + f(H_2, I_2, V_2) V_2 \), \( f(H_2, I_2, V_2) V_2 = \delta e^{\alpha_{1} I_2} \), \( a e^{-\alpha_2 I_2} I_2 = \beta D_2 + \delta D_2 \) and \( \beta e^{-\alpha_2 I} D_2 = c V_2 \) have been used. Consequently, adding (19) and (20), we obtain

\[
\frac{dL}{dt} = \int_\Omega \left( \frac{\partial L_1}{\partial t} + \frac{\partial L_2}{\partial t} \right) d\Omega
\]

where

\[
\frac{dL}{dt} = \int_\Omega \left( \mu H_2 \left( 1 - \frac{H}{H_2} \right) \left( 1 - \frac{f(H_2, I_2, V_2)}{f(H, I, V)} \right) + \delta \frac{(\beta + \delta)}{a} e^{\alpha_1 I_2 + \alpha_2 I_2 + \alpha_3 I_3} \left( 1 - \frac{V}{V_2} \right) \right) d\Omega
\]

and

\[
\frac{dL}{dt} = \int_\Omega \left( \mu H_2 \left( 1 - \frac{H}{H_2} \right) \left( 1 - \frac{f(H_2, I_2, V_2)}{f(H, I, V)} \right) + \delta \frac{(\beta + \delta)}{a} e^{\alpha_1 I_2 + \alpha_2 + \alpha_2 I_2 + \alpha_3 I_3} \left( 1 - \frac{V}{V_2} \right) \right) d\Omega
\]

The hypothesis (T1) implies the function \( f(H, I, V) \) is strictly increasing in \( H \), and so

\[
\left( 1 - \frac{H}{H_2} \right) \left( 1 - \frac{f(H_2, I_2, V_2)}{f(H, I, V)} \right) \leq 0.
\]
On the basis of the assumption (T2), we have
\[ -1 - \frac{V}{V_2} \div \frac{f(H, I_2, V_2)}{f(H, I, V)} + \frac{V}{V_2} \div \frac{f(H, I, V)}{f(H, I, V)} = \left(1 - \frac{f(H, I, V)}{f(H, I_2, V_2)}\right) \left(\frac{f(H, I_2, V_2)}{f(H, I, V)} - \frac{V}{V_2}\right) \leq 0. \]

Using the Neumann boundary condition (5) and the Divergence theorem, we obtain
\[ \int_{\Omega} \Delta V dx = 0 \quad \text{and} \quad \int_{\Omega} \frac{\Delta V}{V} dx = \int_{\Omega} \frac{\|\nabla V\|^2}{V^2} dx \geq 0. \]

Further \( R(z) \geq 0 \) for any \( z > 0 \) implies that \( \frac{dL}{dt} \leq 0 \) with equality if and only if \( H = H_2, I = I_2, D = D_2 \) and \( V = V_2 \). Thus, the largest compact invariant set in \( \{(H, I, D, V) | \frac{dL}{dt} = 0\} \) is the singleton \( E_2 \). By LaSalle invariance principle [10], we show that the chronic infection equilibrium \( E_2 \) is globally asymptotically stable when \( R_0 > 1 \).

5. Numerical simulations. In this section, our object is to apply theoretical results obtained in the Section 3 and 4 to the following delayed reaction-diffusion system:

\[
\begin{align*}
\frac{\partial H}{\partial t} &= s - \mu H(x, t) - \frac{kH(x, t)V(x, t)}{1 + b_1 H(x, t) + b_2 V(x, t)}, \\
\frac{\partial I}{\partial t} &= e^{-\alpha_1 \tau_1} \frac{kH(x, t - \tau_1)V(x, t - \tau_1)}{1 + b_1 H(x, t - \tau_1) + b_2 V(x, t - \tau_1)} - \delta I(x, t), \\
\frac{\partial D}{\partial t} &= a e^{-\alpha_2 \tau_2} I(x, t - \tau_2) - \beta D(x, t) - \delta D(x, t), \\
\frac{\partial V}{\partial t} &= d e \Delta V + \beta e^{-\alpha_3 \tau_3} D(x, t - \tau_3) - c V(x, t),
\end{align*}
\]

with initial conditions
\[ H(x, \theta) = 5 \times 10^8, I(x, \theta) = 1.3 \times 10^7, D(x, \theta) = 2 \times 10^9, V(x, \theta) = 3.6 \times 10^8, \]

for \( x \in [0, 1] \) and \( \theta \in [-\tau, 0] \)

and homogeneous Neumann boundary conditions
\[ \frac{\partial V}{\partial n} = 0, \quad t > 0, \quad x = 0, 1. \]

Obviously, the model (21)-(23), a particular case of model (3)-(5), contains the Beddington-DeAngelis incidence \( \frac{kH}{1 + b_1 H + b_2 V} \) that was used by Yang and Xu [39] in order to study the global stability of viral model with diffusion and delay. In addition, when \( f(H, I, V) = \frac{kH}{1 + b_1 H + b_2 V} \), it is easy to see that the hypotheses (T1) and (T2) are verified. It is worth saying that, from the biological point of view, the basic reproduction number \( R_0 = \frac{a \beta e^{-\alpha_1 \tau_1 - \alpha_2 \tau_2 - \alpha_3 \tau_3}}{c b (\beta + \delta)} \left(\frac{ks}{\mu + \delta h_1}\right) \) of model (21)-(23) is not proportional to \( \frac{s}{n} \), whereas the basic reproduction number \( R_0 = \frac{a \beta s}{\mu c (\beta + \delta)} \) presented in model (2) is proportional to \( \frac{s}{n} \) which denotes the number of all cells in the liver. Thus, compared to system (2), our system describes more realistically the dynamics of HBV infection.

Now, we perform some numerical simulations to illustrate the above main results. First, based on experimental data and literatures [21, 22, 11, 40, 39], we set \( s = \)
Then by the direct computation, we get a unique infection-free equilibrium $E_1$:

$$(H_1, I_1, D_1, V_1) = (2.6 \times 10^9, 0, 0, 0)$$

and $R_0 = 0.285 < 1$. Numerical simulations for $E_1$ are shown in Fig. 3 which show that $E_1$ is asymptotically stable. This confirms the result in Theorem 3.2.

Next, we choose $k = 1.67 \times 10^{-4}$ and do not change the other parameter values. It follows from the direct calculation that $R_0 = 1.587 > 1$. In this case, model (21)-(23) has an infection-free equilibrium $E_1 : (H_1, I_1, D_1, V_1) = (2.6 \times 10^9, 0, 0, 0)$ and a chronic infection equilibrium $E_2 : (H_2, I_2, D_2, V_2) = (1.61 \times 10^9, 2.53 \times 10^7, 4.12 \times 10^9, 9.43 \times 10^8)$. As shown in Fig. 4, $E_2$ is asymptotically stable which confirms our results in Theorem 4.1.

Based upon the above analysis, we know that the extinction and persistence of viral infections crucially depend on the basic reproduction number $R_0$. What is more, it is evident that $R_0$ is a decreasing function on death rates $\alpha_1$, $\alpha_2$ and $\alpha_3$. Hence, the neglect of death rates must result in increase in size of $R_0$, as shown in model (2). In Fig. 5, we remark that $R_0$ becomes large enough when death rates $\alpha_1$, $\alpha_2$ and $\alpha_3$ tend to 0, which confirms the result in Remark 1.

On the other hand, when the basic reproduction number $R_0$ is less than one, the viruses are cleared and the infection dies out (the case when $E_1$ is globally asymptotically stable). Moreover, by the precise expression of $R_0$, we find that we can reduce $R_0$ to below one by increasing delays $\tau_1$, $\tau_2$ and $\tau_3$. Thus, a good strategy to control the HBV should focus on any drugs that can prolong the values of three delays. Numerical simulation for the relationship between $R_0$ and three delays are shown in Fig. 6.
Figure 4. The numerical approximations of system (21)-(23) with parameters $s = 2.6 \times 10^7$, $\mu = 0.01$, $\delta = 0.053$, $a = 150$, $\beta = 0.87$, $c = 3.8$, $d_v = 0.01$, $b_1 = b_2 = 0.01$, $\alpha_1 = 0.2$, $\alpha_2 = 0.28$, $\alpha_3 = 0.1$, $\tau_1 = 10$, $\tau_2 = 0$, $\tau_3 = 0$ and $k = 1.67 \times 10^{-4}$, showing that solution trajectories converge to the chronic infection equilibrium $E_2 : (H_2, I_2, D_2, V_2) = (1.61 \times 10^9, 2.53 \times 10^7, 4.12 \times 10^3, 9.43 \times 10^8)$.

Figure 5. The graphs of the basic reproduction number $R_0$ in terms of some parameters: (a) $R_0$ in terms of $\alpha_1$ and $\alpha_2$, (b) $R_0$ as a function of $\alpha_1$ and $\alpha_3$, and (c) $R_0$ in terms of $\alpha_2$ and $\alpha_3$. Here, $s = 2.6 \times 10^7$, $\mu = 0.01$, $\delta = 0.053$, $a = 150$, $\beta = 0.87$, $c = 3.8$, $b_1 = 0.01$, $\tau_1 = 5.8$, $\tau_2 = 6$, $\tau_3 = 4$ and $k = 2.4 \times 10^{-3}$.

6. Conclusion and discussion. In this paper, based on the fact of HBV infection [19, 25, 22] and motivated by the works [13, 23, 24, 2], we assume that only the viruses move freely in liver, and then establish a 4-dimensional diffusion HBV model with three delays and a general incidence rate. For this mathematical model, we define the basic reproduction number $R_0$ that acts as a threshold to predict whether the disease persist in the host. When the general incidence function $f$ is assumed to meet biologically reasonable conditions (T1) and (T2), we discussed the global stability of the infection-free equilibrium $E_1$ and the chronic infection equilibrium $E_2$ by constructing suitable Lyapunov functionals and using LaSalle invariance principle. More precisely, we have shown that $E_1$ is globally asymptotically stable whenever $R_0 < 1$. In this case, all positive solutions converge to $E_1$. 
and the disease can be eradicated ultimately. When $R_0 > 1$, $E_1$ becomes unstable and there appears a chronic infection equilibrium $E_2$ which is globally asymptotically stable. In this case, all positive solutions converge to $E_2$ and the disease will be persistent in the host. Compared with model (2), these results imply that the diffusion of free viruses and time delays have no effect on the global stability of the HBV infection model under homogeneous Neumann boundary conditions. On the other hand, notice that $R_0$ is a decreasing function of the three delays. Hence, we can reduce the value of $R_0$ to a level lower than one by increasing three delays in an effort to prevent the viruses. Moreover, ignoring the mortalities during the three delays and the third delay in model (3) will overestimate $R_0$. Thus, this study is more realistic and may help to analyze the dynamical behavior of other models including commonly used incidence rates [2, 20, 5, 38].

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