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*Research Article*

# Dynamics of a Diffusive HBV Infection Model with Capsids, Two Delays, and Cell-to-Cell Transmissions

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This article aims to study a hepatitis B virus (HBV) infection model incorporating two nonlinear incidences and spatial diffusion in capsids, virus, and cytotoxic T lymphocyte (CTL) immune response. Three equilibria which are infection-free, immune-free, and infection with CTL immunity are calculated under rational assumptions. Furthermore, two reproduction numbers are verified to assert the global stability of the HBV model. In the end, the theoretical results on HBV dynamics are further illustrated by performing numerical simulations.

## 1. Introduction

Hepatitis B is a disease induced by HBV attacking the hepatocytes [1–3], which has attracted worldwide attention. Mathematical models play an important role in practical applications, such as the Kopel model [4], Hindmarsh–Rose model [5], and Lotka–Volterra model [6], especially in viral infection mechanism, trends, and control strategy of infectious diseases. Recently, Manna and Chakrabarty [7] considered capsids into the HBV infection model and discussed the global properties. It was supposed in above models that the cells and virus are fully mixed in space. Besides, the effect of spatial heterogeneity is neglected. Therefore, the movement of cells and virus is essential. Recently, mathematical models with reaction diffusion have been designed to study its impact of the mobility of cells and viruses [8–10].

Compared with virus-to-cell infection, an available way of virus transmission is cell-to-cell transmission, which is mentioned in [11, 12]. Virus models considering two infection modes have been studied [13, 14]. Meanwhile, the time delay cannot be ignored in numerous biological phenomena. On the basis of the model in [15], Manna et al. [16, 17] introduced HBV models with capsids in which the cell-to-cell transmission has not been included. As discussed in [18], a delayed HBV model presented by Guo et al. [19] has neglected CTL immune response and cell-to-cell transmission. Since then, many complicated dynamical behaviors about delayed HBV infection models are revealed in [20–28]. Thus, it is necessary to introduce a diffused HBV model with two viral infection modes.

Motivated by Shu et al. [14], Manna et al. [8, 15], Connell and Yang [29], Yang and Xu [30], we establish the following diffused HBV model:

$$\begin{aligned}
\frac{\partial P}{\partial t} &= \varrho - \omega P(x,t) - h_1(P(x,t),K(x,t)) - h_2(P(x,t),J(x,t)),\\
\frac{\partial J}{\partial t} &= e^{-m_1\tau_1}\left[h_1\left(P\left(x,t-\tau_1\right),K\left(x,t-\tau_1\right)\right)\right.\\
&\quad \left.+ h_2\left(P\left(x,t-\tau_1\right),J\left(x,t-\tau_1\right)\right)\right] - \sigma J(x,t) - rJ(x,t)H(x,t),\\
\frac{\partial L}{\partial t} &= d_1\Delta L(x,t) + \varepsilon e^{-m_2\tau_2}J\left(x,t-\tau_2\right) - (a+\sigma)L(x,t),\\
\frac{\partial K}{\partial t} &= d_2\Delta K(x,t) + aL(x,t) - cK(x,t),\\
\frac{\partial H}{\partial t} &= d_3\Delta H(x,t) + gJ(x,t)H(x,t) - bH(x,t),
\end{aligned} \tag{1}$$

with initial conditions

$$\begin{aligned}
&P(x,\theta) = \phi_1(x,\theta) \geq 0, J(x,\theta) = \phi_2(x,\theta) \geq 0,\\
&L(x,\theta) = \phi_3(x,\theta) \geq 0, K(x,\theta) = \phi_4(x,\theta) \geq 0,\\
&H(x,\theta) = \phi_5(x,\theta) \geq 0, x \in \overline{\Omega}, \theta \in [-\tau,0], \tau = \max\{\tau_1,\tau_2\},
\end{aligned} \tag{2}$$

and homogeneous Neumann boundary conditions

$$\frac{\partial L}{\partial \overrightarrow{n}} = \frac{\partial K}{\partial \overrightarrow{n}} = \frac{\partial H}{\partial \overrightarrow{n}} = 0, t > 0, x \in \partial\Omega, \tag{3}$$

where $\Omega$ is a bounded domain in $\mathbb{R}^n$ with smooth boundary $\partial\Omega$ and $(\partial/\partial\overrightarrow{n})$ denotes the outward normal derivative on $\partial\Omega$. $\triangle$ is the Laplacian operator where $\Delta = \Sigma_{i=1}^{n}(\partial^2/\partial x_i^2)$. $P(x,t)$, $J(x,t)$, $L(x,t)$, $K(x,t)$, and $H(x,t)$ denote the densities of the uninfected hepatocytes, infected hepatocytes, intracellular HBV DNA-containing capsids, virus, and CTL cells at position $x$ and at time $t$, respectively, and other parameters are described in Table 1.

We assume that the incidences $h_1(P,K)$ and $h_2(P,J)$ satisfy the following conditions:

$(A_1)$ $h_i(P,\zeta)$ is continuously differentiable; $h_i(P,\zeta) > 0$, $P \in (0,\infty), \zeta \in (0,\infty)$; $h_i(P,\zeta) = 0 \Leftrightarrow P = 0$ or $\zeta = 0$.

$(A_2)$ $(\partial h_i(P,\zeta)/\partial P) > 0$ and $(\partial h_i(P,\zeta)/\partial\zeta) > 0$, $\forall P > 0, \zeta > 0, i = 1,2$.

Specifically, the main contributions of this work are as follows. Firstly, the novelty of this model is that it includes two viral transmission modes, two types of delays, and spatial diffusion. Meanwhile, the global stability of feasible equilibrium basis of $(A_1) - (A_3)$ is investigated. Secondly, to understand the viral pathogenesis and disease diffusion better, the spatial effects and Fickian diffusion for capsids, virus, and CTL cells are introduced. Compared with existing works [31], it is more general to consider spatial diffusion in this paper. Thirdly, the cell-to-cell transmission in the HBV model helps to increase $\mathscr{R}_0$. So, the effect of cell-to-cell transmission is assumed as a key factor.

This paper is organized as follows. In Section 2, we study the existence of feasible equilibria which depend on two reproduction numbers. In Section 3, the global stabilities of three equilibria are established. In Section 4, numerical simulations are presented to validate the theoretical results. In Section 5, a summary is given.

## 2. Positivity, Boundedness, and Equilibrium

Let $\mathbb{Y} = C(\overline{\Omega},\mathbb{R}^5)$ be the Banach space with the supremum norm. For $\tau \geq 0$, define $C = C([-\tau,0],\mathbb{Y})$, which is a Banach space of continuous functions from $[-\tau,0]$ into $\mathbb{Y}$ with the norm $\|\varphi\| = \max_{\eta\in[-\tau,0]}\|\varphi(\eta)\|_{\mathbb{Y}}$. If $\gamma > 0$ and $\nu(\cdot)$: $[-\tau,\gamma) \longrightarrow \mathbb{Y}$, then $\nu_t \in C$ is defined by $\nu_t(\kappa) = \nu(t+\kappa), \kappa \in [-\tau,0]$.

**Theorem 1.** *For any given initial condition $\psi \in C$ satisfying (2), there exists a unique nonnegative solution of models (1)–(3) defined on $\overline{\Omega} \times [0,+\infty)$ and this solution remains bounded for all $t \geq 0$.*

*Proof.* For any $\psi = (\psi_1,\psi_2,\psi_3,\psi_4,\psi_5)^T \in C$ and $x \in \overline{\Omega}$, we define $\mathbb{H} = (\mathbb{H}_1,\mathbb{H}_2,\mathbb{H}_3,\mathbb{H}_4,\mathbb{H}_5)$: $C \longrightarrow \mathbb{Y}$ by

$$\begin{aligned}
\mathbb{H}_1(\psi)(x) &= \varrho - \omega\psi_1(x,0) - h_1(\psi_1(x,0),\psi_4(x,0)) - h_2(\psi_1(x,0)\psi_2(x,0)),\\
\mathbb{H}_2(\psi)(x) &= e^{-m_1\tau_1}\left[h_1\left(\psi_1(x,-\tau_1),\psi_4(x,-\tau_1)\right) + h_2\left(\psi_1(x,-\tau_1),\psi_2(x,-\tau_1)\right)\right]\\
&\quad - \sigma\psi_2(x,0) - r\psi_2(x,0)\psi_5(x,0),\\
\mathbb{H}_3(\psi)(x) &= \varepsilon e^{-m_2\tau_2}\psi_2\left(x,-\tau_2\right) - (a+\sigma)\psi_3(x,0),\\
\mathbb{H}_4(\psi)(x) &= a\psi_3(x,0) - c\psi_4(x,0),\\
\mathbb{H}_5(\psi)(x) &= g\psi_2(x,0)\psi_5(x,0) - b\psi_5(x,0).
\end{aligned} \tag{4}$$

Table 1: Definition of parameters in model (1).

| Parameter | Description |
|---|---|
| $d_i, i = 1, 2, 3$ | Diffusion coefficients of capsids, virus, and CTL cells, respectively |
| $\varrho$ | Production rate of uninfected cells |
| $\omega$ | Death rate of uninfected cells |
| $a$ | Replication rate of virus from capsids |
| $\sigma$ | Death rate of capsids and infected cells |
| $c$ | Removal rate of virus |
| $\varepsilon$ | Production rate of capsids from infected cells |
| $r$ | Kill rate of infected cells by CTL cells |
| $g$ | Maturing rate of new CTL cells |
| $b$ | Death rate of CTL cells |
| $m_1$ | Death rate of infected cells during $[t-\tau_1, t]$ |
| $m_2$ | Death rate of virus during $[t-\tau_2, t]$ |
| $\tau_1$ | The time needed for infected cells to produce virions |
| $\tau_2$ | The time in the production of matured capsids |
| $e^{-m_1\tau_1}$ | Probability of surviving during $[t-\tau_1, t]$ |
| $e^{-m_2\tau_2}$ | Probability of survival of immature capsids during $[t-\tau_2, t]$ |

After that, we rewrite models (1)–(3) as follows:

$$\begin{aligned} W'(t) &= \mathbb{B}W + \mathbb{H}(W_t), t > 0, \\ W(0) &= \psi \in \mathbb{Y}, \end{aligned} \tag{5}$$

where $W = (P, J, L, K, H)^T, \psi = (\psi_1, \psi_2, \psi_3, \psi_4, \psi_5)^T$, and $\mathbb{B}W = (0, 0, d_1\Delta L, d_2\Delta K, d_3\Delta H)^T$. Obviously, $\mathbb{H}$ is locally Lipschitz in $\mathbb{Y}$. From [32–34], we deduce that model (4) has a unique local solution on $[0, T_{\max})$, where $T_{\max}$ is the maximal existence time for solution of model (4).

It is obvious that a lower solution of models (1)–(3) is $0 = (0, 0, 0, 0, 0)$. So, we have $P(x,t) \geq 0, J(x,t) \geq 0, L(x,t) \geq 0, K(x,t) \geq 0$, and $H(x,t) \geq 0$.

Let

$$\mathbb{G}_1(x,t) = P(x, t-\tau_1) + e^{m_1\tau_1} J(x,t) + \frac{re^{m_1\tau_1}}{g} H(x,t), \tag{6}$$

and then we can obtain

$$\begin{aligned} \frac{\partial \mathbb{G}_1(x,t)}{\partial t} &= \frac{re^{m_1\tau_1}}{g} d_3\Delta H + \varrho - \omega P(x, t-\tau_1) \\ &\quad - \sigma e^{m_1\tau_1} J(x,t) - \frac{rbe^{m_1\tau_1}}{g} H(x,t) \\ &\leq \frac{re^{m_1\tau_1}}{g} d_3\Delta H + \varrho - \sigma_1 \mathbb{G}_1(x,t), \end{aligned} \tag{7}$$

where $\sigma_1 = \min\{\omega, \sigma, b\}$. Therefore,

$$\mathbb{G}_1(x,t) \leq \max\left\{\frac{\varrho}{\sigma_1}, \max_{x\in\overline{\Omega}}\left\{\psi_1(x,\tau_1) + e^{m_1\tau_1}\psi_2(x,0) + \frac{re^{m_1\tau_1}}{g}\psi_5(x,0)\right\}\right\} = \eta_1, \tag{8}$$

and for $\forall (x,t) \in \overline{\Omega} \times [0, T_{\max})$, $P, J$, and $H$ are bounded.

Using the boundedness of $J$ and models (1)–(3), we obtain

$$\begin{aligned} \frac{\partial L}{\partial t} - d_1\Delta L &\leq \varepsilon e^{-m_2\tau_2}\eta_1 - (a+\sigma)L(x,t), \\ \frac{\partial L}{\partial \vec{n}} &= 0, \\ L(x,0) &= \psi_3(x,0) \geq 0. \end{aligned} \tag{9}$$

If $\overline{L}(t)$ be a solution to the following equation:

$$\begin{aligned} \frac{d\overline{L}}{dt} &= \varepsilon e^{-m_2\tau_2}\eta_1 - (a+\sigma)\overline{L}, \\ \overline{L}(0) &= \max_{x\in\overline{\Omega}} \psi_3(x,0). \end{aligned} \tag{10}$$

Then, we have $\overline{L}(t) \leq \max\left\{(\varepsilon e^{-m_2\tau_2}\eta_1/a+\sigma), \max_{x\in\overline{\Omega}}\{\psi_3(x,0)\}\right\} = \eta_2, \forall t \in [0, T_{\max})$. By the comparison principle [35], $L(x,t) \leq \overline{L}(t)$. Hence,

$$L(x,t) \leq \max\left\{\frac{\varepsilon e^{-m_2\tau_2}\eta_1}{a+\sigma}, \max_{x\in\overline{\Omega}}\{\psi_3(x,0)\}\right\}. \tag{11}$$

Similarly, we have $K(x,t) \le \max\{(a\eta_2/c), \max_{x\in\overline{\Omega}}\{\psi_4(x,0)\}\}$.

Summarizing the inference above and applying [36], we have shown that $P(x,t), J(x,t), L(x,t), K(x,t)$, and $H(x,t)$ are bounded on $\overline{\Omega}\times[0,T_{\max})$. Therefore, by the standard theory for semilinear parabolic systems [37], we have $T_{\max} = +\infty$.

Clearly, model (1) always has an infection-free equilibrium $\widetilde{E}_0 = (P_0, 0, 0, 0, 0)$, where $P_0 = (\varrho/\omega)$. Denote

$$\mathscr{R}_0 = \frac{a\varepsilon e^{-m_1\tau_1 - m_2\tau_2}}{c\sigma(a+\sigma)} \cdot \frac{\partial h_1((\varrho/\omega),0)}{\partial K} + \frac{1}{\sigma} e^{-m_1\tau_1} \cdot \frac{\partial h_2((\varrho/\omega),0)}{\partial J}, \tag{12}$$

which is the basic reproductive number of model (1).

Any equilibrium $E = (P, J, L, K, H)$ of model (1) satisfies the following equations:

$$\begin{aligned} \varrho - \omega P - h_1(P,K) - h_2(P,J) &= 0,\\ e^{-m_1\tau_1}\left(h_1(P,K) + h_2(P,J)\right) - \sigma J - rJH &= 0,\\ \varepsilon e^{-m_2\tau_2} J - (a+\sigma)L &= 0,\\ aL - cK &= 0,\\ gJH - bH &= 0. \end{aligned} \tag{13}$$

If $H = 0$, from model (6), we get

$$J = \frac{(a+\sigma)e^{m_2\tau_2}}{\varepsilon} L, K = \frac{aL}{c}, P = \frac{\varrho}{\omega} - \frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{\varepsilon\omega} L. \tag{14}$$

Define

$$\begin{aligned} \varphi_1(L) = {} & h_1\left(\frac{\varrho}{\omega} - \frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{\varepsilon\omega} L, \frac{aL}{c}\right)\\ & - \frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{\varepsilon} L\\ & + h_2\left(\frac{\varrho}{\omega} - \frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{\varepsilon\omega} L, \frac{(a+\sigma)e^{m_2\tau_2}}{k} L\right). \end{aligned} \tag{15}$$

Then, it follows from $(A_1) - (A_2)$ that $\varphi_1(0) = 0$ and $\varphi_1((s\varepsilon e^{-m_1\tau_1 - m_2\tau_2}/\sigma(a+\sigma))) = -\varrho < 0$. This, together with the expression of $\mathscr{R}_0$ in (12), yields

$$\begin{aligned} \varphi_1'(0) &= \frac{a}{c} \cdot \frac{\partial h_1((\varrho/\omega),0)}{\partial V} + \frac{(a+\sigma)e^{m_2\tau_2}}{\varepsilon} \cdot \frac{\partial h_2((\varrho/\omega),0)}{\partial I} - \frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{\varepsilon}\\ &= \frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{\varepsilon}(\mathscr{R}_0 - 1). \end{aligned} \tag{16}$$

Then, $\varphi_1'(0) < 0$ if $\mathscr{R}_0 > 1$, which implies that there exists $L_1 \in (0, (\varrho\varepsilon e^{-m_1\tau_1 - m_2\tau_2}/\sigma(a+\sigma)))$ such that $\varphi_1(L_1) = 0$. Hence, model (1) has a unique immune-free equilibrium $\widetilde{E}_1 = (P_1, J_1, L_1, K_1, 0)$, where

$$\begin{aligned} P_1 &= \frac{\varrho}{\omega} - \frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}L_1}{\varepsilon\omega}, J_1\\ &= \frac{(a+\sigma)e^{m_2\tau_2}}{k} L_1, K_1 = \frac{aL_1}{c}. \end{aligned} \tag{17}$$

If $H \neq 0$, a short calculation shows that

$$J_2 = \frac{b}{g}, L_2 = \frac{\varepsilon b e^{-m_2\tau_2}}{(a+\sigma)g}, K_2 = \frac{akbe^{-m_2\tau_2}}{c(a+\sigma)g}. \tag{18}$$

Define

$$\varphi_2(P) = \varrho - \omega P - h_1\left(P, \frac{a\varepsilon b e^{-m_2\tau_2}}{c(a+\sigma)g}\right) - h_2\left(P, \frac{b}{g}\right). \tag{19}$$

$H = (\varrho - \omega P - \sigma e^{m_1\tau_1} J/re^{m_1\tau_1} J) \ge 0$ yields $P \le (\varrho - \sigma e^{m_1\tau_1} J/\omega) < (\varrho/d)$. Thus, we have

$$\begin{aligned} &\varphi_2(0) = \varrho > 0, \varphi_2'(P) = -\omega - \frac{\partial h_1(P, V_2)}{\partial P} - \frac{\partial h_2(P, J_2)}{\partial P} < 0,\\ &\varphi_2\left(\frac{\varrho}{\omega}\right) = -h_1\left(\frac{\varrho}{\omega}, \frac{a\varepsilon b e^{-m_2\tau_2}}{c(a+\sigma)g}\right) - h_2\left(\frac{\varrho}{\omega}, \frac{b}{g}\right) < 0. \end{aligned} \tag{20}$$

So, there exists a unique $P_2 \in (0, (\varrho/\omega))$ that satisfies $\varphi_2(P_2) = 0$.

Denote

$$\mathscr{R}_1 = \frac{gJ_1}{b}, \tag{21}$$

which is the CTL immunity reproduction number. Further, from model (6), we can obtain

$$H_2 = \frac{\varrho - \omega P_2 - \sigma e^{m_1\tau_1} J_2}{re^{m_1\tau_1} J_2} = \frac{\sigma}{r}\left(\frac{g(h_1(P_2,K_2) + h_2(P_2,J_2))}{\sigma e^{m_1\tau_1}} - 1\right) = \frac{\sigma}{r}(\mathscr{R}_1 - 1). \tag{22}$$

Thus, if $\mathscr{R}_1 > 1$, model (1) has a unique infection equilibrium with CTL immunity $\widetilde{E}_2 = (P_2, J_2, L_2, K_2, H_2)$, where

$$P_2 \in \left(0, \frac{\varrho}{\omega}\right), J_2 = \frac{b}{g}, L_2 = \frac{\varepsilon b e^{-m_2\tau_2}}{(a+\sigma)g}, K_2 = \frac{a\varepsilon b e^{-m_2\tau_2}}{c(a+\sigma)g}, H_2 = \frac{\sigma}{r}(\mathscr{R}_1 - 1). \tag{23}$$

□

## 3. Stability Analysis

For convenience, for any solution $(P(x,t), J(x,t), L(x,t), K(x,t), H(x,t))$ of model (1), we let

$$\begin{aligned} P(x,t) = P, J(x,t) = J, K(x,t) = K, L(x,t) = L, H(x,t) = H, \\ J(x,t-\tau_2) = J_{\tau_2}, h_1(P(x,t-\tau_1), K(x,t-\tau_1)) = h_1\left(P_{\tau_1}, K_{\tau_1}\right), \\ h_2(P(x,t-\tau_1), J(x,t-\tau_1)) = h_2\left(P_{\tau_1}, J_{\tau_1}\right). \end{aligned} \tag{24}$$

**Theorem 2.** *If $\mathscr{R}_0 \le 1$, then the infection-free equilibrium $\widetilde{E}_0$ is globally asymptotically stable.*

*Proof.* Define a Lyapunov functional

$$\begin{aligned} U_0(t) = \int_\Omega \Bigg\{ & e^{m_1\tau_1} J + \frac{\sigma e^{m_1\tau_1 + m_2\tau_2}}{k} L + \frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{ak} K \\ & + \frac{r e^{m_1\tau_1}}{g} H + \int_{t-\tau_1}^{t} \left(h_1(P(x,\theta), K(x,\theta)) + h_2(P(x,\theta), J(x,\theta))\right) \mathrm{d}\theta \\ & + \sigma e^{m_1\tau_1} \int_{t-\tau_2}^{\infty} J(x,\theta)\mathrm{d}\theta \Bigg\} \mathrm{d}x. \end{aligned} \tag{25}$$

Calculating the time derivative of $U_0(t)$ along the solution, we obtain

$$\begin{aligned} \frac{\mathrm{d}U_0(t)}{\mathrm{d}t} = \int_\Omega \Bigg\{ & \frac{d_1\sigma e^{m_1\tau_1+m_2\tau_2}}{\varepsilon}\Delta L + \frac{d_2\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{a\varepsilon}\Delta K + \frac{d_3 r e^{m_1\tau_1}}{g}\Delta H \\ & + h_1(P,K) - \frac{c\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{a\varepsilon} K - \frac{r b e^{m_1\tau_1}}{g} H \Bigg\} \mathrm{d}x. \end{aligned} \tag{26}$$

Condition $(A_1)$ and the expression of $\mathscr{R}_0$ given in (12) imply that

$$\begin{aligned} & h_1(P,K) - \frac{c\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{a\varepsilon} K \\ & \le \frac{c\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{a\varepsilon} K \left( \frac{a\varepsilon}{c\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}} \cdot \frac{\partial h_1((\varrho/\omega), 0)}{\partial V} - 1 \right) \\ & \le \frac{c\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{a\varepsilon} K(\mathscr{R}_0 - 1). \end{aligned} \tag{27}$$

Using the divergence theorem, we get

$$\int_{\Omega}\Delta L\mathrm{d}x=\int_{\partial\Omega}\frac{\partial L}{\partial\overrightarrow{n}}\mathrm{d}x=0,\ \int_{\Omega}\Delta K\mathrm{d}x=\int_{\partial\Omega}\frac{\partial K}{\partial\overrightarrow{n}}\mathrm{d}x=0,$$
$$\int_{\Omega}\Delta H\mathrm{d}x=\int_{\partial\Omega}\frac{\partial H}{\partial\overrightarrow{n}}\mathrm{d}x=0. \tag{28}$$

Thus, we have

$$\frac{\mathrm{d}U_0(t)}{\mathrm{d}t}\le\int_{\Omega}\left\{\frac{c\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{\varepsilon a}(\mathscr{R}_0-1)K-\frac{rbe^{m_1\tau_1}}{g}H\right\}\mathrm{d}x. \tag{29}$$

Therefore, $(\mathrm{d}U_0(t)/\mathrm{d}t)\le 0$. $(\mathrm{d}U_0(t)/\mathrm{d}t)=0\Leftrightarrow P=P_0$, $J=0, L=0, K=0, H=0$. From LaSalle's invariance principle [38], $\tilde{E}_0$ is globally asymptotically stable when $\mathscr{R}_0\le 1$.

$(A_3)$ Assume that $h_1(P,K)$ and $h_2(P,J)$ satisfy

$$h_1(P_i,K_i)\left(1-\frac{h_1(P,K)P_iK_i}{h_1(P_i,K_i)PK}\right)\left(\frac{h_1(P_i,K_i)PK}{h_1(P,K)P_iK_i}-\frac{K}{K_i}\right)<0,$$
$$h_2(P_i,J_i)\left(1-\frac{h_2(P,J)P_iK_i}{h_2(P_i,J_i)PK}\right)\left(\frac{h_2(P_i,J_i)PK}{h_2(P,J)P_iK_i}-\frac{K}{K_i}\right)<0,\ i=1,2. \tag{30}$$

**Theorem 3.** *If $\mathscr{R}_0>1$, $\mathscr{R}_1\le 1$, and $(A_1)$–$(A_3)$ hold, then the immune-free equilibrium $\tilde{E}_1$ is globally asymptotically stable.*

*Proof.* Let $G(\rho)=\rho-1-\ln\rho$, and we have $G(\rho)\ge 0, \forall\rho>0$, $G(\rho)=0\Leftrightarrow\rho=1$. Define a Lyapunov functional

$$\begin{aligned}U_1(t)=\int_{\Omega}\Bigg\{&P_1G\left(\frac{P}{P_1}\right)+e^{m_1\tau_1}I_1G\left(\frac{J}{J_1}\right)+\frac{re^{m_1\tau_1}}{g}H\\&+\frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{a\varepsilon}V_1G\left(\frac{K}{K_1}\right)\\&+\frac{\sigma e^{m_1\tau_1+m_2\tau_2}}{\varepsilon}L_1G\left(\frac{L}{L_1}\right)\\&+h_1(P_1,K_1)\int_{t-\tau_1}^{t}G\left(\frac{h_1(P(x,\theta),K(x,\theta))}{h_1(P_1,K_1)}\right)\mathrm{d}\theta\\&+h_2(P_1,J_1)\int_{t-\tau_1}^{t}G\left(\frac{h_2(P(x,\theta),J(x,\theta))}{h_2(P_1,J_1)}\right)\mathrm{d}\theta\\&+\sigma e^{m_1\tau_1}\int_{t-\tau_2}^{t}G\left(\frac{J(x,\theta)}{J_1}\right)\mathrm{d}\theta\Bigg\}\mathrm{d}x.\end{aligned} \tag{31}$$

□

Calculating the time derivative of $U_1(t)$ along the solution, we obtain

$$\begin{aligned}\frac{\mathrm{d}U_1(t)}{\mathrm{d}t}=\int_{\Omega}\Bigg\{&\frac{-\omega(P-P_1)^2}{P}+h_1(P_1,K_1)\left[4-\frac{P_1}{P}+\frac{h_1(P,K)P_1}{h_1(P_1,K_1)P}\right.\\&\left.-\frac{h_1(P_{\tau_1},K_{\tau_1})J_1}{h_1(P_1,K_1)J}-\frac{J_{\tau_2}L_1}{J_1L}-\frac{K}{K_1}-\frac{LK_1}{L_1K}+\ln\frac{h_1(P_{\tau_1},K_{\tau_1})}{h_1(P_1,K_1)}+\ln\frac{J_{\tau_2}}{J_1}\right]\\&+h_2(P_1,J_1)\left[4-\frac{P_1}{P}+\frac{h_2(P,J)P_1}{h_2(P_1,J_1)P}-\frac{h_2(P_{\tau_1},J_{\tau_1})J_1}{h_2(P_1,J_1)J}-\frac{J_{\tau_2}L_1}{J_1L}-\frac{K}{K_1}\right.\\&\left.-\frac{LK_1}{L_1K}+\ln\frac{h_2(P_{\tau_1},J_{\tau_1})}{h_2(P_1,J_1)}+\ln\frac{J_{\tau_2}}{J_1}\right]+re^{m_1\tau_1}H\left(J_1-\frac{b}{g}\right)+\frac{re^{m_1\tau_1}}{g}d_3\Delta H\\&+\frac{\sigma(a+\sigma)e^{m_1\tau_1+m_2\tau_2}}{a\varepsilon}\left(1-\frac{K_1}{K}\right)d_2\Delta K\\&+\frac{\sigma e^{m_1\tau_1+m_2\tau_2}}{\varepsilon}\left(1-\frac{L_1}{L}\right)d_1\Delta L\Bigg\}\mathrm{d}x.\end{aligned} \tag{32}$$

By divergence theorem, we get

$$\int_{\Omega} \Delta L \mathrm{d}x = \int_{\partial\Omega} \frac{\partial L}{\partial \vec{n}} \mathrm{d}x = 0, \int_{\Omega} \Delta K \mathrm{d}x = \int_{\partial\Omega} \frac{\partial K}{\partial \vec{n}} \mathrm{d}x = 0,$$

$$\int_{\Omega} \Delta H \mathrm{d}x = \int_{\partial\Omega} \frac{\partial H}{\partial \vec{n}} \mathrm{d}x = 0,$$

$$\int_{\Omega} \frac{\Delta J}{J} \mathrm{d}x = \int_{\Omega} \frac{\|\nabla J\|^2}{J^2} \mathrm{d}x, \int_{\Omega} \frac{\Delta K}{K} \mathrm{d}x = \int_{\Omega} \frac{\|\nabla K\|^2}{K^2} \mathrm{d}x. \tag{33}$$

Thus, we have

$$\begin{aligned}
\frac{\mathrm{d}U_1(t)}{\mathrm{d}t} = \int_{\Omega} \Bigg\{ & \frac{-\omega(P-P_1)^2}{P} - h_1(P_1,K_1)\left[G\left(\frac{P_1}{P}\right) + G\left(\frac{h_1(P_1,K_1)PK}{h_1(P,K)P_1K_1}\right)\right. \\
& \left. + G\left(\frac{h_1\left(P_{\tau_1},K_{\tau_1}\right)J_1}{h_1(P_1,K_1)J}\right) + G\left(\frac{J_{\tau_2}L_1}{J_1L}\right) + G\left(\frac{LK_1}{L_1K}\right)\right] \\
& - h_2(P_1,J_1)\left[G\left(\frac{P_1}{P}\right) + G\left(\frac{h_2(P_1,J_1)PK}{h_2(P,J)P_1K_1}\right) + G\left(\frac{LK_1}{L_1K}\right)\right. \\
& \left. + G\left(\frac{h_2\left(P_{\tau_1},J_{\tau_1}\right)J_1}{h_2(P_1,J_1)J}\right) + G\left(\frac{J_{\tau_2}L_1}{J_1L}\right)\right] \\
& + h_1(P_1,K_1)\left(1 - \frac{h_1(P,K)P_1K_1}{h_1(P_1,K_1)PK}\right)\left(\frac{h_1(P_1,V_1)PK}{h_1(P,K)P_1K_1} - \frac{K}{K_1}\right) \\
& + h_2(P_1,J_1)\left(1 - \frac{h_2(P,J)P_1K_1}{h_2(P_1,J_1)PK}\right)\left(\frac{h_2(P_1,J_1)PK}{h_2(P,J)P_1K_1} - \frac{K}{K_1}\right) \\
& + \frac{rbe^{m_1\tau_1}}{g}(R_1-1)H\Bigg\}\mathrm{d}x - \frac{\sigma(a+\sigma)d_2e^{m_1\tau_1+m_2\tau_2}K_1}{a\varepsilon}\int_{\Omega}\frac{\|\nabla K\|^2}{K^2}\mathrm{d}x \\
& - \frac{\sigma d_1e^{m_1\tau_1+m_2\tau_2}L_1}{\varepsilon}\int_{\Omega}\frac{\|\nabla L\|^2}{L^2}\mathrm{d}x.
\end{aligned} \tag{34}$$

Therefore, using condition $(A_3)$, we have $(dU_1(t)/dt) \le 0$. $(dU_1(t)/dt) = 0 \Leftrightarrow P = P_1, J = J_1, L = L_1, K = K_1, H = 0$. From LaSalle's invariance principle [38], $\widetilde{E}_1$ is globally asymptotically stable when $\mathscr{R}_0 > 1$ and $\mathscr{R}_1 \le 1$. □

**Theorem 4.** *If $\mathscr{R}_1 > 1$ and $(A_1) - (A_3)$ hold, then the infection equilibrium $\widetilde{E}_2$ with CTL immunity is globally asymptotically stable.*

*Proof.* Define a Lyapunov functional

$$
\begin{aligned}
U_2(t) = \int_{\Omega} \Bigg\{ & P_2 G\left(\frac{P}{P_2}\right) + e^{m_1\tau_1} J_2 G\left(\frac{J}{J_2}\right) + \frac{r e^{m_1\tau_1}}{g} H_2 G\left(\frac{H}{H_2}\right) \\
& + \frac{\sigma(a+\sigma) e^{m_1\tau_1 + m_2\tau_2}}{a\varepsilon} K_2 G\left(\frac{K}{K_2}\right) + \frac{\sigma e^{m_1\tau_1 + m_2\tau_2}}{\varepsilon} D_2 G\left(\frac{L}{L_2}\right) \\
& + h_1(P_2, K_2) \int_{t-\tau_1}^{t} G\left(\frac{h_1(P(x,\theta), K(x,\theta))}{h_1(P_2, K_2)}\right) \mathrm{d}\theta \\
& + h_2(P_2, J_2) \int_{t-\tau_1}^{t} G\left(\frac{h_2(P(x,\theta), J(x,\theta))}{h_2(P_2, J_2)}\right) \mathrm{d}\theta \\
& + \sigma e^{m_1\tau_1} J_2 \int_{t-\tau_2}^{t} G\left(\frac{J(x,\theta)}{J_2}\right) \mathrm{d}\theta \Bigg\} \mathrm{d}x.
\end{aligned} \tag{35}
$$

Similarly, we have

$$
\begin{aligned}
\frac{\mathrm{d}U_2(t)}{\mathrm{d}t} = \int_{\Omega} \Bigg\{ & \frac{-\omega(P-P_2)^2}{P} - h_1(P_2, K_2) \left[ G\left(\frac{P_2}{P}\right) + G\left(\frac{h_1(P_2, K_2) PK}{h_1(P, K) P_2 K_2}\right) \right. \\
& \left. + G\left(\frac{h_1\left(P_{\tau_1}, K_{\tau_1}\right) J_2}{h_1(P_2, K_2) J}\right) + G\left(\frac{J_{\tau_2} L_2}{J_2 L}\right) + G\left(\frac{L K_2}{L_2 K}\right) \right] \\
& - h_2(P_2, J_2) \left[ G\left(\frac{P_2}{P}\right) + G\left(\frac{h_2(P_2, J_2) PK}{h_2(P, J) P_2 K_2}\right) + G\left(\frac{L K_2}{L_2 K}\right) \right. \\
& \left. + G\left(\frac{h_2\left(P_{\tau_1}, J_{\tau_1}\right) J_2}{h_2(P_2, J_2) J}\right) + G\left(\frac{J_{\tau_2} L_2}{J_2 L}\right) \right] \\
& + h_1(P_2, K_2) \left(1 - \frac{h_1(P, K) P_2 K_2}{h_1(P_2, K_2) PK}\right) \left(\frac{h_1(P_2, K_2) PK}{h_1(P, K) P_2 K_2} - \frac{K}{K_2}\right) \\
& + h_2(P_2, J_2) \left(1 - \frac{h_2(P, J) P_2 K_2}{h_2(P_2, J_2) PK}\right) \left(\frac{h_2(P_2, J_2) PK}{h_2(P, J) P_2 K_2} - \frac{K}{K_2}\right) \Bigg\} \mathrm{d}x \\
& - \frac{\sigma(a+\sigma) d_2 e^{m_1\tau_1 + m_2\tau_2} K_2}{a\varepsilon} \int_{\Omega} \frac{\|\nabla K\|^2}{K^2} \mathrm{d}x \\
& - \frac{\sigma d_1 e^{m_1\tau_1 + m_2\tau_2} L_2}{\varepsilon} \int_{\Omega} \frac{\|\nabla L\|^2}{L^2} \mathrm{d}x - \frac{r d_3 e^{m_1\tau_1} H_2}{g} \int_{\Omega} \frac{\|\nabla H\|^2}{H^2} \mathrm{d}x.
\end{aligned} \tag{36}
$$

Therefore, $(\mathrm{d}U_2(t)/\mathrm{d}t) \le 0$. $(\mathrm{d}U_2(t)/\mathrm{d}t) = 0 \Leftrightarrow P = P_2$, $J = J_2, L = L_2, K = K_2, H = H_2$. From LaSalle's invariance principle [38], $\tilde{E}_2$ is globally asymptotically stable when $\mathscr{R}_1 > 1$. □

## 4. Numerical Simulations

In this section, we numerically validate the results obtained in Section 3. Let $h_1(P, K) = (\alpha_1 PK/1 + a_1 P + b_1 K)$ and

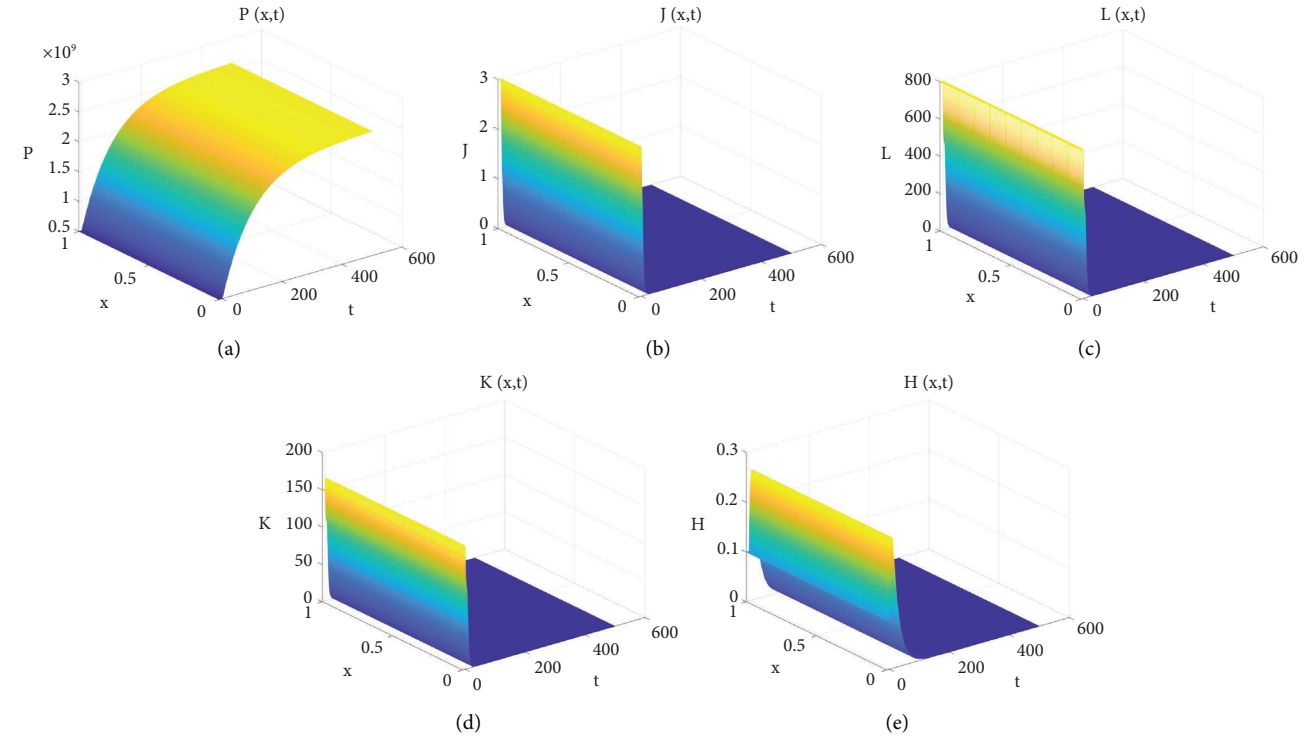



Figure 1: Choosing $\alpha_1 = 3 \times 10^{-13}, \alpha_2 = 2 \times 10^{-12}, b = 0.05, a_1 = 1 \times 10^{-2}, a_2 = 1 \times 10^{-2}$, and $g = 0.12$, we have $\mathscr{R}_0 = 0.0933 < 1$, and $\tilde{E}_0 = (2.6 \times 10^9, 0, 0, 0, 0)$ is globally asymptotically stable.

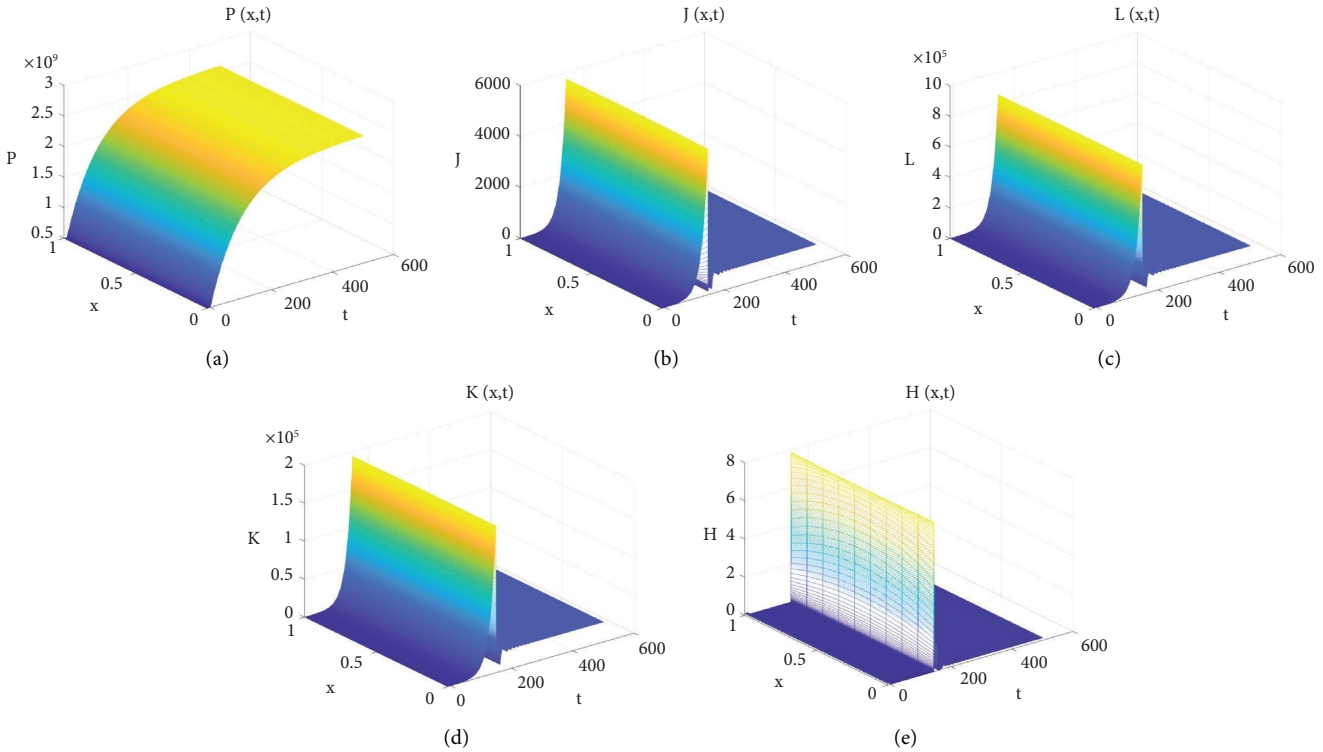



Figure 2: Choosing $\alpha_1 = 1.67 \times 10^{-12}, \alpha_2 = 2 \times 10^{-8}, b = 1.5, a_1 = 1 \times 10^{-4}, a_2 = 1 \times 10^{-7}$, and $g = 0.002$, we have $\mathscr{R}_0 = 933.2817 > 1$ and $\mathscr{R}_1 \leq 1$, and $\tilde{E}_1 = (2.5848 \times 10^9, 750, 1.1594 \times 10^5, 2.6545 \times 10^4, 0)$ is globally asymptotically stable.

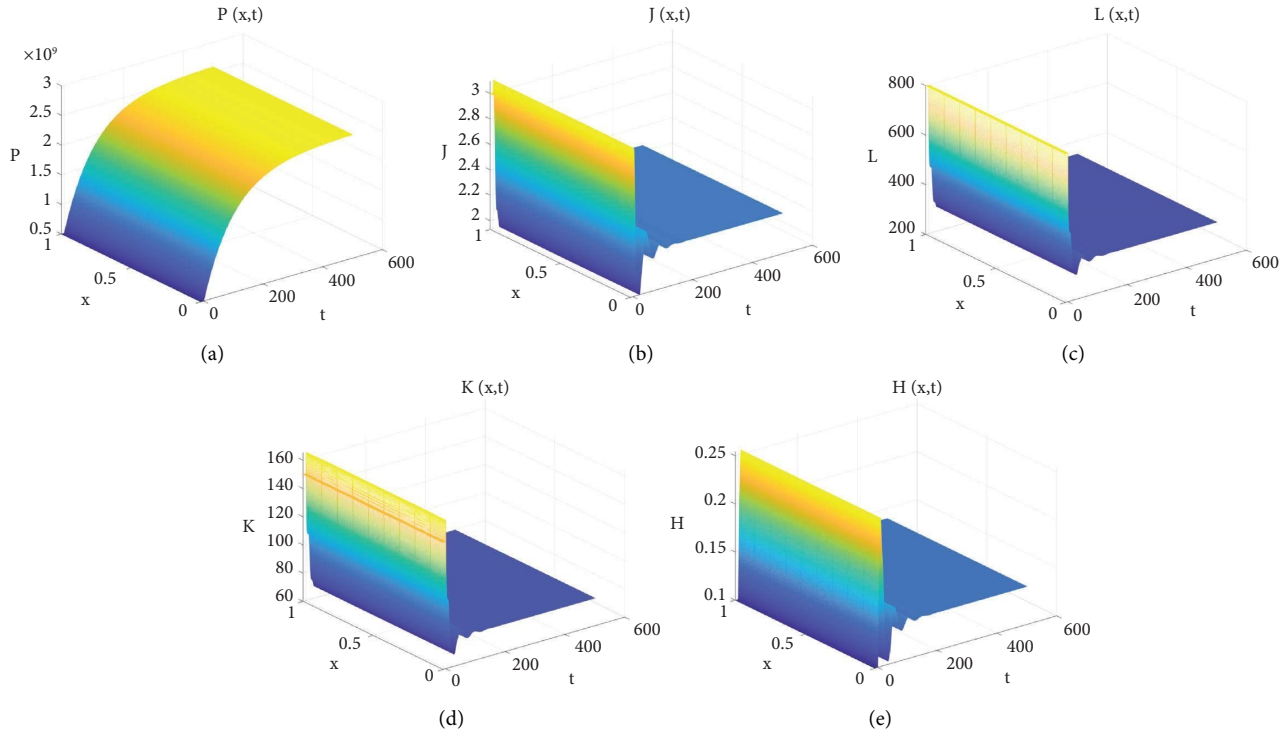



Figure 3: Choosing $\alpha_1 = 1.67 \times 10^{-10}, \alpha_2 = 2 \times 10^{-8}, b = 0.45, a_1 = 1 \times 10^{-6}, a_2 = 1 \times 10^{-7}$, and $g = 0.2$, we have $\mathscr{R}_0 = 933.3826 > 1$ and $\mathscr{R}_1 = 333.3 > 1$, and $\tilde{E}_2 = (2.5850 \times 10^9, 2.25, 347.8225, 79.6331, 0.1395)$ is global asymptotically stable.

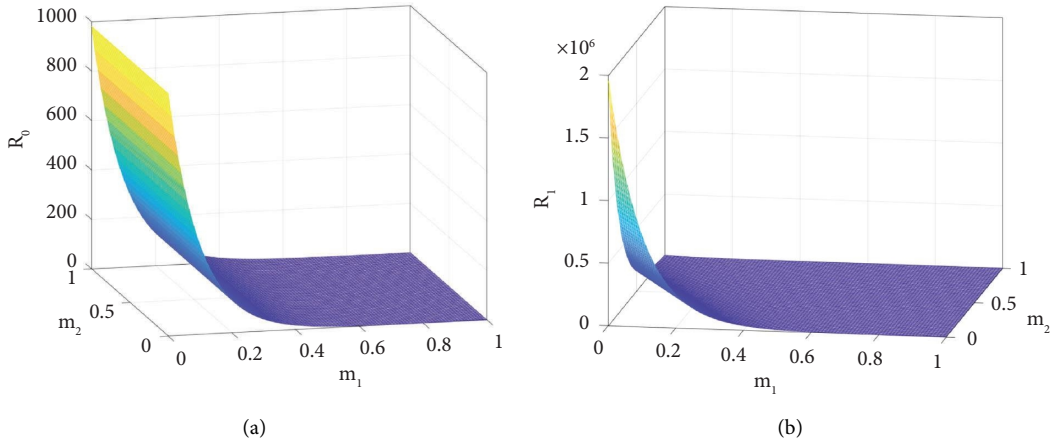


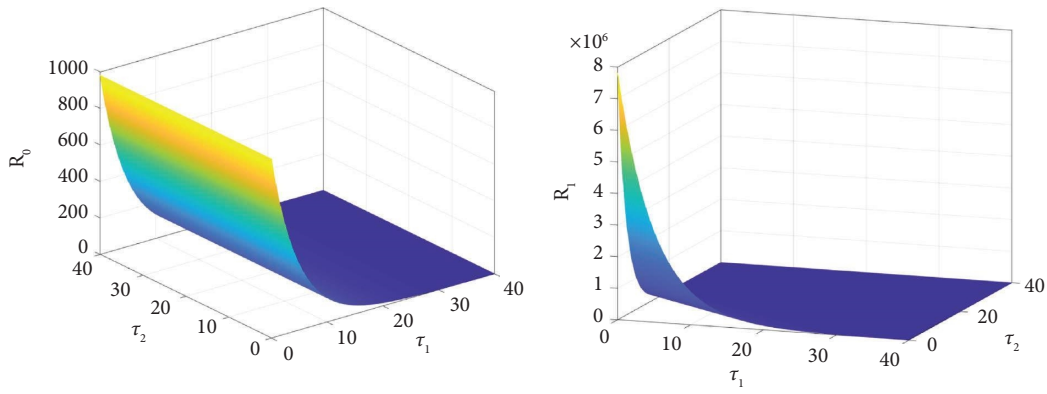

Figure 4: The graphs of $\mathscr{R}_0$ and $\mathscr{R}_1$ in terms of $m_1$ and $m_2$.

$h_2(P, J) = (\alpha_2 PJ/1 + a_2 J)$. One can easily verify that $h_1(P, K)$ and $h_2(P, J)$ satisfy $(A_1) - (A_3)$. Following [7], we select $\varrho = 2.6 \times 10^7, \omega = 0.01, a = 0.87, \sigma = 0.053, c = 3.8, \varepsilon = 150, r = 0.95, m_1 = 0.01, m_2 = 0.01, b_1 = 0.01, d_1 = 0.5, d_2 = 0.1, d_3 = 0.1, \tau_1 = 10, \tau_2 = 5$, and $\Omega = [0, 1]$. Moreover, $\alpha_1, \alpha_2, b, a_1, a_2$, and $g$ are chosen as free parameters. In Figures 1–3, part labels (a), (b), (c), (d), and (e) denote time-series figures of $P(x, t)$, $J(x, t)$, $L(x, t)$, $K(x, t)$, and $H(x, t)$.

$\mathscr{R}_0$ and $\mathscr{R}_1$ also have two impacts on the dynamical behavior of the HBV model. For one thing, we can observe from Figure 4 that $\mathscr{R}_0$ and $\mathscr{R}_1$ become large enough when $m_1$ and $m_2$ approach 0. For another, by the expressions of $\mathscr{R}_0$ and $\mathscr{R}_1$, as we can see in Figure 5, $\mathscr{R}_0$ and $\mathscr{R}_1$ become smaller as $\tau_1$ and $\tau_2$ increase. Therefore, the strategy of controlling HBV should refer to drugs that can lengthen the two delays.

## 5. Discussion

This paper investigated a diffused HBV model with two time delays and CTL immune response, in which two infection modes $h_1(P, K)$ and $h_2(P, J)$ are considered. Under $(A_1) - (A_3)$ on two general incidence functions, the global dynamics of model (1) are established by basic reproduction




(a) (b)

FIGURE 5: The graphs of $\mathscr{R}_0$ and $\mathscr{R}_1$ in terms of $\tau_1$ and $\tau_2$.

numbers $\mathscr{R}_0$ and $\mathscr{R}_1$. If $\mathscr{R}_0 \leq 1$, $\tilde{E}_0$ is globally asymptotically stable; if $\mathscr{R}_0 > 1$ and $\mathscr{R}_1 \leq 1$, $\tilde{E}_1$ is globally asymptotically stable; if $\mathscr{R}_1 > 1$, $\tilde{E}_2$ is globally asymptotically stable. $\mathscr{R}_0$ and $\mathscr{R}_1$ are irrelevant to $d_1$, $d_2$, and $d_3$, Meanwhile, two delays $\tau_1$ and $\tau_2$ have no influence on the global stability of $\tilde{E}_0$, $\tilde{E}_1$, and $\tilde{\tilde{E}}_2$. Hence, the results obtained extend the work in [7].

Numerical simulations graphically show the stability analysis for model (1). It is worth pointing out that $\mathscr{R}_0$ and $\mathscr{R}_1$ are decreasing functions on death rates $m_1$ and $m_2$, delaying $\tau_1$ and $\tau_2$. Therefore, for virus clearance, $\tau_1$ and $\tau_2$ exert a prominent role. This has brought some effects to explore new drugs to stop the virus infection or inhibit virus production. Since $h_1(P, K)$ and $h_2(P, J)$ lead to the virus infection, ignoring one of them would contribute to an underestimated basic reproduction number. Based on this, the strategy of prevention and treatment cannot eliminate virus infection. As discussed in [28, 39, 40], applying these methods to fractional-order or age-structured HBV models is our future work.

## Data Availability

No data were used to support this study.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

HM proved the stability of equilibria. MJ was responsible for validation.

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