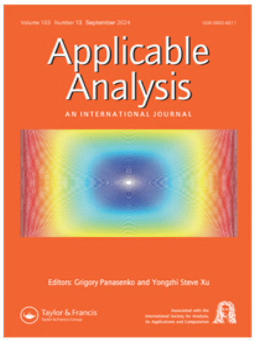

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Analysis of a delayed spatiotemporal model of HBV infection with logistic growth

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ABSTRACT

In this paper, following previous works of ours, we deal with a mathematical model of hepatitis B virus (HBV) infection. We assume spatial diffusion of free HBV particles, logistic growth for both healthy and infected hepatocytes, and use the standard incidence function for viral infection. Moreover, one time delay is introduced to account for actual virus production. Another time delay is used to account for virus maturation. The existence, uniqueness, positivity and boundedness of solutions are established. Analyzing the model qualitatively and using a Lyapunov functional, we establish the existence of a threshold $\mathcal{T}_0$ such that, if the basic reproduction number $\mathcal{R}_0$ verifies $\mathcal{R}_0 \leq \mathcal{T}_0 < 1$, the infection-free equilibrium is globally asymptotically stable. When $\mathcal{R}_0$ is greater than one, we discuss the local asymptotic stability of the unique endemic equilibrium and the occurrence of a Hopf bifurcation. Also, when $\mathcal{R}_0$ is greater than one, the system is uniformly persistent, which means that the HBV infection is endemic. Finally, we carry out some relevant numerical simulations to clarify and interpret the theoretical results.

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1. Introduction

Many people suffer enormously from hepatitis B virus (HBV) infection worldwide. It is a disease affecting the hepatocytes (or the liver cells) [1], which can evolve to acute and chronic stages. The most deadly complications of HBV infection are hepatocellular carcinoma, cirrhosis and liver failure [2]. According to the World Health Organization (WHO), more than 350 million people have chronic HBV infection, and about 600,000 people die every year due to its above mentioned complications [3]. It is now well known that mathematical models can contribute to a better understanding of HBV infection in order to design good strategies for its treatment.

The modeling of processes in a viral infection mainly takes into account: the dynamics of target cells, the viral transmission pathways and the production of free virions. Viral transmissions can occur by different routes, including cell-to-virus transmission, direct cell-to-cell contacts with neighboring cells or mitotic transmission mechanism [4]. It seems reasonable and biologically more meaningful to assume, as in most biological processes, that the different stages of the evolution of HBV in the hepatocytes do not take place at the same time. In order to take into consideration the time necessary to observe the production of new virions after viral entry into a target hepatocyte, mathematical models with time delays have been proposed [5–7]. Dahari and co-workers [8] proposed a basic model

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of hepatitis B virus dynamics with logistic hepatocytes proliferation and noncytolytic loss of infected hepatocytes. In [4], the authors extended the basic model proposed in [8] by incorporating a saturated infection response rate, and a discrete intracellular delay. For the model obtained, they investigated the global asymptotic stability of equilibria by using the Lyapunov method, established the occurrence of a Hopf bifurcation, determined conditions for the permanence of the model, and the length of the delay to preserve stability. Tridane and his collaborators [9] studied the dynamical behavior of HBV infection model with logistic hepatocytes proliferation, antiviral therapy and CTL immune defense delay. The three models mentioned above assume that cells and free viruses are well mixed in the domain with no spatial variations, and they ignored the mobility of cells and free virus particles, whereas the mobility of cells or organisms plays an important role in many biological phenomena [10]. Wang et al. [6] considered a time delay between the infection of a hepatocyte and the production of new virions, and they studied the asymptotic stability of equilibria of the model obtained. For the same model, the traveling wave solutions results were established by Gan and co-workers [11]. Xu and Ma [7] studied the global dynamics of an HBV model with a saturation response and a time delay for virus production. Zhang and Xu [12] investigated a delayed HBV diffusive model with antibody immune response. Yang and Xu [13] relied on the works by Zhu and Zou [14] and Wang et al. [15] to study a diffusive delayed model with Beddington-DeAngelis incidence function and cytotoxic T lymphocytes immune response. Hattaf and Yousfi [16] considered a general HBV model, with spatial diffusion, a general incidence rate and two time delays. Dixit et al. [5] estimated that the time delay for virus production is approximately one day.

In our earlier work [17], based on some previous papers [18–20], we formulated and completely analyzed the following nonlinear PDE model with a logistic growth of hepatocytes and a standard incidence function for describing HBV infection:

$$\begin{cases} \dfrac{\partial H}{\partial t} = s_0 - d_1 H(x,t) + r_1 H(x,t)\left(1 - \dfrac{H(x,t)+I(x,t)}{K_H}\right) - \dfrac{\alpha H(x,t)V(x,t)}{H(x,t)+I(x,t)}, \\ \dfrac{\partial I}{\partial t} = \dfrac{\alpha H(x,t)V(x,t)}{H(x,t)+I(x,t)} - \delta I(x,t) + r_2 I(x,t)\left(1 - \dfrac{H(x,t)+I(x,t)}{K_H}\right), \\ \dfrac{\partial V}{\partial t} = D\Delta V(x,t) + kI(x,t) - \mu V(x,t) - \dfrac{\alpha u H(x,t)V(x,t)}{H(x,t)+I(x,t)}, \end{cases} \tag{1}$$

where $t \geq 0$ denotes time and $x = (x_1, x_2, x_3)$ is a position in Ω, a subset of $\mathbb{R}^3$ representing the liver. $H(x,t), I(x,t)$ and $V(x,t)$ stand for the densities of healthy hepatocytes, infected hepatocytes and free HBV particles at position x and time t, respectively. All the parameters are assumed to be positive constants and independent of the position in the liver. Healthy hepatocytes are fabricated at rate s_0, perish at rate $d_1 H$ and become infected at rate $\alpha HV/(H+I)$. They are assumed to grow logistically, with homeostatic carrying capacity K_H. r_1 is the maximal per capita growth rate or the proliferation rate. Infected hepatocytes die at rate δ per day so that $1/\delta$ is the life-expectancy of HBV infected hepatocytes. r_2 is the proliferation rate or maximal rate of growth per capita of HBV infected hepatocytes. Free viruses are liberated from infected hepatocytes at rate kI and die at rate μV. The population of virions decreases due to the infection at the rate $\alpha u HV/(H+V)$, where $u \in [0,1]$ is a modification parameter. The motion of the virus follows the Fickian diffusion; D is the diffusion coefficient. $\Delta V = \sum_{i=1}^{n} \partial^2 V/\partial x_i^2$, $n = 1, 2, 3$, is the Laplace operator. The PDE system (1) is supplemented by the Neumann homogeneous boundary condition:

$$\frac{\partial V}{\partial \eta} = 0 \quad \text{on } \partial\Omega \times [0,T], \tag{2}$$

where $\frac{\partial}{\partial \eta}$ stands for the outward normal derivative on $\partial\Omega$, and the following initial conditions

$$H(x,0) = H_0(x), \quad I(x,0) = I_0(x), \quad V(x,0) = V_0(x) \quad \text{in } \Omega. \tag{3}$$

It is worth mentioning that, in a recent work [21], we proposed two non-standard finite difference schemes for PDE system (1), and analyzed their dynamic properties. Then, to achieve the main objective of this study, the initial boundary value problem (1)–(3) will be extended to incorporate two time delays.

In this paper, motivated by the works in [6,7,22], we consider the following partially degenerate delayed reaction-diffusion system:

$$\begin{cases} \dfrac{\partial H}{\partial t} = s_0 - d_1 H(x,t) + r_1 H(x,t)\left(1 - \dfrac{H(x,t)+I(x,t)}{K_H}\right) - \dfrac{\alpha H(x,t)V(x,t)}{H(x,t)+I(x,t)}, \\ \dfrac{\partial I}{\partial t} = \mathrm{e}^{-\gamma_1\tau_1}\dfrac{\alpha H(x,t-\tau_1)V(x,t-\tau_1)}{H(x,t-\tau_1)+I(x,t-\tau_1)} - \delta I(x,t) + r_2 I(x,t)\left(1 - \dfrac{H(x,t)+I(x,t)}{K_H}\right), \\ \dfrac{\partial V}{\partial t} = D\Delta V(x,t) + kI(x,t-\tau_2)\,\mathrm{e}^{-\gamma_2\tau_2} - \mu V(x,t) - \dfrac{\alpha u H(x,t)V(x,t)}{H(x,t)+I(x,t)}, \end{cases} \tag{4}$$

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

$$\begin{aligned} &H(x,\theta) = \phi_1(x,\theta) \geq 0, \qquad I(x,\theta) = \phi_2(x,\theta) \geq 0, \\ &V(x,\theta) = \phi_3(x,\theta) \geq 0, \qquad x \in \overline{\Omega},\ \theta \in [-\tau, 0],\ \tau = \max\{\tau_1,\tau_2\} \end{aligned} \tag{5}$$

and homogeneous Neumann boundary condition

$$\frac{\partial V}{\partial \eta} = 0 \quad \text{on } \partial\Omega \times (0,T). \tag{6}$$

We assume as in [23] that at time $t-\tau_1$, the virus contacts a healthy hepatocyte and the cell actively evolves at the infected state at time t. That is, the first parameter τ_1 denotes the time delay for new virus particles production. Note that the hepatocytes that are infected at time t are not those that were infected at time $t-\tau_1$, but rather those that have been added at this time. Also, of the $\frac{\alpha H(x,t-\tau_1)V(x,t-\tau_1)}{H(x,t-\tau_1)+I(x,t-\tau_1)}$ infected hepatocytes added at time $t-\tau_1$, only a fraction $\mathrm{e}^{-\gamma_1\tau_1}$ will be, in life at time t, able to produce free virions. This infers that, from time $t-\tau_1$ to time t the probability of newly surviving produced virions is given by the quantity $\mathrm{e}^{-\gamma_1\tau_1}$. γ_1 denote the death rate for infected hepatocytes but not yet producing free liver virions. The last time parameter τ_2 is the maturation time of newly produced virions. The quantity $\mathrm{e}^{-\gamma_2\tau_2}$ is the probability of survival of immature virions, so that the $1/\gamma_2$ is the average life time of an immature virus, with γ_2 the death rate of immature virions newly produced. Now, it is worth noting that as the total number of hepatocytes, $H+I$, approaches the carrying capacity K_H, one assumes proliferation slows down thanks to a homeostasis mechanism in which only the total hepatocytes number matters, not whether they are infected [8]. The use of the standard incidence function is due to the fact that an average human liver is constituted of billions of hepatocytes [24]. The rate $u\alpha HV/(H+I)$, which corresponds to the decreasing number of free virions population due to the infection, describes the absorption phenomenon [25]. Epidemiologically, the force of infection by virions denoted by $\alpha V/(H+I)$ means that for $V=0$, this force of infection is zero. This indicates that the HBV pathogenesis cannot spread on the human liver if there is no infection. As noted in [18], it is worth recalling that one advantage of the standard incidence function is that it eliminates the biologically unrealistic dependence of the susceptibility to HBV infection on the liver mass that occurs when a mass action function is assumed for describing HBV infection. The justification of the assumption concerning the use of logistic functions to describe the growth of healthy and infected hepatocytes has been emphasized in [19]. For the analysis of the model obtained, we assume that the domain Ω is connected and bounded in $\mathbb{R}^3$ and that its boundary, $\partial\Omega$, is smooth. We also assume that the functions $\phi_i(x,\theta)(i=1,2,3)$ are Hölder continuous in $\overline{\Omega}\times[-\tau,0]$ and ϕ_3 satisfies the compatibility condition $\partial\phi_3/\partial\eta = 0$ on $\partial\Omega\times[-\tau,0]$. The homogeneous Neumann condition (6) means that free virions do not move across the boundary of the liver.

The remainder of the paper is outlined as follows. In Section 2, by using the parabolic maximum principle combined with other relevant arguments from functional analysis, we prove that there exists a unique bounded positive global solution to the model considered. Section 3 is devoted to the local stability analysis of equilibria and to the Hopf bifurcation of the endemic equilibrium. The main concern of Section 4 is the global stability of the steady states. Numerical simulations are performed in Section 5 to illustrate the theoretical results. We conclude the work in Section 6.

2. Positivity, boundedness, existence and uniqueness of solution

In this Section, we mainly use the techniques set up in [18], to study the positivity, boundedness, existence and uniqueness of the solution to PDE-model problem (4)–(6). Let $\mathbb{X} = C(\bar{\Omega}, \mathbb{R}^3)$ be a Banach space of continuous functions from $\bar{\Omega}$ to $\mathbb{R}^3$ and $\mathcal{C} = C([-\tau, 0], \mathbb{X})$ be the Banach space of continuous functions from $[-\tau, 0]$ to $\mathbb{X}$ equipped with the usual supremum norm. We will identify an element $\phi \in \mathcal{C}$ as a function from $\bar{\Omega} \times [-\tau, 0]$ to $\mathbb{R}^3$ defined by $\phi(x, s) = \phi(s)(x)$. Also, we define $\omega_t \in \mathcal{C}$ by $\omega_t(s) = \omega(t + s), s \in [-\tau, 0]$ for any continuous function $\omega : [-\tau, \tau_0) \to \mathbb{X}$, where $\tau_0 > 0$. We further assume that the initial conditions of system (4) satisfy:

$$\begin{aligned} &\phi_1(x,\theta)>0, \quad \phi_2(x,\theta)>0, \quad \phi_3(x,\theta)>0, \\ &K_H \geq N_0(x,\theta) = \phi_1(x,\theta) + \phi_2(x,\theta) > C, \quad x \in \bar{\Omega},\ \theta \in [-\tau, 0], \end{aligned} \tag{7}$$

where C is a positive real constant. Assumption (7) means that we are not interested by the initial processes of infection but by HBV pathogenesis. The boundary condition (6) implies that free virus particles do not move across the boundary $\partial\Omega$.

Theorem 2.1: *For any given initial data $\phi \in \mathcal{C}$ satisfying the condition* (7)*, there exists a unique solution of the PDE problem* (4)–(6) *defined on* $[0, \infty)$*, and this solution remains positive and bounded for all* $t \geq 0$.

To prove Theorem 2.1, we shall make use of the following result, which is an immediate consequence of the positivity lemma for parabolic equations, see [26, Lemma 2.2.1] or an immediate consequence of the maximum principle for parabolic equations, see [27, from p.187] (see also [28] for other possible methods).

Lemma 2.2: *Let L be an elliptic operator, for instance $L = \Delta$. If u is continuous in $\Omega \times (0, T)$ and*

$$\begin{cases} \dfrac{\partial u}{\partial t} - Lu = f(u) \leq g(u), & \text{in } \Omega \times (0, T), \\ \dfrac{\partial u}{\partial \eta} = 0 \leq h, & \text{on } \partial\Omega \times (0, T), \\ u = u_0 \leq l, & \text{in } \Omega \end{cases}$$

and w is a continuous solution of:

$$\begin{cases} \dfrac{\partial w}{\partial t} - Lw = g(w), & \text{in } \Omega \times (0, T), \\ \dfrac{\partial w}{\partial \eta} = h, & \text{on } \partial\Omega \times (0, T), \\ w = l, & \text{in } \Omega, \end{cases}$$

then

$$u \leq w, \quad \text{in } \overline{\Omega} \times [0, T).$$

Proof: Define $y = u - w$. Then, it follows that y satisfies:

$$\begin{cases} \dfrac{\partial y}{\partial t} - Ly = f(u) - g(w) \leq 0, & \text{in } \Omega \times (0, T), \\ \dfrac{\partial y}{\partial \eta} = -h \leq 0, & \text{on } \partial\Omega \times (0, T), \\ y = u_0 - l \leq 0, & \text{in } \Omega. \end{cases}$$

Then, the positivity lemma or the maximum principle guarantees that $y \leq 0$ and therefore $u \leq w$ and the proof is done. ■

Proof of Theorem 2.1: Define $\mathbb{H} = \{(\phi_1, \phi_2, \phi_3) \in \mathcal{C} : \phi_1(\cdot, \theta) \geq C>0, \phi_2(\cdot, \theta) \geq C>0, \theta \in [-\tau, 0]\}$. Then for any initial conditions $\phi = (\phi_1, \phi_2, \phi_3)^T \in \mathbb{H}$ and $x \in \bar{\Omega}$, we define $F = (F_1, F_2, F_3) : \mathbb{H} \to \mathbb{X}$ by

$$F_1(\phi)(x) = s_0 - d_1\phi_1(x, 0) + r_1\phi_1(x, 0)\left(1 - \frac{\phi_1(x, 0) + \phi_2(x, 0)}{K_H}\right) - \frac{\alpha\phi_1(x, 0)\phi_3(x, 0)}{\phi_1(x, 0) + \phi_2(x, 0)},$$

$$F_2(\phi)(x) = \frac{\alpha\, \mathrm{e}^{-\gamma_1\tau_1}\phi_1(x, -\tau_1)\phi_3(x, -\tau_1)}{\phi_1(x, -\tau_1) + \phi_2(x, -\tau_1)} - \delta\phi_2(x, 0) + r_2\phi_2(x, 0)\left(1 - \frac{\phi_1(x, 0) + \phi_2(x, 0)}{K_H}\right),$$

$$F_3(\phi)(x) = k\phi_2(x, -\tau_2)\, \mathrm{e}^{-\gamma_2\tau_2} - \mu\phi_3(x, 0) - \frac{\alpha u\phi_1(x, 0)\phi_3(x, 0)}{\phi_1(x, 0) + \phi_2(x, 0)}.$$

In this case, problem (4)–(6) can be rewritten as the following abstract functional differential equation:

$$\begin{cases} \dfrac{\mathrm{d}W(t)}{\mathrm{d}t} = AW + F(W_t), & t>0, \\ W(0) = \phi \in \mathbb{X}, \end{cases} \tag{8}$$

where $W = (H, I, V)^T$, $\phi = (\phi_1, \phi_2, \phi_3)^T$ and $A\omega = (0, 0, D\Delta V)^T$.

Now, we prove that F is locally Lipschitz in $\mathbb{X}$.

Let $\phi = (\phi_1, \phi_2, \phi_3), \varphi = (\varphi_1, \varphi_2, \varphi_3) \in \mathbb{H}$. By calculation, we have

$$\begin{aligned} &F_1(\phi)(x) - F_1(\varphi)(x) \\ &\quad = d_1(\varphi_1(x, 0) - \phi_1(x, 0)) + r_1(\phi_1(x, 0) - \varphi_1(x, 0)) + \frac{r_1}{K_H}[(\varphi_1(x, 0) + \phi_1(x, 0) + \varphi_2(x, 0)) \\ &\qquad \times (\varphi_1(x, 0) - \phi_1(x, 0)) + \phi_1(x, 0)(\varphi_2(x, 0) - \phi_2(x, 0))] \\ &\qquad + \frac{\alpha(\varphi_1(x, 0)\phi_1(x, 0) + \varphi_1(x, 0)\phi_2(x, 0))(\varphi_3(x, 0) - \phi_3(x, 0))}{\varphi_1(x, 0)\phi_1(x, 0) + \varphi_1(x, 0)\phi_2(x, 0) + \varphi_2(x, 0)\phi_1(x, 0) + \varphi_2(x, 0)\phi_2(x, 0)} \\ &\qquad + \frac{\alpha\varphi_1(x, 0)\phi_3(x, 0)(\phi_2(x, 0) - \varphi_2(x, 0))}{\varphi_1(x, 0)\phi_1(x, 0) + \varphi_1(x, 0)\phi_2(x, 0) + \varphi_2(x, 0)\phi_1(x, 0) + \varphi_2(x, 0)\phi_2(x, 0)} \\ &\qquad + \frac{\alpha\varphi_2(x, 0)\phi_3(x, 0)(\varphi_1(x, 0) - \varphi_1(x, 0))}{\varphi_1(x, 0)\phi_1(x, 0) + \varphi_1(x, 0)\phi_2(x, 0) + \varphi_2(x, 0)\phi_1(x, 0) + \varphi_2(x, 0)\phi_2(x, 0)}. \end{aligned} \tag{9}$$

From (9), it follows that

$$
\begin{aligned}
&\|F_1(\phi)(x) - F_1(\varphi)(x)\|_{\mathbb{X}} \\
&\quad \le \left(d_1 + r_1 + \frac{r_1 n_0}{K_H}\right)\|\varphi_1 - \phi_1\|_{\mathcal{C}} + \frac{r_1 n_1}{K_H}\|\varphi_2 - \phi_2\|_{\mathcal{C}} + \left\| \frac{\alpha n_2 \varphi_2 \phi_2 (\varphi_1 - \phi_1)}{\varphi_1\phi_1 + \varphi_1\phi_2 + \varphi_2\phi_1 + \varphi_2\phi_2} \right\|_{\mathcal{C}} \\
&\qquad + \left\| \frac{\alpha n_2 \varphi_1 \phi_2 (\phi_2 - \varphi_2)}{\varphi_1\phi_1 + \varphi_1\phi_2 + \varphi_2\phi_1 + \varphi_2\phi_2} \right\|_{\mathcal{C}} + \left\| \frac{\alpha (\varphi_1\phi_1 + \varphi_1\phi_2)(\varphi_3 - \phi_3)}{\varphi_1\phi_1 + \varphi_1\phi_2 + \varphi_2\phi_1 + \varphi_2\phi_2} \right\|_{\mathcal{C}},
\end{aligned}
$$

where

$$
\begin{aligned}
n_0 &= \|\varphi_1 + \phi_1 + \varphi_2\|_\infty = \sup_{x\in\bar{\Omega}}\{\varphi_1(x,0) + \phi_1(x,0) + \varphi_2(x,0)\}, \\
n_1 &= \|\phi_1\|_\infty = \sup_{x\in\bar{\Omega}}\{\phi_1(x,0)\}, \\
n_2 &= \left\|\frac{\phi_3}{\phi_2}\right\|_\infty = \sup_{x\in\bar{\Omega}}\left\{\frac{\phi_3(x,0)}{\phi_2(x,0)}\right\}.
\end{aligned}
$$

Now, by using the fact that

$$
\frac{\varphi_1\phi_2}{\varphi_1\phi_1 + \varphi_1\phi_2 + \varphi_2\phi_1 + \varphi_2\phi_2} < 1, \quad \frac{\varphi_2\phi_2}{\varphi_1\phi_1 + \varphi_1\phi_2 + \varphi_2\phi_1 + \varphi_2\phi_2} < 1,
$$
$$
\frac{\varphi_1\phi_1 + \varphi_1\phi_2}{\varphi_1\phi_1 + \varphi_1\phi_2 + \varphi_2\phi_1 + \varphi_2\phi_2} < 1,
$$

we obtain

$$
\begin{aligned}
&\|F_1(\phi)(x) - F_1(\varphi)(x)\|_{\mathbb{X}} \\
&\quad < \left(d_1 + r_1 + \alpha n_2 + \frac{r_1 n_0}{K_H}\right)\|\varphi_1 - \phi_1\|_{\mathcal{C}} + \left(\frac{r_1 n_1}{2K_H} + \alpha n_2\right)\|\varphi_2 - \phi_2\|_{\mathcal{C}} + \alpha\|\varphi_3 - \phi_3\|_{\mathcal{C}} \\
&\quad < \sum_{i=1}^{3} N_i^1 \|\phi_i - \varphi_i\|_{\mathcal{C}},
\end{aligned}
$$

where $N_1^1 = d_1 + r_1 + \alpha n_2 + \frac{r_1 n_0}{K_H}$, $N_2^1 = \frac{r_1 n_1}{2K_H} + \alpha n_2$ and $N_3^1 = \alpha$. In a similar manner, we get

$$
\|F_2(\phi)(x) - F_2(\varphi)(x)\|_{\mathbb{X}} < \sum_{i=1}^{3} N_i^2 \|\phi_i - \varphi_i\|_{\mathcal{C}},
$$

where

$$
\begin{aligned}
N_1^2 &= \alpha n_5\, \mathrm{e}^{-\gamma_1\tau_1} + \frac{r_2 n_4}{K_H}, N_2^2 = \delta + r_2 + \alpha n_5\, \mathrm{e}^{-\gamma_1\tau_1} + \frac{r_2 n_3}{K_H}, N_3^2 = \alpha\, \mathrm{e}^{-\gamma_1\tau_1}, \\
n_3 &= \|\varphi_2 + \phi_2 + \varphi_1\|_\infty = \sup_{x\in\bar{\Omega}}\{\varphi_2(x,0) + \phi_2(x,0) + \varphi_1(x,0)\}, \\
n_4 &= \|\phi_2\|_\infty = \sup_{x\in\bar{\Omega}}\{\phi_2(x,0)\}, \\
n_5 &= \left\|\frac{\varphi_3}{\varphi_2}\right\|_\infty = \sup_{x\in\bar{\Omega}}\left\{\frac{\varphi_3(x,-\tau_1)}{\varphi_2(x,-\tau_1)}\right\},
\end{aligned}
$$

$$\|F_3(\phi)(x) - F_3(\varphi)(x)\|_{\mathbb{X}} < \sum_{i=1}^{3} N_i^3 \, \|\phi_i - \varphi_i\|_C \,,$$

where $N_1^3 = \alpha u n_2$, $N_2^3 = k e^{-\gamma_2\tau_2} + \alpha u n_2$ and $N_3^3 = \mu + \alpha u$. Thus, F is locally Lipschitz in $\mathbb{X}$. Hence, thanks to Proposition 2.1 in [29], there exists a unique local solution for system (4) on the interval $[0, T_{\max})$, where $T_{\max}$ is the maximal time of existence of a solution of system (4).

Next, we show that the solution (H, I, V) of problem (4)–(6) remains positive on $\bar{\Omega} \times [0, T_{\max})$. Let $[0, T_+)$ denote the maximal subinterval of $[0, T_{\max})$ where the solution remains positive. We first prove that the solution is bounded on $\bar{\Omega} \times [0, T_+)$. In order to prove the boundedness of solutions, define the following functional

$$L(x,t) = \mathrm{e}^{-\gamma_1\tau_1} H(x, t-\tau_1) + I(x,t), \quad (x,t) \in \bar{\Omega} \times [0, T_+).$$

This implies

$$\begin{aligned}
\frac{\partial L(x,t)}{\partial t} &= \mathrm{e}^{-\gamma_1\tau_1} s_0 - \mathrm{e}^{-\gamma_1\tau_1} d_1 H(x,t-\tau_1) - \delta I(x,t) + r_2 I(x,t)\left(1 - \frac{H(x,t)+I(x,t)}{K_H}\right) \\
&\quad + \mathrm{e}^{-\gamma_1\tau_1} r_1 H(x,t-\tau_1)\left(1 - \frac{H(x,t-\tau_1)+I(x,t-\tau_1)}{K_H}\right) \\
&= s_0\,\mathrm{e}^{-\gamma_1\tau_1} + \frac{K_H r_1\,\mathrm{e}^{-\gamma_1\tau_1}}{4} + \frac{K_H r_1}{4} - \mathrm{e}^{-\gamma_1\tau_1} d_1 H(x,t-\tau_1) - \delta I(x,t) - \frac{r_2}{K_H}\left(I - \frac{K_H}{2}\right)^2 \\
&\quad - \frac{r_1\,\mathrm{e}^{-\gamma_1\tau_1}}{K_H}\left(H(x,t-\tau_1) - \frac{K_H}{2}\right)^2 - \frac{r_1\,\mathrm{e}^{-\gamma_1\tau_1}}{K_H} H(x,t-\tau_1) I(x,t-\tau_1) - \frac{r_2}{K_H} HI \\
&\le \frac{(4s_0 + K_H r_1)\,\mathrm{e}^{-\gamma_1\tau_1} + K_H r_2}{4} - q_0 L,
\end{aligned}$$

where $q_0 = \min\{d_1, \delta\}$. Thus, it follows that

$$L(x,t) \le \max\left\{\frac{(4s_0 + K_H r_1)\,\mathrm{e}^{-\gamma_1\tau_1} + K_H r_2}{4q_0}, \max_{x\in\bar{\Omega}}\{\,\mathrm{e}^{-\gamma_1\tau_1}\phi_1(x,-\tau_1) + \phi_2(x,0)\}\right\} := M_1.$$

This implies that H and I are bounded on $\bar{\Omega} \times [0, T_+)$.

Now, from the boundedness of I and system (4)–(6), we deduce that V satisfies the following system

$$\begin{cases}
\dfrac{\partial V}{\partial t} - D\Delta V = kI(x,t-\tau_2)\,\mathrm{e}^{-\gamma_2\tau_2} - \mu V(x,t) - \dfrac{\alpha u H(x,t) V(x,t)}{H(x,t)+I(x,t)} \le k M_1\,\mathrm{e}^{-\gamma_2\tau_2} - \mu V, \\
\dfrac{\partial V}{\partial \eta} = 0, \\
V(x,0) = \phi_3(x,0) > 0,
\end{cases} \tag{10}$$

where $M_1 = \max\{\dfrac{(4s_0 + K_H r_1)\,\mathrm{e}^{-\gamma_1\tau_1} + K_H r_2}{4q_0}, \max_{x\in\bar{\Omega}}\{\,\mathrm{e}^{-\gamma_1\tau_1}\phi_1(x,-\tau_1) + \phi_2(x,0)\}\}$.

Thus by Corollary 2.2, the solution $\tilde{v}(t)$ of problem (11) below

$$\begin{cases}
\dfrac{\partial \tilde{v}}{\partial t} = k M_1\,\mathrm{e}^{-\gamma_2\tau_2} - \mu\tilde{v} \\
\tilde{v}(0) = \max\limits_{x\in\overline{\Omega}} \phi_3(x,0)
\end{cases} \tag{11}$$

satisfies $V(x,t) \le \tilde{v}(t)$. By Gronwall's inequality in differential form [30, Lemma 2.3], the solution is

$$\tilde{v}(t) = \max_{x\in\overline{\Omega}} \phi_3(x,0)\,\mathrm{e}^{-\mu t} + \frac{kM_1\,\mathrm{e}^{-\gamma_2\tau_2}}{\mu}(1-\mathrm{e}^{-\mu t}), \quad \text{for all } t\in[0,T_+) \text{ and hence}$$

$$V(x,t) \le \max\left\{\frac{kM_1\,\mathrm{e}^{-\gamma_2\tau_2}}{\mu}, \max_{x\in\overline{\Omega}}\phi_3(x,0)\right\}, \quad \forall\,(x,t)\in\overline{\Omega}\times[0,T_+).$$

From the above discussion, we have proved that $H(x,t)$, $I(x,t)$ and $V(x,t)$ are positive and bounded on $\overline{\Omega}\times[0,T_+)$.

Now, let

$$B(x,t) = \frac{r_1}{K_H}(H(x,t)+I(x,t)) + \frac{\alpha V(x,t)}{H(x,t)+I(x,t)}. \tag{12}$$

It follows from the first equation in system (4) that

$$\frac{\partial H}{\partial t} = s_0 - (B(x,t)+d-r_1)H(x,t). \tag{13}$$

This reads as

$$\frac{\partial}{\partial t}\left[H(x,t)\exp\left\{(d-r_1)t+\int_0^t B(x,s)\,\mathrm{d}s\right\}\right] = s_0\exp\left\{(d-r_1)t+\int_0^t B(x,s)\,\mathrm{d}s\right\}.$$

Thus,

$$H(x,t)\exp\left\{(d-r_1)t+\int_0^t B(x,s)\,\mathrm{d}s\right\} - \phi_1(x,0) = \int_0^t s_0\exp\left\{(d-r_1)t+\int_0^t B(x,s)\,\mathrm{d}s\right\}\mathrm{d}t.$$

From the above result, we obtain the following formula for H

$$\begin{aligned} H(x,t) &= \phi_1(x,0)\exp\left\{-(d-r_1)t-\int_0^t B(x,s)\,\mathrm{d}s\right\} \\ &\quad + \left[\exp\left\{-(d-r_1)t-\int_0^t B(x,s)\,\mathrm{d}s\right\}\right]\int_0^t s_0\exp\left\{(d-r_1)t+\int_0^t B(x,s)\,\mathrm{d}s\right\}\mathrm{d}t. \end{aligned} \tag{14}$$

Note for instance that (14) is valid when $(x,t)\in\bar{\Omega}\times[0,T_+)$. We formally set

$$B_1(x,t) = \frac{r_2}{K_H}(H(x,t)+I(x,t)). \tag{15}$$

By the second equation of system (4), we get

$$\frac{\partial I}{\partial t} = \frac{\alpha\,\mathrm{e}^{-\gamma_1\tau_1}H(x,t-\tau_1)V(x,t-\tau_1)}{H(x,t-\tau_1)+I(x,t-\tau_1)} - (B_1(x,t)+\delta-r_2)I(x,t). \tag{16}$$

This leads to

$$\begin{aligned} &\frac{\partial}{\partial t}\left[I(x,t)\exp\left\{(\delta-r_2)t+\int_0^t B_1(x,s)\,\mathrm{d}s\right\}\right] \\ &\quad = \frac{\alpha\,\mathrm{e}^{-\gamma_1\tau_1}H(x,t-\tau_1)V(x,t-\tau_1)}{H(x,t-\tau_1)+I(x,t-\tau_1)}\exp\left\{(\delta-r_2)t+\int_0^t B_1(x,s)\,\mathrm{d}s\right\}. \end{aligned}$$

It follows that

$$I(x,t) = \phi_3(x,0)\exp\left\{-(\delta - r_2)t - \int_0^t B_1(x,s)\,\mathrm{d}s\right\}$$
$$+ \int_0^t \frac{\alpha\,\mathrm{e}^{-\gamma_1\tau_1}H(x,\theta-\tau)V(x,\theta-\tau)}{H(x,\theta-\tau)+V(x,\theta-\tau)}\,\mathrm{e}^{(\delta-r_2)(\theta-t)}\exp\left\{-\int_\theta^t B_1(x,s)\,\mathrm{d}s\right\}\mathrm{d}\theta. \quad (17)$$

Owing to the initial condition, it follows that $I(x,t)>0$ for $(x,t)\in\bar{\Omega}\times[0,\tau]$.

Now we prove that $V(x,t)>0$ for $(x,t)\in\bar{\Omega}\times[0,\tau]$.

From the third equation of system (4), the zero-flux boundary condition (6) and the initial condition (7), we have

$$\frac{\partial V}{\partial t} - D\Delta V(x,t) = kI(x,t-\tau_2)\,\mathrm{e}^{-\gamma_2\tau_2} - \mu V(x,t) - \frac{\alpha u H(x,t)V(x,t)}{H(x,t)+I(x,t)},$$
$$V(x,0) = \phi_3(x,0)>0,$$
$$\frac{\partial V}{\partial \eta} = 0, \quad \text{on } \partial\Omega\times[0,\infty).$$

By contradiction, assume that there exists $(x_0,t_0)\in\bar{\Omega}\times[0,\tau]$, such that $V(x,t)\le 0$. For this, define

$$t_1 = \inf\{t\in[0,\tau] : \exists x_1\in\bar{\Omega} \quad \text{such that } V(x_1,t)=0\}.$$

Due to $V(x,0)=\phi_3(x,0)>0$ for $x\in\bar{\Omega}$, and from the continuity of V, it follows that $t_1>0$. Therefore, for $t\in[0,t_1)$, one can define the following function $h(x,t)=\ln V(x,t)$. To get a contradiction it is sufficient to show that the function h is bounded from below on $\bar{\Omega}\times[0,t_1)$. By direct calculation, we obtain

$$\begin{aligned}
\frac{\partial h(x,t)}{\partial t} - D\Delta h(x,t) &= \frac{1}{V(x,t)}\left(\frac{\partial V(x,t)}{\partial t} - D\Delta V(x,t)\right) + D\frac{|\nabla V(x,t)|^2}{V(x,t)^2},\\
&= \frac{1}{V(x,t)}\left(kI(x,t-\tau_2)\ \mathrm{e}^{-\gamma_2\tau_2} - \mu V(x,t) - \frac{\alpha u H(x,t)V(x,t)}{H(x,t)+I(x,t)}\right)\\
&\quad + D\frac{|\nabla V(x,t)|^2}{V(x,t)^2},\\
&= -\mu - \frac{\alpha u H(x,t)}{H(x,t)+I(x,t)} + \frac{kI(x,t-\tau_2)\ \mathrm{e}^{-\gamma_2\tau_2}}{V(x,t)} + D\frac{|\nabla v(x,t)|^2}{v(x,t)^2},\\
&\ge -\|\chi\|_\infty, \qquad (18)
\end{aligned}$$

where $\chi(x,t)=\mu+\frac{\alpha u H(x,t)}{H(x,t)+I(x,t)}$. Due to (18), we deduce that

$$h(x,0) = \ln\phi_3(x,0) \ge -\|\ln\phi_3\|_\infty.$$

The Neumann condition in (6) implies that $\dfrac{\partial h}{\partial \eta}=0$. Now, for a sufficiently small $\epsilon>0$, define

$$h_\epsilon(x,t) = h(x,t) + \|\chi\|_\infty t + \|\ln\phi_4\|_\infty + \frac{\epsilon}{2}(t+1),$$

so that the following inequality holds

$$\frac{\partial h_\epsilon(x,t)}{\partial t} - D\Delta h_\epsilon(x,t) \geq \frac{\epsilon}{2},$$

with positive initial condition and homogeneous Neumann boundary condition

$$h_\epsilon(x,0) \geq \frac{\epsilon}{2} \quad \text{and} \quad \frac{\partial h_\epsilon}{\partial \eta} = 0,$$

respectively. Note that for h to be bounded from below, it suffices to show that $h_\epsilon \geq 0$. So, we again proceed by contradiction. Then, define

$$t_2 = \inf\{t \in [0,t_1) : \exists x_1 \in \bar{\Omega} \quad \text{such that } h_\epsilon(x_1,t) = 0\}.$$

Clearly, $t_2>0$. Then, from the definition of t_2, the function $x \mapsto h_\epsilon(x,t_2)$ has a minimum on $\bar{\Omega}$ at x_1. If $x_1 \in \Omega$, then $\Delta h_\epsilon(x,t_2) \geq 0$. Thus, $\frac{\partial h_\epsilon(x,t)}{\partial t}>0$, which indicates that on the left neighborhood of t_2, $h_\epsilon(x_1,t)<0$. This contradicts the definition of t_2. On the other hand, if $x_1 \in \partial\Omega$, one has a minimum on $\partial\Omega$ and accordingly $\nabla h_\epsilon(x_1,t_2)$ is orthogonal to the tangent plane at x_1. But, from the boundary condition, we have $\frac{\partial h_\epsilon}{\partial \eta}(x_1,t_2) = 0$. Thus $\Delta h_\epsilon(x_1,t_2) \geq 0$, which also gives a contradiction. It is obvious that, for a sufficiently small $\epsilon>0$, $h_\epsilon>0$ on $\bar{\Omega} \times [0,t_1)$. So, by letting $\epsilon \to 0$ in the definition of h_ϵ, we get

$$h(x,t) \geq -\|\chi\|_\infty t_1 - \|\ln \phi_4\|_\infty \quad \text{for all } (x,t) \in \bar{\Omega} \times [0,t_1).$$

With this last conclusion, we deduce that $V(x,t)>0$ for all $(x,t) \in \bar{\Omega} \times [0,\tau]$. Now, since $I(x,t)>0$ for all $(x,t) \in \bar{\Omega} \times [0,\tau]$, it follows, in view of (12) and (14), that B is bounded on $\bar{\Omega} \times [0,\tau]$ and $H(x,t)>0$ for all $(x,t) \in \bar{\Omega} \times [0,\tau]$.

Repeating the above arguments, it follows that I and V are positive on $\bar{\Omega} \times [n\tau,(n+1)\tau]$, $n = 1,2,\ldots$. Thus $I(x,t)>0$ and $V(x,t)>0$ for all $(x,t) \in \bar{\Omega} \times [0,T_{\max})$. In view of (12) and (14), since I and V are positive on $\bar{\Omega} \times [0,T_{\max})$, it follows that B is bounded and H is positive on $\bar{\Omega} \times [0,T_{\max})$. From this, we easily obtain the boundedness of H, I and V on $\bar{\Omega} \times [0,T_{\max})$ as on $\bar{\Omega} \times [0,T_+)$. From the above investigation and the standard theory of semilinear parabolic systems [31], we deduce that $T_+ = T_{\max} = \infty$. This completes the proof. ∎

3. Local stability analysis of steady states

This Section is devoted to the local stability of HBV-free equilibrium and HBV-infected equilibrium of problem (4)–(6). For this purpose we will thoroughly analyze the characteristic equations.

If $r_1>d_1$, then PDE system (4) always has an HBV-free equilibrium

$$E_0 = (\Lambda,0,0), \quad \text{with } \Lambda = \frac{K_H}{2r_1}\left[(r_1-d_1) + \sqrt{(r_1-d_1)^2 + \frac{4s_0r_1}{K_H}}\right].$$

In the following theorem, whose proof is similar to that of Theorem 4.2 in [17], we give the expression of the basic reproduction number $\mathcal{R}_0$, which is defined as the average number of newly infected hepatocytes at the beginning of the infectious process [12].

Theorem 3.1: *If the diffusion coefficient of the mature free virions D is a positive constant and $\delta>r_2$, then the basic reproductive number $\mathcal{R}_0$ of PDE-model* (4) *is*

$$\mathcal{R}_0 = \frac{\alpha k e^{-\gamma_1\tau_1-\gamma_2\tau_2}}{(\mu+\alpha u)\left[\delta + r_2\left(\frac{\Lambda}{K_H}-1\right)\right]}. \tag{19}$$

Biologically speaking, $\frac{1}{\delta+r_2(\frac{\Lambda}{K_H}-1)}$ denotes the average survival period of infected hepatocytes which is less than $\frac{1}{\delta}$ since proliferation of infected hepatocytes slows down according to a homeostasis process. During this period an infected cell produces k virions per unit time. $\frac{1}{\mu+\alpha u}$ is the average surviving period of free virions that is less than $\frac{1}{\mu}$ because free viruses decrease due to the infection following an absorption effect with a modification u. α stands for the rate of newly infected cells which are infected by the first free virions. The fraction $e^{-\gamma_1\tau_1}$ represents the probability of surviving of hepatocytes infected from $t-\tau_1$ to t, while the quotients $e^{-\gamma_2\tau_2}$ is the probability of surviving for immature free viruses from time $t-\tau_2$ to time t. Thus, $\mathcal{R}_0$ of our PDE model (4) has an interesting biological meaning. Note that, the basic reproduction number $\mathcal{R}_0$ is independent of the diffusion coefficient D. Also, $\mathcal{R}_0$ decreases as the delays τ_1 and τ_2 increase. Hence, neglecting one of these delays leads to an overestimate of the infection risk.

From Proposition 4.6 of [17], PDE model (4) has a unique positive constant endemic equilibrium $E^* = (H^*, I^*, V^*)$, given by

$$H^* = \frac{K_H X\left[(\mu+\alpha u)\left(\delta + r_2\left(\frac{\Lambda}{K_H}-1\right)\right)(\mathcal{R}_0-1)X + \mu(r_2-\delta)(1-X) + \frac{r_2\Lambda}{K_H}(\mu+\alpha u)X\right]}{r_2(\mu+\alpha u X)}, \tag{20}$$

$$I^* = \frac{(1-X)K_H\left[(\mu+\alpha u)\left(\delta + r_2\left(\frac{\Lambda}{K_H}-1\right)\right)(\mathcal{R}_0-1)X + \mu(r_2-\delta)(1-X) + \frac{r_2\Lambda}{K_H}(\mu+\alpha u)X\right]}{r_2(\mu+\alpha u X)} \tag{21}$$

and

$$V^* = \frac{\begin{array}{c}(1-X)kK_H\left[(\mu+\alpha u)\left(\delta + r_2\left(\frac{\Lambda}{K_H}-1\right)\right)\right. \\ \left.(\mathcal{R}_0-1)X + \mu(r_2-\delta)(1-X) + \frac{r_2\Lambda}{K_H}(\mu+\alpha u)X\right]\end{array}}{r_2(\mu+\alpha u X)^2}, \tag{22}$$

with $0<X\leq 1$ satisfying the following equation:

$$b_3X^3 + b_2X^2 + b_1X + b_0 = 0, \tag{23}$$

where

$$\begin{aligned}
b_0 &= s_0(\mu r_2)^2>0,\\
b_1 &= 2s_0\alpha u\mu r_2^2 + \mu K_H(r_2-\delta)[\mu(r_1\delta - r_2 d_1) - r_2\alpha k e^{-\gamma_2\tau_2}],\\
b_2 &= s_0(\alpha u r_2)^2 + \alpha[\mu r_2 K_H(r_1-d_1) - r_2\alpha k K_H - 2\mu r_1 K_H][ke^{-\gamma_1\tau_1-\gamma_2\tau_2} + u(r_2-\delta)]\\
&\quad + \mu r_2\alpha K_H(r_2-\delta)(ke^{-\gamma_2\tau_2} + u(r_1-d_1)),\\
b_3 &= \alpha K_H[r_2\alpha(ke^{-\gamma_2\tau_2} + u(r_1-d_1)) - r_1][ke^{-\gamma_1\tau_1-\gamma_2\tau_2} + u(r_2-\delta)].
\end{aligned}$$

Note that for all $X\in(0,1]$, $H^*, I^*, V^*>0$ if $\mathcal{R}_0>1$ and the constant equilibrium with infection $E^* = (H^*, I^*, V^*)$ is unique if $b_3<0, b_2<0, b_1>0$ or if $b_i<0$ for all $i\in\{1,2,3\}$.

Now, let $E = (H_0, I_0, V_0)$ be any feasible steady state of PDE system (4). Then linearizing (4) at $E = (H_0, I_0, V_0)$ yields

$$\begin{cases} \dfrac{\partial H}{\partial t} = \left(r_1 - d_1 - \dfrac{2r_1}{K_H}H_0 - \dfrac{r_1}{K_H}I_0 - \dfrac{\alpha I_0 V_0}{(H_0+I_0)^2}\right)H(x,t) \\ \quad + \left(-\dfrac{r_1}{K_H}H_0 + \dfrac{\alpha H_0 V_0}{(H_0+I_0)^2}\right)I(x,t) - \dfrac{\alpha H_0}{H_0+I_0}V(x,t), \\ \dfrac{\partial I}{\partial t} = \dfrac{\alpha\, \mathrm{e}^{-\gamma_1\tau_1} I_0 V_0}{(H_0+I_0)^2}H(x,t-\tau_1) - \dfrac{r_2}{K_H}I_0 H(x,t) + \left(r_2 - \delta - \dfrac{r_2}{K_H}H_0 - \dfrac{2r_2}{K_H}I_0\right)I(x,t) \\ \quad - \dfrac{\alpha\, \mathrm{e}^{-\gamma_1\tau_1} H_0 V_0}{(H_0+I_0)^2}I(x,t-\tau_1) + \dfrac{\alpha\, \mathrm{e}^{-\gamma_1\tau_1} H_0}{H_0+I_0}V(x,t-\tau_1), \\ \dfrac{\partial V}{\partial t} = D\Delta V - \dfrac{\alpha u I_0 V_0}{(H_0+I_0)^2}H(x,t) + k e^{-\gamma_2\tau_2} I(x,t-\tau_2) \\ \quad + \dfrac{\alpha u H_0 V_0}{(H_0+I_0)^2}I(x,t) - \left(\mu + \dfrac{\alpha u H_0}{H_0+I_0}\right)V(x,t). \end{cases} \tag{24}$$

for $t>0$, $x \in \Omega$. Let $-\Delta$ be the operator, with eigenvalues $0 = \mu_1 < \mu_2 \leq \mu_3 \leq \cdots$, on Ω subject to the homogeneous Neumann boundary condition. Let E_{μ_i} be the eigenspace associated to μ_i in $C^1(\Omega)$. Consider, on $\mathbb{X} = [C^1(\Omega)]^3$, the following orthogonal basis $\{\varphi_{ij}, j = 1, \ldots, \dim E_{\mu_i}\}$ of the eigenspace E_{μ_i}, and set $\mathbb{X}_{ij} = \{\varphi_{ij}c, \ / \ c \in \mathbb{R}^3\}$. Hence

$$\mathbb{X} = \bigoplus_{i=1}^{\infty} \mathbb{X}_i \quad \text{and} \quad \mathbb{X}_i = \bigoplus_{j=1}^{\dim E_{\mu_i}} \mathbb{X}_{ij}.$$

Inserting $H(x,t) = \mathrm{e}^{\lambda t}\varphi_1(x), I(x,t) = \mathrm{e}^{\lambda t}\varphi_2(x)$, and $V(x,t) = \mathrm{e}^{\lambda t}\varphi_3(x)$ into (24), we get the following eigenvalue problem

$$\begin{cases} \lambda\varphi_1(x) = \left(r_1 - d_1 - \dfrac{2r_1}{K_H}H_0 - \dfrac{r_1}{K_H}I_0 - \dfrac{\alpha I_0 V_0}{(H_0+I_0)^2}\right)\varphi_1(x) \\ \quad + \left(-\dfrac{r_1}{K_H}H_0 + \dfrac{\alpha H_0 V_0}{(H_0+I_0)^2}\right)\varphi_2(x) - \dfrac{\alpha H_0}{H_0+I_0}\varphi_3(x), \\ \lambda\varphi_2(x) = \dfrac{\alpha I_0 V_0}{(H_0+I_0)^2}\,\mathrm{e}^{-(\lambda+\gamma_1)\tau_1}\varphi_1(x) - \dfrac{r_2}{K_H}I_0\varphi_1(x) + \left(r_2 - \delta - \dfrac{r_2}{K_H}H_0 - \dfrac{2r_2}{K_H}I_0\right)\varphi_2(x) \\ \quad - \dfrac{\alpha H_0 V_0}{(H_0+I_0)^2}\,\mathrm{e}^{-(\lambda+\gamma_1)\tau_1}\varphi_2(x) + \dfrac{\alpha H_0}{H_0+I_0}\,\mathrm{e}^{-(\lambda+\gamma_1)\tau_1}\varphi_3(x), \\ \lambda\varphi_3(x) = D\varphi_3''(x) - \dfrac{\alpha u I_0 V_0}{(H_0+I_0)^2}\varphi_1(x) + k e^{-(\lambda+\gamma_2)\tau_2}\varphi_2(x) \\ \quad + \dfrac{\alpha u H_0 V_0}{(H_0+I_0)^2}\varphi_2(x) - \left(\mu + \dfrac{\alpha u H_0}{H_0+I_0}\right)\varphi_3(x). \end{cases} \tag{25}$$

3.1. Local stability of the HBV-free equilibrium

In this subsection, we investigate the local stability of infection-free equilibrium $E_0 = (\Lambda, 0, 0)$ by analyzing the corresponding characteristic equation.

We have the following result.

Theorem 3.2: *The HBV-free equilibrium $E_0(\Lambda, 0, 0)$ of PDE-model (4) is locally asymptotically stable If $\mathcal{R}_0 < 1$, and becomes unstable if $\mathcal{R}_0 > 1$.*

Proof: At the HBV-free equilibrium E_0, system (25) becomes

$$\begin{cases} \lambda\varphi_1(x) = \left(r_1 - d_1 - \dfrac{2r_1}{K_H}\Lambda\right)\varphi_1(x) - \dfrac{r_1}{K_H}\Lambda\varphi_2(x) - \alpha\varphi_3(x), \\ \lambda\varphi_2(x) = \left(r_2 - \delta - \dfrac{r_2}{K_H}\Lambda\right)\varphi_2(x) + \alpha\,\mathrm{e}^{-(\lambda+\gamma_1)\tau_1}\varphi_3(x), \\ \lambda\varphi_3(x) = D\varphi_3''(x) + ke^{-(\lambda+\gamma_2)\tau_2}\varphi_2(x) - (\mu+\alpha u)\varphi_3(x). \end{cases} \tag{26}$$

Lemma 2.2 in [32] and Lemma 3.1 in [33] imply that (26) admits a principal eigenvalue λ^*, which verifies the following characteristic equation

$$\begin{aligned} &\left(r_1\left(1-\frac{2\Lambda}{K_H}\right) - d_1 - \lambda\right)\left\{\lambda^2 + \left[\delta - r_2\left(1-\frac{\Lambda}{K_H}\right) + \mu_i D + \mu + \alpha u\right]\lambda \right. \\ &\qquad \left. + \left(\delta - r_2\left(1-\frac{\Lambda}{K_H}\right)\right)(\mu_i D + \mu + \alpha u) - k\alpha\,\mathrm{e}^{-(\lambda+\gamma_1)\tau_1-(\lambda+\gamma_2)\tau_2}\right\} = 0. \end{aligned} \tag{27}$$

It is easy to see that, for any $i \geq 1$, Equation (27) always has the negative real root $\lambda_0 = -\sqrt{(r_1-d_1)^2 + \frac{4r_1 s_0}{K_H}} < 0$. All other roots of Equation (27) satisfy the following equation

$$\begin{aligned} &\lambda^2 + \left[\delta - r_2\left(1-\frac{\Lambda}{K_H}\right) + \mu_i D + \mu + \alpha u\right]\lambda \\ &\quad + \left(\delta - r_2\left(1-\frac{\Lambda}{K_H}\right)\right)(\mu_i D + \mu + \alpha u) - k\alpha\,\mathrm{e}^{-(\lambda+\gamma_1)\tau_1-(\lambda+\gamma_2)\tau_2} = 0. \end{aligned} \tag{28}$$

Now, set

$$\begin{aligned} h_1(\lambda) = {} & \lambda^2 + \left[\delta - r_2\left(1-\frac{\Lambda}{K_H}\right) + \mu_i D + \mu + \alpha u\right]\lambda \\ & + \left(\delta - r_2\left(1-\frac{\Lambda}{K_H}\right)\right)(\mu_i D + \mu + \alpha u) - k\alpha\,\mathrm{e}^{-(\lambda+\gamma_1)\tau_1-(\lambda+\gamma_2)\tau_2}. \end{aligned}$$

If $\mathcal{R}_0 > 1$, then for $\lambda \in \mathbb{R}$ and $i = 1$ (which implies that $\mu_1 = 0$), one has

$$h_1(0)|_{i=1} = (\mu + \alpha u)\left(\delta - r_2\left(1-\frac{\Lambda}{K_H}\right)\right) - k\alpha\,\mathrm{e}^{-\gamma_1\tau_1-\gamma_2\tau_2} < 0 \quad \text{and} \quad \lim_{\lambda\to+\infty} h_1(\lambda) = +\infty.$$

Thus, Equation (28) has a positive real root. Consequently, there is a characteristic root λ with positive real part. Hence, if $\mathcal{R}_0 > 1$, the infection-free equilibrium $E_0(\Lambda, 0, 0)$ is unstable. If $\mathcal{R}_0 < 1$, set

$$\begin{aligned} p = {} & \delta - r_2\left(1-\frac{\Lambda}{K_H}\right) + \mu_i D + \mu + \alpha u, \\ & q = (\mu_i D + \mu + \alpha u)\left[\delta - r_2\left(1-\frac{\Lambda}{K_H}\right)\right] \text{ and } q_0 = -k\alpha\,\mathrm{e}^{-\gamma_1\tau_1-\gamma_2\tau_2}. \end{aligned}$$

Then, Equation (28) becomes

$$\lambda^2 + p\lambda + q + q_0\,\mathrm{e}^{-\lambda(\tau_1+\tau_2)} = 0. \tag{29}$$

Now, by admitting that $i\omega$ (with $\omega > 0$) is a solution to (29) and setting $\tau = \tau_1 + \tau_2$,, we easily obtain after separating real and imaginary parts

$$\begin{cases} \omega^2 - q = q_0 \cos\omega\tau, \\ p\omega = q_0 \sin\omega\tau. \end{cases} \tag{30}$$

After squaring and adding equations of (30), we get the following biquadratic equation

$$\omega^4 + (p^2 - 2q)\omega^2 + q^2 - q_0^2 = 0. \tag{31}$$

From Equation (31), taking $z = \omega^2$, it follows that

$$z^2 + (p^2 - 2q)z + q^2 - q_0^2 = 0, \tag{32}$$

with

$$p^2 - 2q = \left[\delta - r_2\left(1 - \frac{\Lambda}{K_H}\right)\right]^2 + (\mu_i D + \mu + \alpha u)^2 > 0$$

and

$$\begin{aligned} q^2 - q_0^2 = &\left\{(\mu_i D + \mu + \alpha u)\left[\delta - r_2\left(1 - \frac{\Lambda}{K_H}\right)\right] + k\alpha\, \mathrm{e}^{-\gamma_1\tau_1 - \gamma_2\tau_2}\right\} \\ &\times \left\{\mu_i D\left[\delta - r_2\left(1 - \frac{\Lambda}{K_H}\right)\right] + (\mu + \alpha u)\left[\delta - r_2\left(1 - \frac{\Lambda}{K_H}\right)\right](1 - \mathcal{R}_0)\right\} > 0. \end{aligned}$$

When $\tau_1 = \tau_2 = 0$, $\mathcal{R}_0 = \dfrac{k\alpha}{(\mu + \alpha u)(\delta + r_2(\frac{\Lambda}{K_H} - 1))}$ and Equation (28) becomes

$$\lambda^2 + p_1\lambda + p_0 = 0, \tag{33}$$

with

$$p_1 = \delta - r_2\left(1 - \frac{\Lambda}{K_H}\right) + \mu_i D + \mu + \alpha u > 0 \quad \text{and}$$

$$p_0 = \mu_i D\left(\delta - r_2\left(1 - \frac{\Lambda}{K_H}\right)\right) + (\mu + \alpha u)\left(\delta - r_2\left(1 - \frac{\Lambda}{K_H}\right)\right)(1 - \mathcal{R}_0) > 0.$$

Therefore, if $\mathcal{R}_0 < 1$, by the signs rule of Descartes it follows that Equations (32) and (33) have no positive roots. By a similar argument as above, it can be shown that when $\tau_1 = 0$ and $\tau_2 \geq 0$ and when $\tau_1 \geq 0$ and $\tau_2 = 0$, the infection-free equilibrium, E_0, is locally asymptotically stable. Accordingly, if $\mathcal{R}_0 < 1$, the infection-free equilibrium $E_0 = (\Lambda, 0, 0)$ is locally asymptotically stable for all $\tau_1, \tau_2 \geq 0$. This completes the proof ■

3.2. Local stability of the equilibrium with infection and occurence of Hopf bifurcation

Here, we discuss the local stability behavior of the endemic equilibrium E^* when $\mathcal{R}_0 > 1$ for PDE-model (4). Moreover, we explore the impact of the delays τ_1 and τ_2 according to the analysis of the distribution of the roots of associated transcendental characteristic equations.

Using the equilibrium condition

$$r_1 - d_1 = -\frac{s_0}{H^*} + \frac{r_1(H^* + I^*)}{K_H} + \frac{\alpha V^*}{H^* + I^*},$$

$$r_2 - \delta = -\frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)I^*} + \frac{r_2(H^* + I^*)}{K_H},$$

at the equilibrium with infection E^*, the principal eigenvalue λ^* satisfies the following associated transcendental characteristic equation

$$\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 + (B_2\lambda^2 + B_1\lambda + B_0)\,e^{-\lambda\tau_1} + C_0\,e^{-\lambda\tau_2} + (P_1\lambda + P_0)\,e^{-\lambda(\tau_1+\tau_2)} = 0, \quad (34)$$

where

$$A_2 = \mu + \mu_i D + \frac{s_0}{H^*} + \frac{r_1 H^*}{K_H} + \frac{r_2 I^*}{K_H} + \frac{\alpha u H^*}{H^* + I^*} + \frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)I^*} - \frac{\alpha H^* V^*}{(H^* + I^*)^2},$$

$$\begin{aligned} A_1 = {} & \left(\mu + \mu_i D + \frac{\alpha u H^*}{H^* + I^*}\right)\left(\frac{r_2 I^*}{K_H} + \frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)I^*}\right) + \left(\frac{s_0}{H^*} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right) \\ & \times \left(\mu + \mu_i D + \frac{r_2 I^*}{K_H} + \frac{\alpha u H^*}{H^* + I^*} + \frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)I^*}\right) \\ & + \frac{r_1 H^*}{K_H}\left(\mu + \mu_i D + \frac{\alpha u H^*}{H^* + I^*} + \frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)I^*}\right) + \frac{r_2 \alpha H^* I^* V^*}{K_H (H^* + I^*)^2} - \frac{\alpha^2 u H^* I^* V^*}{(H^* + I^*)^3}, \end{aligned}$$

$$\begin{aligned} A_0 = {} & \frac{s_0}{H^*}\left(\mu + \mu_i D + \frac{\alpha u H^*}{H^* + I^*}\right)\left(\frac{r_2 I^*}{K_H} + \frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)I^*}\right) + \left(\frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right) \\ & \times \left(\mu + \mu_i D + \frac{\alpha u H^*}{H^* + I^*}\right)\frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)I^*} - \frac{\alpha^2 u H^* I^* V^*}{(H^* + I^*)^3} \\ & \times \left(\frac{r_2 I^*}{K_H} + \frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)I^*}\right) - \frac{r_2 \alpha^2 u (H^*)^2 I^* V^*}{K_H (H^* + I^*)^3}, \end{aligned}$$

$$\begin{aligned} B_0 = {} & (\mu + \mu_i D)\left\{\left(\frac{s_0}{H^*} + \frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right)\frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)^2} \right. \\ & \left. + \left(\frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right)\frac{e^{-\gamma_1\tau_1}\alpha I^* V^*}{(H^* + I^*)^2}\right\}, \end{aligned}$$

$$\begin{aligned} B_1 = {} & \left(\mu + \mu_i D + \frac{s_0}{H^*} + \frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right)\frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)^2} \\ & + \left(\frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right)\frac{e^{-\gamma_1\tau_1}\alpha I^* V^*}{(H^* + I^*)^2}, \end{aligned}$$

$$B_2 = \frac{e^{-\gamma_1\tau_1}\alpha H^* V^*}{(H^* + I^*)^2}, \quad C_0 = -\frac{k\alpha r_2 H^* I^*\,e^{-\gamma_2\tau_2}}{K_H (H^* + I^*)} \quad P_1 = -\frac{k\alpha H^*}{H^* + I^*}\,e^{-\gamma_1\tau_1 - \gamma_2\tau_2},$$

$$P_0 = -\left(\frac{s_0}{H^*} + \frac{r_1 H^*}{K_H} - \frac{\alpha V^*}{H^* + I^*}\right)\frac{k\alpha H^*}{H^* + I^*}\,e^{-\gamma_1\tau_1 - \gamma_2\tau_2},$$

with $A_i = A_i(\tau_1, \tau_2)$, $B_i = B_i(\tau_1, \tau_2)$, $C_0 = C_0(\tau_1, \tau_2)$, $P_i = P_i(\tau_1, \tau_2)$.

When $\tau_1 = \tau_2 = 0$, Equation (34) becomes

$$\lambda^3 + (A_2 + B_2)\lambda^2 + (A_1 + B_1 + P_1)\lambda + A_0 + B_0 + C_0 + P_0 = 0. \tag{35}$$

Note that

$$D_2 = A_2 + B_2 = \mu + \mu_i D + \frac{s_0}{H^*} + \frac{r_1 H^*}{K_H} + \frac{r_2 I^*}{K_H} + \frac{\alpha u H^*}{H^* + I^*} + \frac{\alpha H^* V^*}{(H^* + I^*)I^*} > 0,$$

$$\begin{aligned}
D_1 &= A_1 + B_1 + P_1 \\
&= \left(\mu + \mu_i D + \frac{\alpha u H^*}{H^* + I^*}\right)\left(\frac{r_2 I^*}{K_H} + \frac{\alpha H^* V^*}{(H^* + I^*)I^*}\right) + \left(\frac{s_0}{H^*} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right) \\
&\quad \times \left(\mu + \mu_i D + \frac{r_2 I^*}{K_H} + \frac{\alpha u H^*}{H^* + I^*} + \frac{\alpha H^* V^*}{(H^* + I^*)I^*}\right) - \frac{k\alpha H^*}{H^* + I^*} \\
&\quad + \frac{r_1 H^*}{K_H}\left(\mu + \mu_i D + \frac{\alpha u H^*}{H^* + I^*} + \frac{\alpha H^* V^*}{(H^* + I^*)I^*}\right) + \frac{r_2 \alpha H^* I^* V^*}{K_H (H^* + I^*)^2} - \frac{\alpha^2 u H^* I^* V^*}{(H^* + I^*)^3} \\
&\quad + \left(\mu + \mu_i D + \frac{s_0}{H^*} + \frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right)\frac{\alpha H^* V^*}{(H^* + I^*)^2} \\
&\quad + \left(\frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right)\frac{\alpha I^* V^*}{(H^* + I^*)^2},
\end{aligned}$$

$$\begin{aligned}
D_0 &= A_0 + B_0 + C_0 + P_0 \\
&= \frac{s_0}{H^*}\left(\mu + \mu_i D + \frac{\alpha u H^*}{H^* + I^*}\right)\left(\frac{r_2 I^*}{K_H} + \frac{\alpha H^* V^*}{(H^* + I^*)I^*}\right) + \left(\frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right) \\
&\quad \times \left(\mu + \mu_i D + \frac{\alpha u H^*}{H^* + I^*}\right)\frac{\alpha H^* V^*}{(H^* + I^*)I^*} - \frac{\alpha^2 u H^* I^* V^*}{(H^* + I^*)^3} \\
&\quad \times \left(\frac{r_2 I^*}{K_H} + \frac{\alpha H^* V^*}{(H^* + I^*)I^*}\right) - \frac{r_2 \alpha^2 u (H^*)^2 I^* V^*}{K_H (H^* + I^*)^3} \\
&\quad + (\mu + \mu_i D)\left\{\left(\frac{s_0}{H^*} + \frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right)\frac{\alpha H^* V^*}{(H^* + I^*)^2}\right. \\
&\quad \left. + \times \left(\frac{r_1 H^*}{K_H} - \frac{\alpha H^* V^*}{(H^* + I^*)^2}\right)\frac{\alpha I^* V^*}{(H^* + I^*)^2}\right\} \\
&\quad - \frac{k\alpha r_2 H^* I^*}{K_H (H^* + I^*)} - \left(\frac{s_0}{H^*} + \frac{r_1 H^*}{K_H} - \frac{\alpha V^*}{H^* + I^*}\right)\frac{k\alpha H^*}{H^* + I^*},
\end{aligned}$$

$$\begin{aligned}
D_3 &= D_1 D_2 - D_0, \\
&= \left(\alpha u c_* H^* + \alpha c_*^2 I^* V^* + d_1 - r_1 + \frac{2r_1}{K_H}H^* + \frac{r_1}{K_H}I^*\right) D_1 + (\mu_i D + \mu)\left[(\mu_i D + \mu)\left(d_1 - r_1\right.\right. \\
&\quad \left. + \frac{2r_1}{K_H}H^* + \frac{r_1}{K_H}I^* + \alpha c_*^2 I^* V^*\right) + \left(\mu_i D + \mu + \alpha u c_* H^* + d_1 - r_1 + \frac{2r_1}{K_H}H^* + \alpha c_*^2 I^* V^*\right)
\end{aligned}$$

$$\times\left(\delta-r_2+\frac{r_2}{K_H}H^*+\frac{2r_2}{K_H}I^*\right)+\alpha uc_*H^*\left(d_1-r_1+\frac{2r_1}{K_H}H^*+\frac{r_1}{K_H}I^*\right)$$

$$+\frac{r_1}{K_H}I^*\left(\delta-r_2+\frac{2r_2}{K_H}I^*\right)+\frac{\alpha r_2}{K_H}c_*^2H^*I^*V^*-k\alpha c_*H^*$$

$$+\alpha c_*^2H^*V^*\left(\mu_iD+\mu+d_1-r_1+\frac{2r_1}{K_H}H^*+\frac{r_1}{K_H}I^*\right)\Bigg]+\alpha^2c_*^4H^*I^*V^*(\mu_iD+\mu)$$

$$+\alpha c_*^2H^*V^*\Bigg[(\mu_iD+\mu+\alpha uc_*H^*)\left(\delta-r_2+\frac{r_2}{K_H}H^*+\frac{r_2}{K_H}I^*\right)+\frac{\alpha r_2}{K_H}c_*^2H^*I^*V^*$$

$$+\left(\delta-r_2+\frac{r_2}{K_H}H^*+\frac{2r_2}{K_H}I^*\right)\left(d_1-r_1+\frac{2r_1}{K_H}H^*+\alpha c_*^2I^*V^*\right)+\frac{r_1}{K_H}I^*\left(\delta-r_2+\frac{2r_2}{K_H}I^*\right)$$

$$+\alpha uc_*H^*\left(d_1-r_1+\frac{2r_1}{K_H}H^*+\frac{r_1}{K_H}I^*\right)+\frac{\alpha r_1}{K_H}c_*^2H^*I^*V^*-k\alpha c_*H^*$$

$$+\alpha c_*^2H^*V^*\left(\mu_iD+\mu+d_1-r_1+\frac{2r_1}{K_H}H^*+\frac{r_1}{K_H}I^*\right)\Bigg]$$

$$+\left(\delta-r_2+\frac{r_2}{K_H}H^*+\frac{2r_2}{K_H}I^*\right)\Bigg[\left(\mu_iD+\mu+\alpha uc_*H^*+d_1-r_1+\frac{2r_1}{K_H}H^*+\alpha c_*^2I^*V^*\right)$$

$$\times\left(\delta-r_2+\frac{r_2}{K_H}H^*+\frac{2r_2}{K_H}I^*\right)+\frac{r_1}{K_H}I^*\left(\delta-r_2+\frac{2r_2}{K_H}I^*\right)+\frac{\alpha r_2}{K_H}c_*^2H^*I^*V^*$$

$$+\alpha c_*^2H^*V^*+\left(\mu_iD+\mu+d_1-r_1+\frac{2r_1}{K_H}H^*+\frac{r_1}{K_H}I^*\right)+\frac{\alpha r_1}{K_H}c_*^2H^*I^*V^*-k\alpha c_*H^*\Bigg]$$

$$+\frac{r_1r_2}{K_H^2}H^*I^*(\mu_iD+\mu+\alpha uc_*H^*)+\frac{\alpha^2ur_1}{K_H}c_*^2H^*I^*V^*+\frac{k\alpha r_2}{K_H}c_*H^*I^*$$

$$+\alpha^3uc_*^4I^*(H^*V^*)^2(1-c_*)+k\alpha c_*H^*(1-\alpha c_*^2I^*V^*), \tag{36}$$

where $c_*=H^*/(H^*+I^*)$. By the Routh-Hurwitz criterion, it can be seen that all solutions of (35) have negative real parts if and only if $D_0>0$ and $D_1D_2>D_0$. Therefore, we have the following result.

Theorem 3.3: *Consider PDE-model (4) with $\tau_1=\tau_2=0$. If $\mathcal{R}_0>1$, the equilibrium point with infection E^* exists and is locally asymptotically stable provided that $D_0>0$ and $D_1D_2>D_0$.*

We consider (34) with $\tau_1=0$ and $\tau_2>0$. So, Equation (34) is reduced to

$$\lambda^3+E_2\lambda^2+E_1\lambda+E_0+(F_1\lambda+F_0)\,\mathrm{e}^{-\lambda\tau_2}=0, \tag{37}$$

where $E_0=A_0+B_0$, $E_1=A_1+B_1$, $E_2=A_2+B_2$, $F_0=C_0+P_0$ and $F_1=P_1$. Equation (37) can be rewritten as

$$P(\lambda,0,\tau_2)+Q(\lambda,0,\tau_2)\,\mathrm{e}^{-\lambda\tau_2}=0, \tag{38}$$

where

$$P(\lambda,0,\tau_2)=\lambda^3+E_2\lambda^2+E_1\lambda+E_0 \quad \text{and} \quad Q(\lambda,0,\tau_2)=F_1\lambda+F_0. \tag{39}$$

Now, we discuss the existence of purely imaginary roots $\lambda = i\omega$ ($\omega>0$) to (37), taking the form of a third-degree exponential polynomial in λ. In [34] the authors established a geometrical criterion which gives the existence of purely imaginary roots of a characteristic equation with delay dependent coefficients.

In order to apply the Beretta and Kuang criterion [34], we need to verify the following properties for all $\tau_2 \in [0,\tau_2^0)$, where τ_2^0 is the maximum value for which E^* exists.

(a) $P(0,0,\tau_2)+Q(0,0,\tau_2)\neq 0$,
(b) $P(i\omega,0,\tau_2)+Q(i\omega,0,\tau_2)\neq 0$, for all $\omega\in\mathbb{R}$,
(c) $\limsup\{|\frac{Q(\lambda,0,\tau_2)}{P(\lambda,0,\tau_2)}| : |\lambda|\to\infty,\ Re\lambda\geq 0\}<1$,
(d) $F(\omega,0,\tau_2)=|P(i\omega,0,\tau_2)|^2-|Q(i\omega,0,\tau_2)|^2$ admits a finite number of zeros,
(e) each positive root ω of $F(\omega,0,\tau_2)=0$ is continuous and differentiable in τ_2 if it exists.

Let $\tau_2\in[0,\tau_2^0)$ and $\omega\in\mathbb{R}$. Then $P(0,0,\tau_2)+Q(0,0,\tau_2)=E_0+F_0=A_0+B_0+C_0+P_0=D_0$. This indicates that item (a) is satisfied if $D_0\neq 0$. Moreover, a direct calculation shows that

$$P(i\omega,0,\tau_2)+Q(i\omega,0,\tau_2)=D_0-D_2\omega^2+i\omega(D_1-\omega^2).$$

Thus, one easily sees that item (b) is satisfied if $D_0-D_1D_2\neq 0$. From (39) it is known that

$$\lim_{|\lambda|\to\infty}\left|\frac{Q(\lambda,0,\tau_2)}{P(\lambda,0,\tau_2)}\right|=\lim_{|\lambda|\to\infty}\left|\frac{F_1\lambda+F_0}{\lambda^3+E_2\lambda^2+E_1\lambda+E_0}\right|=\lim_{|\lambda|\to\infty}\left|\frac{F_1}{3\lambda^2+2E_2\lambda+E_1}\right|=0.$$

Thus, (c) follows.

Let F be defined as in (d). From

$$|P(i\omega,0,\tau_2)|^2=\omega^6+(E_2^2-2E_1)\omega^4+(E_1^2-2E_0E_2)\omega^2+E_0^2 \quad \text{and} \quad |Q(i\omega,0,\tau_2)|^2=F_0^2+F_1^2\omega^2,$$

we get

$$F(\omega,0,\tau_2)=\omega^6+k_1\omega^4+k_2\omega^2+k_3,$$

where $k_1=E_2^2-2E_1$, $k_2=E_1^2-2E_0E_2-F_1^2$ and $k_3=E_0^2-F_0^2$.

Letting $\omega^2=z$, we obtain

$$G(z)=z^3+k_1z^2+k_2z+k_3=0. \tag{40}$$

If Equation (40) has no positive roots, then when $\mathcal{R}_0>1$, E^* is locally asymptotically stable for all $\tau_2\geq 0$.

We assume that (40) has positive roots, then it follows that (d) is valid, and according to the Implicit Function Theorem, (e) is also verified.

Now, by admitting that $\lambda=i\omega$ ($\omega>0$) is a root of (37), then substituting $\lambda=i\omega$ in (37), we obtain after separating in real and imaginary parts

$$\begin{cases} E_0-E_2\omega^2=-F_0\cos\omega\tau_2-F_1\omega\sin\omega\tau_2,\\ E_1\omega-\omega^3=-F_1\omega\cos\omega\tau_2+F_0\sin\omega\tau_2. \end{cases} \tag{41}$$

From system (41), we have

$$\sin\omega\tau_2=\frac{(E_2F_1-F_0)\omega^3+(E_1F_0-E_0F_1)\omega}{F_0^2+F_1^2\omega^2}, \tag{42}$$

$$\cos\omega\tau_2 = \frac{F_1\omega^4 + (E_2F_0 - E_1F_1)\omega^2 - E_0F_0}{F_0^2 + F_1^2\omega^2}. \tag{43}$$

Now, using the definitions of $P(\lambda, 0, \tau_2)$ and $Q(\lambda, 0, \tau_2)$ given in (39), and applying the property (a), (42) and (43) can be written easily as

$$\sin\omega\tau_2 = \mathrm{Im}\frac{P(i\omega, 0, \tau_2)}{Q(i\omega, 0, \tau_2)} \quad \text{and} \quad \cos\omega\tau_2 = -\mathrm{Re}\frac{P(i\omega, 0, \tau_2)}{Q(i\omega, 0, \tau_2)}. \tag{44}$$

This reads as

$$|P(i\omega, 0, \tau_2)|^2 = |Q(i\omega, 0, \tau_2)|^2.$$

Denote by $I \subseteq \mathbb{R}_{+0}$ the set of τ_2 for which positive solutions, $\omega(\tau_2)$, exist for the following equation:

$$F(\omega, 0, \tau_2) = |P(i\omega, 0, \tau_2)|^2 - |Q(i\omega, 0, \tau_2)|^2 = 0.$$

If $I \neq \emptyset$, then E^* is stable for $\tau_2 \geq 0$. We note that

$$F(0, 0, \tau_2) = (A_0 + B_0)^2 - (C_0 + P_0)^2 \quad \text{and} \quad \lim_{\omega\to\infty} F(\omega, 0, \tau_2) = \infty.$$

A direct computation gives

$$\begin{aligned}
A_0 + B_0 + C_0 + P_0 = {} & (\mu_i D + \mu)\left(d_1 - r_1 + \frac{2r_1}{K_H}H^* + \frac{r_1}{K_H}I^* + \alpha c_*^2 I^* V^*\right) \\
& \times \left(\delta - r_2 + \frac{r_2}{K_H}H^* + \frac{2r_2}{K_H}I^*\right) \\
& + \alpha u c_* H^*\left(d_1 - r_1 + \frac{2r_1}{K_H}H^* + \frac{r_1}{K_H}I^*\right)\left(\delta - r_2 + \frac{r_2}{K_H}H^* + \frac{2r_2}{K_H}I^*\right) \\
& + \frac{r_2}{K_H}I^*(\mu_i D + \mu + \alpha u c_* H^*)\left(\alpha c_*^2 H^* V^* - \frac{r_1}{K_H}H^*\right) - \frac{\alpha^2 u r_1}{K_H}c_*^2 H^* I^* V^* \\
& + \alpha c_*^2 H^* V^*(\mu_i D + \mu)\left(d_1 - r_1 + \frac{2r_1}{K_H}H^* + \frac{r_1}{K_H}I^*\right) \\
& + \frac{\alpha r_1}{K_H}c_*^2 H^* I^* V^*(\mu_i D + \mu) + \alpha^3 u c_*^5 I^*(H^* V^*)^2(H^* + I^* - 1) \\
& - \frac{\alpha r_2}{K_H}k c_* H^* I^*\, \mathrm{e}^{-\gamma_2\tau_2} + k\alpha c_* H^*(\alpha c_*^2 I^* V^* - 1)\, \mathrm{e}^{-\gamma_2\tau_2},
\end{aligned} \tag{45}$$

$$\begin{aligned}
A_0 + B_0 - C_0 - P_0 = {} & (\mu_i D + \mu)\left(d_1 - r_1 + \frac{2r_1}{K_H}H^* + \frac{r_1}{K_H}I^* + \alpha c_*^2 I^* V^*\right) \\
& \times \left(\delta - r_2 + \frac{r_2}{K_H}H^* + \frac{2r_2}{K_H}I^*\right) \\
& + \alpha u c_* H^*\left(d_1 - r_1 + \frac{2r_1}{K_H}H^* + \frac{r_1}{K_H}I^* *\right)\left(\delta - r_2 + \frac{r_2}{K_H}H^* + \frac{2r_2}{K_H}I^*\right) \\
& + \frac{r_2}{K_H}I^*(\mu_i D + \mu + \alpha u c_* H^*)\left(\alpha c_*^2 H^* V^* - \frac{r_1}{K_H}H^*\right) + \frac{\mu\alpha r_1}{K_H}c_* H^* V^*
\end{aligned}$$

$$+\alpha c_*^2 H^* V^* (\mu_i D + \mu)\left(d_1 - r_1 + \frac{2r_1}{K_H} H^* + \frac{r_1}{K_H} I^*\right)$$
$$+\frac{\alpha r_1}{K_H} c_*^2 H^* I^* V^* (\mu_i D + \mu) + \alpha^3 u c_*^5 I^* (H^* V^*)^2 (H^* + I^* - 1)$$
$$+ k\alpha c_* H^* (1 - \alpha c_*^2 I^* V^*)\, \mathrm{e}^{-\gamma_2 \tau_2} > 0. \tag{46}$$

Therefore, if

$A_0 + B_0 + C_0 + P_0 < 0$, we have $I \neq \emptyset$ and $F(\omega, 0, \tau_2) = 0$ has at least a positive solution.

From (44), we choose an angle $\theta \in [0, 2\pi)$ such that

$$\sin\theta\tau_2 = \mathrm{Im}\frac{P(i\omega, 0, \tau_2)}{Q(i\omega, 0, \tau_2)} \quad \text{and} \quad \cos\theta\tau_2 = -\mathrm{Re}\frac{P(i\omega, 0, \tau_2)}{Q(i\omega, 0, \tau_2)}. \tag{47}$$

From (44) and (47), we get

$$\omega\tau_2 = \theta + 2\pi n, \quad n \in \{0, 1, 2, \ldots\}.$$

Therefore, we can define the maps $\tau_n : I \to \mathbb{R}_{+0}$ as

$$\tau_n(\tau_2) = \frac{\theta(\tau_2) + 2\pi n}{\omega(\tau_2)}, \quad \tau_2 \in I,\ n \in \{0, 1, 2, \ldots\},$$

where $\omega(\tau_2)$ is a positive root of Equation (37).

Define the functions $S_n : I \to \mathbb{R}$ by

$$S_n(\tau_2) = \tau_2 - \frac{\theta(\tau_2) + 2\pi n}{\omega(\tau_2)}, \quad \tau_2 \in I,\ n = 0, 1, 2, \ldots$$

that are continuous and differentiable in τ_2. Therefore, Equation (37) admits a purely imaginary root $\lambda = i\omega(\tau_2^*)$ at delay $\tau_2 = \tau_2^*$ with $\omega(\tau_2^*) > 0$ whenever τ_2^* is a solution of equation $S_n(\tau_2) = 0$ for some $n \in \mathbb{N}$. Thus, proceeding as in [34], we get the following result.

Theorem 3.4: *Assume that $D_0 < 0$ and $D_0 - D_1 D_2 \neq 0$. Then the characteristic Equation (37) has a pair of simple conjugate pure imaginary roots, $\pm i\omega(\tau_2^*)$, at $\tau_2 = \tau_2^*$ with $\omega(\tau_2^*) > 0$ if $S_n(\tau_2^*) = 0$ for some $n \in \mathbb{N}$, and these roots cross the imaginary axis from left to right if $\sigma_2(\tau_2^*) > 0$ and from right to left if $\sigma(\tau_2^*) < 0$, where*

$$\sigma_2(\tau_2^*) = sign\left\{\left.\frac{dRe\lambda}{d\tau_2}\right|_{\lambda = i\omega(\tau_2^*)}\right\} = sign\{F'_\omega(\omega\tau_2^*, \tau_2^*)\} \times sign\left\{\left.\frac{dS_n(\tau_2)}{d\tau_2}\right|_{\tau_2 = \tau_2^*}\right\}.$$

By applying Theorem 3.4 and the Hopf bifurcation theorem for functional differential equations [35], we get the existence of a Hopf bifurcation given in the following result.

Theorem 3.5: *Assume that $\mathcal{R}_0 > 1$, $D_0 < 0$ and $D_0 - D_1 D_2 \neq 0$. Then, for PDE system (4), there exists $\tau_2^* \in I$ such that the endemic equilibrium E^* is locally asymptotically stable when $0 \le \tau_2 < \tau_2^*$, and becomes unstable when τ_2 stays in some right neighborhood of τ_2^*. Therefore, a Hopf bifurcation occurs at $\tau_2 = \tau_2^*$.*

We now consider the case $\tau_1 > 0$ and $\tau_2 = 0$. Then Equation (34) becomes

$$\lambda^3 + A_{22}\lambda^2 + A_{21}\lambda + A_{20} + (B_{22}\lambda^2 + B_{21}\lambda + B_{20})\, \mathrm{e}^{-\lambda\tau_1} = 0, \tag{48}$$

where

$$A_{22} = A_2, \quad A_{21} = A_1, \quad A_{20} = A_0 + C_0, \quad B_{22} = B_2, \quad B_{21} = B_1 + P_1, \quad B_{20} = B_0 + P_0.$$

Equation (48) can be rewritten as

$$P_1(\lambda, \tau_1, 0) + Q_1(\lambda, \tau_1, 0)\, \mathrm{e}^{-\lambda\tau_1} = 0, \tag{49}$$

where

$$P_1(\lambda, \tau_1, 0) = \lambda^3 + A_{22}\lambda^2 + A_{21}\lambda + A_{20} \quad \text{and} \quad Q(\lambda, \tau_1, 0) = B_{22}\lambda^2 + B_{21}\lambda + B_{20}. \tag{50}$$

Let $\lambda = i\omega_1$ ($\omega_1 > 0$) be a root of Equation (48). Then

$$\begin{cases} A_{20} - A_{22}\omega_1^2 = -(B_{20} - B_{22}\omega_1^2)\cos\omega_1\tau_1 - B_{21}\omega_1 \sin\omega_1\tau_1, \\ A_{21}\omega_1 - \omega_1^3 = -B_{21}\omega_1 \cos\omega_1\tau_1 + (B_{20} - B_{22}\omega_1^2)\sin\omega_1\tau_1. \end{cases} \tag{51}$$

It follows from system (51) that

$$\sin\omega_1\tau_1 = \frac{B_{22}\omega_1^5 + (A_{22}B_{21} - B_{20} - A_{21}B_{22})\omega_1^3 + (A_{21}B_{20} - A_{20}B_{21})\omega_1}{B_{21}^2\omega_1^2 + (B_{20} - B_{22}\omega_1^2)^2}, \tag{52}$$

$$\cos\omega_1\tau_1 = -\frac{(A_{22}B_{22} - B_{21})\omega_1^4 + (A_{21}B_{21} - A_{22}B_{20} - A_{20}B_{22})\omega_1^2 + A_{20}B_{20}}{B_{21}^2\omega_1^2 + (B_{20} - B_{22}\omega_1^2)^2}. \tag{53}$$

Note that

$$\sin\omega_1\tau_1 = \mathrm{Im}\frac{P_1(i\omega_1, \tau_1, 0)}{Q_1(i\omega_1, \tau_1, 0)} \quad \text{and} \quad \cos\omega_1\tau_1 = -\mathrm{Re}\frac{P_1(i\omega_1, \tau_1, 0)}{Q_1(i\omega_1, \tau_1, 0)}, \tag{54}$$

which gives

$$|P_1(i\omega_1, \tau_1, 0)|^2 = |Q_1(i\omega_1, \tau_1, 0)|^2.$$

Define

$$\tilde{F}_1(\omega_1) = |P_1(i\omega_1, \tau_1, 0)|^2 - |Q_1(i\omega_1, \tau_1, 0)|^2. \tag{55}$$

Let

$$I_1 = \{\tau_1 \in \mathbb{R}_{+0} : \tilde{F}_1(\omega_1, \tau_1, 0) = 0\, and\, \mathbb{R}_{+0}\}. \tag{56}$$

Thus I_1 is the set of τ_1 for which positive solutions, $\omega_1(\tau_1)$, exist for the equation $\tilde{F}_1(\omega_1, \tau_1, 0) = 0$. From (54), we choose $\theta_1 \in [0, 2\pi)$ such that

$$\sin\theta_1\tau_1 = \mathrm{Im}\frac{P_1(i\omega_1, \tau_1, 0)}{Q_1(i\omega, \tau_1, 0)} \quad \text{and} \quad \cos\theta_1\tau_1 = -\mathrm{Re}\frac{P_1(i\omega_1, \tau_1, 0)}{Q_1(i\omega_1, \tau_1, 0)}. \tag{57}$$

From (54) and (57), we have

$$\omega_1\tau_1 = \theta_1 + 2\pi n, \quad n \in \{0, 1, 2, \ldots\}.$$

Therefore, we can define the maps $\tau_n^1 : I_1 \to \mathbb{R}_{+0}$ as

$$\tau_n^1(\tau_1) = \frac{\theta_1(\tau_1) + 2\pi n}{\omega_1(\tau_1)}, \quad \tau_1 \in I_1,\ n \in \{0, 1, 2, \ldots\},$$

where I_1 is defined in (56) and $\omega_1(\tau_1)$ is a positive root of Equation (48).

Define the functions $S_n^1 : I_1 \to \mathbb{R}$

$$S_n^1(\tau_1) = \tau_1 - \frac{\theta_1(\tau_1) + 2\pi n}{\omega_1(\tau_1)}, \quad \tau_1 \in I_1,\ n \in \{0, 1, 2, \ldots\}$$

that are continuous and differentiable in τ_1, with I_1 defined in (56). Therefore, Equation (48) admits a purely imaginary root $\lambda = i\omega_1(\tau_1^*)$ at delay $\tau_1 = \tau_1^*$ with $\omega_1(\tau_1^*)>0$ whenever τ_1^* is a solution of equation $S_n^1(\tau_1) = 0$ for some $n \in \mathbb{N}$. Thus, proceeding as in [34], we get the following result.

Theorem 3.6: *Assume that $\omega_1(\tau_1)$ is a positive root of (48) defined for $\tau_1 \in I_1 \subseteq \mathbb{B}_{+0}$ and for some $\tau_1^* \in I_1$, $S_n^1(\tau_1^*) = 0$ for some $n \in \mathbb{N}$. Then the characteristic Equation (48) has a pair of simple conjugate purely imaginary roots, $\pm i\omega_1(\tau_1^*)$, at $\tau_1 = \tau_1^*$, which cross the imaginary axis from left to right if $\sigma_1(\tau_1^*)>0$ and from right to left if $\sigma_1(\tau_1^*)<0$, where*

$$\sigma_1(\tau_1^*) = sign\left\{ \frac{dRe\lambda}{d\tau_1}\bigg|_{\lambda=i\omega_1(\tau_1^*)} \right\} = sign\{\tilde{F}'_{1_{\omega_1}}(\omega_1\tau_1^*, \tau_1^*)\} \times sign\left\{ \frac{dS_n^1(\tau_1)}{d\tau_1}\bigg|_{\tau_1=\tau_1^*} \right\}.$$

By applying Theorem 3.6 and the Hopf bifurcation theorem for functional differential equations [35], we get the existence of a Hopf bifurcation given in the following result.

Theorem 3.7: *Assume that $\mathcal{R}_0>1$. Then, for PDE system (4), there exists $\tau_1^* \in I_1$, such that the endemic equilibrium E^* is locally asymptotically stable when $0 \le \tau_1<\tau_1^*$, and becomes unstable when τ_1 stays in some right neighborhood of τ_1^*. Therefore, a Hopf bifurcation occurs at $\tau_1 = \tau_1^*$.*

Let now $\tau_1>0$ and $\tau_2 \in (0, \tau_2^0)$. Then Equation (34) reads

$$\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 + C_0\,e^{-\lambda\tau_2^0} + (B_2\lambda^2 + B_1\lambda + B_0 + (P_1\lambda + P_0)\,e^{-\lambda\tau_2^0})\,e^{-\lambda\tau_1} = 0. \tag{58}$$

Let $\lambda = i\omega_2$ ($\omega_2>0$) be a root of Equation (58). Then

$$\begin{cases} N_1\cos\omega_2\tau_1 + N_2\sin\omega_2\tau_1 = R_1, \\ N_2\cos\omega_2\tau_1 + N_1\sin\omega_2\tau_1 = R_2, \end{cases} \tag{59}$$

where

$$N_1 = B_0 - B_2\omega_2^2 + P_1\omega_2\sin\omega_2\tau_2^0 + P_0\cos\omega_2\tau_2^0,$$

$$N_2 = B_1\omega_2 + P_1\omega_2\cos\omega_2\tau_2^0 - P_0\sin\omega_2\tau_2^0,$$

$$R_1 = -(A_0 - A_2\omega_2^2 + C_0\cos\omega_2\tau_2^0),$$

$$R_2 = -(A_1\omega_2 - \omega_2^3 - C_0\sin\omega_2\tau_2^0).$$

It follows from system (59) that

$$\sin\omega_2\tau_1 = \frac{N_2R_1 - N_1R_2}{N_1^2 + N_2^2} \quad \text{and} \quad \cos\omega_1\tau_1 = \frac{N_1R_1 + N_2R_2}{N_1^2 + N_2^2}. \tag{60}$$

Squaring and adding (60) yields

$$\tilde{F}_2(\omega_2, \tau_1, \tau_2^0) := \omega_2^6 + q_4\omega_2^4 + q_3\omega_2^3 + q_2\omega_2^2 + q_1\omega_2 + q_0, \tag{61}$$

where

$$
\begin{aligned}
q_4 &= A_2^2 - 2A_1 - B_2^2,\\
q_3 &= 2(C_0 + B_2P_1)\sin\omega_2\tau_2^0,\\
q_2 &= A_1^2 + B_0B_2 - B_1^2 - 2A_0A_2 - P_1^2 + 2(B_2P_0 - A_2C_0 - B_1P_1)\cos\omega_2\tau_2^0,\\
q_1 &= 2(B_1P_0 - A_1C_0 - B_0P_1)\sin\omega_2\tau_2^0,\\
q_0 &= A_0^2 + C_0^2 - B_0^2 - P_0^2 + 2(A_0C_0 - B_0P_0)\cos\omega_2\tau_2^0.
\end{aligned}
$$

Let

$$
I_2 = \{\tau_1 \in \mathbb{R}_{+0} : \tilde{F}_2(\omega_2, \tau_1, \tau_2^0) = 0 \; and \; \omega_2(\tau_1, \tau_2^0) > 0\}. \tag{62}
$$

Thus I_2 is the set of τ_1 for which positive solutions, $\omega_2(\tau_1, \tau_2^0)$, exist for the equation $\tilde{F}_2(\omega_2, \tau_1, \tau_2^0) = 0$. If $I_2 \neq \emptyset$, then E^* is stable for $\tau_2 = \tau_2^0$ and $\tau_1 \geq 0$. We note that

$$
\tilde{F}_2(0, \tau_1, \tau_2^0) = (A_0 + C_0)^2 - (B_0 + P_0)^2 \quad \text{and} \quad \lim_{\omega_2 \to \infty} \tilde{F}_2(\omega_2, \tau_1, \tau_2^0) = \infty.
$$

Now, we choose $\theta_2(\tau_1) \in [0, 2\pi)$ such that

$$
\sin\theta_2(\tau_1) = \frac{N_2R_1 - N_1R_2}{N_1^2 + N_2^2} \quad \text{and} \quad \cos\theta_2(\tau_1) = \frac{N_1R_1 + N_2R_2}{N_1^2 + N_2^2}. \tag{63}
$$

Define the functions $S_n^2 : I_2 \to \mathbb{R}$

$$
S_n^2(\tau_1) = \tau_1 - \frac{\theta_2(\tau_1) + 2\pi n}{\omega_2(\tau_1)}, \quad \tau_1 \in I_2,\ n = 0, 1, 2, \ldots
$$

that are continuous and differentiable in τ_1, with I_2 defined in (62). Therefore, Equation (58) has a purely imaginary root $\lambda = i\omega(\tau_{11}^*, \tau_2^0)$ at delay $\tau_1 = \tau_{11}^*$ with $\omega(\tau_{11}^*, \tau_2^0) > 0$ if and only if τ_{11}^* is a solution of equation $S_n^2(\tau_1) = 0$ for some $n \in \mathbb{N}$. Thus, proceeding as in [34], we get the following result, whose proof is given in details.

Theorem 3.8: *Assume that $\omega_2(\tau_1)$ is a positive root of* (58) *defined for $\tau_1 \in I_2 \subseteq \mathbb{R}_{+0}$ and for some $\tau_{11}^* \in I_2$, $S_n^2(\tau_{11}^*) = 0$ for some $n \in \mathbb{N}$. Then the characteristic Equation* (58) *admits a simple conjugate purely imaginary root $\lambda = i\omega_2(\tau_{11}^*)$ at $\tau_1 = \tau_{11}^*$ which crosses the imaginary axis from left to right if $\sigma_2(\tau_{11}^*) > 0$ and from right to left if $\sigma_2(\tau_{11}^*) < 0$, where*

$$
\sigma_2(\tau_{11}^*) = sign\left\{ \left.\frac{dRe\lambda}{d\tau_1}\right|_{\lambda = i\omega_2(\tau_{11}^*, \tau_2^0)} \right\} = sign\{\tilde{F}'_{2_{\omega_2}}(\omega_2, \tau_{11}^*, \tau_2^0)\} \cdot sign\left\{ \left.\frac{dS_n^2(\tau_1)}{d\tau_1}\right|_{\tau_1 = \tau_{11}^*} \right\}.
$$

Proof: Equation (58) can be rewritten as

$$
G_0 + G_1\, e^{-\lambda\tau_2^0} + \left(G_2 + G_3\, e^{-\lambda\tau_2^0}\right) e^{-\lambda\tau_1} = 0, \tag{64}
$$

where

$$
\begin{aligned}
&G_0 = \lambda^3 + A_2\lambda^2 + A_1\lambda + A_0, \quad G_1 = C_0, \quad G_2 = B_2\lambda^2 + B_1\lambda + B_0,\\
&G_3 = P_1\lambda + P_0, \quad G_i = G_i(\lambda, \tau_1, \tau_2^0).
\end{aligned}
$$

It is worth noting that $G_1 = C_0$ depends neither on λ nor on τ_1. Therefore, if $\tau_2 = \tau_2^0$ is fixed, then G_1 is a real constant.

For a fixed delay $\tau_2 = \tau_2^0$, let $\lambda = i\omega_2(\tau_1, \tau_2^0)$ be a root of (64). Then system (59) can be rewritten as

$$\begin{cases} N_{11} \cos \omega_2 \tau_1 + N_{22} \sin \omega_2 \tau_1 = R_{11}, \\ N_{22} \cos \omega_2 \tau_1 + N_{11} \sin \omega_2 \tau_1 = R_{22}. \end{cases} \tag{65}$$

where

$$\begin{aligned} &N_{11} = G_{2R} + G_{3R} \cos \omega_2 \tau_2^0 + G_{3I} \sin \omega_2 \tau_2^0, \quad N_{22} = G_{2I} - G_{3R} \sin \omega_2 \tau_2^0 + G_{3I} \cos \omega_2 \tau_2^0, \\ &R_{11} = -G_{0R} - G_{1R} \cos \omega_2 \tau_2^0, \quad R_{22} = -G_{0I} + G_{1R} \sin \omega_2 \tau_2^0, \end{aligned} \tag{66}$$

with $G_{jR} = \mathrm{Re} G_i$ and $G_{jI} = \mathrm{Im} G_i, j = 0, 1, 2, 3$. Then, one has

$$\cos \omega_2 \tau_2^0 = -\frac{\varphi}{\left|G_2 + G_3\, \mathrm{e}^{-i\omega_2 \tau_2^0}\right|^2} \quad \text{and} \quad \sin \omega_2 \tau_2^0 = \frac{\psi}{\left|G_2 + G_3\, \mathrm{e}^{-i\omega_2 \tau_2^0}\right|^2}, \tag{67}$$

where

$$\begin{aligned} \varphi &= (G_{2R} + G_{3R} \cos \omega_2 \tau_2^0 + G_{3I} \sin \omega_2 \tau_2^0)(G_{0R} + G_{1R} \cos \omega_2 \tau_2^0) \\ &\quad + (G_{2I} - G_{3R} \sin \omega_2 \tau_2^0 + G_{3I} \cos \omega_2 \tau_2^0)(G_{0I} - G_{1R} \sin \omega_2 \tau_2^0), \\ \psi &= -(G_{2I} - G_{3R} \sin \omega_2 \tau_2^0 + G_{3I} \cos \omega_2 \tau_2^0)(G_{0R} + G_{1R} \cos \omega_2 \tau_2^0) \\ &\quad + (G_{2R} + G_{3R} \cos \omega_2 \tau_2^0 + G_{3I} \sin \omega_2 \tau_2^0)(G_{0I} - G_{1R} \sin \omega_2 \tau_2^0). \end{aligned}$$

Note that

$$\cos \omega_2 \tau_2^0 = -\mathrm{Re}\left(\frac{G_0 + G_1\, \mathrm{e}^{-i\omega_2 \tau_2^0}}{G_2 + G_3\, \mathrm{e}^{-i\omega_2 \tau_2^0}}\right) \quad \text{and} \quad \sin \omega_2 \tau_2^0 = \mathrm{Im}\left(\frac{G_0 + G_1\, \mathrm{e}^{-i\omega_2 \tau_2^0}}{G_2 + G_3\, \mathrm{e}^{-i\omega_2 \tau_2^0}}\right).$$

This reads as

$$\left|G_0 + G_1\, \mathrm{e}^{-i\omega_2 \tau_2^0}\right|^2 = \left|G_2 + G_3\, \mathrm{e}^{-i\omega_2 \tau_2^0}\right|^2. \tag{68}$$

Define

$$\tilde{F}_3(\omega_2, \tau_1, \tau_2^0) = \left|G_0 + G_1\, \mathrm{e}^{-i\omega_2 \tau_2^0}\right|^2 - \left|G_2 + G_3\, \mathrm{e}^{-i\omega_2 \tau_2^0}\right|^2. \tag{69}$$

Thus $\omega_2(\tau_1, \tau_2^0)$ in (67) is a positive root of $\tilde{F}_3(\omega_2, \tau_1, \tau_2^0) = 0$ and consequently, $I_2 \neq \emptyset$. Then for any $\tau_1 \in I_2$, differentiating (69) with respect to τ_1 yields

$$\tilde{F}'_{3_{\omega_2}}(\omega_2, \tau_1, \tau_2^0)\omega'_2 + \tilde{F}'_{3_{\tau_2}}(\omega_2, \tau_1, \tau_2^0) = 0, \tag{70}$$

where

$$\begin{aligned} \tilde{F}'_{3_{\omega_2}} &= 2[G_{0R} G'_{0R_{\omega_2}} + G_{0I} G'_{0I_{\omega_2}} - G_{2R} G'_{2R_{\omega_2}} - G_{2I} G'_{2I_{\omega_2}} \\ &\quad - G_{3R} G'_{3R_{\omega_2}} - G_{3I} G'_{3I_{\omega_2}} + \cos \omega_2 \tau_2^0 (G_{1R} G'_{0R_{\omega_2}} \end{aligned}$$

$$
\begin{aligned}
&- G_{3R}G'_{2R_{\omega_2}} - G_{2R}G'_{3R_{\omega_2}} - G_{3I}G'_{2I_{\omega_2}} - G_{2I}G'_{3I\omega_2})\\
&+ \tau_2^0 \cos\omega_2\tau_2^0(G_{2I}G_{3R} - G_{0I}G_{1R} - G_{2R}G_{3I})\\
&+ \sin\omega_2\tau_2^0(G_{3R}G'_{2I_{\omega_2}} - G_{3I}G'_{2R_{\omega_2}} - G_{2R}G'_{3I_{\omega_2}} + G_{2I}G'_{3R_{\omega_2}} - G_{1I}G'_{0I_{\omega_2}})]\\
&+ \tau_2^0 \sin\omega_2\tau_2^0(G_{2R}G'_{3R_{\omega_2}} + G_{2I}G_{3I} - G_{0R}G_{1R\omega_2})],
\end{aligned}
$$

$$
\begin{aligned}
\tilde{F}'_{3_{\tau_2}} = 2[&G_{0R}G'_{0R_{\tau_1}} + G_{0I}G'_{0I_{\tau_1}} - G_{2R}G'_{2R_{\tau_1}} - G_{2I}G'_{2I_{\tau_1}} - G_{3R}G'_{3R_{\tau_1}} - G_{3I}G'_{3I_{\tau_1}}\\
&+ \cos\omega_2\tau_2^0(G_{1R}G'_{0R_{\tau_1}} - G_{3R}G'_{2R_{\tau_1}} - G_{2R}G'_{3R_{\tau_1}} - G_{3I}G'_{2I_{\tau_1}} - G_{2I}G'_{3I_{\tau_1}})\\
&+ \sin\omega_2\tau_2^0(G_{3R}G'_{2I_{\tau_1}} + G_{2I}G'_{3R_{\tau_1}} - G_{3I}G'_{2R_{\tau_1}} - G_{2R}G'_{3I_{\tau_1}} - G_{1R}G'_{0I_{\tau_1}})].
\end{aligned}
$$

For $\tau_1 \in I_2$ and $\omega_2(\tau_1, \tau_2^0)$, by (67), we get that $\theta_2(\tau_1)$ chosen in (63) satisfies

$$
\cos\theta_2(\tau_1) = -\frac{\varphi}{\left|G_2 + G_3\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^2} \quad \text{and} \quad \sin\theta_2(\tau_1) = \frac{\psi}{\left|G_2 + G_3\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^2}. \tag{71}
$$

Because $S_n^2(\tau_{11}^*) = 0$ for some $n \in \mathbb{N}$, we have $\omega_2(\tau_{11}^*, \tau_2^0)\tau_{11}^* = \theta(\tau_{11}^*) + 2\pi n$. Moreover, (67) and (71) imply $\tilde{F}_3(\omega_2, \tau_{11}^*, \tau_2^0) = 0$. Thus, $\pm i\omega_2(\tau_{11}^*, \tau_2^0)$ are roots of (64). Now, we prove the criterion for direction of the geometric crossing. Differentiating (64) with respect to τ_1, we have

$$
\frac{\mathrm{d}\lambda}{\mathrm{d}\tau_1} = \frac{\lambda(G_2 + G_3\,\mathrm{e}^{-\lambda\tau_2^0})\,\mathrm{e}^{-\lambda\tau_1} - G'_{0_{\tau_1}} - (G'_{2_{\tau_1}} + G'_{3_{\tau_1}}\,\mathrm{e}^{-\lambda\tau_2^0})\,\mathrm{e}^{-\lambda\tau_1}}{G'_{0_\lambda} - \tau_2^0 G_1\,\mathrm{e}^{-\lambda\tau_2^0} + (G'_{2_\lambda} - \tau_1 G_2)\,\mathrm{e}^{-\lambda\tau_1} + [(G'_{3_\lambda} - \tau_2^0 G_3 - \tau_1 G_3)\,\mathrm{e}^{-\lambda\tau_2^0}]\,\mathrm{e}^{-\lambda\tau_1}},
$$

where the variables $(\lambda, \tau_1, \tau_2^0)$ of functions $G_j, j = 0, 1, 2, 3$ and their derivatives are omitted for concision. From (64), we have $\mathrm{e}^{-\lambda\tau_1} = -\frac{G_0 + G_1\,\mathrm{e}^{-\lambda\tau_2^0}}{G_2 + G_3\,\mathrm{e}^{-\lambda\tau_2^0}}$. It then follows that

$$
\frac{\mathrm{d}\lambda}{\mathrm{d}\tau_1} = \frac{\lambda + \dfrac{G'_{0_{\tau_1}}}{G_0 + G_1\,\mathrm{e}^{-\lambda\tau_2^0}} - \dfrac{G'_{2_{\tau_1}} + G'_{3_{\tau_1}}\,\mathrm{e}^{-\lambda\tau_2^0}}{G_2 + G_3\,\mathrm{e}^{-\lambda\tau_2^0}}}{-\dfrac{G'_{0_\lambda} - \tau_2^0 G_1\,\mathrm{e}^{-\lambda\tau_2^0}}{G_0 + G_1\,\mathrm{e}^{-\lambda\tau_2^0}} + \dfrac{G'_{2_\lambda}}{G_2 + G_3\,\mathrm{e}^{-\lambda\tau_2^0}} - \tau_1 + \dfrac{(G'_{3_\lambda} - \tau_2^0 G_3)\,\mathrm{e}^{-\lambda\tau_2^0}}{G_2 + G_3\,\mathrm{e}^{-\lambda\tau_2^0}}}.
$$

From the equality (68) and the property $\frac{1}{z} = \frac{\bar{z}}{|z|^2}$, the above equality becomes

$$
\left.\frac{\mathrm{d}\lambda}{\mathrm{d}\tau_1}\right|_{\lambda = i\omega_2} = \frac{\mathbb{T}}{\mathbb{H}},
$$

where

$$
\mathbb{T} = i\omega_2|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}|^2 + G'_{0_{\tau_1}}\overline{(G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0})} - (G'_{2_{\tau_1}} + G'_{3_{\tau_1}}\,\mathrm{e}^{-i\omega_2\tau_2^0})\overline{(G_2 + G_3\,\mathrm{e}^{-i\omega_2\tau_2^0})},
$$

$$
\begin{aligned}
\mathbb{J} = [&-G'_{0_\lambda} + \tau_2^0 G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}]\overline{(G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0})} + G'_{2_\lambda}\overline{(G_2 + G_3\,\mathrm{e}^{-i\omega_2\tau_2^0})} - \tau_1|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}|^2\\
&+ [(G'_{3_\lambda} - \tau_2^0 G_3)\,\mathrm{e}^{-i\omega_2\tau_2^0}]\overline{(G_2 + G_3\,\mathrm{e}^{-i\omega_2\tau_2^0})}.
\end{aligned}
$$

Accordingly,

$$\operatorname{sign}\left\{\frac{\mathrm{dRe}\lambda}{\mathrm{d}\tau_1}\bigg|_{\lambda=i\omega_2(\tau_{11}^*,\tau_2^0)}.\right\}=\operatorname{sign}\left\{\operatorname{Re}\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau_1}\right)^{-1}\bigg|_{\lambda=i\omega_2(\tau_{11}^*,\tau_2^0)}\right\}=\operatorname{sign}\left\{\operatorname{Re}\left(\frac{\mathbb{J}}{\mathbb{T}}\right)\right\}. \tag{72}$$

By tedious computation and employing the fact that

$$iG'_{j_\lambda}(i\omega_2,\tau_1,\tau_2^0)=G'_{j_{\omega_2}}(i\omega_2,\tau_1,\tau_2^0),\quad \text{for } j=0,1,2,3,$$

we get

$$\begin{aligned}
\mathbb{J}_1 &= \left[-G'_{0_\lambda}+\tau_2^0 G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}\right]\overline{(G_0+G_1\,\mathrm{e}^{-i\omega_2\tau_2^0})}+G'_{2_\lambda}\overline{(G_2+G_3\,\mathrm{e}^{-i\omega_2\tau_2^0})}\\
&\quad+[(G'_{3_\lambda}-\tau_2^0G_3)\,\mathrm{e}^{-i\omega_2\tau_2^0}]\overline{(G_2+G_3\,\mathrm{e}^{-i\omega_2\tau_2^0})}\\
&=\Big\{-G'_{0I_{\omega_2}}(G_{0R}+G_{1R}\cos\omega_2\tau_2^0)+G'_{0R_{\omega_2}}(G_{0I}-G_{1R}\sin\omega_2\tau_2^0)\\
&+G'_{2I_{\omega_2}}(G_{2R}+G_{3R}\cos\omega_2\tau_2^0+G_{3I}\sin\omega_2\tau_2^0)\\
&\quad-G'_{2R_{\omega_2}}(G_{2I}+G_{3I}\cos\omega_2\tau_2^0-G_{3R}\sin\omega_2\tau_2^0)+\tau_2^0G_{1R}(G_{0R}\cos\omega_2\tau_2^0\\
&\quad-G_{0I}\sin\omega_2\tau_2^0)+(G'_{3I_{\omega_2}}-\tau_2^0G_{3R})(G_{3R}+G_{2R}\cos\omega_2\tau_2^0-G_{2I}\sin\omega_2\tau_2^0)\\
&\quad-(G'_{3R_{\omega_2}}+\tau_2^0G_{3I})(G_{3I}+G_{2R}\cos\omega_2\tau_2^0+G_{2R}\sin\omega_2\tau_2^0)\Big\}\\
&\quad+i\Big\{G'_{0I_{\omega_2}}(G_{0I}-G_{1R}\sin\omega_2\tau_2^0)+G'_{0R_{\omega_2}}(G_{0R}+G_{1R}\cos\omega_2\tau_2^0)-G'_{2I_{\omega_2}}(G_{2I}+G_{3I}\cos\omega_2\tau_2^0\\
&\quad-G_{3R}\sin\omega_2\tau_2^0)-G'_{2R_{\omega_2}}(G_{2R}+G_{3R}\cos\omega_2\tau_2^0+G_{3I}\sin\omega_2\tau_2^0)-\tau_2^0G_{1R}(G_{0I}\cos\omega_2\tau_2^0\\
&\quad+G_{0R}\sin\omega_2\tau_2^0)-(G'_{3I_{\omega_2}}-\tau_2^0G_{3R})(G_{3I}+G_{2R}\cos\omega_2\tau_2^0+G_{2R}\sin\omega_2\tau_2^0)\\
&\quad-(G'_{3R_{\omega_2}}+\tau_2^0G_{3I})(G_3+G_{2R}\cos\omega_2\tau_2^0-G_{2I}\sin\omega_2\tau_2^0)\Big\},
\end{aligned}$$

$$\begin{aligned}
\mathbb{T}_1 &= G'_{0_{\tau_1}}\overline{(G_0+G_1\,\mathrm{e}^{-i\omega_2\tau_2^0})}-(G'_{2_{\tau_1}}+G'_{3_{\tau_1}}\,\mathrm{e}^{-i\omega_2\tau_2^0})\overline{(G_2+G_3\,\mathrm{e}^{-i\omega_2\tau_2^0})}\\
&=\Big\{G'_{0R_{\tau_1}}(G_{0R}+G_{1R}\cos\omega_2\tau_2^0)+G'_{0I_{\tau_1}}(G_{0I}-G_{1R}\sin\omega_2\tau_2^0)-G'_{2R_{\tau_1}}(G_{2R}+G_{3R}\cos\omega_2\tau_2^0\\
&\quad+G_{3I}\sin\omega_2\tau_2^0)-G'_{2I_{\tau_1}}(G_{2I}+G_{3I}\cos\omega_2\tau_2^0-G_{3R}\sin\omega_2\tau_2^0)-G'_{3R_{\tau_1}}(G_{3R}+G_{2R}\cos\omega_2\tau_2^0\\
&\quad-G_{2I}\sin\omega_2\tau_2^0)-G'_{3I_{\tau_1}}(G_{3I}+G_{2I}\cos\omega_2\tau_2^0+G_{2R}\sin\omega_2\tau_2^0)\Big\}\\
&\quad+i\Big\{-G'_{0R_{\tau_1}}(G_{0I}-G_{1R}\sin\omega_2\tau_2^0)+G'_{0I_{\tau_1}}(G_{0R}+G_{1R}\cos\omega_2\tau_2^0)+G'_{2R_{\tau_1}}(G_{2I}+G_{3I}\cos\omega_2\tau_2^0\\
&\quad-G_{3R}\sin\omega_2\tau_2^0)-G'_{2I_{\tau_1}}(G_{2R}+G_{3R}\cos\omega_2\tau_2^0-G_{3I}\sin\omega_2\tau_2^0)+G'_{3R_{\tau_1}}(G_{3I}+G_{2I}\cos\omega_2\tau_2^0\\
&\quad+G_{2R}\sin\omega_2\tau_2^0)-G'_{3I_{\tau_1}}(G_{3R}+G_{2R}\cos\omega_2\tau_2^0-G_{2I}\sin\omega_2\tau_2^0)\Big\}.
\end{aligned}$$

Thanks to expression of $\tilde{F}'_{3\omega_2}$ and $\tilde{F}'_{3\tau_2}$ in (70), $\mathbb{T}_1$ and $\mathbb{J}_1$ can be rewritten as

$$\mathbb{T}_1 = \frac{\tilde{F}'_{3_{\tau_1}}}{2} + iU \quad \text{and} \quad \mathbb{J}_1 = L + i\frac{\tilde{F}'_{3_{\omega_2}}}{2}, \tag{73}$$

where U denotes the imaginary part of $\mathbb{T}_1$ and L the real part of $\mathbb{J}_1$. Then, combining (70), (72) and (73), we get

$$\begin{aligned}
\operatorname{sign}\left\{ \frac{\mathrm{dRe}\lambda}{\mathrm{d}\tau_1}\bigg|_{\lambda=i\omega_2(\tau_{11}^*,\tau_2^0)} \right\} &= \operatorname{signRe}\left\{ \frac{2L - 2\tau_1|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}|^2 + i\tilde{F}'_{3_{\omega_2}}}{\tilde{F}'_{3_{\tau_1}} + i(2U + 2\omega_2|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}|^2)} \right\} \\
&= \operatorname{sign}\Big\{\tilde{F}'_{3_{\tau_1}}(2L - 2\tau_1|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}|^2) + \tilde{F}'_{3_{\omega_2}}(2U \\
&\quad +2\omega_2|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}|^2)\Big\} \\
&= \operatorname{sign}\{\tilde{F}'_{3_{\omega_2}}\}\cdot\operatorname{signRe}\left\{\tau_{11}^*\omega_2' + \omega_2 + \frac{U - L\omega_2'}{|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}|^2)}\right\}.
\end{aligned} \tag{74}$$

On the other hand, we have $S_n^2(\tau_{11}^*) = 0$, which implies

$$(S_n^2)'(\tau_{11}^*) = \frac{\mathrm{d}}{\mathrm{d}\tau_1}\left(\tau_1 - \frac{\theta_2(\tau_1) + 2\pi n}{\omega_2(\tau_1)}\right)\bigg|_{\tau_1=\tau_{11}^*} = \frac{\omega_2(\tau_{11}^*,\tau_2^0) + \tau_{11}^*\omega_2'(\tau_{11}^*,\tau_2^0) - \theta_2'(\tau_{11}^*)}{\omega_2(\tau_{11}^*,\tau_2^0)}.$$

It then follows that

$$\operatorname{sign}\left\{(S_n^2)'(\tau_{11}^*)\right\} = \operatorname{sign}\left\{\omega_2(\tau_{11}^*,\tau_2^0) + \tau_{11}^*\omega_2'(\tau_{11}^*,\tau_2^0) - \theta_2'(\tau_{11}^*)\right\}. \tag{75}$$

From (67) and (68), we have

$$(\varphi(\omega_2,\tau_{11}^*,\tau_2^0))^2 + (\psi(\omega_2,\tau_{11}^*,\tau_2^0))^2 = \left|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^4 = \left|G_2 + G_3\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^4,$$

for $\tau_1 \in I_2$, where $\theta(\tau_1)$ is defined in (71). Then, a simple computation gives

$$\theta_2'(\tau_1,\tau_2^0) = \frac{\psi\varphi'_{\tau_1} - \varphi\psi'_{\tau_1}}{\left|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^4}, \tag{76}$$

where

$$\varphi'_{\tau_1} = -AR_{11} + BN_{11} - CR_{22} + DN_{22} \quad \text{and} \quad \psi'_{\tau_1} = CR_{11} - BN_{22} - AR_{22} + DN_{11},$$

with N_{11}, N_{22}, R_{11} and R_{22} defined as in (66), and

$$\begin{aligned}
A &= G'_{2R_{\omega_2}}\omega_2' + G'_{2R_{\tau_1}} + (G'_{3R_{\omega_2}}\omega_2' + G'_{3R_{\tau_1}} + \tau_2^0 G_{3I}\omega_2')\cos\omega_2\tau_2^0 + (G'_{3I_{\omega_2}}\omega_2' \\
&\quad + G'_{3I_{\tau_1}} - \tau_2^0 G_{3R}\omega_2')\sin\omega_2\tau_2^0, \\
B &= G'_{0R_{\omega_2}}\omega_2' + G'_{0R_{\tau_1}} - \tau_2^0 G_{1R}\omega_2'\sin\omega_2\tau_2^0, \\
C &= G'_{2I_{\omega_2}}\omega_2' + G'_{2I_{\tau_1}} - (G'_{3R_{\omega_2}}\omega_2' + G'_{3R_{\tau_1}} + \tau_2^0 G_{3I}\omega_2')\sin\omega_2\tau_2^0 + (G'_{3I_{\omega_2}}\omega_2'
\end{aligned}$$

$$+ G'_{3I_{\tau_1}} - \tau_2^0 G_{3R}\omega'_2) \cos\omega_2\tau_2^0,$$

$$D = G'_{0I_{\omega_2}}\omega'_2 + G'_{0I_{\tau_1}} - \tau_2^0 G_{1R}\omega'_2 \cos\omega_2\tau_2^0.$$

Knowing that

$$N_{11}^2 + N_{22}^2 = \left|G_2 + G_3\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^2 = \left|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^2 = R_{11}^2 + R_{22}^2,$$

it follows that

$$\begin{aligned}\psi\varphi'_{\tau_1} - \varphi\psi'_{\tau_1} &= (N_{11}^2 + N_{22}^2)(DR_{11} - BR_{22}) + (R_{11}^2 + R_{22}^2)(CN_{11} - AN_{22})\\ &= \left|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^2 \Big\{\omega'_2\Big[R_{11}(G'_{0I_{\omega_2}} - \tau_2^0 G_{1R}\cos\omega_2\tau_2^0)\\ &\quad - R_{22}(G'_{0R_{\omega_2}} - \tau_2^0 G_{1R}\sin\omega_2\tau_2^0)\\ &\quad + N_{11}(G'_{2I_{\omega_2}} - (G'_{3R_{\omega_2}} + \tau_2^0 G_{3I})\sin\omega_2\tau_2^0 + (G'_{3I_{\omega_2}} - \tau_2^0 G_{3R})\cos\omega_2\tau_2^0)\\ &\quad - N_{22}(G'_{2R_{\omega_2}} + (G'_{3R_{\omega_2}} + \tau_2^0 G_{3I})\cos\omega_2\tau_2^0 + (G'_{3I_{\omega_2}} - \tau_2^0 G_{3R})\sin\omega_2\tau_2^0)\Big]\\ &\quad + R_{11}G'_{0I_{\tau_1}} - R_{22}G'_{0R_{\tau_1}} + N_{11}(G'_{2I_{\tau_1}} - G'_{3R_{\tau_1}}\sin\omega_2\tau_2^0 + G'_{3I_{\tau_1}}\cos\omega_2\tau_2^0)\\ &\quad - N_{22}(G'_{2R_{\tau_1}} + G'_{3R_{\tau_1}}\cos\omega_2\tau_2^0 + G'_{3I_{\tau_1}}\sin\omega_2\tau_2^0)\Big\}.\end{aligned}$$

From the expressions of L and U in (73), the equality above becomes

$$\psi\varphi'_{\tau_1} - \varphi\psi'_{\tau_1} = \left|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^2 (L\omega'_2 - U).$$

From this last equality and (76), we obtain

$$\theta'_2(\tau_1, \tau_2^0) = \frac{L\omega'_2 - U}{\left|G_0 + G_1\,\mathrm{e}^{-i\omega_2\tau_2^0}\right|^2}. \tag{77}$$

Finally, combining (74), (75) and (77) yields

$$\operatorname{sign}\left\{\frac{\mathrm{dRe}\lambda}{\mathrm{d}\tau_1}\bigg|_{\lambda=i\omega_2(\tau_{11}^*,\tau_2^0)}\right\} = \operatorname{sign}\{\tilde{F}'_{2_{\omega_2}}(\omega_2, \tau_{11}^*, \tau_2^0)\}\cdot\operatorname{sign}\left\{\frac{\mathrm{d}S_n^2(\tau_1)}{\mathrm{d}\tau_1}\bigg|_{\tau_1=\tau_{11}^*}\right\}.$$

This completes the Proof. ■

Applying Theorem 3.8 and the Hopf bifurcation theorem for functional differential equations [35], we get the existence of a Hopf bifurcation given in the following result.

Theorem 3.9: *Assume that $\mathcal{R}_0>1$. Then, for PDE system (4), there exists $\tau_{11}^* \in I_2$, such that the endemic equilibrium E^* is locally asymptotically stable when $0 \le \tau_1<\tau_{11}^*$, and becomes unstable when τ_1 stays in some right neighborhood of τ_{11}^*. Therefore, a Hopf bifurcation occurs at $\tau_1 = \tau_{11}^*$.*

By similar arguments as above, we have the following result, where I_3 is defined mutatis mutandis as I, I_1 and I_2.

Theorem 3.10: *Assume that $\mathcal{R}_0>1$. Then, for PDE system (4), there exists $\tau_{22}^* \in I_3$, such that the endemic equilibrium E^* is locally asymptotically stable when $0 \le \tau_2<\tau_{22}^*$, and becomes unstable when τ_2 staying in some right neighborhood of τ_{22}^*. Therefore, a Hopf bifurcation occurs at $\tau_2 = \tau_{22}^*$.*

4. Global stability of equilibria

In this Section, we construct a Lyapunov functional and rely on LaSalle's invariance principle to study the global stability of the HBV-free equilibrium E_0 of PDE-model (4)–(6). After proving that the PDE-model (4)–(6) is uniformly persistent, we apply the fluctuation method of Thieme and Zhao [36], to prove that the unique equilibrium with infection, E^*, is globally attractive.

4.1. Global stability of the HBV-free equilibrium E_0

This subsection is devotes to the global stability of the HBV-free equilibrium E_0 of PDE-model system (4)–(6). We have the following result. For convenience, as in our earlier work [17], we start by setting

$$\mathcal{T}_0 = \frac{k\alpha\, \mathrm{e}^{-\gamma_1\tau_1-\gamma_2\tau_2}}{(\mu+\alpha u)(\delta-r_2)},$$

to gain

$$\frac{k\alpha\, \mathrm{e}^{-\gamma_1\tau_1-\gamma_2\tau_2}}{(\mu+\alpha u)(\delta-r_2+\frac{r_2\Lambda}{K_H})} \le \frac{k\alpha\, \mathrm{e}^{-\gamma_1\tau_1-\gamma_2\tau_2}}{(\mu+\alpha u)(\delta-r_2)},$$

that is

$$\mathcal{R}_0 \le \mathcal{T}_0. \tag{78}$$

So, as in [37] and [17], we use $\mathcal{T}_0$ to prove the global stability of the infection-free equilibrium $E_0(\Lambda,0,0)$ of problem (4)–(6). The result stands as follows.

Theorem 4.1: *The HBV-free equilibrium $E_0(\Lambda,0,0)$ of problem (4)–(6) is globally asymptotically stable if $\mathcal{R}_0 \le \mathcal{T}_0 < 1$.*

Proof: Let $(H(x,t), I(x,t), V(x,t))$ be a positive solution to (4)–(6). We define a Lyapunov functional $L(t)$ as

$$\begin{aligned} L(t) = \int_\Omega \Bigg\{ & \mathrm{e}^{\gamma_1\tau_1} I(x,t) + \frac{(\delta-r_2)\,\mathrm{e}^{\gamma_1\tau_1+\gamma_2\tau_2}}{k} V(x,t)\ \mathrm{d}x \\ & + \int_{t-\tau_1}^{t} \frac{\alpha H(x,\theta)V(x,\theta)}{H(x,\theta)+I(x,\theta)}\,\mathrm{d}\theta + (\delta-r_2)\ \mathrm{e}^{\gamma_1\tau_1} \int_{t-\tau_2}^{t} I(x,\theta)\,\mathrm{d}\theta \Bigg\}\,\mathrm{d}x. \end{aligned} \tag{79}$$

For the sake of notational convenience, we set $y = y(x,t)$ and $y_\tau = y(x,t-\tau)$, for all $y \in \{H, I, V\}$. It is clear that $L(t)$ is nonnegative definite in $\overline{\Omega} \times [-\tau, 0]$, with respect to E_0. The time derivative of $L(t)$ along the solution to problem (4)–(6) is calculated as follows:

$$\begin{aligned} \frac{\mathrm{d}L(t)}{\mathrm{d}t} = \int_\Omega \Bigg\{ & \frac{\alpha H_{\tau_1} V_{\tau_1}}{H_{\tau_1}+I_{\tau_1}} - \delta\, \mathrm{e}^{\gamma_1\tau_1} I + r_2\, \mathrm{e}^{\gamma_1\tau_1} I \left(1 - \frac{H+I}{K_H}\right) \\ & + \frac{D(\delta-r_2)\,\mathrm{e}^{\gamma_1\tau_1+\gamma_2\tau_2}}{k} \Delta V + (\delta-r_2)\ \mathrm{e}^{\gamma_1\tau_1} I_{\tau_2} \\ & - \frac{\mu(\delta-r_2)\,\mathrm{e}^{\gamma_1\tau_1+\gamma_2\tau_2}}{k} V + \frac{\alpha u(\delta-r_2)\,\mathrm{e}^{\gamma_1\tau_1+\gamma_2\tau_2}}{k} \frac{HV}{H+I} + \frac{\alpha HV}{H+I} - \frac{\alpha H_{\tau_1} V_{\tau_1}}{H_{\tau_1}+I_{\tau_1}} \\ & + (\delta-r_2)\ \mathrm{e}^{\gamma_1\tau_1} I - (\delta-r_2)\ \mathrm{e}^{\gamma_1\tau_1} I_{\tau_2} \Bigg\}\,\mathrm{d}x \end{aligned}$$

$$
\begin{aligned}
&= \int_\Omega \left\{ \frac{\alpha HV}{H+I} - \frac{(\mu+\alpha u)(\delta-r_2)\,e^{\gamma_1\tau_1+\gamma_2\tau_2}}{k}\frac{HV}{H+I} - \frac{\mu(\delta-r_2)\,e^{\gamma_1\tau_1+\gamma_2\tau_2}}{k}\frac{IV}{H+I} \right.\\
&\quad \left. - \frac{r_2\,e^{\gamma_1\tau_1}}{K_H} I(H+I) + \frac{D(\delta-r_2)\,e^{\gamma_1\tau_1+\gamma_2\tau_2}}{k}\Delta V \right\} dx\\
&= \int_\Omega \left\{ \frac{(\mu+\alpha u)(\delta-r_2)\,e^{\gamma_1\tau_1+\gamma_2\tau_2}}{k}\frac{HV}{H+I}(\mathcal{T}_0-1) - \frac{r_2\,e^{\gamma_1\tau_1}}{K_H} I(H+I) \right.\\
&\quad \left. - \frac{\mu(\delta-r_2)\,e^{\gamma_1\tau_1+\gamma_2\tau_2}}{k}\frac{IV}{H+I} \right\} dx + \int_\Omega \frac{D(\delta-r_2)\,e^{\gamma_1\tau_1+\gamma_2\tau_2}}{k}\Delta V\, dx. \qquad (80)
\end{aligned}
$$

From the Divergence Theorem and the homogeneous Neumann boundary conditions (6), we obtain

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

and thus, Equation (80) becomes

$$
\begin{aligned}
\frac{dL(t)}{dt} &= (\mathcal{T}_0-1)\frac{(\mu+\alpha u)(\delta-r_2)\,e^{\gamma_1\tau_1+\gamma_2\tau_2}}{k}\int_\Omega \frac{HV}{H+I}\, dx - \int_\Omega \left\{ \frac{r_2\,e^{\gamma_1\tau_1}}{K_H} I(H+I) \right.\\
&\quad \left. + \frac{\mu(\delta-r_2)\,e^{\gamma_1\tau_1+\gamma_2\tau_2}}{k}\frac{IV}{H+I} \right\} dx.
\end{aligned}
$$

From condition $\mathcal{T}_0<1$, we are sure that $\frac{dL(t)}{dt} \le 0$, for all $H, I, V \ge 0$. Moreover, $\frac{dL(t)}{dt} = 0$ if and only if $I = 0$, $V = 0$. Combining this to PDE-model (4), we get $H = \Lambda$. It follows that the largest compact invariant set in $\{(H, I, V) \in \mathbb{R}^3_+ : \frac{dL(t)}{dt} = 0\}$ is $\{E_0\}$. By LaSalle's invariant principle [38, Theorem 5.3.1], if $\mathcal{T}_0 \le 1$, the positive solution to problem (4)–(6) converges to the HBV-free equilibrium E_0. Since, if $\mathcal{R}_0 \le 1$, $E_0(\Lambda, 0, 0)$ is locally asymptotically stable, we obtain a sufficient condition $\mathcal{R}_0 \le \mathcal{T}_0$ which ensures that the infection-free equilibrium E_0 of problem (4)–(6) is globally asymptotically stable if $\mathcal{T}_0<1$. This completes the proof. ■

The biological implication of Theorem 4.1 is that if the condition $\mathcal{R}_0 \le \mathcal{T}_0<1$ holds, free HBV particles will be wiped out from the liver. Therefore, for the delayed diffusive model (4)–(6), the condition $\mathcal{R}_0 \le \mathcal{T}_0<1$ is necessary and sufficient for infection eradication.

4.2. *Uniform persistence result for problem (eqn4)–(eqn6)*

In this subsection, we provide a uniform persistence result for problem (4)–(6) by using techniques developed in [38]. So, we will need the following definitions and notations. Set $\tau = \max\{\tau_1, \tau_2\}$. Consider the Banach space of continuous functions $\mathbb{X} := C(\overline{\Omega}, \mathbb{R}^3)$, equipped with sup-norm $\|\cdot\|_{\mathbb{X}}$. Define $\mathbb{X}_+ := C(\overline{\Omega}, \mathbb{R}^3_+)$. Let $\mathbb{Y} = C(\overline{\Omega}, \mathbb{R})$ and $\mathbb{Y}_+ = C(\overline{\Omega}, \mathbb{R}_+)$. Let $\mathcal{X}_\tau = C([-\tau, 0], \mathbb{X}_+)$ be the Banach space of continuous functions, endowed with the sup-norm. Denote

$$
\mathcal{X}^0 = \{(\phi_1, \phi_2, \phi_3) \in \mathcal{X}_\tau \ : \ \phi_2(\cdot, \theta)>0, \phi_3(\cdot, \theta)>0,\ \theta \in [-\tau, 0]\},
$$

$$
\mathcal{X}_0 = \partial\mathcal{X}_\tau = \mathcal{X}_\tau/\mathcal{X}^0 = \{(\phi_1, \phi_2, \phi_3) \in \mathcal{X}_\tau \ : \ \phi_2(\cdot, \theta) = 0, \text{ or } \phi_3(\cdot, \theta) = 0,\ \theta \in [-\tau, 0]\}.
$$

For $t \geq 0$, let $\Phi(t)$ be the family of solution operators associated to system (4). By the parabolic maximum principle, one has $\Phi(t)\mathcal{X}^0 \subset \mathcal{X}^0$. We define the ω–limit as

$$\omega(z) := \{y \in \mathcal{X}_\tau \ : \ \text{there is a sequence } t_n \to \infty \text{ as } n \to \infty \text{ with } \Phi(t_n)z \to y \text{ as } n \to \infty\}.$$

Recall that, for $\mathcal{R}_0 \leq 1$, the HBV-free equilibrium $E_0(\Lambda, 0, 0)$ is the only equilibrium and that it is globally asymptotically stable in the feasible region

$$\Gamma_1 = \left\{(H, I, V)^T \in \mathcal{X}_\tau \ : \ H \leq M_1, \, I \leq M_1, \, V \leq M_2\right\}.$$

When $\mathcal{R}_0>1$, E_0 loses its stability and a unique locally asymptotically stable equilibrium with infection E^* emerges in the interior of Γ_1.

Lemma 4.2 below follows from Theorem 4.2 of [38].

Lemma 4.2: *Assume the following:*

(i) *$\mathcal{X}^0$ is open and dense in $\mathcal{X}_\tau$ with $\mathcal{X}^0 \subset \mathcal{X}_\tau$, $\mathcal{X}_0 \subset \mathcal{X}_\tau$, $\mathcal{X}^0 \bigcup \mathcal{X}_0 = \mathcal{X}_\tau$ and $\mathcal{X}^0 \bigcap \mathcal{X}_0 = \emptyset$,*
(ii) *the solution operators $\Phi(t)$ satisfy $\Phi(t) : \mathcal{X}^0 \to \mathcal{X}^0$; $\Phi(t) : \mathcal{X}_0 \to \mathcal{X}_0$,*
(iii) *The family of solution operators $\Phi(t)$ is point dissipative in $\mathcal{X}_\tau$,*
(iv) *If U is bounded in $\mathcal{X}_\tau$, then the orbit $\gamma^+(U)$ is bounded in $\mathcal{X}_\tau$,*
(v) *$\Phi(t)$ is asymptotically smooth;*
(vi) *$\Omega_2 = \bigcup_{z \in Y_2} \omega(z)$ is isolated and has acyclic covering N, where Y_2 is the global attractor of $\Phi(t)$ restricted to $\mathcal{X}_0$ and $N = \bigcap_{i=1}^k N_i$,*
(vii) *for each N_i; $W^s(N_i) \bigcap \mathcal{X}^0 = \emptyset$, where W^s refers to the stable set, i.e. $W^s(A) = \{z \in \mathcal{X}_\tau : \omega(z) \neq \emptyset \text{ and } \omega(z) \subset A\}$.*

Then, the family of solution operators $\Phi(t)$ is a uniform repeller with respect to $\mathcal{X}_0$. This means that, there exits a real constant $\eta_0>0$ such that for any $z \in \mathcal{X}_0$, one has

$$\liminf_{t \to \infty} d(\Phi(t), \mathcal{X}_0) \geq \eta_0.$$

Hence, we have the following result.

Theorem 4.3: *Problem (4)–(6) is uniformly persistent in Γ_1 when $\mathcal{R}_0>1$, that is, there exists $\eta_0>0$, such that every solution $(H(x,t), I(x,t), V(x,t))$ of (4)–(6) with $(\phi_1(x,\theta), \phi_2(x,\theta), \phi_3(x,\theta))$ in the interior of Γ_1 and $\phi_i(x,0) \not\equiv 0, i = 1, 2, 3$, satisfies*

$$\liminf_{t\to\infty} \min_{x\in\bar{\Omega}} H(x,t) \geq \eta_0, \quad \liminf_{t\to\infty} \min_{x\in\bar{\Omega}} I(x,t) \geq \eta_0, \quad \liminf_{t\to\infty} \min_{x\in\bar{\Omega}} V(x,t) \geq \eta_0.$$

Proof: Let $(H(x,t), I(x,t), V(x,t))$ be a solution to problem (4)–(6), $\phi_i(x,0) \not\equiv 0, i = 1, 2, 3$. We have $H(x,t)>0, I(x,t)>0, V(x,t)>0$ and bounded for all $x \in \overline{\Omega}, t>0$. Then, it is easy to verify that assumptions (i)-(v) of Lemma 4.2 are satisfied. Thus, to end the proof of Theorem 4.3, it suffices to verify the hypotheses (vi) and (vii) of Lemma 4.2. Define

$$\mathcal{M}_\partial = \{\phi \in \mathcal{X}_\tau \ : \ \Phi(t)\phi \text{ verifies (4) and } \Phi(t)\phi \in \partial\mathcal{X}_\tau, \quad \forall\, t \geq 0\}. \tag{1}$$

We are going to show that $\mathcal{M}_\partial = \{(\Lambda, 0, 0)\}$. For this, assume that $\Phi(t) \in \mathcal{M}_\partial, \forall t \geq 0$. Thus, to ensure that $\mathcal{M}_\partial = \{(\Lambda, 0, 0)\}$, we need to prove that $I(x,t) = V(x,t) = 0, \forall x \in \overline{\Omega}, t \geq 0$. We show this by contradiction. Suppose that, there is $t_0>0$ such that either $(*)$: $I(x,t_0)>0, V(x,t_0) = 0$; or $(**)$: $I(x,t_0) = 0, V(x,t_0)>0$, holds uniformly for all $x \in \overline{\Omega}$.

For the case $(*)$, in view of the third equation of (4), one gets

$$\frac{\partial V(x,t)}{\partial t} - D\Delta V(x,t)\Big|_{(x,t)=(x,t_0)} = ke^{-\gamma_2\tau_2} I(x, t_0 - \tau_2) > 0.$$

From this last inequality, it follows that for $(x,t) = (x, t_0)$, we have

$$\int_\Omega \left(\frac{\partial V(x,t)}{\partial t} - D\Delta V(x,t)\,\mathrm{d}x \right) > 0,$$

which gives $\int_\Omega \frac{\partial V(x,t)}{\partial t}\,\mathrm{d}x > 0$, since $\int_\Omega \Delta V(x,t)\,\mathrm{d}x = 0$. It follows that

$$\frac{\partial V(x,t)}{\partial t}\Big|_{(x,t)=(x,t_0)} > 0.$$

Therefore, there exists a sufficiently small constant $\varepsilon_0 > 0$ such that $V(x,t) > 0$, $\forall (x,t) \in \overline{\Omega} \times (t_0, t_0 + \varepsilon_0)$. Now, using the fact that $I(x,t_0) > 0$, we get a positive ε_1 $(0 < \varepsilon_1 < \varepsilon_0)$ such that $I(x,t) > 0$, $V(x,t) > 0$, $\forall (x,t) \in \overline{\Omega} \times (t_0, t_0 + \varepsilon_1)$. This contradicts the fact that $(H(x,t), I(x,t), V(x,t)) \in M_\partial$, $\forall x \in \overline{\Omega}$, $t \geq 0$. With the same arguments, it can be shown that $(**)$ does not also hold.

Letting $\Omega_2 = \bigcup_{z \in Y_2} \omega(z)$, with Y_2 representing the global attractor of the family of solution operators $\Phi(t)$ restricted to $\partial \mathcal{X}_\tau$, we prove that $\Omega_2 = \{E_0\}$. This follows from $\Omega_2 \subseteq M_\partial$ and system (4). We have $\lim_{t\to\infty} H(x,t) = \Lambda$, uniformly for $x \in \overline{\Omega}$. Accordingly, $\{E_0\}$ is the isolated invariant set in $\mathcal{X}_\tau$.

Lastly, we prove that $W^s(E_0) \bigcap \mathcal{X}^0 = \emptyset$.

By contradiction, assume that there is a positive orbit $(H(x,t), I(x,t), V(x,t)) \in \mathcal{X}^0$ of (4) such that

$$\lim_{t\to\infty} H(x,t) = \Lambda, \quad \lim_{t\to\infty} I(x,t) = 0, \quad \lim_{t\to\infty} V(x,t) = 0, \quad \text{uniformly for } x \in \overline{\Omega}. \tag{82}$$

Thus, for every sufficiently small constant $\varepsilon > 0$, there is a positive constant $T_0 = T_0(\varepsilon)$, such that

$$\Lambda - \varepsilon < H(x,t) < \Lambda + \varepsilon, \quad 0 < I(x,t) < \varepsilon, \quad 0 < V(x,t) < \varepsilon, \quad \forall\, x \in \overline{\Omega},\ t \geq T_0. \tag{83}$$

Thus, from the last two Equation (4), for $\varepsilon > 0$, $x \in \overline{\Omega}$, $t \geq T_0 + \tau$, one has

$$\begin{aligned} \frac{\partial I}{\partial t} &\geq \alpha\, \mathrm{e}^{-\gamma_1\tau_1} V(x, t-\tau_1) - \delta I(x,t) + r_2 I(x,t)\left(1 - \frac{\Lambda + 2\epsilon}{K_H}\right), \\ \frac{\partial V}{\partial t} &\geq D\Delta V(x,t) + ke^{-\gamma_2\tau_2} I(x, t-\tau_2) - \mu V(x,t) - \frac{\alpha u(\Lambda+\varepsilon) V(x,t)}{\Lambda + 2\varepsilon}. \end{aligned} \tag{84}$$

Consider the matrix defined by

$$B_\epsilon = \begin{pmatrix} r_2\left(1 - \frac{\Lambda+2\epsilon}{K_H}\right) - \delta & \alpha\, \mathrm{e}^{-\gamma_1\tau_1} \\ ke^{-\gamma_2\tau_2} & -\mu - \mu_i D - \frac{\alpha u(\Lambda+\varepsilon)}{\Lambda+2\varepsilon} \end{pmatrix}.$$

Since B_ϵ has positive off-diagonal elements, the Perron-Frobenius Theorem implies that there exists a positive eigenvector $\tilde{v}$ for the maximum principal eigenvalue λ^* of B_ϵ. Furthermore, since $\mathcal{R}_0 > 1$, we have

$$\left(\delta - r_2\left(1 - \frac{\Lambda + 2\epsilon}{K_H}\right)\right)\left(\mu + \mu_i D + \frac{\alpha u(\Lambda+\varepsilon)}{\Lambda + 2\varepsilon}\right) - k\alpha\, \mathrm{e}^{-\gamma_1\tau_1 - \gamma_2\tau_2} < 0,$$

for ϵ small enough. By a simple calculation we see that λ^* is positive.

Consider the problem below:

$$
\begin{aligned}
\frac{\partial \nu_2^{(1)}}{\partial t} &= \alpha\, \mathrm{e}^{-\gamma_1\tau_1} \nu_3^{(1)}(x,t-\tau_1) - \delta \nu_2^{(1)}(x,t) + r_2 \nu_2^{(1)}(x,t)\left(1-\frac{\Lambda+2\epsilon}{K_H}\right),\\
\frac{\partial \nu_3^{(1)}}{\partial t} &= D\Delta \nu_3^{(1)}(x,t) + k e^{-\gamma_2\tau_2}\nu_2^{(1)}(x,t-\tau_2) - \mu \nu_3^{(1)}(x,t)\\
&\quad - \frac{\alpha u(\Lambda+\varepsilon)\nu_3^{(1)}(x,t)}{\Lambda+2\varepsilon}, \quad t>T_0+\tau,\ x\in\Omega\\
\frac{\partial \nu_2^{(1)}}{\partial \eta} &= \frac{\partial \nu_3^{(1)}}{\partial \eta} = 0, \quad t>T_0+\tau,\ x\in\partial\Omega\\
\nu_2^{(1)}(x,t) &= \frac{1}{2}I(x,t), \quad \nu_3^{(1)}(x,t) = \frac{1}{2}V(x,t),\ t\in[T_0,T_0+\varepsilon],\ x\in\overline{\Omega}.
\end{aligned}
\tag{85}
$$

Let $(\nu_2(t),\nu_3(t))$ be the unique positive solution of the following problem:

$$
\begin{aligned}
\dot{\nu}_2(t) &= \alpha\, \mathrm{e}^{-\gamma_1\tau_1}\nu_3(t-\tau_1) - \delta\nu_2(t) + r_2\nu_2(t)\left(1-\frac{\Lambda+2\epsilon}{K_H}\right),\\
\dot{\nu}_3(t) &= k e^{-\gamma_2\tau_2}\nu_2(t-\tau_2) - \mu\nu_3(t) - \frac{\alpha u(\Lambda+\varepsilon)\nu_3(t)}{\Lambda+2\varepsilon},\\
\nu_2(t) &= \frac{1}{2}\min_{x\in\overline{\Omega}} I(x,t), \quad \nu_3(t) = \frac{1}{2}\min_{x\in\overline{\Omega}} V(x,t), \quad t\in[T_0,T_0+\varepsilon].
\end{aligned}
\tag{86}
$$

Then $(\nu_2(t),\nu_3(t))$ is a lower solution of problem (85).

Define

$$(f_1(x,t,\phi_2),f_2(x,t,\phi_3)) = (I(x,t,\phi_2),V(x,t,\phi_3)),\ \text{and}\ (\mathrm{g}_1(t,\phi_2),\mathrm{g}_2(t,\phi_3)) = (\nu_2(t,\phi_2),\nu_3(t,\phi_3)).$$

From Theorem 2.1, we have that $(I(x,t),V(x,t))$ is bounded. Hence, from (84) and (86) it is evident that $(f_1(x,t,\phi_2),f_2(x,t,\phi_3))$ and $(\mathrm{g}_1(t,\phi_2),\mathrm{g}_2(t,\phi_3))$ are continuous, Lipschitz on each compact subset of $\mathcal{X}_\tau$, and thanks to boundedness of solutions, $(f_1(x,t,\phi_2),f_2(x,t,\phi_3))$ satisfies the assumption (Q): if $\phi_i\le\psi_i$ and $\phi_i(0)=\psi_i(0)$ for some $i=1,2$, then $f(\phi)\le f(\psi)$. Thus in (84), all the conditions of Theorem 5.1.1 in [39] hold. Since in (82), one supposes that $I(x,t)\to 0$ and $V(x,t)\to 0$ as $t\to\infty$ uniformly for $x\in\overline{\Omega}$, by a comparison principle one deduces that the solution of system (86), $(\nu_2(t),\nu_3(t))$, with the above initial conditions, converge to $(0,0)$.

Let

$$
\begin{aligned}
\widetilde{M}(t) = {}& \mathrm{e}^{\gamma_1\tau_1}\nu_2(t) + \frac{1}{k}\left[\delta - r_2\left(1-\frac{\Lambda+2\epsilon}{K_H}\right)\right]\mathrm{e}^{\gamma_1\tau_1+\gamma_2\tau_2}\nu_3(t)\\
&+\alpha\int_{t-\tau_1}^{t}\nu_3(\theta)\,\mathrm{d}\theta + \left[\delta - r_2\left(1-\frac{\Lambda+2\epsilon}{K_H}\right)\right]\mathrm{e}^{\gamma_1\tau_1}\int_{t-\tau_2}^{t}\nu_2(\theta)\,\mathrm{d}\theta.
\end{aligned}
$$

Since $(\nu_2(t),\nu_3(t))\to(0,0)$ as $t\to\infty$, we get

$$\lim_{t\to+\infty}\widetilde{M}(t) = 0. \tag{87}$$

In the same vein, by computing the time derivative of $\widetilde{M}(t)$ along the positive solution to problem (86), one can choose a sufficiently small constant ε such that

$$\frac{\mathrm{d}\widetilde{M}(t)}{\mathrm{d}t}\Big|_{86} = \left\{\frac{k\alpha(\Lambda+2\epsilon)\,\mathrm{e}^{-\gamma_1\tau_1-\gamma_2\tau_2}}{(\alpha u(\Lambda+\epsilon)+\mu(\Lambda+2\epsilon))\left[\delta - r_2\left(1-\frac{\Lambda+2\epsilon}{K_H}\right)\right]} - 1\right\}$$

$$\times \frac{1}{k(\Lambda+2\epsilon)}(\alpha u(\Lambda+\epsilon)+\mu(\Lambda+2\epsilon))\left[\delta - r_2\left(1-\frac{\Lambda+2\epsilon}{K_H}\right)\right]v_3(t).$$

Since $\mathcal{R}_0 > 1$, we can choose a sufficiently small constant ϵ such that

$$\frac{k\alpha(\Lambda+2\epsilon)\,\mathrm{e}^{-\gamma_1\tau_1-\gamma_2\tau_2}}{(\alpha u(\Lambda+\epsilon)+\mu(\Lambda+2\epsilon))\left[\delta - r_2\left(1-\frac{\Lambda+2\epsilon}{K_H}\right)\right]} - 1 > 0.$$

Therefore, $\widetilde{M}(t)$ tends to either infinity or a nonnegative number when $t \to \infty$. This contradicts Equation (87). Hence, we have $W^s(E_0) \bigcap \mathcal{X}^0 = \emptyset$. Lemma 4.2 implies that, for some constant $\eta_1 > 0$, one has $\liminf_{t\to\infty} \min_{x\in\bar{\Omega}} I(x,t) > \eta_1$, and $\liminf_{t\to\infty} \min_{x\in\bar{\Omega}} V(x,t) > \eta_1$.

For any solution (H, I, V) of PDE system (4), one has

$$\limsup_{t\to\infty} \max_{x\in\bar{\Omega}} H(x,t) \le H_0 = \frac{K_H}{2r_1}\left[(r_1-d_1)+\sqrt{(r_1-d_1)^2+\frac{4s_0r_1}{K_H}}\right].$$

Then, for all $\epsilon > 0$, there is a $t_1 > 0$ such that $H(x,t) < H_0 + \epsilon$, for all $t > t_1$, $x \in \bar{\Omega}$.

Let

$$M_I = \limsup_{t\to\infty} \max_{x\in\bar{\Omega}} I(x,t) \quad \text{and} \quad M_V = \limsup_{t\to\infty} \max_{x\in\bar{\Omega}} V(x,t)$$

which we know are finite quantities according to Theorem 2.1. Assume that $s_0 - \alpha M_V > 0$. The first equation of PDE system (4) satisfies, for some $t_1 > 0$,

$$\frac{\partial H}{\partial t} \ge s_0 - d_1 H + r_1 H\left(1-\frac{H+M_I}{K_H}\right) - \alpha M_V,$$

which implies that

$$\liminf_{t\to+\infty} \min_{x\in\bar{\Omega}} H(x,t) \ge \frac{K_H}{2r_1}\left[\left(r_1-d_1-\frac{r_1M_I}{K_H}\right)+\sqrt{\left(r_1-d_1-\frac{r_1M_I}{K_H}\right)^2+\frac{4r_1(s_0-\alpha M_V)}{K_H}}\right].$$

This proves that $H(x,t)$ is uniformly bounded away from zero. This means that there exists a constant $\eta_2 > 0$ such that $\liminf_{t\to\infty} \min_{x\in\bar{\Omega}} H(x,t) > \eta_2$, uniformly for all $x \in \overline{\Omega}$. This achieves the proof of Theorem 4.3. ■

4.3. Global stability of the equilibrium point with infection E*

In this subsection, we investigate the global stability of the equilibrium point with infection E^*.

Using Theorem 4.3, we obtain the following result.

Theorem 4.4: *Let $(H(x,t), I(x,t), V(x,t))$ be a solution to problem (4)–(6), $\phi_i(x,0) \not\equiv 0$, $i = 1,2,3$. If $\mathcal{R}_0 > 1$ and $r_1 - d_1 > 0$, then for $\tau_1 \in [0, \tau_{11}^*)$ and $\tau_2 \in [0, \tau_{22}^*)$, $\lim_{t\to\infty}(H(x,t), I(x,t), V(x,t)) = (H^*, I^*, V^*)$, uniformly for $x \in \overline{\Omega}$, i.e. the positive equilibrium point with infection E^* is globally asymptotically stable for $\tau_1 \in [0, \tau_{11}^*)$ and $\tau_2 \in [0, \tau_{22}^*)$.*

Proof: Here, we suppose that healthy hepatocytes stop growing at $H = K_H$. So, the compatibility condition $K_H > s_0/d_1$ is needed. Under this condition and the fact that $\Lambda = \frac{K_H}{2r_1}[(r_1 - d_1) +$

$\sqrt{(r_1-d_1)^2+\frac{4s_0r_1}{K_H}}]$, we have the relation $\Lambda \le K_H$. Since we proved that $\lim_{t\to\infty}(H(x,t), I(x,t)) \le \Lambda_e$, uniformly for all $x \in \overline{\Omega}$, where $\Lambda_e = \frac{(4s_0+K_Hr_1)\,\mathrm{e}^{-\gamma_1\tau_1}+K_Hr_2}{4q_0}$, it is clear that $\Lambda_e \le K_H$. One can then deduce from Γ_1 that the set

$$\Gamma_2 = \left\{(H,I,V) \in \mathcal{X}_\tau \,:\, I(x,\theta) \le \Lambda_e,\ V(x,\theta) \le \frac{k\Lambda_e}{\mu}\,\mathrm{e}^{-\gamma_2\tau_2}, \quad \forall\,\theta \in [-\tau,0],\ x \in \overline{\Omega}\right\}$$

is positively invariant for the family of solution operators $\Phi(t)$ and any forward orbit eventually enters into Γ_2. Accordingly, we will investigate the dynamics of (4)–(6) in Γ_2.

Since $\mathcal{R}_0>1$, there exists a unique constant equilibrium point with infection $E^*=(H^*,I^*,V^*)$, with H^*, I^* and V^* given by (20), (21) and (22) respectively.

We can choose a sufficiently large number $a_0>0$ so that the function $a_0H+s_0-d_1H+r_1H(1-\frac{H+I}{K_H})-\frac{\alpha HV}{H+I}$ increases monotonically with respect to H for all $(H,I,V) \in [0,K_H]^2 \times [0, \frac{k\Lambda_e}{\mu}\,\mathrm{e}^{-\gamma_2\tau_2}]$. It then follows that

$$\begin{aligned} H(x,t) &= \mathrm{e}^{-a_0t}H(x,0)+\int_0^t \mathrm{e}^{-a_0s}\{a_0H(x,t-s)+s_0-d_1H(x,t-s) \\ &\quad +r_1H(x,t-s)\left(1-\frac{H(x,t-s)+I(x,t-s)}{K_H}\right)-\frac{\alpha H(x,t-s)V(x,t-s)}{H(x,t-s)+I(x,t-s)}\right\}\mathrm{d}s. \end{aligned}$$

Set

$$\begin{aligned} H^\infty(x) &:= \limsup_{t\to\infty} H(x,t), & H_\infty(x) &:= \liminf_{t\to\infty} H(x,t), \\ I^\infty(x) &:= \limsup_{t\to\infty} I(x,t), & I_\infty(x) &:= \liminf_{t\to\infty} I(x,t), \\ V^\infty(x) &:= \limsup_{t\to\infty} V(x,t), & V_\infty(x) &:= \liminf_{t\to\infty} V(x,t). \end{aligned} \tag{88}$$

Then, by Theorem 4.3, there exists $\eta_0>0$ such that

$$H^\infty(x) \ge H_\infty(x) \ge \eta_0, \quad I^\infty(x) \ge I_\infty(x) \ge \eta_0, \quad V^\infty(x) \ge V_\infty(x) \ge \eta_0, \quad \forall x \in \overline{\Omega}. \tag{89}$$

By Fatou's Lemma, we obtain

$$\begin{aligned} H^\infty(x) &\le \int_0^\infty \mathrm{e}^{-a_0s}\left\{a_0H^\infty(x)+s_0-d_1H^\infty(x)\right. \\ &\quad \left.+r_1H^\infty(x)\left(1-\frac{H^\infty(x)+I_\infty(x)}{K_H}\right)-\frac{\alpha H^\infty(x)V_\infty(x)}{H^\infty(x)+I_\infty(x)}\right\}\mathrm{d}s. \end{aligned}$$

Also, set

$$\begin{aligned} \beta_1^\infty &:= \sup_{x\in\overline{\Omega}} H^\infty(x), & \beta_{1\infty} &:= \inf_{x\in\overline{\Omega}} H_\infty(x), \\ \beta_2^\infty &:= \sup_{x\in\overline{\Omega}} I^\infty(x), & \beta_{2\infty} &:= \inf_{x\in\overline{\Omega}} I_\infty(x), \\ \beta_3^\infty &:= \sup_{x\in\overline{\Omega}} V^\infty(x), & \beta_{3\infty} &:= \inf_{x\in\overline{\Omega}} V_\infty(x). \end{aligned} \tag{90}$$

It is clear that

$$\beta_1^\infty \ge \beta_{1\infty} \ge \eta_0, \quad \beta_2^\infty \ge \beta_{2\infty} \ge \eta_0, \quad \beta_3^\infty \ge \beta_{3\infty} \ge \eta_0, \tag{91}$$

and

$$\beta_{1\infty} \leq \beta_1^{\infty} \leq K_H, \quad \beta_{2\infty} \leq \beta_2^{\infty} \leq K_H. \tag{92}$$

We thus have

$$\begin{aligned}\beta_1^{\infty} &\leq \int_0^{\infty} \mathrm{e}^{-a_0 s}\left\{a_0\beta_1^{\infty} + s_0 - d_1\beta_1^{\infty} + r_1\beta_1^{\infty}\left(1 - \frac{\beta_1^{\infty} + \beta_{2\infty}}{K_H}\right) - \frac{\alpha\beta_1^{\infty}\beta_{3\infty}}{\beta_1^{\infty} + \beta_2^{\infty}}\right\}\mathrm{d}s,\\ &= \frac{1}{a_0}\left\{a_0\beta_1^{\infty} + s_0 - d_1\beta_1^{\infty} + r_1\beta_1^{\infty}\left(1 - \frac{\beta_1^{\infty} + \beta_{2\infty}}{K_H}\right) - \frac{\alpha\beta_1^{\infty}\beta_{3\infty}}{\beta_1^{\infty} + \beta_2^{\infty}}\right\},\end{aligned}$$

and hence,

$$0 \leq s_0 - d_1\beta_1^{\infty} + r_1\beta_1^{\infty}\left(1 - \frac{\beta_1^{\infty} + \beta_{2\infty}}{K_H}\right) - \frac{\alpha\beta_1^{\infty}\beta_{3\infty}}{\beta_1^{\infty} + \beta_2^{\infty}}. \tag{93}$$

Similarly, we have the following inequality:

$$0 \geq s_0 - d_1\beta_{1\infty} + r_1\beta_{1\infty}\left(1 - \frac{\beta_{1\infty} + \beta_2^{\infty}}{K_H}\right) - \frac{\alpha\beta_{1\infty}\beta_3^{\infty}}{\beta_{1\infty} + \beta_{2\infty}}. \tag{94}$$

By employing the second equation of (4), with arguments similar to those above, we further get

$$0 \leq \frac{\alpha\,\mathrm{e}^{-\gamma_1\tau_1}\beta_1^{\infty}\beta_3^{\infty}}{\beta_1^{\infty} + \beta_2^{\infty}} - \delta\beta_2^{\infty} + r_2\beta_2^{\infty}\left(1 - \frac{\beta_{1\infty} + \beta_2^{\infty}}{K_H}\right), \tag{95}$$

$$0 \geq \frac{\alpha\,\mathrm{e}^{-\gamma_1\tau_1}\beta_{1\infty}\beta_{3\infty}}{\beta_{1\infty} + \beta_{2\infty}} - \delta\beta_{2\infty} + r_2\beta_{2\infty}\left(1 - \frac{\beta_1^{\infty} + \beta_{2\infty}}{K_H}\right). \tag{96}$$

From the third equation of (4), with arguments similar to those above, we have

$$\begin{aligned}&V(x,t) = \mathrm{e}^{-a_0 t}\int_{\Omega}\Gamma(x,y,Dt)V(y,0)\,\mathrm{d}y + \int_0^t \mathrm{e}^{-a_0 s}\int_{\Omega}\Gamma(x,y,Ds)\\ &\left(a_0V(y,t-s) + kI(y,t-\tau_2-s)\,\mathrm{e}^{-\gamma_2\tau_2} - \mu V(y,t-s) - \frac{\alpha u H(y,t-s)V(y,t-s)}{H(y,t-s) + I(y,t-s)}\right)\mathrm{d}y\,\mathrm{d}s,\end{aligned}$$

where Γ is the Green function associated with Δ and the Neumann boundary condition (6). Thus, by (88), (89), Fatou's Lemma, (90), (91), (92) and using the fact that $\int_{\Omega}\Gamma(x,y,Ds) = 1$ for all $x \in \overline{\Omega}, s>0$, we then get

$$0 \leq ke^{-\gamma_2\tau_2}\beta_2^{\infty} - \mu\beta_3^{\infty} - \frac{\alpha u\beta_1^{\infty}\beta_3^{\infty}}{\beta_{1\infty} + \beta_{2\infty}}, \tag{97}$$

$$0 \geq ke^{-\gamma_2\tau_2}\beta_{2\infty} - \mu\beta_{3\infty} - \frac{\alpha u\beta_{1\infty}\beta_{3\infty}}{\beta_1^{\infty} + \beta_2^{\infty}}. \tag{98}$$

Now, from (93) and (94) we have

$$\beta_{3\infty} \leq \frac{s_0}{\alpha} + \frac{r_1 - d}{\alpha} + \frac{s_0}{\alpha}\frac{\beta_2^{\infty}}{\beta_1^{\infty}} + \frac{r_1 - d}{\alpha}\frac{\beta_2^{\infty}}{\beta_1^{\infty}} \tag{99}$$

and

$$\beta_3^{\infty} \geq \frac{s_0}{\alpha} + \frac{r_1 - d}{\alpha} + \frac{s_0}{\alpha}\frac{\beta_{2\infty}}{\beta_{1\infty}} + \frac{r_1 - d}{\alpha}\frac{\beta_{2\infty}}{\beta_{1\infty}}, \tag{100}$$

respectively. Making (100) minus (99), we readily obtain

$$0 \geq \beta_{1\infty}\beta_1^{\infty}(\beta_{3\infty} - \beta_3^{\infty}) + \left(\frac{s_0}{\alpha} + \frac{r_1 - d_1}{\alpha}\right)\beta_{2\infty}(\beta_1^{\infty} - \beta_{1\infty}) + \left(\frac{s_0}{\alpha} + \frac{r_1 - d_1}{\alpha}\right)\beta_{1\infty}(\beta_{2\infty} - \beta_2^{\infty}). \tag{101}$$

Similarly, from (91), inequalities (97) and (98) imply

$$0 \leq k e^{-\gamma_2\tau_2}\beta_2^{\infty} - \mu\beta_3^{\infty} - \frac{\alpha u \beta_{1\infty}\beta_3^{\infty}}{\beta_{1\infty} + \beta_{2\infty}} \tag{102}$$

and

$$0 \geq k e^{-\gamma_2\tau_2}\beta_{2\infty} - \mu\beta_{3\infty} - \frac{\alpha u \beta_{1\infty}\beta_{3\infty}}{\beta_{1\infty} + \beta_{2\infty}}, \tag{103}$$

respectively. (103) minus (102) gives

$$0 \geq k e^{-\gamma_2\tau_2}(\beta_{2\infty} - \beta_2^{\infty}) + \left(\mu + \frac{\alpha u \beta_{1\infty}}{\beta_{1\infty} + \beta_{2\infty}}\right)(\beta_3^{\infty} - \beta_{3\infty}). \tag{104}$$

In the same vein, from (91), inequalities (95) and (96) imply

$$0 \leq \frac{\alpha\, e^{-\gamma_1\tau_1}\beta_1^{\infty}\beta_3^{\infty}}{\beta_1^{\infty} + \beta_2^{\infty}} - \delta\beta_2^{\infty} + r_2\beta_2^{\infty} - r_2\beta_{2\infty}\left(\frac{\beta_{1\infty} + \beta_2^{\infty}}{K_H}\right)$$

and

$$0 \geq \frac{\alpha\, e^{-\gamma_1\tau_1}\beta_1^{\infty}\beta_3^{\infty}}{\beta_1^{\infty} + \beta_2^{\infty}} - \delta\beta_{2\infty} + r_2\beta_{2\infty} - r_2\beta_{2\infty}\left(\frac{\beta_{1\infty} + \beta_{2\infty}}{K_H}\right),$$

respectively. Subtracting the first inequality from the second one, we get

$$0 \geq \left(\delta - r_2 + \frac{r_2\beta_{2\infty}}{K_H}\right)(\beta_2^{\infty} - \beta_{2\infty}). \tag{105}$$

Since $r_1 - d_1 > 0$ and $r_2 < \delta$, we must have $\beta_1^{\infty} = \beta_{1\infty}$, $\beta_2^{\infty} = \beta_{2\infty}$ and $\beta_3^{\infty} = \beta_{3\infty}$, for inequalities (101), (104) and (105) to hold. It then follows that

$$\lim_{t\to\infty}(H(x,t,\phi_1), I(x,t,\phi_2), V(x,t,\phi_3)) = (\beta_1^{\infty}, \beta_2^{\infty}, \beta_3^{\infty}), \quad \forall\, x \in \overline{\Omega}. \tag{106}$$

Now, we find $\lim_{t\to\infty}(H(x,t,\phi_1), I(x,t,\phi_2), V(x,t,\phi_3)) = (\beta_1^{\infty}, \beta_2^{\infty}, \beta_3^{\infty})$, uniformly for all $x \in \overline{\Omega}$. For any $\psi \in \omega(\phi)$, there is a sequence $t_n \to \infty$ such that $\Phi(t_n)\phi \to \psi$ in $\mathcal{X}_\tau$ as $n \to \infty$. Thus

$$\lim_{n\to\infty}(H(x,t_n+\theta,\phi_1), I(x,t_n+\theta,\phi_2), V(x,t_n+\theta,\phi_3)) = \psi(x,\theta),$$

uniformly for all $(x,\theta) \in \overline{\Omega} \times [-\tau, 0]$. Hence, by (106), $\psi(x,\theta) = (\beta_1^{\infty}, \beta_2^{\infty}, \beta_3^{\infty}), \forall (x,\theta) \in \overline{\Omega} \times [-\tau, 0]$. Therefore $\omega(\phi) = \{(\beta_1^{\infty}, \beta_2^{\infty}, \beta_3^{\infty})\}$, which infers that $(H(x,t,\phi_1), I(x,t,\phi_2), V(x,t,\phi_3))$ converges to $(\beta_1^{\infty}, \beta_2^{\infty}, \beta_3^{\infty})$ in Γ_2. Since the ω-limit $(\omega(\phi))$ is invariant for $\Phi(t)$ for all $t \geq 0$, it directly follows that $(\beta_1^{\infty}, \beta_2^{\infty}, \beta_3^{\infty})$ is a positive constant equilibrium point of problem (4)–(6). Since E^* is locally asymptotically stable for $\tau_1 \in [0, \tau_{11}^*)$ and $\tau_2 \in [0, \tau_{22}^*)$, it follows that, the largest compact invariant subset of Γ_2 is the singleton $\{(H^*, I^*, V^*)\}$. So, by LaSalle's invariant principle [38, Theorem 5.3.1], $(\beta_1^{\infty}, \beta_2^{\infty}, \beta_3^{\infty}) = (H^*, I^*, V^*)$, that is, the unique equilibrium point with infection, E^*, is globally attractive. This ends the proof of Theorem 4.4. ■

Table 1. Biological description of the parameters of model (4).

Parameters	Description	Value	Unit	Source
s_0	Production rate of healthy hepatocytes HBV	5.04×10^5	cells $\mathrm{mm}^{-3}\,\mathrm{day}^{-1}$	[16]
d_1	Decay rate of healthy hepatocytes HBV	0.0039	day^{-1}	[16]
α	Rate of transmission of infection	0.0014	cells $(\mathrm{day\,virus})^{-1}$	[18]
δ	Decay rate of HBV infected cells	0.0693	day^{-1}	[16,18]
μ	Decay rate of HBV virions	0.693	day^{-1}	[16,18]
r_1	Maximal rate of growth per capita of healthy hepatocytes	1	cells ml^{-1}	[18]
r_2	Maximal rate of growth per capita of infected hepatocytes	0.01	cells ml^{-1}	Estimated
K_H	Homeostatic carrying capacity of healthy HBV cells	2×10^{11}	cells ml^{-1}	[18]
k	Rate of replication of HBV virions produced by HBV infected cells	280	virus $(\mathrm{day\,cells})^{-1}$	[18]
γ_1	Death rate for new infected hepatocytes during $[t-\tau_1, t]$	0.01	day^{-1}	Assumed
γ_2	Death rate for new virion during $[t-\tau_2, t]$	0.01	day^{-1}	Assumed
u	Modification parameter	0.08	day^{-1}	[17,21]
D	Free HBV virion diffusion coefficient	0.01	$\mathrm{mm}^2\,\mathrm{day}^{-1}$	[16]

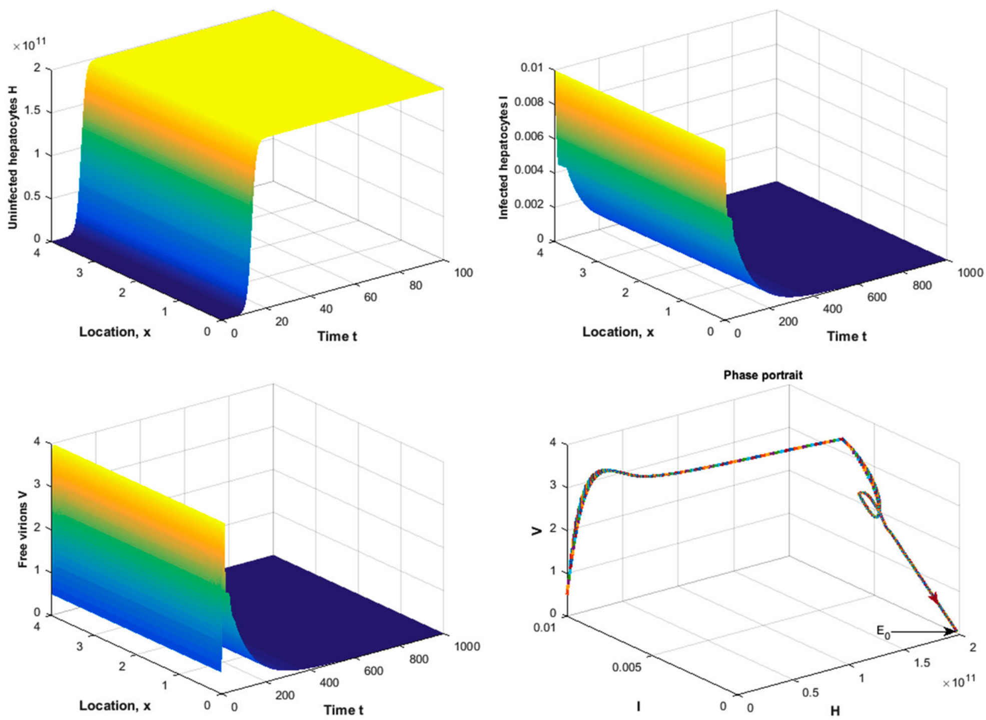

Figure 1. Dynamical behavior of PDE problem (4)–(6) with the set of parameter values of Table 1 and $\alpha = 0.00014$, $\tau_1 = 15$, $\tau_2 = 2$, so that $\mathcal{R}_0 = 0.6898 < \mathcal{T}_0 = 0.8048 < 1$.

5. Numerical simulations

In this section, we carry out numerical simulations in order to illustrate theoretical analytical results obtained in the preceding sections. The numerical implementation is performed using a standard finite difference method. The one-dimensional bounded spatial domain is taken as $\Omega = [0, 4]$ and the time window is chosen according to the expected observation. The spatial and temporal directions grid sizes used are $\Delta x = 0.05$ and $\Delta t = 0.08$, respectively. By considering the experimental data available in the literature [16–18], we list the parameter values used in Table 1 to explore PDE

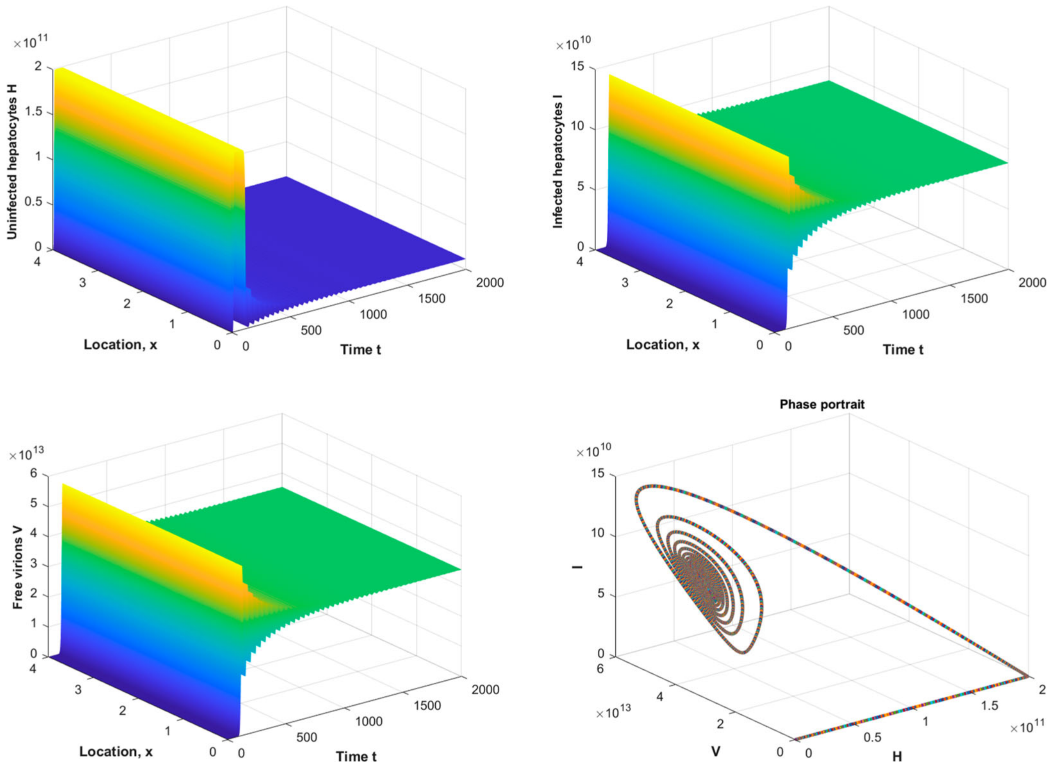

Figure 2. Dynamical behavior of PDE problem (4)–(6) with the set of parameter values of Table 1 and $\tau_1 = 0$, $\tau_2 = 0.6$, so that $\mathcal{R}_0 = 8.1169 > 1$. The endemic equilibrium E^* is asymptotically stable when $\tau_2 < \tau_2^* = 0.8000$.

system (4) and illustrate the stability properties of constant equilibria. For all the numerical implementation scenarios, we choose the initial conditions as $(H(x,\theta), I(x,\theta), V(x,\theta)) = (50, 0.01, 0.5)$, for $x \in \Omega, \theta \in [-\tau, 0]$, $\tau = \max\{\tau_1, \tau_2\}$.

First, we let $\tau_1 = 15$, $\tau_2 = 2$ and keep the other parameter values as in Table 1 except for $\alpha = 0.00014$, which implies $\mathcal{R}_0 = 0.6898 < \mathcal{T}_0 = 0.8048 < 1$. In this case, the HBV-free equilibrium E_0 is globally asymptotically stable. It can be seen from Figure 1 that this is indeed the case and the solution trajectories converge towards the infection-free equilibrium $E_0 = (1.9767 \times 10^{11}, 0, 0)$. Here, we observe that healthy hepatocytes increase and approach the carrying capacity $K_H = 2 \times 10^{11}$. Meanwhile, the other viral infection components converge to zero after small oscillations. This confirms the result stated in Theorem 4.1 and it then follows that the infection is wiped out. Now, we fix $\tau_1 = 0$ and vary the value of the delay parameter τ_2 to see the effect of one delay on the dynamical behavior of PDE-model (4)–(6). Through numerical computation, we obtain two critical values of the delay parameter τ_2, represented by $\tau_2^* = 0.8000$ and $\tau_2^{**} = 29.9217$. Figure 2 depicts the local asymptotic stability of the endemic equilibrium E^* for $\tau_2 = 0.6 < \tau_2^*$ as attested by Theorem 3.5. Figures 3 and 4 plot the solutions trajectories of the PDE-model (4)–(6) when $\tau_2 = 5 \in (\tau_2^*, \tau_2^{**})$ and $\tau_2 = 27 \in (\tau_2^*, \tau_2^{**})$, respectively, and show that the endemic equilibrium E^* becomes unstable whenever $\tau_2 \in (\tau_2^*, \tau_2^{**})$. Figure 5 plots the solutions trajectories of PDE-model (4)–(6) when $\tau_2 = 32 > \tau_2^{**}$ and illustrates the fact that the endemic equilibrium E^* regains its stability for $\tau_2 > \tau_2^{**}$. From these arguments, we can see that the endemic equilibrium E^* is locally asymptotically stable for $\tau_2 \in [0, \tau_2^*)$. This indicates that PDE-model (4)–(6) undergoes Hopf bifurcation at $\tau_2 = \tau_2^*$ and the endemic equilibrium E^* losses its stability for $\tau_2 \in (\tau_2^*, \tau_2^{**})$, afterwards, E^* regains its stability for $\tau_2 > \tau_2^{**}$. Accordingly, the Hopf bifurcation occurs at τ_2^* and τ_2^{**}.

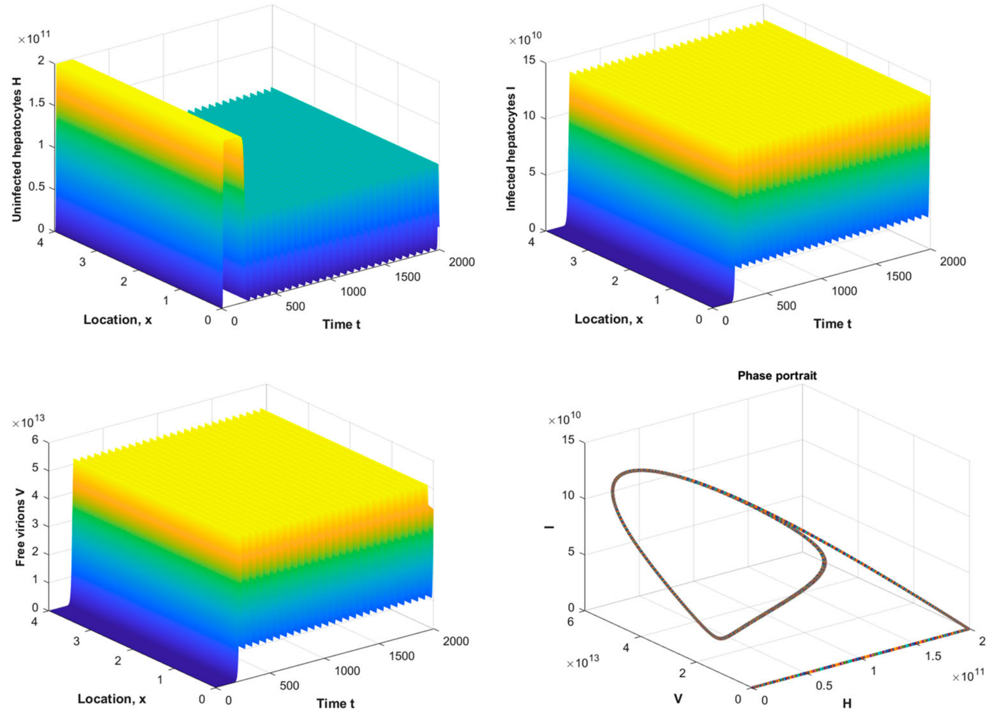

Figure 3. Dynamical behavior of PDE problem (4)–(6) with the set of parameter values of Table 1 and $\tau_1 = 0$, $\tau_2 = 5$, so that $\mathcal{R}_0 = 7.7675 > 1$. The endemic equilibrium E^* becomes unstable and a Hopf bifurcation occurs when $\tau_2 \in (\tau_2^*, \tau_2^{**})$, where $\tau_2^{**} = 29,9217$.

Next, we fix $\tau_2 = 0$ and vary the value of τ_1 to see its effect on the dynamical behavior of PDE-model (4)–(6). By numerical calculation, we first find one critical value of τ_1, denoted by $\tau_1^* = 0.8400$. We observe from the phase portrait on Figure 6 that the endemic equilibrium E^* is locally asymptotically stable for $\tau_1 \in [0, \tau_1^*)$. It losses its stability for $\tau_1 \in (\tau_1^*, \tau_1^{**})$, and recovers it after τ_1^{**}. In this case, it is confirmed that PDE-model (4)–(6) undergoes Hopf bifurcation at τ_1^* and τ_1^{**}.

Now, it is worth noting that, the dynamical behavior of PDE-model (4)–(6) is completely arbitrated by the basic reproduction number $\mathcal{R}_0$. Then, it follows that a good strategy to control HBV infection is to reduce the value of $\mathcal{R}_0$ below one. In this case, the infection-free equilibrium E_0 is globally asymptotically stable. From the expression $\mathcal{R}_0 = \mathcal{R}_0(\tau_1, \tau_2) = \alpha k e^{-\gamma_1 \tau_1 - \gamma_2 \tau_2}/(\mu + \alpha u)[\delta + r_2(\frac{\Lambda}{K_H} - 1)]$, we can conclude that $\mathcal{R}_0$ is a nonincreasing function of the delays parameters τ_1 and τ_2, so that $\mathcal{R}_0(\infty, \tau_2) = \mathcal{R}_0(\tau_1, \infty) = \mathcal{R}_0(\infty, \infty) = 0$. Figure 7 designs the basic reproduction number $\mathcal{R}_0$ as a function of the time delays τ_1 and τ_2. From this graphical result, we see that sufficient large values of delays τ_1 and τ_2 reduce $\mathcal{R}_0$ below one. This leads to the conclusion that the time delays τ_1 and τ_2 are relevant in the eradication of free HBV from the liver.

Additionally, the expression of $\mathcal{R}_0$ shows that it is independent of the diffusion coefficient D, which indicates that the mobility of free virions in the liver has no effect on the global dynamical behavior of the model established. However, the sub-figures of Figure 8 show that large diffusion coefficients destabilize the endemic equilibrium. This means that the fast mobility of free virions in the liver can make HBV infection uncontrollable in the liver of an infected patient.

6. Concluding remarks

The study of HBV infection is a hot research topic. Following a recent work of ours [17], we have formulated and analyzed a two-time-delayed reaction-diffusion model of HBV infection within a

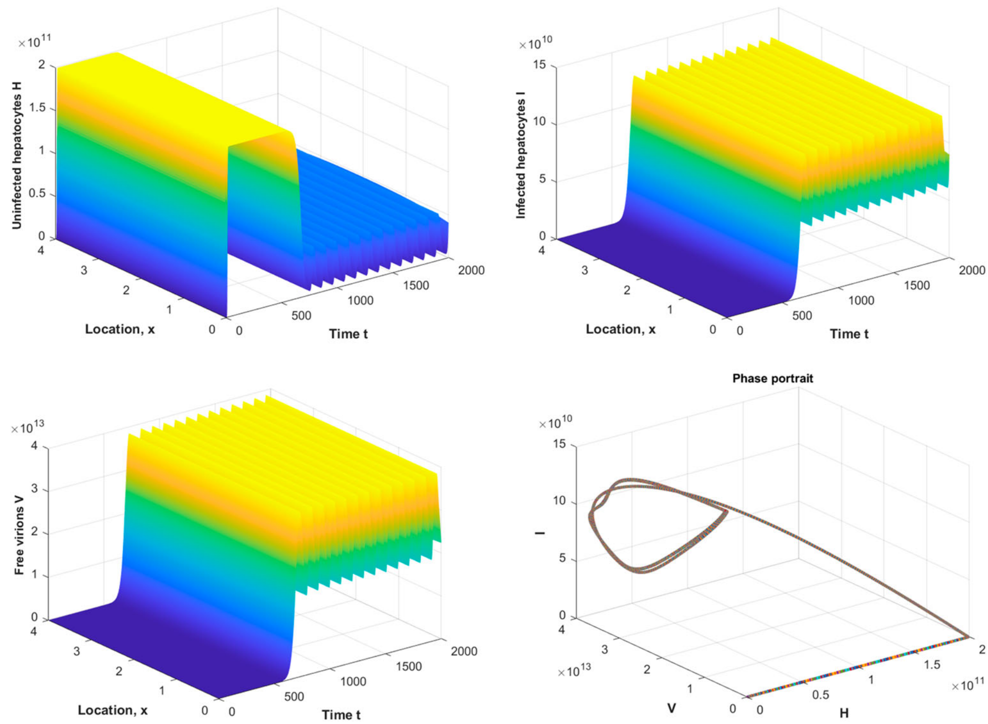

Figure 4. The space and time histories and the phase trajectory of PDE problem (4)–(6) after Hopf bifurcation occurs for the parameter values of Table 1 with $\tau_1 = 0$, $\tau_2 = 27$. Here the basic reproduction number is $\mathcal{R}_0 = 6.2335$.

host. The two time delays are introduced to account, respectively, for actual virus production and virus maturation. After establishing the well-posedness of this mathematical model, we derived a biologically meaningful threshold, the basic reproduction number $\mathcal{R}_0$, and discussed the asymptotic stability of the infection-free equilibrium and the endemic equilibrium. We showed that the infection will not invade the liver if there exists a threshold parameter $\mathcal{T}_0$ such that $\mathcal{R}_0 \leq \mathcal{T}_0 < 1$ and the infection persists in previously infected hepatocytes if $\mathcal{R}_0 > 1$. Using a fluctuation method developed by Thieme and Zhao [36], we obtained a set of sufficient conditions to insure that the HBV infection will become established and stabilized at a unique endemic equilibrium. In particular, if $\mathcal{R}_0 > 1$ is large enough, the positive endemic equilibrium is globally attractive. We investigated the local asymptotic stability of the endemic equilibrium in particular cases with one positive delay and in a general case with both positive delays. We found that a nondecreasing HBV production and HBV maturation delays can stabilize or destabilize the endemic equilibrium, yielding stability switches. Therefore, the HBV production and HBV maturation delays cause the occurrence of Hopf bifurcation and provoke appearance of viral oscillations. Clinically, these oscillations patterns resemble to the blips of the different phases of chronic HBV infection, and they provide an alternative interpretation of these observable events.

From the numerical results, we saw that oscillations also occur when the diffusion coefficient is large. This signifies that the fast mobility of free virions in the liver can make HBV infection uncontrollable.

We proved that the intracellular replication delay τ_1 and the virus maturation delay τ_2 can reduce the basic reproduction number $\mathcal{R}_0$ if hepatocytes die during the delays periods. Then we deduced that neglecting one of these time delays leads to an overestimate of HBV infection risk. Finally, on Figure 7, we noticed that $\mathcal{R}_0$ becomes less than one when all parameters are fixed and time delays τ_1 and τ_2 are sufficiently large. From there, we saw that the time delays τ_1 and τ_2 play an important role in the

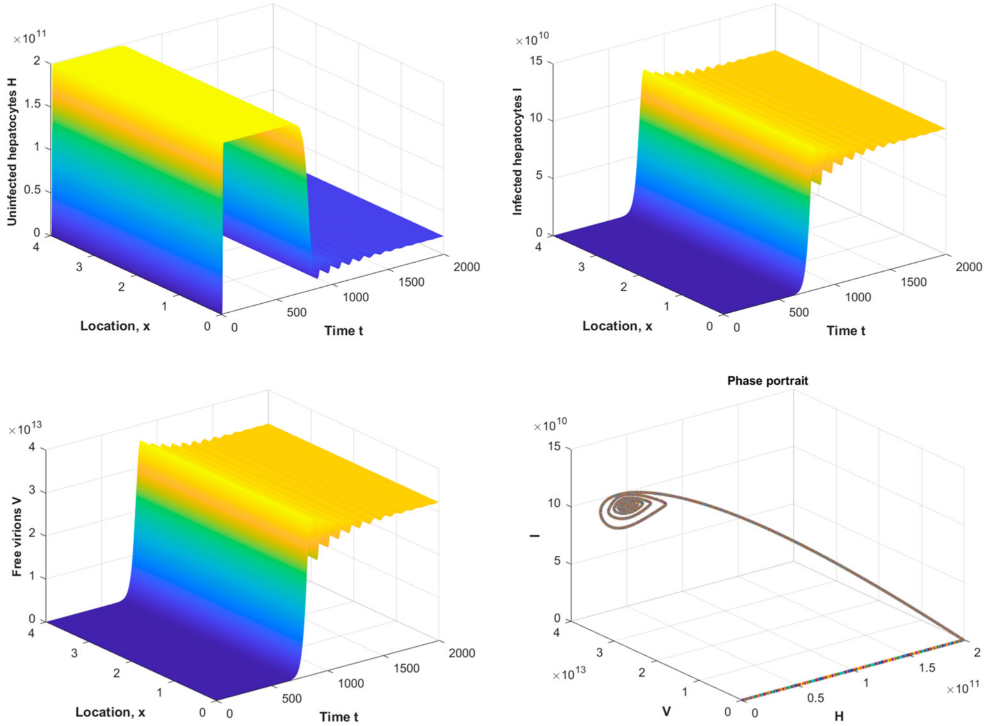

Figure 5. For the parameter values of Table 1 with $\tau_1 = 0$, and $\tau_2 = 32$, the endemic equilibrium E^* of PDE problem (4)–(6) is asymptotically stable. Here the basic reproduction number is $\mathcal{R}_0 = 5.9295$.

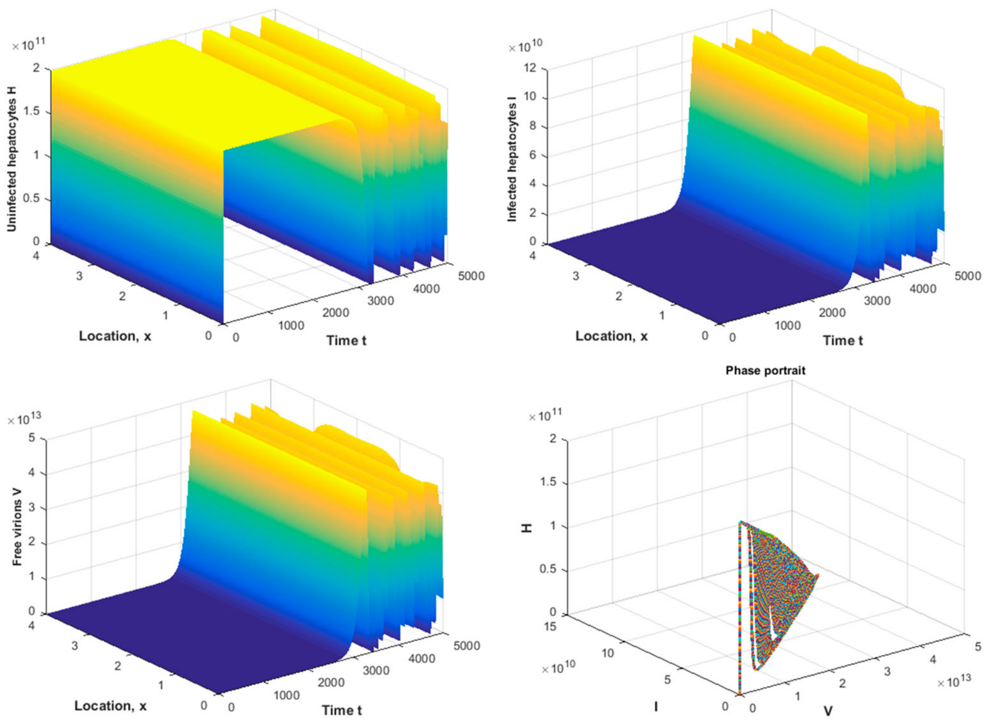

Figure 6. The space and time histories and the phase trajectory of PDE problem (4)–(6) after Hopf bifurcation occurs for the parameter values of Table 1 with $\tau_1 = 100$, $\tau_2 = 0$. Here the basic reproduction number is $\mathcal{R}_0 = 3.0040$.

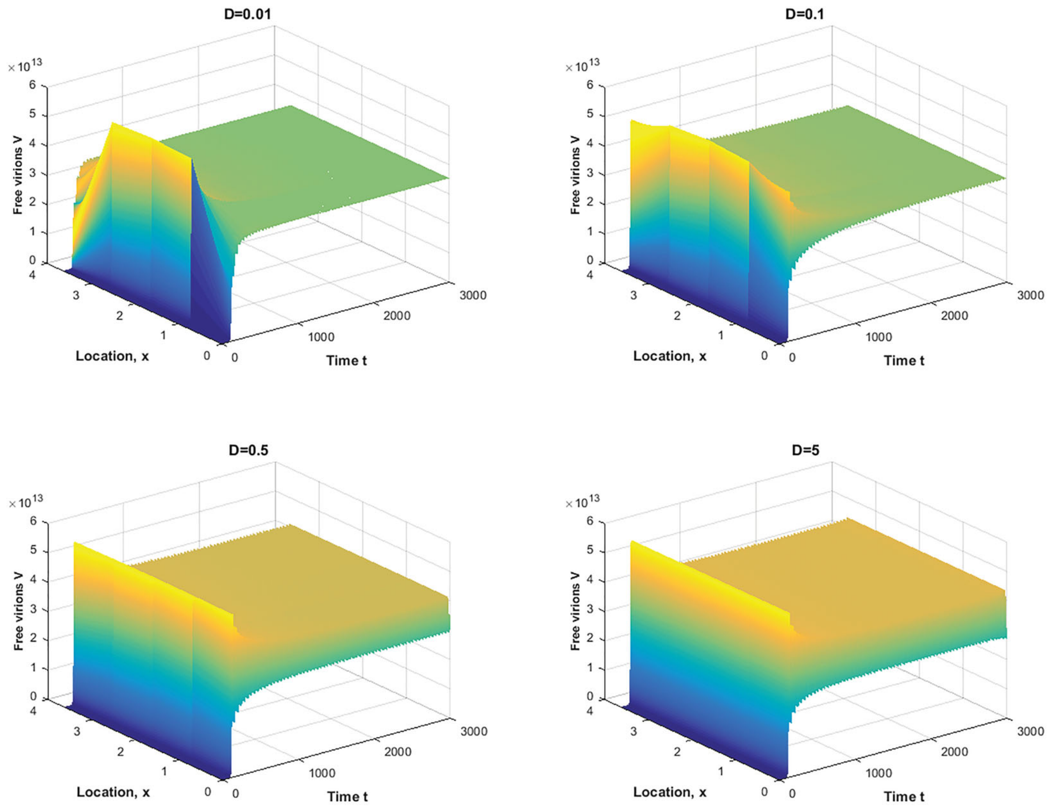

Figure 7. Plot of the basic reproduction number $\mathcal{R}_0$ as a function of the time delays τ_1 and τ_2, using the parameter values of Table 1.

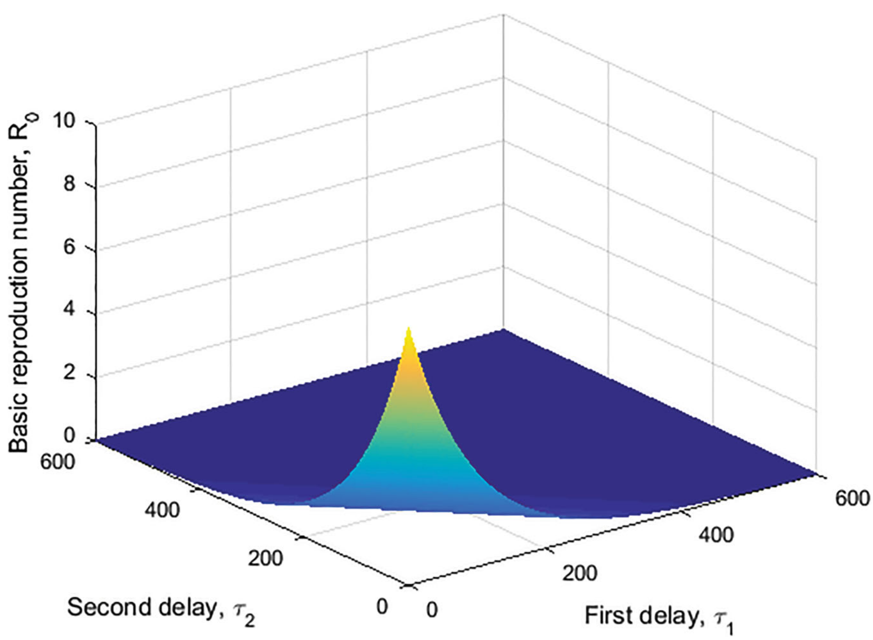

Figure 8. Distribution of free virus under different diffusion coefficients, with $\tau_1 = 0.15$, and $\tau_2 = 0.6$.

eradication of free HBV from the liver. From the mathematical analysis and numerical simulations, we think that the model studied in the present paper can be used to design better strategies for mitigating HBV infection.

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Data availability statement

The codes written to run most of the simulations presented in this work can be available upon simple request to the authors.

Disclosure statement

The authors declare that they have no known personal relationships or competing financial interests that could have appeared to influence the work made in this paper.

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