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Research Article

Analysis of a New Delayed HBV Model with Exposed State and Immune Response to Infected Cells and Viruses

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We propose a comprehensive delayed HBV model, which not only considers the immune response to both infected cells and viruses and a time delay for the immune system to clear viruses but also incorporates an exposed state and the proliferation of hepatocytes. We prove the positivity and boundedness of solutions and analyze the global stability of two boundary equilibria and then study the local asymptotic stability and Hopf bifurcation of the positive (infection) equilibrium and also the stability of the bifurcating periodic solutions. Moreover, we illustrate how the factors such as the time delay, the immune response to infected cells and viruses, and the proliferation of hepatocytes affect the dynamics of the model by numerical simulation.

1. Introduction

Hepatitis B virus (HBV) has become one of the serious infectious diseases threatening global human health, which can cause chronic liver infection and further result in liver inflammation, fibrosis, cirrhosis, or even cancer [1]. Each year more than 1 million people die of end-stage liver diseases like cancer due to the HBV infection [2].

Mathematical modeling and analysis of the dynamics of such infectious viruses as HBV play important roles in understanding the factors that govern the infectious disease progression and offering insights into developing treatment strategies and guiding antiviral drug therapies [3]. So far, there have been plenty of mathematical models proposed to describe and analyze virus infection, immune responses, and antiretroviral treatment [4–10].

Among these works, the development of virus models with immune responses is gaining much attention [3, 11, 12]. The immune system is essential in controlling the level of virus reproduction in terms of the strength of the Cytotoxic T Lymphocyte (CTL) response. A small change of the CTL response may have a large effect on virus production and infected cells load. As to this aspect, typical work can be summarized as follows. Chen et al. [12] indicated that the immunity system can not only clear free viruses but also kill infected cells. Elaiw and AlShamrani [3] proposed a four-dimensional model with humoral immunity response and general function and analyzed the global asymptotic stability of all equilibria based on the general function. However, both models in [3, 12] do not consider time delay. In order to characterize the time of a body's immune response after the virus infection of target cells, time delay has been taken into account [13–16]. For example, Zhu et al. [16] proposed an HIV infection model with CTL response delay and analyzed the effect of time delay on the stability of equilibria. Besides, a latent period would be necessary to be incorporated into a virus model because when viruses infect a healthy organ like liver, it will not be pathogenetic at once, as it takes about six weeks to six months from the infection to the incidence [17–20]. For example, Medley et al. [17] proposed an HBV model with an exposed state, namely, infected but not yet infectious. Moreover, it was modeled in [21, 22] that the liver can regenerate cells and compensate the lost infected hepatocytes by the proliferation of hepatocytes.

In this paper, we will propose a more comprehensive model than those existing ones, which not only considers the immune response to both infected cells and viruses and a time delay for the immune system to clear viruses but also incorporates an exposed state and the proliferation of

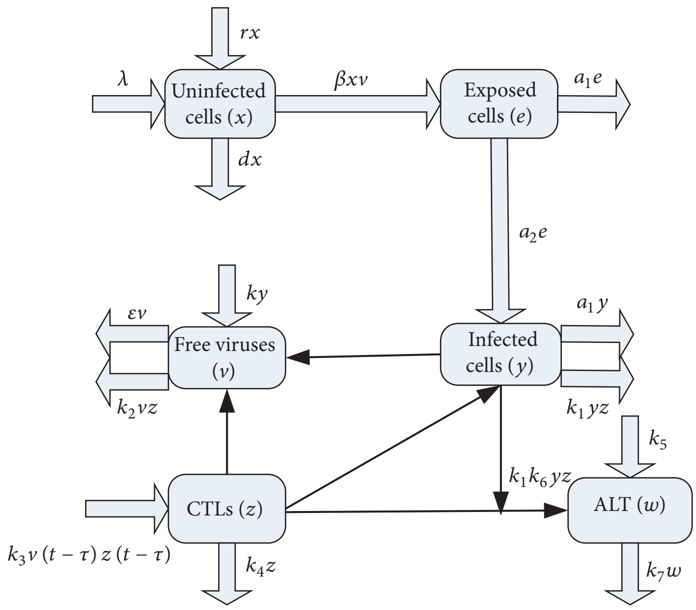

Figure 1: The mechanism of our model.

hepatocytes. We first discuss the existence of two boundary equilibria and one positive (infection) equilibrium. We then analyze the global stability of the two boundary equilibria, the local asymptotic stability and Hopf bifurcation of the positive equilibrium and also the stability of the bifurcating periodic solutions. Moreover, we perform numerical simulations to illustrate some of the theoretical results we obtain and also illustrate how the factors such as the immune response to infected cells and viruses and the proliferation of hepatocytes affect the dynamics of the model under time delay.

The paper is structured as follows. In Section 2, a delayed mathematical model is proposed, and the positivity and boundedness of solutions, existence of two boundary equilibria, and one positive equilibrium are discussed, followed by the global stability analysis of these two boundary equilibria and the local asymptotic stability and Hopf bifurcation of the positive equilibrium in Section 3. The stability of the bifurcating periodic solutions is studied in Section 4. In Section 5, some numerical simulations and discussions are given. Finally, a conclusion is given in Section 6.

2. Mathematical Model

Wang et al. [23] proposed a virus infection model of four-dimensional equations with delayed humoral immune response, which, however, does not involve an exposed state and consider the proliferation of hepatocytes. Although it considers the immune response to viruses, it does not involve the immune response to infected cells.

Based on this model, we propose a new and comprehensive HBV model, which not only considers the immune response to both infected cells and viruses and a time delay for the immune system to clear viruses but also incorporates an exposed state and the proliferation of hepatocytes. To better understand our model, we illustrate its mechanism in Figure 1.

The model is then given as follows:

$$\begin{aligned} \dot{x}(t) &= \lambda + rx(t) - dx(t) - \beta x(t) v(t), \\ \dot{e}(t) &= \beta x(t) v(t) - a_1 e(t) - a_2 e(t), \\ \dot{y}(t) &= a_2 e(t) - a_1 y(t) - k_1 y(t) z(t), \\ \dot{v}(t) &= ky(t) - \varepsilon v(t) - k_2 v(t) z(t), \\ \dot{z}(t) &= k_3 v(t-\tau) z(t-\tau) - k_4 z(t), \\ \dot{w}(t) &= k_5 + k_1 k_6 y(t) z(t) - k_7 w(t), \end{aligned} \tag{1}$$

where x, e, y, v, z, and w denote the number of uninfected cells, exposed cells, infected cells, free viruses, CTLs, and alanine aminotransferases (ALT), respectively. The parameter λ represents the natural production rate of uninfected cells. rx is a new term which is introduced to represent the proliferation of hepatocytes, where r is the proliferation rate. Parameters d, (and the following) a_1, ε, k_4, and k_7 represent the natural death rate of uninfected cells, exposed cells, infected cells, free viruses, CTLs, and ALT, respectively. β represents the infection rate from uninfected cells to exposed cells and a_2 the transfer rate from exposed cells to infected cells. The production rate of free viruses from infected cells is denoted by k, and the production rate of CTLs by k_3. k_5 represents the production rate of ALT from the extrahepatic tissue and k_1k_6 the production rate of ALT when the infected hepatocytes are killed by CTL. The immunity-induced clearance for infected cells is modeled by a term k_1yz, where k_1 represents the clearance rate of infected cells. Similarly, the immunity-induced clearance for free viruses is modeled by k_2vz, where k_2 represents the clearance rate of free viruses. τ is time delay. All the parameters in this paper are positive and $d > r$. For convenience, we define new parameter $\rho = d - r$.

2.1. Positivity and Boundedness of Solutions. In this subsection, we prove the positivity and the boundedness of solutions of system (1).

We denote $x(0) \geq 0$, $e(0) \geq 0$, $y(0) \geq 0$, $w(0) \geq 0$, $v(t) \geq 0$, $z(t) \geq 0$, $t \in [-\tau, 0]$. From the first equation of system (1), we have $x(t) = e^{-\int_0^t (\rho+\beta v(s))ds} x(0) + \lambda \int_0^t e^{-\int_s^t [\rho+\beta v(\xi)]d\xi} ds$; therefore, $x(t) \geq 0$ for $\forall t > 0$ if $x(0) \geq 0$. Next, we consider the second, third, and fourth equation in system (1) as a nonautonomous system for $e(t)$, $y(t)$, $v(t)$:

$$\begin{aligned} \dot{e} &= \beta x v - (a_1 + a_2) e(t), \\ \dot{y} &= a_2 e - (a_1 + k_1 z) y(t), \\ \dot{v} &= k y - (\varepsilon + k_2 z) v(t). \end{aligned} \tag{2}$$

Based on Theorem 2.1 in [24], we have $e(t) \geq 0$, $y(t) \geq 0$, $v(t) \geq 0$ if $e(0) \geq 0$, $y(0) \geq 0$, $z(0) \geq 0$.

$z(t) = e^{-k_4 t} y(0) + \int_0^t k_3 v(t-\gamma) z(t-\gamma) e^{-k_4(t-\gamma)} d\gamma$, we have $z(t) \geq 0$, $\forall t > 0$ if $z(t) \geq 0$, $t \in [-\tau, 0]$.

$w(t) = e^{-k_7 t} w(0) + e^{-k_7 t} \int_0^t [(k_5 + k_1 k_6 y(s) z(s)] e^{-k_7 t} ds$, because $y(t), z(t) \geq 0$, so we have $w(t) \geq 0$, $\forall t > 0$ if $w(0) \geq 0$.

Hence, the nonnegative is proved. In what follows, we will study the boundedness of solutions. We define $G(t)$ as a linear combination of x, e, y, v, z:

$$\begin{aligned} G(t) &= x(t) + e(t) + y(t) + \frac{a_1}{2k} v(t) \\ &\quad + \frac{a_1 k_2}{2k k_3} z(t+\tau), \\ \delta &= \min\left\{d - r, \frac{a_1}{2}, a_1, \varepsilon, k_4\right\}, \\ \frac{dG(t)}{dt} &= (\lambda - \rho x - \beta x v) + (\beta x v - a_1 e - a_2 e) \\ &\quad + (a_2 e - a_1 y - k_1 y z) + \frac{a_1}{2k}(k y - \varepsilon v - k_2 v z) \\ &\quad + \frac{a_1 k_2}{2k k_3}(k_3 v(t) z(t) - k_4 z(t+\tau)) \\ &= \lambda - (d - r) x - \frac{a_1}{2} e - a_1 y - \frac{a_1 \varepsilon}{2k} v \\ &\quad - \frac{a_1 k_2 k_4}{2k k_3} z(t+\tau) - k_1 y z \leq \lambda - \delta G(t). \end{aligned} \tag{3}$$

Therefore, we obtain $\lim_{t\to\infty} G(t) \leq \lambda/\delta$, namely, $x(t) + e(t) + y(t) + (a_1/2k) v(t) + (a_1 k_2 / 2k k_3) z(t+\tau) \leq \lambda/\delta$. So we have $0 \leq x(t), e(t), y(t), v(t), z(t) \leq \lambda/\delta$ Because the boundedness of $x(t), e(t), y(t), v(t), z(t)$, $\lim_{t\to\infty} w(t) \leq (k_5 + k_1 k_6)\lambda^2 / k_7 \delta^2$.

The boundedness is proved.

2.2. Equilibrium. In this subsection, we study the equilibria of system (1). The method to obtain equilibria is setting $\dot{x} = \dot{e} = \dot{y} = \dot{v} = \dot{z} = \dot{w} = 0$ and computes the following:

$$\begin{aligned} \lambda - \rho x - \beta x v &= 0, \\ \beta x v - a_1 e - a_2 e &= 0, \\ a_2 e - a_1 y - k_1 y z &= 0, \\ k y - \varepsilon v - k_2 v z &= 0, \\ k_3 v(t-\tau) z(t-\tau) - k_4 z &= 0, \\ k_5 + k_1 k_6 y z - k_7 w &= 0. \end{aligned} \tag{4}$$

The system (1) has two boundary equilibria (an infection-free equilibrium E_{00} in which $x \neq 0$, $w \neq 0$, $e = y = v = z = 0$ and an equilibrium without immune response E_{11} in which $x \neq 0$, $e \neq 0$, $y \neq 0$, $v \neq 0$, $w \neq 0$, $z = 0$) and a positive (infection) equilibrium E_{22} in which $x \neq 0$, $E \neq 0$, $y \neq 0$, $v \neq 0$, $z \neq 0$, $w \neq 0$.

The infection-free equilibrium is $E_{00} = (x_0, 0, 0, 0, 0, w_0)$, where $x_0 = \lambda/\rho$, and $w_0 = k_5/k_7$, and the basic reproductive number is obtained by the following method.

Based on integral operator spectral radius, the basic reproductive number is $R_0 = \rho(FV^{-1})$, where

$$\begin{aligned} F &= \begin{bmatrix} 0 & 0 & \beta x_0 \\ a_2 & 0 & 0 \\ 0 & k & 0 \end{bmatrix}, \\ V &= \begin{bmatrix} a_1 + a_2 & 0 & 0 \\ 0 & a_1 + k_1 z_0 & 0 \\ 0 & 0 & \varepsilon \end{bmatrix}. \end{aligned} \tag{5}$$

Hence, we have the basic reproductive number being $R_0 = a_2 k x_0 \beta / a_1 \varepsilon (a_1 + a_2)$.

The equilibrium without immune response is $E_{11} = (x_1, e_1, y_1, v_1, 0, w_1)$, where $x_1 = a_1 \varepsilon (a_1 + a_2)/a_2 k \beta$, $e_1 = (a_1 \varepsilon / a_2 k) v_1$, $y_1 = (\varepsilon/k) v_1$, $v_1 = a_2 k \lambda / a_1 \varepsilon (a_1 + a_2) - \rho/\beta$, and $w_1 = k_5/k_7$. Similarly, we have the basic reproductive number is $R_1 = k_3 v_1 / k_4 + k k_3 y_1 k_1 / a_1 k_2 k_4$ at $E_{11} = (x_1, e_1, y_1, v_1, 0, w_1)$.

The infected positive equilibrium is $E_{22} = (x_2, e_2, y_2, v_2, z_2, w_2)$, where

$$\begin{aligned} v_2 &= \frac{k_4}{k_3}, \\ x_2 &= \frac{\lambda}{\rho + \beta v_2}, \\ e_2 &= \frac{\beta x_2 v_2}{a_1 + a_2}, \\ y_2 &= \frac{A + \sqrt{A^2 + 4B}}{2}, \end{aligned}$$

$$A = \frac{a_1 k_2 k_4 - k_1 k_3 \varepsilon v_2}{k k_1 k_3},$$
$$B = \frac{a_2 k_2 k_4}{k k_1 k_3} > 0,$$
$$z_2 = \frac{k_3 (k y_2 - \varepsilon v_2)}{k_2 k_4},$$
$$w_2 = \frac{k_5 + k_1 k_6 y_2 z_2}{k_7}. \quad (6)$$

3. Analysis

3.1. Global Stability Analysis of the Two Boundary Equilibria. In this section, we will employ the direct Lyapunov method and LaSalle's invariance principle to establish the global asymptotic stability of the two boundary equilibria.

Theorem 1. *The infection-free equilibrium E_{00} is globally asymptotically stable if and only if $R_0 < 1$.*

See Appendix A for proof.

Theorem 2. *The equilibrium without immune response E_{11} is globally asymptotically stable if and only if $R_1 < 1$.*

See Appendix B for proof.

3.2. Local Asymptotic Stability and Hopf Bifurcation of the Positive Equilibrium. In this section, we will discuss the local asymptotic stability and Hopf bifurcation of the positive equilibrium E_{22}.

The characteristic equation of system (1) at E_{22} is as follows:

$$H(\lambda;\tau) = \begin{vmatrix} \lambda+\rho+\beta v_2 & 0 & 0 & \beta x_2 & 0 & 0 \\ -\beta v_2 & \lambda+a_1+a_2 & 0 & -\beta x_2 & 0 & 0 \\ 0 & -a_2 & \lambda+a_1+k_1 z_2 & 0 & k_1 y_2 & 0 \\ 0 & 0 & -k & \lambda+\varepsilon+k_2 z_2 & k_2 v_2 & 0 \\ 0 & 0 & 0 & -k_3 z_2 e^{-\lambda\tau} & \lambda - k_3 v_2 e^{-\lambda\tau} + k_4 & 0 \\ 0 & 0 & -k_1 k_6 z_2 & 0 & -k_1 k_6 y_2 & \lambda + k_7 \end{vmatrix} = 0. \quad (7)$$

Define

$$A_1 = 2a_1 + a_2 + k z_2,$$
$$A_2 = (a_1 + a_2)(a_1 + k z_2),$$
$$A_3 = \varepsilon + k_4 - k_2 z_2,$$
$$A_4 = k_4 (\varepsilon - k_2 z_2),$$
$$A_5 = a_2 k \beta x_2,$$
$$A_6 = a_2 k k_4 \beta x_2,$$
$$M_1 = -k_3 v_2,$$
$$M_2 = (2 k_2 z_2 - \varepsilon) k_3 v_2,$$
$$M_3 = k k_1 k_3 y_2 z_2,$$
$$M_4 = -a_2 k k_3 \beta x_2 v_2 + k k_1 k_3 y_2 z_2 (a_1 + a_2),$$
$$s_1 = A_1 + A_3,$$
$$s_2 = A_2 + A_4 + A_1 A_3,$$
$$s_3 = A_5 + A_1 A_4 + A_2 A_3,$$
$$s_4 = A_6 + A_2 A_4,$$
$$s_5 = M_1,$$
$$s_6 = M_2 + A_1 M_1,$$
$$s_7 = A_1 M_2 + A_2 M_1 + M_3,$$
$$s_8 = A_2 M_2 + M_4,$$
$$s_9 = \rho + \beta v_2,$$
$$s_{10} = \beta^2 x_2 v_2 a_2 k,$$
$$s_{11} = \beta^2 x_2 v_2 a_2 k k_4,$$
$$s_{12} = -\beta^2 x_2 v_2^2 a_2 k k_3,$$
$$B_1 = s_1 + s_9,$$
$$B_2 = s_2 + s_1 s_9,$$
$$B_3 = s_3 + s_2 s_9,$$
$$B_4 = s_4 + s_3 s_9 + s_{10},$$
$$B_5 = s_{11} + s_4 s_9,$$
$$B_6 = s_5,$$
$$B_7 = s_6 + s_5 s_9,$$
$$B_8 = s_7 + s_6 s_9,$$
$$B_9 = s_8 + s_7 s_9,$$

$$
\begin{aligned}
B_{10} &= s_{12} + s_8 s_9,\\
D_1 &= B_1 + k_7,\\
D_2 &= B_2 + B_1 k_7,\\
D_3 &= B_3 + B_2 k_7,\\
D_4 &= B_4 + B_3 k_7,\\
D_5 &= B_5 + B_4 k_7,\\
D_6 &= B_6 + B_5 k_7,\\
S_1 &= B_6,\\
S_2 &= B_7 + B_6 k_7,\\
S_3 &= B_8 + B_7 k_7,\\
S_4 &= B_9 + B_8 k_7,\\
S_5 &= B_{10} + B_9 k_7,\\
S_6 &= B_{10} k_7.
\end{aligned} \tag{8}
$$

Then the characteristic equation $H(\lambda;\tau)$ above becomes

$$
\begin{aligned}
H(\lambda;\tau) = {} & \lambda^6 + D_1\lambda^5 + D_2\lambda^4 + D_3\lambda^3 + D_4\lambda^2 + D_5\lambda\\
& + D_6 + S_1\lambda^5 e^{-\lambda\tau} + S_2\lambda^4 e^{-\lambda\tau} + S_3\lambda^3 e^{-\lambda\tau}\\
& + S_4\lambda^2 e^{-\lambda\tau} + S_5\lambda e^{-\lambda\tau} + S_6 e^{-\lambda\tau} = 0.
\end{aligned} \tag{9}
$$

When $\tau = 0$, (9) further becomes

$$
\begin{aligned}
H(\lambda;\tau) = {} & \lambda^6 + n_1\lambda^5 + n_2\lambda^4 + n_3\lambda^3 + n_4\lambda^2 + n_5\lambda + n_6\\
& = 0,
\end{aligned} \tag{10}
$$

where

$$
\begin{aligned}
n_1 &= D_1 + S_1,\\
n_2 &= D_2 + S_2,\\
n_3 &= D_3 + S_3,\\
n_4 &= D_4 + S_4,\\
n_5 &= D_5 + S_5,\\
n_6 &= D_6 + S_6.
\end{aligned} \tag{11}
$$

Using the Routh-Hurwitz criterion [23], we obtain the following lemma.

Lemma 3. *If (10) satisfies* $\Delta_1 \equiv n_1 > 0$, $\Delta_2 \equiv \begin{vmatrix} n_1 & 1 \\ n_3 & n_2 \end{vmatrix} > 0$, $\Delta_3 \equiv \begin{vmatrix} n_1 & 1 & 0 \\ n_3 & n_2 & n_1 \\ n_5 & n_4 & n_3 \end{vmatrix} > 0$ *and* $\Delta_4 = \begin{vmatrix} n_1 & 1 & 0 & 0 \\ n_3 & n_2 & n_1 & 1 \\ n_5 & n_4 & n_3 & n_2 \\ 0 & n_6 & n_5 & n_4 \end{vmatrix} > 0$, *then the positive equilibrium* E_{22} *is locally asymptotically stable when* $\tau = 0$.

Proof. By the Routh-Hurwitz criterion, if the four conditions are satisfied, then all roots of (10) have negative real parts. Therefore, the positive equilibrium E_{22} is locally asymptotically stable when $\tau = 0$. For more details, we refer the readers to [25, 26].

From Lemma 3, we know that all roots of $H(\lambda;\tau)$ lie to the left of the imaginary axis when $\tau = 0$. However, with τ increasing from zero, some of its roots may cross the imaginary axis to the right. In this case, there are some roots having positive real parts, and therefore the equilibrium E_{22} becomes unstable. Next, we will discuss the stability of system (1) at E_{22} when $\tau > 0$.

We first divide (9) into two parts and obtain

$$
\begin{aligned}
& \left|\lambda^6 + D_1\lambda^5 + D_2\lambda^4 + D_3\lambda^3 + D_4\lambda^2 + D_5\lambda + D_6\right|^2\\
& \quad = \left|S_1\lambda^5 + S_2\lambda^4 + S_3\lambda^3 + S_4\lambda^2 + S_5\lambda + S_6\right|^2 \left|e^{-\lambda\tau}\right|^2.
\end{aligned} \tag{12}
$$

Suppose (9) has a purely imaginary root $\lambda = i\omega$ ($\omega > 0$). Substituting $\lambda = i\omega$ into (12) yields

$$
\begin{aligned}
& \left|-\omega^6 + D_1\omega^5 i + D_2\omega^4 - D_3\omega^3 i - D_4\omega^2 + D_5\omega i\right.\\
& \quad \left. + D_6\right|^2 = \left|S_1\omega^5 i + S_2\omega^4 - S_3\omega^3 i - S_4\omega^2 + S_5\omega i\right.\\
& \quad \left. + S_6\right|^2.
\end{aligned} \tag{13}
$$

By separating the real part and imaginary part, the following real part is obtained:

$$
\begin{aligned}
& \omega^{12} + C_1\omega^{10} + C_2\omega^8 + C_3\omega^6 + C_4\omega^4 + C_5\omega^2 + C_6\\
& \quad = 0,
\end{aligned} \tag{14}
$$

where

$$
\begin{aligned}
C_1 &= -D_1^2 - 2D_2 + S_1^2,\\
C_2 &= D_2^2 + 2D_4 + 2D_1D_3 - S_2^2 - 2S_1S_3,\\
C_3 &= -D_3^2 - 2D_6 - 2D_1D_5 - 2D_2D_4 + S_3^2 + 2S_1S_5\\
&\quad + 2S_2S_4,\\
C_4 &= D_4^2 + 2D_2D_6 + 2D_3D_5 - S_4^2 - 2S_2S_6 - 2S_3S_5,\\
C_5 &= -D_5^2 - 2D_4D_6 + S_5^2 + 2S_4S_6,\\
C_6 &= D_6^2 - S_6^2.
\end{aligned} \tag{15}
$$

Let

$$
\begin{aligned}
G(x) = {} & x^6 + C_1x^5 + C_2x^4 + C_3x^3 + C_4x^2 + C_5x\\
& + C_6.
\end{aligned} \tag{16}
$$

Therefore, if (9) has a purely imaginary root $i\omega$, it is equivalent to the fact that $G(x) = 0$ has a positive real root ω^2. □

Theorem 4. *If* $G(x) = 0$ *has no positive real roots, then the positive equilibrium* E_{22} *is locally asymptotically stable for any* $\tau > 0$.

Proof. If $G(x) = 0$ has no positive real roots, then obviously (9) has no positive real roots. Therefore, the positive equilibrium E_{22} is locally asymptotically stable for any $\tau > 0$.

Substituting $\lambda = i\omega$ into (22), we obtain the real part,

$$\begin{aligned} &-\omega^6 + D_2\omega^4 - D_4\omega^2 + D_6 \\ &\quad + \left(S_1\omega^5 - S_3\omega^3 + S_5\omega\right)\sin\omega\tau \\ &\quad + \left(S_2\omega^4 - S_4\omega^2 + S_6\right)\cos\omega\tau = 0, \end{aligned} \tag{17}$$

and imaginary part,

$$\begin{aligned} &D_1\omega^5 - D_3\omega^3 + D_5\omega + \left(-S_2\omega^4 + S_4\omega^2 - S_6\right)\sin\omega\tau \\ &\quad + \left(S_1\omega^5 - S_3\omega^3 + S_5\omega\right)\cos\omega\tau = 0. \end{aligned} \tag{18}$$

Assuming that $G(x) = 0$ has $\tilde{n}(1 \le \tilde{n} \le 6)$ positive real roots, denoted by x_n $(1 \le n \le \tilde{n})$. As $\sqrt{x_n} = \omega$, we then have

$$\begin{aligned} \cos\left(\sqrt{x_n}\tau\right) &= Q_n \\ &= \frac{\left(-S_2x_n^2 + S_4x_n - S_6\right)\left(-x_n^3 + D_2x_n^2 - D_4x_n + D_6\right)}{\left(S_2x_n^2 - S_4x_n + S_6\right)^2 + \left(S_1x_n^2\sqrt{x_n} - S_3x_n\sqrt{x_n} + S_5\sqrt{x_n}\right)^2} \\ &\quad - \frac{\left(S_1x_n^2\sqrt{x_n} - S_3x_n\sqrt{x_n} + S_5\sqrt{x_n}\right)\left(D_1x_n^2\sqrt{x_n} - D_3x_n\sqrt{x_n} + D_5\sqrt{x_n}\right)}{\left(S_2x_n^2 - S_4x_n + S_6\right)^2 + \left(S_1x_n^2\sqrt{x_n} - S_3x_n\sqrt{x_n} + S_5\sqrt{x_n}\right)^2}, \\ \sin\left(\sqrt{x_n}\tau\right) &= P_n \\ &= \frac{\left(S_2x_n^2 - S_4x_n + S_6\right)\left(D_1x_n^2\sqrt{x_n} - D_3x_n\sqrt{x_n} + D_5\sqrt{x_n}\right)}{\left(S_2x_n^2 - S_4x_n + S_6\right)^2 + \left(S_1x_n^2\sqrt{x_n} - S_3x_n\sqrt{x_n} + S_5\sqrt{x_n}\right)^2} \\ &\quad - \frac{\left(S_1x_n^2\sqrt{x_n} - S_3x_n\sqrt{x_n} + S_5\sqrt{x_n}\right)\left(-x_n^3 + D_2x_n^2 - D_4x_n + D_6\right)}{\left(S_2x_n^2 - S_4x_n + S_6\right)^2 + \left(S_1x_n^2\sqrt{x_n} - S_3x_n\sqrt{x_n} + S_5\sqrt{x_n}\right)^2}. \end{aligned} \tag{19}$$

Let

$$\tau_n^{(j)} = \begin{cases} \dfrac{1}{\sqrt{x_n}}\left[\arccos\left(Q_n\right) + 2j\pi\right], & \text{if } P_n \ge 0, \\ \dfrac{1}{\sqrt{x_n}}\left[2\pi - \arccos\left(Q_n\right) + 2j\pi\right], & \text{if } P_n < 0, \end{cases} \tag{20}$$

where $1 \le n \le \tilde{n}$ and $j = 0, 1, 2, \ldots$.

Therefore, the characteristic equation $H(\lambda; \tau_n^{(j)}) = 0$ has a pair of purely imaginary roots $\pm i\sqrt{x_n}$. For every integer j and $1 \le n \le \tilde{n}$, define $\lambda_n^{(j)}(\tau) = \alpha_n^{(j)}(\tau) + i\omega_n^{(j)}(\tau)$ as the root of (9) near $\tau_n^{(j)}$, satisfying $\alpha_n^{(j)}(\tau_n^{(j)}) = 0$ and $\omega_n^{(j)}(\tau_n^{(j)}) = \sqrt{x_n}$. Then the following theorem is obtained. □

Theorem 5. *If $G(x) = 0$ has some positive real roots, then E_{22} is locally asymptotically stable for $\tau \in [0, \tau_{n_0}^{(0)})$, where*

$$\tau_{n_0}^{(0)} = \min\left\{\tau_n^{(j)} \mid 1 \le n \le \tilde{n},\ j = 0, 1, 2, \ldots\right\}. \tag{21}$$

Proof. For $\tau_{n_0}^{(0)} = \min\{\tau_n^{(j)} \mid 1 \le n \le \tilde{n}, j = 0, 1, 2, \ldots\}$, $G(x) = 0$ has no positive real roots when $\tau \in [0, \tau_{n_0}^{(0)})$, which means that all the roots of (9) have strictly negative real parts when $\tau \in [0, \tau_{n_0}^{(0)})$. Therefore, E_{22} is locally asymptotically stable for $\tau \in [0, \tau_{n_0}^{(0)})$. □

Theorem 6. *If x_{n_0} is a simple root of $G(x) = 0$, then there is a Hopf bifurcation for the system as τ increases past $\tau_{n_0}^{(0)}$.*

See Appendix C for proof.

4. Stability of the Bifurcating Periodic Solutions

In this section, we will continue to derive the explicit formulas for determining the stability, direction, and other properties of the Hopf bifurcation at a critical value $\tau_{n_0}^{(0)}$ by means of the normal form and the center manifold theory [27].

First, we make the following hypotheses.

(1) Equation (9) has a pair of purely imaginary roots $\pm i\omega_0$ at $\tau = \tau_0$, where $\tau_0 \in \{\tau_n^{(j)} \mid 1 \le n \le \tilde{n},\ j = 0, 1, 2, \ldots\}$.

(2) The remaining roots of (22) have strictly negative real parts.

(3) ω_0 is a simple root of $G(x) = 0$.

We use $u = \tau - \tau_0$ to represent a new bifurcation parameter. Let $X(t) = (x - x_2, e - e_2, y - y_2, v - v_2, z - z_2, w - w_2)^T$, and $X_t(\theta) = X(t + \theta)$, where $\theta \in [-\tau, 0]$. Therefore, system (1) can be written as the following functional differential equation:

$$\dot{X}(t) = L_u X_t + f\left(X_t(\cdot), u\right), \tag{22}$$

where

$$L_u\phi = F_1\phi(0) + F_2\phi(-\tau),$$
$$F_1 = \begin{bmatrix} -\rho-\beta v_2 & 0 & 0 & -\beta x_2 & 0 & 0 \\ \beta v_2 & -a_1-a_2 & 0 & \beta x_2 & 0 & 0 \\ 0 & a_2 & -a_1-k_1z_2 & 0 & -k_1y_2 & 0 \\ 0 & 0 & k & -\varepsilon-k_2z_2 & -k_2v_2 & 0 \\ 0 & 0 & 0 & 0 & -k_4 & 0 \\ 0 & 0 & k_1k_6z_2 & 0 & k_1k_6y_2 & -k_7 \end{bmatrix},$$
$$F_2 = \begin{bmatrix} 0&0&0&0&0&0\\0&0&0&0&0&0\\0&0&0&0&0&0\\0&0&0&0&0&0\\0&0&0&k_3z_2&k_3v_2&0\\0&0&0&0&0&0 \end{bmatrix}, \tag{23}$$
$$f(\phi,u) = \begin{bmatrix} -\beta\phi_1(0)\phi_4(0) \\ \beta\phi_1(0)\phi_4(0) \\ -k_1\phi_3(0)\phi_5(0) \\ -k_2\phi_4(0)\phi_5(0) \\ k_3\phi_4(-\tau)\phi_5(-\tau) \\ k_1k_6\phi_3(0)\phi_5(0) \end{bmatrix}.$$

By the Riesz representation theorem [28], there exists a 6×6 matrix-valued function such that

$$L_u\phi = \int_{-\tau}^{0} d\eta(\theta,u)\,\phi(\theta), \tag{24}$$

where $d\eta(\theta,u) = F_1\delta(\theta)d\theta + F_2\delta(\theta+\tau)d\theta$.

For $\phi \in C([-\tau,0],R^6)$, we further define

$$A(u)\phi(\theta) = \begin{cases} \dfrac{d\phi(\theta)}{d\theta}, & \text{if } \theta\in[-\tau,0), \\ \displaystyle\int_{-\tau}^{0} d\eta(\xi,u)\,\phi(\xi) \equiv L_u\phi, & \text{if } \theta = 0, \end{cases} \tag{25}$$
$$R(u)\phi(\theta) = \begin{cases} 0, & \text{if}\,\theta\in[-\tau,0), \\ f(\phi,u), & \text{if}\,\theta=0. \end{cases}$$

Then system (22) can be written as

$$\dot{X}_t(\theta) = A(u)X_t(\theta) + R(u)X_t(\theta). \tag{26}$$

For $\varphi\in C([-\tau,0],R^6)$, define

$$A^*(0)\varphi(s) = \begin{cases} \dfrac{d\phi(s)}{ds}, & \text{if } s\in[-\tau,0), \\ \displaystyle\int_{-\tau}^{0} d\eta^T(\xi,0)\,\varphi(-\xi), & \text{if } s=0, \end{cases} \tag{27}$$

and an inner product of ϕ,φ

$$\langle\varphi,\phi\rangle = \overline{\varphi}^T(0)\,\phi(0) - \int_{\theta=-\tau}^{0}\int_{\xi=0}^{\theta} \overline{\varphi}^T(\xi-\theta)\,d\eta(\theta)\,\phi(\xi)\,d\xi, \tag{28}$$

where $\eta(\theta) = \eta(\theta,0)$ and $\phi\in C([-\tau,0],R^6)$. Then $A(0)$ and $A^*(0)$ are adjoint operators.

Let $h(\theta)$ and $h^*(s)$ be the eigenvectors of $A(0)$ and $A^*(0)$ corresponding to the eigenvalues $i\omega_0$ and $-i\omega_0$, respectively. We choose $h(\theta)$ and $h^*(s)$ as

$$h(\theta) = (1,h_2,h_3,h_4,h_5,h_6)^T e^{i\omega_0\theta},$$
$$h^*(s) = D(1,h_2^*,h_3^*,h_4^*,h_5^*,h_6^*)^T e^{i\omega_0 s}, \tag{29}$$

so that $\langle h^*(s),h(\theta)\rangle = 1$ is satisfied. We give the detailed computation of (29) in Appendix D.

In the following, we will compute the coefficients, g_{20}, g_{11}, g_{02}, and g_{21}, using the method given in [27]. The detailed computation of g_{20}, g_{11}, g_{02}, and g_{21} is presented in Appendix E.

Then the following values can be computed:

$$c_1(0) = \frac{i}{2\omega_0}\left(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2},$$
$$u_2 = -\frac{\operatorname{Re}(c_1(0))}{\operatorname{Re}(\lambda'(\tau_0))}, \tag{30}$$
$$\beta_2 = 2\operatorname{Re}(c_1(0)).$$

The signs of u_2, β_2 determine the direction of the Hopf bifurcation and the stability of bifurcating periodic solutions, respectively [27]. From (C.11) of Appendix C, we obtain $\operatorname{sign}[(d\alpha_n^{(j)}(\tau)/d\tau)|_{\tau=\tau_n^j}] = \operatorname{sign}[(dG/dx)|_{x=x_n}]$.

Let $u_2^* = -\operatorname{Re}(c_1(0))/G'(\omega_0^2)$. We obtain the following theorem.

Theorem 7. *Assume the hypotheses (1), (2), and (3) at the beginning of Section 4 hold.*

(1) If $u_2^* > 0$ ($u_2^* < 0$), then the bifurcating periodic solutions exist for $\tau > \tau_0$ ($\tau < \tau_0$) in a τ_0-neighborhood.

(2) If $\beta_2 < 0$ ($\beta_2 > 0$), the bifurcating periodic solutions are orbitally asymptotically stable as $t\to+\infty$ ($t\to-\infty$).

Proof. (1) If $\tau_0 = \tau_{n_0}^{(0)}$, where $\tau_{n_0}^{(0)} = \min\{\tau_n^{(j)} \mid 1\le n\le \tilde{n},\ j = 0,1,2,\ldots\}$, and the hypotheses (1), (2), and (3) hold, then, from Theorem 6, we draw the conclusion that the existence and stability of the bifurcating periodic solutions are only determined by $\operatorname{Re}(c_1(0))$.

(2) If $\beta_2 < 0$, namely, $\operatorname{Re}(c_1(0)) < 0$, then there exist stable periodic solutions for $\tau > \tau_{n_0}^{(0)}$ in a τ_0-neighborhood. So the bifurcating periodic solutions are orbitally asymptotically stable as $t\to+\infty$. □

5. Simulation and Discussions

In this section, we will numerically illustrate the theoretical results obtained above and also discuss how the factors such as the immune response to infected cells and viruses and the proliferation of hepatocytes affect the dynamics of the model under time delay.

For the following simulations, we choose the parameter values for system (1) as follows:

$$\begin{aligned} \lambda &= 4.0551, \\ r &= 0.6933, \\ d &= 4.4096, \\ \beta &= 4.6178, \\ a_1 &= 0.0638, \\ a_2 &= 1.8858, \\ k_1 &= 0.8391, \\ k &= 2.7011, \\ \varepsilon &= 0.5083, \\ k_2 &= 0.1963, \\ k_3 &= 4.6661, \\ k_4 &= 4.8580, \\ k_5 &= 1.8046, \\ k_6 &= 3.2210, \\ k_7 &= 0.3397. \end{aligned} \quad (31)$$

We set the initial values to $x(t) = 1$, $e(t) = 1$, $y(t) = 1$, $v(t) = 1$, $z(t) = 1$, and $w(t) = 1$, where $t \in [-\tau, 0]$.

5.1. Hopf Bifurcation and the Stability of Periodic Solutions. With the parameter values given in (31), we have the positive equilibrium $E_{22} = (0.4757, 1.1732, 0.3281, 1.0411, 1.7470, 9.8727)$ and the critical time value $\tau_{n_0}^{(0)} = 0.041$.

When $\tau > 0.041$, we obtain stable bifurcating periodic solutions. For example, when $\tau = 0.05$, the simulation result is shown Figures 2 and 3. Figure 2 indicates that a stable limit cycle is obtained as expected and Figure 3 indicates the state dynamics of uninfected cells, exposed cells, infected cells, free viruses, CTLs, and ALT, which are periodically oscillating.

When $\tau < 0.041$, the bifurcating periodic solutions are unstable. For example, when $\tau = 0.03$, the simulation result is shown in Figures 4 and 5. From Figures 4 and 5, we know that the positive equilibrium E_{22} is asymptotically stable and the system will converge to E_{22}.

With the increasing of time delay (τ), the radius of limit cycle will increase. The simulation result is shown Figure 6.

5.2. The Immune Response to Infected Cells. Here we will investigate the effect of the immune response to infected cells

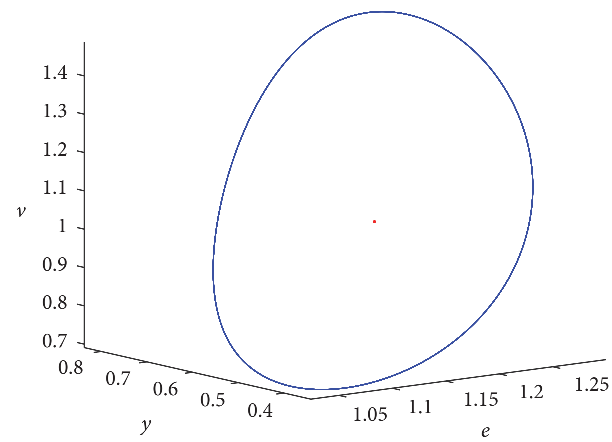

Figure 2: The positive equilibrium E_{22} bifurcates into a periodic solution at $\tau = 0.05$ (a limit cycle).

on the model dynamics under time delay. When we change $k_1 = 0.8391$ to $k_1 = 0.01$ by fixing other values given in (31), we obtain a simulation result at $\tau = 0.05$, illustrated in Figure 7. Comparing Figure 2 when $k_1 = 0.8391$ and Figure 7 when $k_1 = 0.01$, we can see that, with the decrease of k_1, the stable periodic solution becomes unstable, that is, asymptotically stable.

5.3. The Immune Response to Viruses. We continue to investigate the effect of the immune response to viruses on the model dynamics under time delay. When we change $k_2 = 0.1963$ to $k_2 = 0.001$ by fixing other values given in (31), we obtain a simulation result at $\tau = 0.05$, illustrated in Figure 8. Similarly, comparing Figures 2 and 8, we can see that, with the decrease of k_2, the stable periodic solution also becomes unstable, that is, asymptotically stable. We further can see that the effect of the immune response to infected cells on the model dynamics is similar to that of the immune response to viruses.

5.4. Proliferation of Hepatocytes. Then we investigate the effect of proliferation of hepatocytes on the model dynamics under time delay. For this, we still keep $\tau = 0.05$ and change the value of parameter r. When we change $r = 0.6933$ to $r = 0.001$ by fixing other values given in (31), we obtain a simulation result at $\tau = 0.05$, illustrated in Figure 9. Figure 9 shows that when $r = 0.001$, the bifurcating periodic solution is stable, compared with Figure 2 when $r = 0.6933$. We also try other values of parameter rand obtaining similar results. Thus, we can see parameter r has a small effect on the model dynamics, which reflect in periodicity and the positive equilibrium E_{22}.

6. Conclusions

In this paper, we consider a comprehensive delayed HBV model. Different from other existing models, our model not only considers the immune response to both infected cells and viruses and a time delay for the immune system to

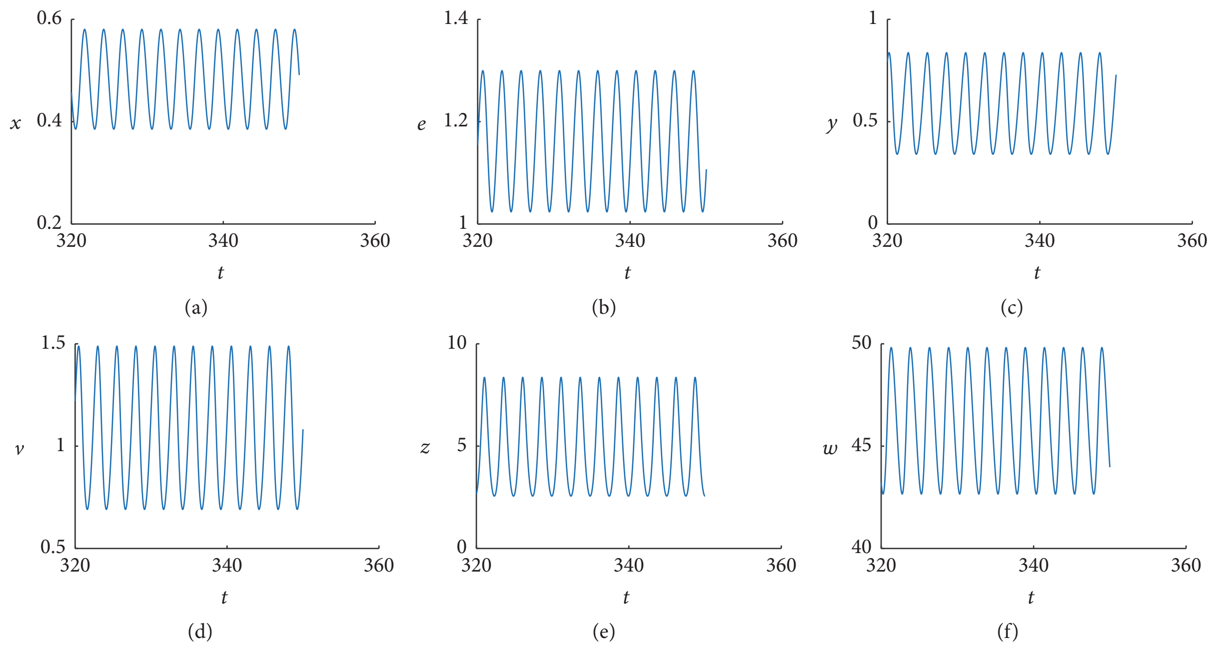

FIGURE 3: The positive equilibrium E_{22} bifurcates into a periodic solution at $\tau = 0.05$.

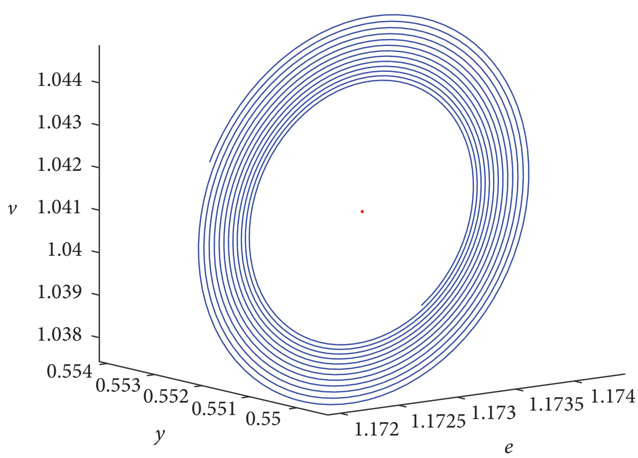

FIGURE 4: The positive equilibrium E_{22} at $\tau = 0.03$.

clear viruses but also incorporates an exposed state and the proliferation of hepatocytes.

We then prove the positivity and boundedness of solutions and analyze the global stability of two boundary equilibria and investigate the local asymptotic stability and Hopf bifurcation of the positive (infection) equilibrium and also the stability of the bifurcating periodic solutions. We also numerically illustrate the Hopf bifurcation and the stability of the bifurcating periodic solutions.

Moreover, we numerically illustrate how the factors such as the time delay, the immune response to infected cells and viruses, and the proliferation of hepatocytes affect the dynamics of the model, which shows that the former two factors have a big effect on the model dynamics, while the latter one does not have a big effect.

Appendix

A. The Proof of Theorem 1

We construct a Lyapunov functional as follows:

$$V_0 = \frac{a_2 k}{a_1 + a_2}\left[x(t) - x_0 - x_0 \ln \frac{x(t)}{x_0}\right] + \frac{a_2 k}{a_1 + a_2} e(t) + k y(t) + a_1 v(t). \tag{A.1}$$

Calculating the derivative of V_0 along with the trajectories of system (1), we obtain

$$\begin{aligned}
\dot{V}_0 = {} & \frac{a_2 k}{a_1 + a_2}\left(1 - \frac{x_0}{x(t)}\right)(\lambda - \rho x - \beta x v) \\
& + \frac{a_2 k}{a_1 + a_2}(\beta x v - a_1 e(t) - a_2 e(t)) \\
& + k(a_2 e(t) - a_1 y - k_1 y z) \\
& + a_1(k y - \varepsilon v - k_2 v z) \\
= {} & -\frac{a_2 k \rho}{a_1 + a_2} \cdot \frac{(x(t) - x_0)^2}{x(t)} - \frac{a_2 k}{a_1 + a_2}\beta x v \\
& + \frac{a_2 k}{a_1 + a_2} \cdot \frac{x_0}{x(t)} \cdot \beta x v + \frac{a_2 k}{a_1 + a_2}\beta x v \\
& - \frac{a_2 k}{a_1 + a_2}(a_1 + a_2) e(t) + k a_2 e(t) - k a_1 y \\
& - k k_1 y z + a_1 k y - a_1 \varepsilon v - a_1 k_2 v z
\end{aligned}$$

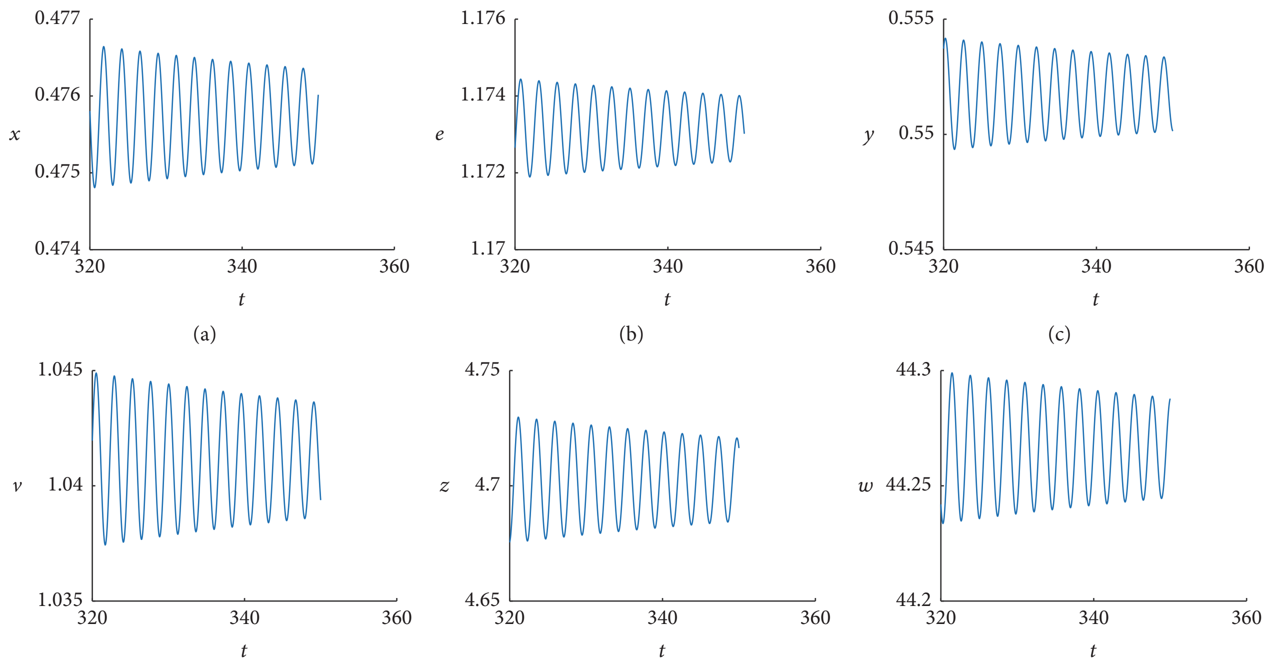

FIGURE 5: The positive equilibrium E_{22} remains stale at $\tau = 0.03$.

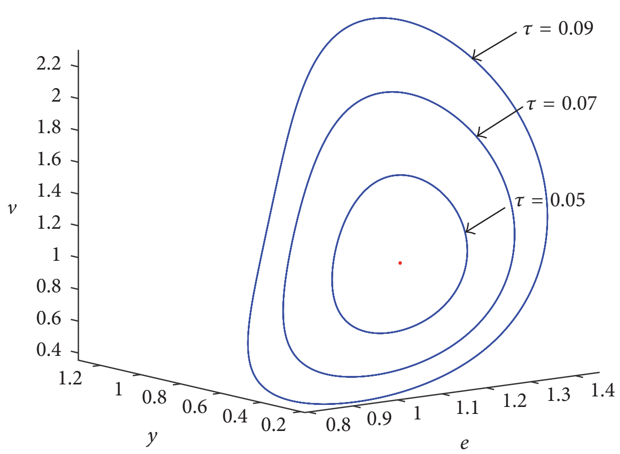

FIGURE 6: The different periodic solutions at $\tau = 0.05$, $\tau = 0.07$ and $\tau = 0.09$ (three limit cycles).

$$\begin{aligned}
&= -\frac{a_2 k\rho}{a_1 + a_2} \cdot \frac{(x(t) - x_0)^2}{x(t)} \\
&\quad - a_1\varepsilon\left(1 - \frac{a_2 k x_0 \beta}{a_1\varepsilon(a_1 + a_2)}\right)v - kk_1 yz - a_1 k_2 vz \\
&= -\frac{a_2 k\rho}{a_1 + a_2} \cdot \frac{(x(t) - x_0)^2}{x(t)} - a_1\varepsilon(1 - R_0)v \\
&\quad - kk_1 yz - a_1 k_2 vz.
\end{aligned} \tag{A.2}$$

Therefore, when $R_0 = a_2 k x_0 \beta / a_1 \varepsilon (a_1 + a_2) < 1$, $\dot{V}_0 \le 0$ holds true. Furthermore, if and only if $x = x_0$, $e = 0$, $y = 0$, $v = 0$, $z = 0$, and $w = w_0$, the Lyapunov functional satisfies $\dot{V}_0 = 0$. According to LaSalle's invariance principle [29], the infection-free equilibrium E_{00} is globally asymptotically stable when $R_0 < 1$. Apparently, when $R_0 > 1$, E_{00} is unstable.

B. The Proof of Theorem 2

Similarly, we define the following Lyapunov functional:

$$\begin{aligned}
V_1 &= \frac{k_3\varepsilon}{\beta x_1}\left[x(t) - x_1 - x_1 \ln\frac{x(t)}{x_1}\right] \\
&\quad + \frac{a_2 k k_3}{a_1(a_1 + a_2)}\left[e(t) - e_1 - e_1 \ln\frac{e(t)}{e_1}\right] \\
&\quad + \frac{kk_3}{a_1}\left[y(t) - y_1 - y_1 \ln\frac{y(t)}{y_1}\right] \\
&\quad + k_3\left[v(t) - v_1 - v_1 \ln\frac{v(t)}{v_1}\right] + k_2 z \\
&\quad + k_2 k_3 \int_{t-\tau}^{t} v(\theta) z(\theta)\, d\theta.
\end{aligned} \tag{B.1}$$

The derivative of V_1 along with the trajectories of system (1) can be calculated as

$$\begin{aligned}
\dot{V}_1 &= \frac{k_3\varepsilon}{\beta x_1}\left(1 - \frac{x_1}{x}\right)(\lambda - \rho x - \beta x v) \\
&\quad + \frac{a_2 k k_3}{a_1(a_1 + a_2)}\left(1 - \frac{e_1}{e(t)}\right)
\end{aligned}$$

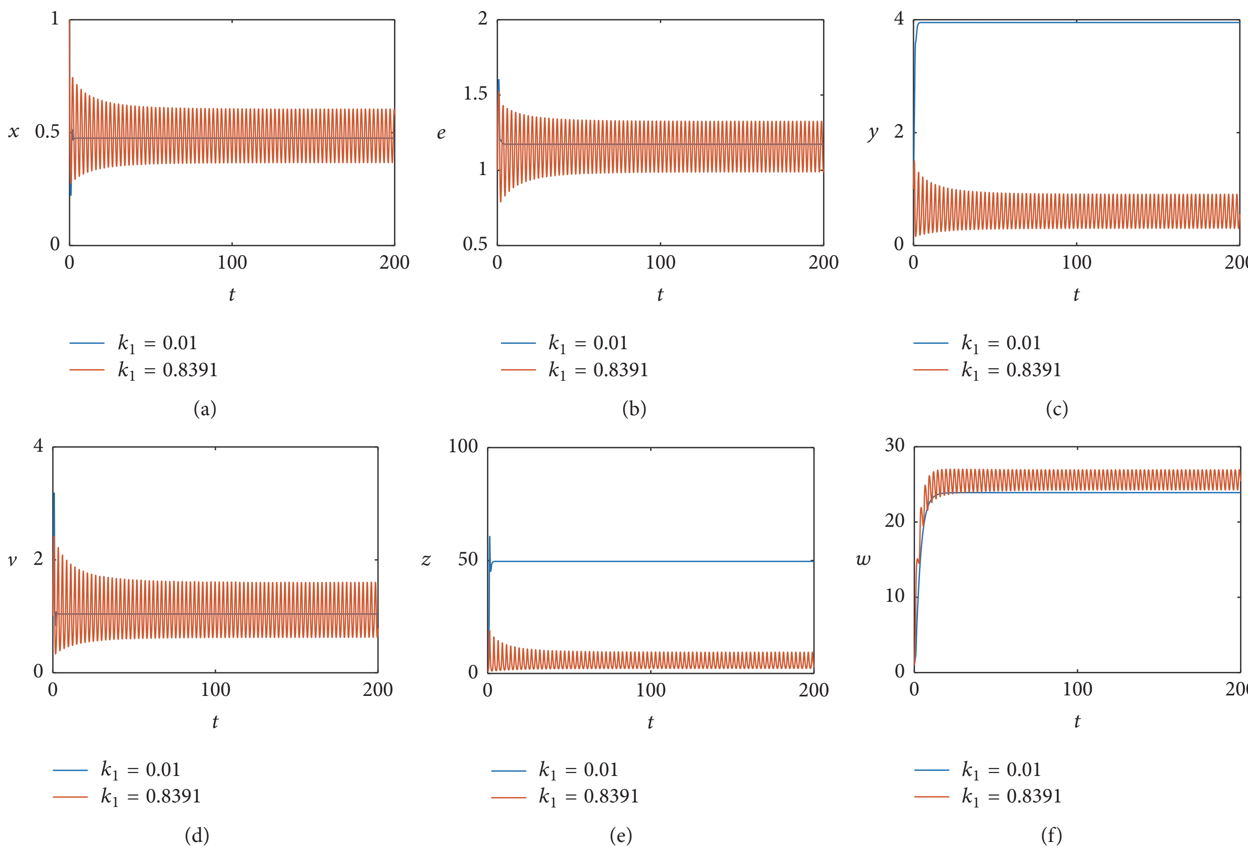

FIGURE 7: The positive equilibrium E_{22} remains stable at $\tau = 0.05$ when $k_1 = 0.01$ (blue line) and exists at stable periodic solutions when $k_1 = 0.8391$ (red line).

$$\cdot\left(\beta x v - a_1 e(t) - a_2 e(t)\right) + \frac{kk_3}{a_1}\left(1-\frac{y_1}{y}\right)$$
$$\cdot\left(a_2 e(t) - a_1 y - k_1 yz\right) + k_3\left(1-\frac{v_1}{v}\right)$$
$$\cdot\left(ky - \varepsilon v - k_2 vz\right)$$
$$+ k_2\left[k_3 v(t-\tau) z(t-\tau) - k_4 z\right]$$
$$+ k_2k_3\int_{t-\tau}^{t} v(\theta) z(\theta)\, d\theta = -\frac{k_3\varepsilon}{\beta x_1}\frac{\rho(x_1-x)^2}{x}$$
$$+\frac{k_3\varepsilon}{\beta x_1}\beta x_1 v_1 - \frac{k_3\varepsilon}{\beta x_1}\beta x v - \frac{m_1\beta x_1^2 v_1}{x} + \frac{k_3\varepsilon}{\beta x_1}\beta x_1 v$$
$$+\frac{a_2kk_3}{a_1(a_1+a_2)}\beta x v - \frac{a_2kk_3}{a_1(a_1+a_2)}a_1 e(t)$$
$$-\frac{a_2kk_3}{a_1(a_1+a_2)}a_2 e(t) - \frac{a_2kk_3}{a_1(a_1+a_2)}\frac{e_1}{e(t)}\beta x v$$
$$+\frac{a_2kk_3}{a_1(a_1+a_2)}a_1 e_1 + \frac{a_2kk_3}{a_1(a_1+a_2)}a_2 e_1 + \frac{kk_3}{a_1}$$
$$\cdot a_2 e(t) - \frac{kk_3}{a_1}a_1 y - \frac{kk_3}{a_1}k_1 yz - \frac{kk_3}{a_1}\frac{y_1 a_2 e(t)}{y}$$
$$+\frac{kk_3}{a_1}y_1 a_1 + \frac{kk_3}{a_1}y_1 k_1 z + k_3 ky - k_3\varepsilon v - k_3 k_2 vz$$
$$-\frac{k_3 v_1 ky}{v} + k_3 v_1\varepsilon + k_3 v_1 k_2 z + k_2 k_3 v(t-\tau)$$
$$\cdot z(t-\tau) - k_2 k_4 z + k_2 k_3 vz - k_2 k_3 v(t-\tau)$$
$$\cdot z(t-\tau) = -\frac{k_3\varepsilon}{\beta x_1}\frac{\rho(x_1-x)^2}{x}$$
$$+k_3\varepsilon v_1\left(4-\frac{x_1}{x}-\frac{y_1 e(t)}{e_1 y}-\frac{x e_1 v}{x_1 e(t) v_1}-\frac{v_1 y}{y_1 v}\right)$$
$$+\left(k_3 v_1 k_2 - k_2 k_4 + \frac{kk_3}{a_1}y_1 k_1\right)z - \frac{kk_3}{a_1}k_1 yz$$
$$= -\frac{a_2kk_3}{a_1(a_1+a_2)}\frac{\rho(x_1-x)^2}{x}$$
$$+k_3\varepsilon v_1\left(4-\frac{x_1}{x}-\frac{y_1 e(t)}{e_1 y}-\frac{x e_1 v}{x_1 e(t) v_1}-\frac{v_1 y}{y_1 v}\right)$$
$$-k_2 k_4\left(1-R_1\right)z - \frac{kk_3}{a_1}k_1 yz. \quad \text{(B.2)}$$

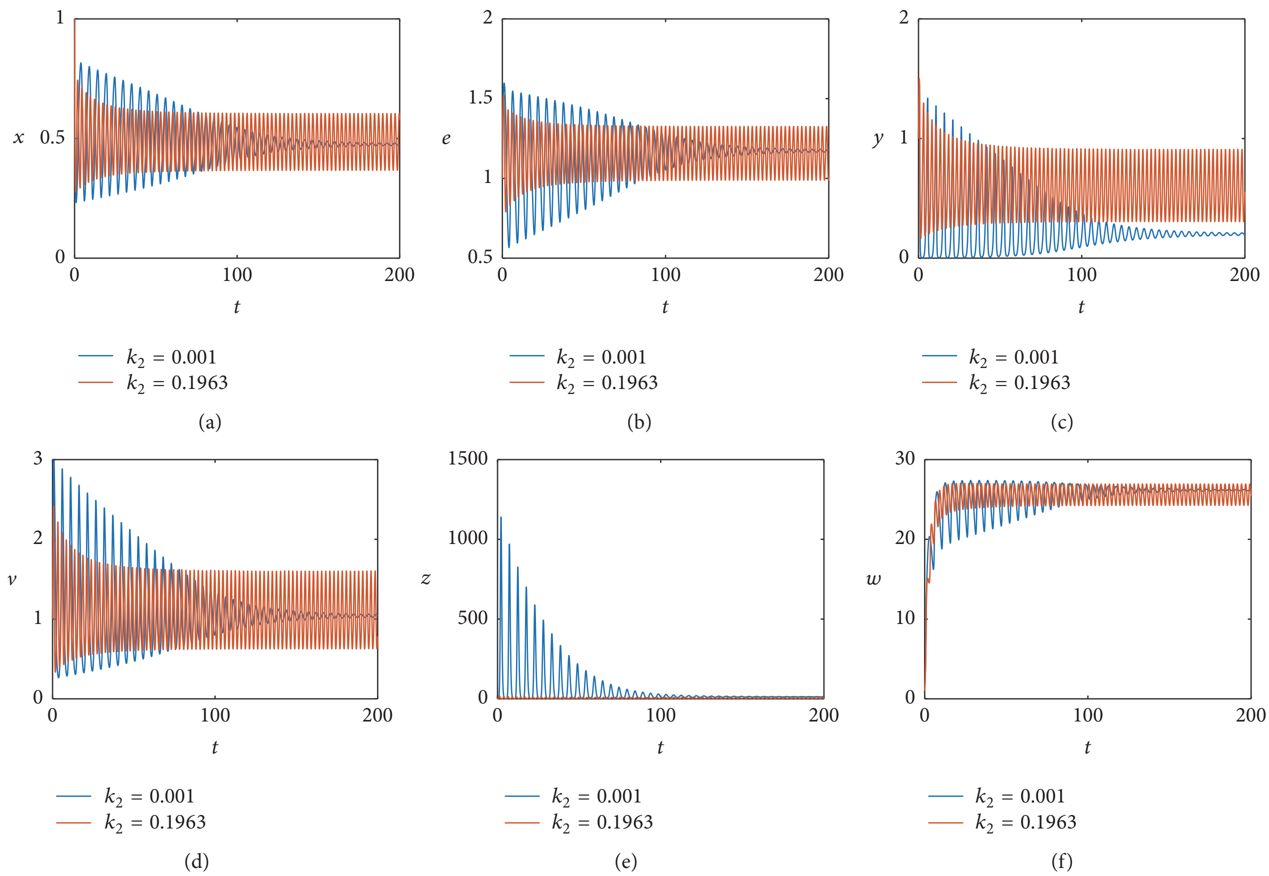

FIGURE 8: The positive equilibrium E_{22} remains stable at $\tau = 0.05$ when $k_2 = 0.001$ (blue line) and exists at stable periodic solutions when $k_2 = 0.1963$ (red line).

Therefore, $R_1 = k_3 v_1/k_4 + kk_3 y_1 k_1/a_1 k_2 k_4 < 1$ ensures that $\dot{V}_0 \leq 0$ holds true. Furthermore, if and only if $x = x_1$, $e = e_1$, $y = y_1$, $v = v_1$, $z = 0$, and $w = w_1$, the Lyapunov functional satisfies $\dot{V}_0 = 0$. Using the LaSalle's invariance principle, we can see that the equilibrium without immune response $E_{11} = (x_1, e_1, y_1, v_1, 0, w_1)$ is globally asymptotically stable.

C. The Proof of Theorem 6

The characteristic equation (9) can be written into the following form:

$$f_0(\lambda) + f_1(\lambda) e^{-\lambda\tau} = 0, \tag{C.1}$$

where

$$\begin{aligned} f_0(\lambda) &= \lambda^6 + D_1\lambda^5 + D_2\lambda^4 + D_3\lambda^3 + D_4\lambda^2 + D_5\lambda \\ &\quad + D_6, \\ f_1(\lambda) &= S_1\lambda^5 + S_2\lambda^4 + S_3\lambda^3 + S_4\lambda^2 + S_5\lambda + S_6, \end{aligned} \tag{C.2}$$

and $f_0(\lambda)$ and $f_1(\lambda)$ are continuously differentiable to λ.

Suppose that one of the roots of (C.1) is $\lambda(\tau) = \alpha(\tau) + i\omega(\tau)$, satisfying $\alpha(\tau_0) = 0$ and $\omega(\tau_0) = \omega_0$ for a positive real number τ_0.

Let

$$\Phi(\omega) = \left|f_0(i\omega)\right|^2 - \left|f_1(i\omega)\right|^2. \tag{C.3}$$

Calculating the derivative of $|f_0(i\omega)|^2$ to ω, we have

$$\begin{aligned} \frac{d}{d\omega}\left(\left|f_0(i\omega)\right|^2\right) &= -2\,\mathrm{Im}\left[\overline{f_0(i\omega)}\dot{f}_0(i\omega)\right] \\ &= 12\omega^{11} + \left(-20D_2 + 10D_1^2\right)\omega^9 \\ &\quad + \left(16D_4 - 16D_1D_3 + 8D_2^2\right)\omega^7 \\ &\quad + \left(12D_1D_5 - 12D_2D_4 + 6D_3^2 - 12D_6\right)\omega^5 \\ &\quad + \left(-8D_3D_5 + 4D_4^2 + 8D_2D_6\right)\omega^3 \\ &\quad + \left(2D_5^2 - 4D_4D_6\right)\omega. \end{aligned} \tag{C.4}$$

Then we have

$$\begin{aligned} \frac{1}{2\omega}\cdot\frac{d\Phi}{d\omega} &= \frac{1}{2\omega}\cdot\frac{d}{d\omega}\left(\left|f_0(i\omega)\right|^2 - \left|f_1(i\omega)\right|^2\right) \\ &= \mathrm{Im}\left[\left|f_1(i\omega)\right|^2\frac{\dot{f}_1(i\omega)}{\omega f_1(i\omega)} - \left|f_0(i\omega)\right|^2\frac{\dot{f}_0(i\omega)}{\omega f_0(i\omega)}\right]. \end{aligned} \tag{C.5}$$

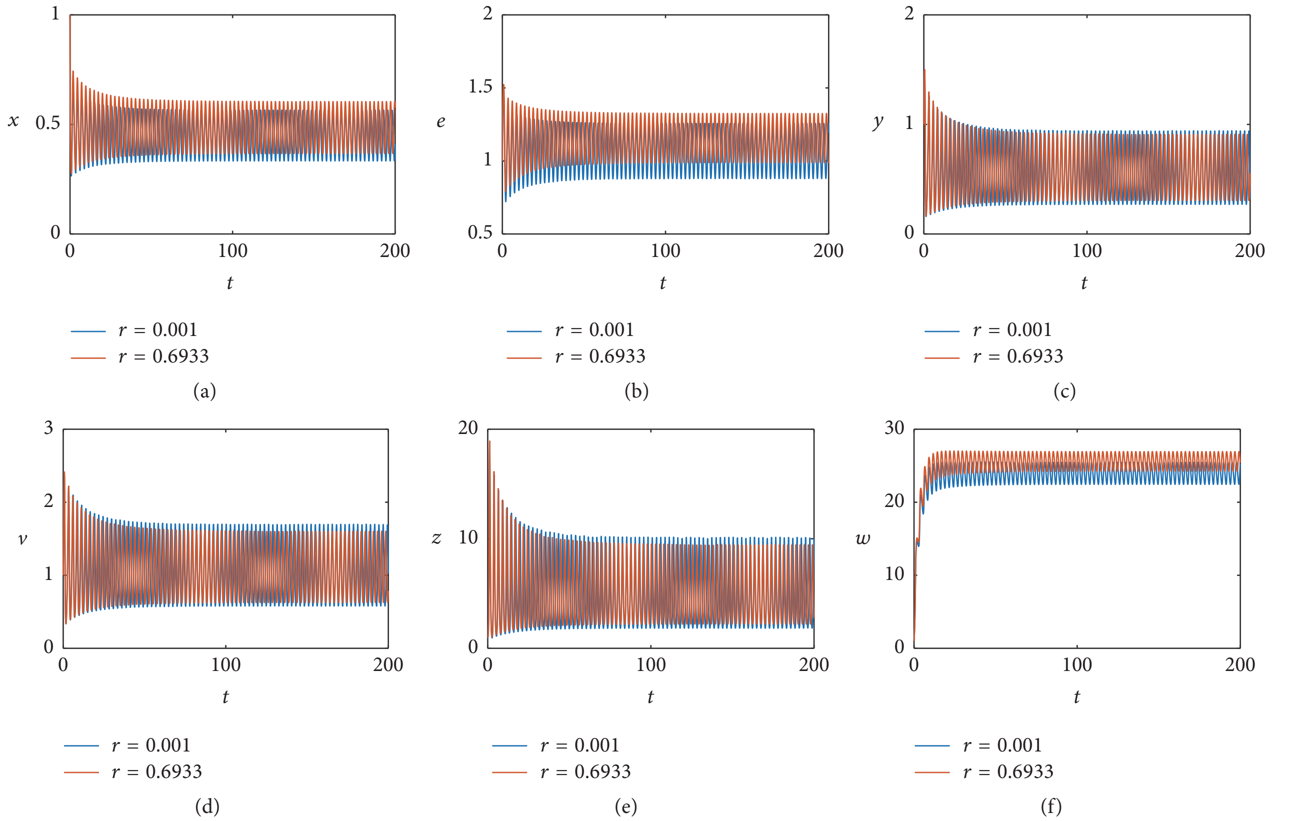

FIGURE 9: The positive equilibrium E_{22} remains stable at $\tau = 0.05$ when $r = 0.001$ (blue line) and exists at stable periodic solutions when $r = 0.6933$ (red line).

Because $|f_0(i\omega_0)|^2 = |f_1(i\omega_0)|^2$, we have

$$\left(\frac{1}{2\omega}\cdot\frac{d\Phi}{d\omega}\right)\bigg|_{\omega=\omega_0} = \left|f_0(i\omega_0)\right|^2 \operatorname{Im}\left[\frac{\dot{f}_1(i\omega_0)}{\omega_0 f_1(i\omega_0)} - \frac{\dot{f}_0(i\omega_0)}{\omega_0 f_0(i\omega_0)}\right]. \quad (C.6)$$

Calculating the derivative of both sides of (C.1) to τ, we have

$$\dot{f}_0(\lambda)\frac{d\lambda}{d\tau} + \dot{f}_1(\lambda)\frac{d\lambda}{d\tau}e^{-\lambda\tau} - \left(\lambda + \tau\frac{d\lambda}{d\tau}\right) f_1(\lambda)e^{-\lambda\tau} = 0. \quad (C.7)$$

Then we have

$$\left[\frac{d\lambda}{d\tau}\right]^{-1} = \frac{\dot{f}_0(\lambda) + \dot{f}_1(\lambda)e^{-\lambda\tau} - \tau f_1(\lambda)e^{-\lambda\tau}}{\lambda f_1(\lambda)e^{-\lambda\tau}} = \frac{\dot{f}_0(\lambda)e^{\lambda\tau} + \dot{f}_1(\lambda)}{\lambda f_1(\lambda)} - \frac{\tau}{\lambda}. \quad (C.8)$$

Since $f_0(i\omega_0) + f_1(i\omega_0)e^{-i\omega_0\tau} = 0$, we obtain

$$\begin{aligned}\operatorname{Re}\left[\frac{ds}{d\tau}\bigg|_{\tau=\tau_0}\right]^{-1} &= \operatorname{Re}\left[\frac{\dot{f}_0(i\omega_0)e^{i\omega_0\tau} + \dot{f}_1(i\omega_0)}{i\omega_0 f_1(i\omega_0)}\right] \\ &= \operatorname{Re}\left[\frac{\dot{f}_0(i\omega_0)}{\omega_0 f_0(i\omega_0)}i\right] + \operatorname{Re}\left[-\frac{\dot{f}_1(i\omega_0)}{\omega_0 f_1(i\omega_0)}i\right] \\ &= \operatorname{Im}\left[\frac{\dot{f}_1(i\omega_0)}{\omega_0 f_1(i\omega_0)} - \frac{\dot{f}_0(i\omega_0)}{\omega_0 f_0(i\omega_0)}\right].\end{aligned} \quad (C.9)$$

Thus, we have

$$\begin{aligned}\operatorname{sign}\left[\frac{d\operatorname{Re}(\lambda)}{d\tau}\bigg|_{\tau=\tau_0}\right] &= \operatorname{sign}\operatorname{Re}\left[\frac{d\lambda}{d\tau}\bigg|_{\tau=\tau_0}\right] \\ &= \operatorname{sign}\operatorname{Re}\left[\frac{d\lambda}{d\tau}\bigg|_{\tau=\tau_0}\right]^{-1} \\ &= \operatorname{sign}\left[\left(\frac{1}{2\omega}\cdot\frac{d\Phi}{d\omega}\right)\bigg|_{\omega=\omega_0}\right].\end{aligned} \quad (C.10)$$

When $\mathrm{Re}(\lambda) = \alpha_n^{(j)}(\tau)$, obviously, we have

$$\operatorname{sign}\left[\left.\frac{d\alpha_n^{(j)}(\tau)}{d\tau}\right|_{\tau=\tau_n^j}\right] = \operatorname{sign}\left[\left.\left(\frac{dG}{dx}\right)\right|_{x=x_n}\right]. \tag{C.11}$$

As x_{n_0} is a simple root of $G(x) = 0$, we know $\dot{G}(x_{n_0}) \neq 0$. From (C.11), we further know $(d\alpha_{n_0}^{(0)}/d\tau)|_{\tau=\tau_{n_0}^{(0)}} \neq 0$. If $(d\alpha_{n_0}^{(0)}/d\tau)|_{\tau=\tau_{n_0}^{(0)}} < 0$; we obtain that the roots of (9) have positive real part when $\tau \in [0, \tau_{n_0}^{(0)})$, which contrasted with Theorem 5. Hence, we can see that $(d\alpha_{n_0}^{(0)}/d\tau)|_{\tau=\tau_{n_0}^{(0)}} > 0$. When $\tau = \tau_{n_0}^{(0)}$, except for the pair of purely imaginary roots, the remaining roots of $H(\lambda;\tau)$ have strictly negative real parts, so the system has Hopf bifurcation.

D. The Detailed Computation of (29)

In what follows, we will compute (29).

Substituting $X = e^{\lambda t}$ into (26), we have

$$\lambda e^{\lambda t} = F_1 e^{\lambda t} + F_2 e^{\lambda t}\left(e^{-\lambda t}\right) \Longrightarrow$$
$$\left(\lambda I - F_1 - F_2 e^{-\lambda t}\right) e^{\lambda t} = 0. \tag{D.1}$$

Therefore, $\det|\lambda I - F_1 - F_2 e^{-\lambda t}| = 0$ is the characteristic equation of $A(0)$.

As $A(0) = F_1 + F_2 e^{-i\omega_0\tau_0}$, we have

$$\left(A(0) - i\omega_0 I\right) h(\theta) = 0, \tag{D.2}$$

where

$$A(0) = \begin{bmatrix} -\rho-\beta v_2 & 0 & 0 & -\beta x_2 & 0 & 0 \\ \beta v_2 & -a_1-a_2 & 0 & \beta x_2 & 0 & 0 \\ 0 & a_2 & -a_1-k_1 z_2 & 0 & -k_1 y_2 & 0 \\ 0 & 0 & k & -\varepsilon-k_2 z_2 & -k_2 v_2 & 0 \\ 0 & 0 & 0 & k_3 z_2 e^{-i\omega_0\tau_0} & -k_4+k_3 v_2 e^{-i\omega_0\tau_0} & 0 \\ 0 & 0 & k_1 k_6 z_2 & 0 & k_1 k_6 y_2 & -k_7 \end{bmatrix}. \tag{D.3}$$

So we have

$$\left(A(0) - i\omega_0 I\right) h(\theta) = \begin{bmatrix} -\rho-\beta v_2-i\omega_0 & 0 & 0 & -\beta x_2 & 0 & 0 \\ \beta v_2 & -a_1-a_2-i\omega_0 & 0 & \beta x_2 & 0 & 0 \\ 0 & a_2 & -a_1-k_1 z_2-i\omega_0 & 0 & -k_1 y_2 & 0 \\ 0 & 0 & k & -\varepsilon-k_2 z_2-i\omega_0 & -k_2 v_2 & 0 \\ 0 & 0 & 0 & k_3 z_2 e^{-i\omega_0\tau_0} & -k_4+k_3 v_2 e^{-i\omega_0\tau_0}-i\omega_0 & 0 \\ 0 & 0 & k_1 k_6 z_2 & 0 & k_1 k_6 y_2 & -k_7-i\omega_0 \end{bmatrix} \begin{bmatrix} 1 \\ h_2 \\ h_3 \\ h_4 \\ h_5 \\ h_6 \end{bmatrix} = 0. \tag{D.4}$$

The eigenvectors of $A(0)$ are

$$\begin{aligned} h_1 &= 1, \\ h_2 &= \frac{-\rho-i\omega_0}{a_1+a_2+i\omega_0}, \\ h_3 &= \frac{a_2(-\rho-i\omega_0)}{(a_1+k_1 z_2+i\omega_0)(a_1+a_2+i\omega_0)} - \frac{k_1 y_2 h_5 k_3 z_2 e^{-i\omega_0\tau_0}(-\rho-\beta v_2-i\omega_0)}{(a_1+k_1 z_2+i\omega_0)\beta x_2(k_4-k_3 z_2 e^{-i\omega_0\tau_0}+i\omega_0)}, \\ h_4 &= \frac{-\rho-\beta v_2-i\omega_0}{\beta x_2}, \\ h_5 &= \frac{k_3 z_2 e^{-i\omega_0\tau_0}(-\rho-\beta v_2-i\omega_0)}{\beta x_2(k_4-k_3 z_2 e^{-i\omega_0\tau_0}+i\omega_0)}, \\ h_6 &= \frac{k_1 k_6 z_2}{k_7+i\omega_0}\left[\frac{a_2(-\rho-i\omega_0)}{(a_1+k_1 z_2+i\omega_0)(a_1+a_2+i\omega_0)} - \frac{k_1 y_2 h_5 k_3 z_2 e^{-i\omega_0\tau_0}(-\rho-\beta v_2-i\omega_0)}{(a_1+k_1 z_2+i\omega_0)\beta x_2(k_4-k_3 z_2 e^{-i\omega_0\tau_0}+i\omega_0)}\right] \\ &\quad + \frac{k_1 k_6 y_2 k_3 z_2 e^{-i\omega_0\tau_0}(-\rho-\beta v_2-i\omega_0)}{(k_7+i\omega_0\beta x_2)(k_4-k_3 z_2 e^{-i\omega_0\tau_0}+i\omega_0)}. \end{aligned} \tag{D.5}$$

Similarly,

$$
\begin{aligned}
&A^*(0) \\
&= \begin{bmatrix} -\rho-\beta v_2 & \beta v_2 & 0 & 0 & 0 & 0 \\ 0 & -a_1-a_2 & a_2 & 0 & 0 & 0 \\ 0 & 0 & -a_1-k_1z_2 & k & 0 & k_1k_6z_2 \\ -\beta x_2 & \beta x_2 & 0 & -\varepsilon-k_2z_2 & k_3z_2e^{-i\omega_0\tau_0} & 0 \\ 0 & 0 & -k_1y_2 & -k_2v_2 & -k_4+k_3v_2e^{-i\omega_0\tau_0} & k_1k_6y_2 \\ 0 & 0 & 0 & 0 & 0 & -k_7 \end{bmatrix} \begin{bmatrix} -\rho-\beta v_2+i\omega_0 & \beta v_2 & 0 & 0 & 0 & 0 \\ 0 & -a_1-a_2+i\omega_0 & a_2 & 0 & 0 & 0 \\ 0 & 0 & -a_1-k_1z_2+i\omega_0 & k & 0 & k_1k_6z_2 \\ -\beta x_2 & \beta x_2 & 0 & -\varepsilon-k_2z_2+i\omega_0 & k_3z_2e^{i\omega_0\tau_0} & 0 \\ 0 & 0 & -k_1y_2 & -k_2v_2 & -k_4+k_3v_2e^{i\omega_0\tau_0}+i\omega_0 & k_1k_6y_2 \\ 0 & 0 & 0 & 0 & 0 & -k_7+i\omega_0 \end{bmatrix} \begin{bmatrix} 1 \\ h_2^* \\ h_3^* \\ h_4^* \\ h_5^* \\ h_6^* \end{bmatrix} \\
&= 0.
\end{aligned} \tag{D.6}
$$

The eigenvectors of $A^*(0)$ are

$$
\begin{aligned}
h_1^* &= 1, \\
h_2^* &= -\frac{-\rho-\beta v_2+i\omega_0}{\beta v_2}, \\
h_3^* &= -\frac{(a_1+a_2-i\omega_0)(-\rho-\beta v_2+i\omega_0)}{a_2\beta v_2}, \\
h_4^* &= -\frac{(a_1+k_1z_2-i\omega_0)(a_1+a_2-i\omega_0)(-\rho-\beta v_2+i\omega_0)}{a_2k\beta v_2}, \\
h_5^* &= -\frac{k_1y_2(a_1+a_2-i\omega_0)(-\rho-\beta v_2+i\omega_0)}{a_2\beta v_2(-k_4+k_3v_2e^{i\omega_0\tau_0}+i\omega_0)} \\
&\quad -\frac{k_2(a_1+k_1z_2-i\omega_0)(a_1+a_2-i\omega_0)(-\rho-\beta v_2+i\omega_0)}{a_2k\beta(-k_4+k_3v_2e^{i\omega_0\tau_0}+i\omega_0)}, \\
h_6^* &= 0.
\end{aligned} \tag{D.7}
$$

Since

$$
\begin{aligned}
1 &= \langle h^*, h\rangle = \overline{D}\left(1, \overline{h}_2^*, \overline{h}_3^*, \overline{h}_4^*, \overline{h}_5^*, \overline{h}_6^*\right)\begin{bmatrix} 1 \\ h_2 \\ h_3 \\ h_4 \\ h_5 \\ h_6 \end{bmatrix} \\
&\quad - \int_{-\tau_0}^{0}\int_{\xi=0}^{\theta} \overline{D}\left(1, \overline{h}_2^*, \overline{h}_3^*, \overline{h}_4^*, \overline{h}_5^*, \overline{h}_6^*\right) \\
&\quad \cdot e^{-i\omega_0(\xi-\theta)}d\eta(\theta)\begin{bmatrix} 1 \\ h_2 \\ h_3 \\ h_4 \\ h_5 \\ h_6 \end{bmatrix} e^{i\omega_0\xi}d\xi = \overline{D}\left(1 + h_2\overline{h}_2^*\right. \\
&\quad \left. + h_3\overline{h}_3^* + h_4\overline{h}_4^* + h_5\overline{h}_5^* + h_6\overline{h}_6^*\right) \\
&\quad - \lim_{n\to\infty}\overline{D}\left(1, \overline{h}_2^*, \overline{h}_3^*, \overline{h}_4^*, \overline{h}_5^*, \overline{h}_6^*\right)\left(\sum_{i=1}^{n} e^{i\omega_0\xi_i}\theta_i\left(\eta(\theta_i)\right.\right. \\
&\quad \left.\left. - \eta(\theta_{i-1})\right)\right)\begin{bmatrix} 1 \\ h_2 \\ h_3 \\ h_4 \\ h_5 \\ h_6 \end{bmatrix} = \overline{D}\left(1 + h_2\overline{h}_2^* + h_3\overline{h}_3^* + h_4\overline{h}_4^*\right. \\
&\quad + h_5\overline{h}_5^* + h_6\overline{h}_6^* - \tau_0e^{-i\omega_0\tau_0}k_3zh_4h_5^* \\
&\quad \left. - \tau_0e^{-i\omega_0\tau_0}k_3vh_5h_5^*\right),
\end{aligned} \tag{D.8}
$$

we have that

$$
\begin{aligned}
D &= \left(1 + h_2\overline{h}_2^* + h_3\overline{h}_3^* + h_4\overline{h}_4^* + h_5\overline{h}_5^* + h_6\overline{h}_6^*\right. \\
&\quad \left. - \tau_0e^{-i\omega_0\tau_0}k_3zh_4h_5^* - \tau_0e^{-i\omega_0\tau_0}k_3vh_5h_5^*\right)^{-1}.
\end{aligned} \tag{D.9}
$$

E. The Detailed Computation of g_{20}, g_{11}, g_{02}, and g_{21}

In the following, we will compute coefficients, g_{20}, g_{11}, g_{02}, and g_{21}, using the method given in [27].

Let

$$
\begin{aligned}
f(\phi, 0) &= \begin{bmatrix} -\beta\phi_1(0)\phi_4(0) \\ \beta\phi_1(0)\phi_4(0) \\ -k_1\phi_3(0)\phi_5(0) \\ -k_2\phi_4(0)\phi_5(0) \\ k_3\phi_4(-\tau)\phi_5(-\tau) \\ k_1k_6\phi_3(0)\phi_5(0) \end{bmatrix} \\
&= (f_{z^2})\frac{z^2}{2} + (f_{z\overline{z}})z\overline{z} + (f_{\overline{z}^2})\frac{\overline{z}^2}{2} \\
&\quad + (f_{z^2\overline{z}})\frac{z^2\overline{z}}{2}, \\
X_t &= \begin{bmatrix} \phi_1 \\ \phi_2 \\ \phi_3 \\ \phi_4 \\ \phi_5 \\ \phi_6 \end{bmatrix} = zh(\theta) + \overline{z}\overline{h}(\theta) + w(z, \overline{z}, \theta) \\
&= z\begin{bmatrix} 1 \\ h_2 \\ h_3 \\ h_4 \\ h_5 \\ h_6 \end{bmatrix} e^{i\omega_0\theta} + \overline{z}\begin{bmatrix} 1 \\ h_2^* \\ h_3^* \\ h_4^* \\ h_5^* \\ h_6^* \end{bmatrix} e^{i\omega_0\theta} + w(z, \overline{z}, \theta),
\end{aligned} \tag{E.1}
$$

where

$$w(z,\overline{z},\theta) = w_{20}(\theta)\frac{z^2}{2} + w_{11}(\theta) z\overline{z} + w_{02}(\theta)\frac{\overline{z}^2}{2} + \cdots. \tag{E.2}$$

Then we have

$$\begin{aligned}
\phi_1(0) &= z + \overline{z} + w_{20}(0)\frac{z^2}{2} + w_{11}(0) z\overline{z} + w_{02}(0)\frac{\overline{z}^2}{2} + \cdots, \\
\phi_3(0) &= zh_3 + \overline{z}\overline{h}_3 + w_{20}^3(0)\frac{z^2}{2} + w_{11}^3(0) z\overline{z} + w_{02}^3(0)\frac{\overline{z}^2}{2} + \cdots, \\
\phi_4(0) &= zh_4 + \overline{z}\overline{h}_4 + w_{20}^4(0)\frac{z^2}{2} + w_{11}^4(0) z\overline{z} + w_{02}^4(0)\frac{\overline{z}^2}{2} + \cdots, \\
\phi_5(0) &= zh_5 + \overline{z}\overline{h}_5 + w_{20}^5(0)\frac{z^2}{2} + w_{11}^5(0) z\overline{z} + w_{02}^5(0)\frac{\overline{z}^2}{2} + \cdots, \\
\phi_4(-\tau) &= zh_4 e^{-i\omega_0\tau} + \overline{z}\overline{h}_4 e^{i\omega_0\tau} + w_{20}^4(-\tau)\frac{z^2}{2} + w_{11}^4(-\tau) z\overline{z} + w_{02}^4(-\tau)\frac{\overline{z}^2}{2} + \cdots, \\
\phi_5(-\tau) &= zh_5 e^{-i\omega_0\tau} + \overline{z}\overline{h}_5 e^{i\omega_0\tau} + w_{20}^5(-\tau)\frac{z^2}{2} + w_{11}^5(-\tau) z\overline{z} + w_{02}^5(-\tau)\frac{\overline{z}^2}{2} + \cdots, \\
\beta\phi_1(0)\phi_4(0) &= 2\beta h_4\frac{z^2}{2} + \beta\left(h_4 + \overline{h}_4\right) z\overline{z} + 2\beta\overline{h}_4\frac{\overline{z}^2}{2} + \beta\left(w_{20}(0)\overline{h}_4 + w_{20}^2(0) + 2w_{11}^2(0) + 2h_4 w_{11}(0)\right)\frac{z^2\overline{z}}{2} + \cdots, \\
-k_1\phi_3(0)\phi_5(0) &= -2k_1h_3h_5\frac{z^2}{2} - k_1\left(h_3\overline{h}_5 + \overline{h}_3 h_5\right) \cdot z\overline{z} - 2k_1\overline{h}_3\overline{h}_5\frac{\overline{z}^2}{2} - k_1\left(2h_3 w_{11}^5(0) + \overline{h}_3 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right)\frac{z^2\overline{z}}{2} + \cdots, \\
k_1k_6\phi_3(0)\phi_5(0) &= 2k_1k_6h_3h_5\frac{z^2}{2} + k_1k_6\left(h_3\overline{h}_5 + \overline{h}_3 h_5\right) z\overline{z} + 2k_1k_6\overline{h}_3\overline{h}_5\frac{\overline{z}^2}{2} + k_1k_6\left(2h_3 w_{11}^5(0) + \overline{h}_3 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right)\frac{z^2\overline{z}}{2} + \cdots, \\
-k_2\phi_4(0)\phi_5(0) &= -2k_2h_4h_5\frac{z^2}{2} - k_2\left(h_4\overline{h}_5 + \overline{h}_4 h_5\right) \cdot z\overline{z} - 2k_2\overline{h}_4\overline{h}_5\frac{\overline{z}^2}{2} - k_2\left(2h_4 w_{11}^5(0) + \overline{h}_4 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right)\frac{z^2\overline{z}}{2} + \cdots, \\
k_3\phi_4(-\tau)\phi_5(-\tau) &= 2k_3h_4h_5 e^{-2i\omega_0\tau}\frac{z^2}{2} + k_3\left(h_4\overline{h}_5 + \overline{h}_4 h_5\right) z\overline{z} + 2k_3\overline{h}_4\overline{h}_5 e^{2i\omega_0\tau}\frac{\overline{z}^2}{2} \\
&\quad + k_3\left(2h_4 w_{11}^5(-\tau) e^{-i\omega_0\tau} + \overline{h}_4 w_{20}^5(-\tau) e^{i\omega_0\tau} + \overline{h}_5 w_{20}^4(-\tau) e^{i\omega_0\tau} + 2h_5 w_{11}^4(-\tau) e^{-i\omega_0\tau}\right)\frac{z^2\overline{z}}{2} + \cdots.
\end{aligned} \tag{E.3}$$

We further obtain

$$f(\phi, 0) = \begin{bmatrix} -2\beta h_4 \\ 2\beta h_4 \\ -2k_1h_3h_5 \\ -2k_2h_4h_5 \\ 2k_3h_4h_5 e^{-2i\omega_0\tau} \\ 2k_1k_6h_3h_5 \end{bmatrix}\frac{z^2}{2} + \begin{bmatrix} -\beta\left(h_4 + \overline{h}_4\right) \\ \beta\left(h_4 + \overline{h}_4\right) \\ -k_1\left(h_3\overline{h}_5 + \overline{h}_3 h_5\right) \\ -k_2\left(h_4\overline{h}_5 + \overline{h}_4 h_5\right) \\ k_3\left(h_4\overline{h}_5 + \overline{h}_4 h_5\right) \\ -k_1k_6\left(h_3\overline{h}_5 + \overline{h}_3 h_5\right) \end{bmatrix} z\overline{z} + \begin{bmatrix} -2\beta\overline{h}_4 \\ 2\beta\overline{h}_4 \\ -2k_1\overline{h}_3\overline{h}_5 \\ -2k_2\overline{h}_4\overline{h}_5 \\ 2k_3\overline{h}_4\overline{h}_5 e^{2i\omega_0\tau} \\ k_1k_6\overline{h}_3\overline{h}_5 \end{bmatrix}\frac{\overline{z}^2}{2}$$

$$+\begin{bmatrix} -\beta\left(w_{20}(0)\overline{h}_4 + w_{20}^2(0) + 2w_{11}^2(0) + 2h_4 w_{11}(0)\right) \\ \beta\left(w_{20}(0)\overline{h}_4 + w_{20}^2(0) + 2w_{11}^2(0) + 2h_4 w_{11}(0)\right) \\ -k_1\left(2h_3 w_{11}^5(0) + \overline{h}_3 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right) \\ -k_2\left(2h_4 w_{11}^5(0) + \overline{h}_4 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right) \\ k_3\left(2h_4 w_{11}^5(-\tau)e^{-i\omega_0\tau} + \overline{h}_4 w_{20}^5(-\tau)e^{i\omega_0\tau} + \overline{h}_5 w_{20}^4(-\tau)e^{i\omega_0\tau} + 2h_5 w_{11}^4(-\tau)e^{-i\omega_0\tau}\right) \\ k_1k_6\left(2h_3 w_{11}^5(0) + \overline{h}_3 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right) \end{bmatrix} \frac{z^2\overline{z}}{2}. \tag{E.4}$$

Using the method [27], we obtain the following coefficients:

$$g_{20} = \overline{h}^*(0) f_{z^2} = \overline{D}\left(1, \overline{h}_2^*, \overline{h}_3^*, \overline{h}_4^*, \overline{h}_5^*, \overline{h}_6^*\right) \begin{bmatrix} -2\beta h_4 \\ 2\beta h_4 \\ -2k_1 h_3 h_5 \\ -2k_2 h_4 h_5 \\ 2k_3 h_4 h_5 e^{-2i\omega_0\tau} \\ 2k_1 k_6 h_3 h_5 \end{bmatrix},$$

$$g_{11} = \overline{h}^*(0) f_{z\overline{z}} = \overline{D}\left(1, \overline{h}_2^*, \overline{h}_3^*, \overline{h}_4^*, \overline{h}_5^*, \overline{h}_6^*\right) \begin{bmatrix} -\beta\left(h_4 + \overline{h}_4\right) \\ \beta\left(h_4 + \overline{h}_4\right) \\ -k_1\left(h_3\overline{h}_5 + \overline{h}_3 h_5\right) \\ -k_2\left(h_4\overline{h}_5 + \overline{h}_4 h_5\right) \\ k_3\left(h_4\overline{h}_5 + \overline{h}_4 h_5\right) \\ -k_1k_6\left(h_3\overline{h}_5 + \overline{h}_3 h_5\right) \end{bmatrix},$$

$$g_{02} = \overline{h}^*(0) f_{\overline{z}^2} = \overline{D}\left(1, \overline{h}_2^*, \overline{h}_3^*, \overline{h}_4^*, \overline{h}_5^*, \overline{h}_6^*\right) \begin{bmatrix} -2\beta\overline{h}_4 \\ 2\beta\overline{h}_4 \\ -2k_1\overline{h}_3\overline{h}_5 \\ -2k_2\overline{h}_4\overline{h}_5 \\ 2k_3\overline{h}_4\overline{h}_5 e^{2i\omega_0\tau} \\ k_1k_6\overline{h}_3\overline{h}_5 \end{bmatrix}, \tag{E.5}$$

$$g_{21} = \overline{h}^*(0) f_{z^2\overline{z}}$$

$$= \overline{D}\left(1, \overline{h}_2^*, \overline{h}_3^*, \overline{h}_4^*, \overline{h}_5^*, \overline{h}_6^*\right) \cdot \begin{bmatrix} -\beta\left(w_{20}(0)\overline{h}_4 + w_{20}^2(0) + 2w_{11}^2(0) + 2h_4 w_{11}(0)\right) \\ \beta\left(w_{20}(0)\overline{h}_4 + w_{20}^2(0) + 2w_{11}^2(0) + 2h_4 w_{11}(0)\right) \\ -k_1\left(2h_3 w_{11}^5(0) + \overline{h}_3 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right) \\ -k_2\left(2h_4 w_{11}^5(0) + \overline{h}_4 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right) \\ k_3\left(2h_4 w_{11}^5(-\tau)e^{-i\omega_0\tau} + \overline{h}_4 w_{20}^5(-\tau)e^{i\omega_0\tau} + \overline{h}_5 w_{20}^4(-\tau)e^{i\omega_0\tau} + 2h_5 w_{11}^4(-\tau)e^{-i\omega_0\tau}\right) \\ k_1k_6\left(2h_3 w_{11}^5(0) + \overline{h}_3 w_{20}^5 + \overline{h}_5 w_{20}^4(0) + 2h_5 w_{11}^4(0)\right) \end{bmatrix},$$

where

$$w_{20}(\theta) = \frac{ig_{20}}{\omega_0} e^{i\omega_0\theta} h(0) + \frac{i\overline{g}_{20}}{3\omega_0} e^{-i\omega_0\theta} \overline{h}(0) + E_{20} e^{2i\omega_0\theta}, \quad \text{(E.6)}$$

$$w_{11}(\theta) = -\frac{ig_{11}}{\omega_0} e^{i\omega_0\theta} h(0) + \frac{i\overline{g}_{11}}{\omega_0} e^{-i\omega_0\theta} \overline{h}(0) + E_{11},$$

where

$$E_{20} = \left[2i\omega_0 I - \int_{-\tau_0}^{0} e^{-2i\omega_0\theta} d\eta(0,\theta)\right]^{-1} f_{z^2} = \left[2i\omega_0 I - \lim_{\lambda\to 0}\left(e^{2i\omega_0\xi_1}(\eta(\theta_1) - \eta(\theta_0)) + \cdots + e^{2i\omega_0\xi_n}(\eta(\theta_n) - \eta(\theta_{n-1}))\right)\right]^{-1} f_{z^2} = \left[2i\omega_0 I - \lim_{\lambda\to 0}\left(e^{2i\omega_0\xi_1} F_2 + e^{2i\omega_0\xi_n} F_1\right)\right]^{-1} f_{z^2} = \left(2i\omega_0 I - F_1 - F_2 e^{-2i\omega_0\tau}\right)^{-1} f_{z^2} = \left(2i\omega_0 I - F_1 - F_2 e^{-2i\omega_0\tau}\right)^{-1} \cdot \begin{bmatrix} -2\beta h_4 \\ 2\beta h_4 \\ -2k_1 h_3 h_5 \\ -2k_2 h_4 h_5 \\ 2k_3 h_4 h_5 e^{-2i\omega_0\tau} \\ 2k_1 k_6 h_3 h_5 \end{bmatrix}, \quad \text{(E.7)}$$

$$E_{11} = -\left[\int_{-\tau_0}^{0} d\eta(0,\theta)\right]^{-1} \cdot f_{z\overline{z}} = -\left[F_1 + F_2\right]^{-1} \cdot f_{z\overline{z}} = -2\left[F_1 + F_2\right]^{-1} \begin{bmatrix} -\beta \operatorname{Re} h_4 \\ \beta \operatorname{Re} h_4 \\ -k_1 \operatorname{Re} h_3 \overline{h}_5 \\ -k_2 \operatorname{Re} h_4 \overline{h}_5 \\ k_3 \operatorname{Re} h_4 \overline{h}_5 \\ -k_1 k_6 \operatorname{Re} h_3 \overline{h}_5 \end{bmatrix}.$$

So far, we have obtained g_{20}, g_{11}, g_{02}, and g_{21}.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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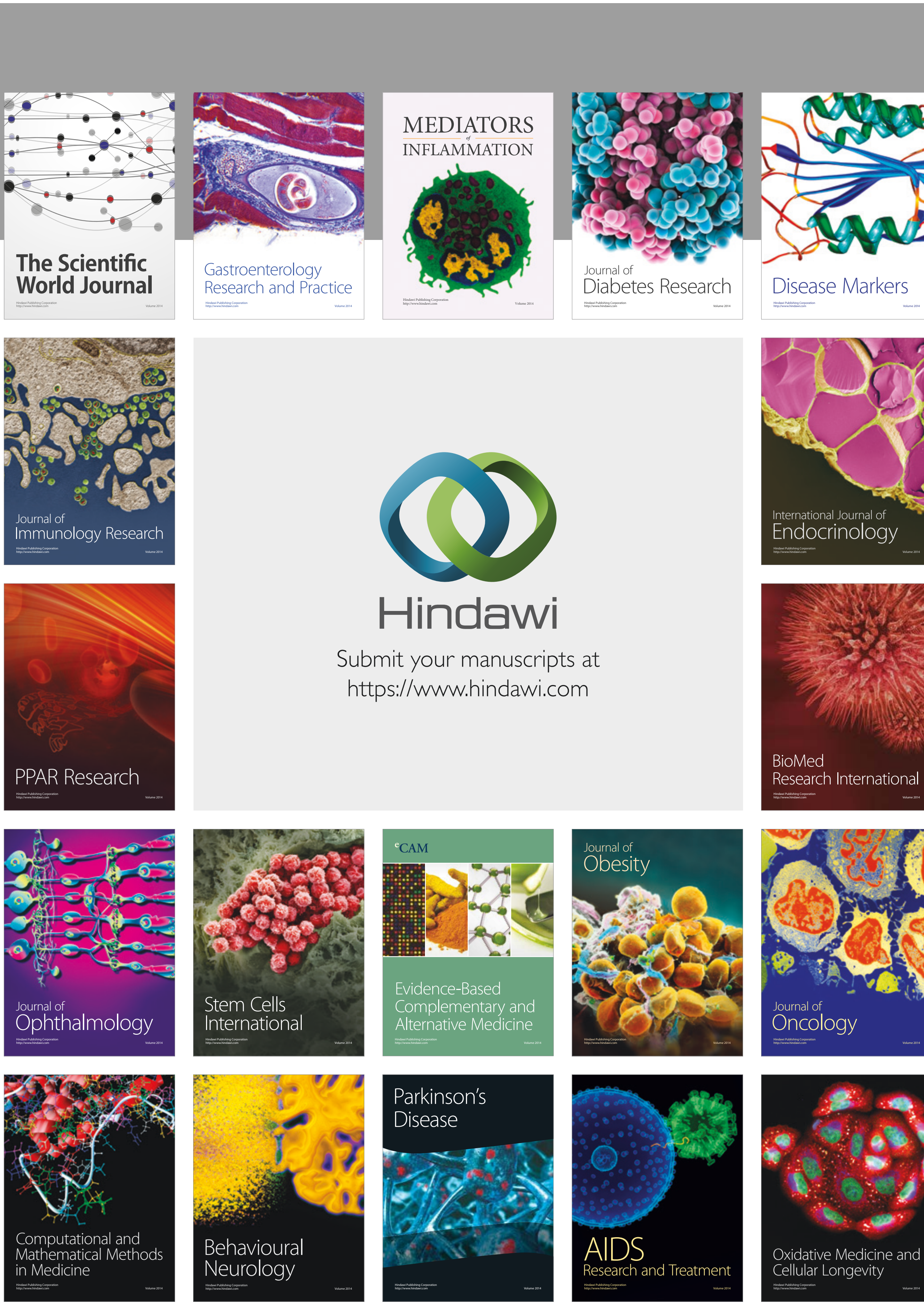
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