HOPF BIFURCATION OF AN HIV-1 VIRUS MODEL WITH TWO DELAYS AND LOGISTIC GROWTH*

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Abstract. The paper establish and investigate an HIV-1 virus model with logistic growth, which also has intracellular delay and humoral immunity delay. The local stability of feasible equilibria are established by analyzing the characteristic equations. The globally stability of infection-free equilibrium and immunity-inactivated equilibrium are studied using the Lyapunov functional and LaSalle's invariance principle. Besides, we prove that Hopf bifurcation will occur when the humoral immune delay pass through the critical value. And the stability of the positive equilibrium and Hopf bifurcations are investigated by using the normal form theory and the center manifold theorem. Finally, we confirm the theoretical results by numerical simulations.

Mathematics Subject Classification. D25, 34C23, 37B25, 34D23.

Received December 28, 2018. Accepted September 8, 2019.

1. INTRODUCTION

For the past few years, HIV-1 infection model has been widely studied (see [4–6, 11, 13, 20]). HIV-1 has two primary infection modes, one is the classical cell-free transmission [6], and the other is direct cell-to-cell transfer of viral particles [5]. A great amount of the studies often only consider one aspect. For instance, Song and Wang [21] and Wang [28] established a viral infection model with lytic and nonlytic immune responses. Li and Wang [15] discussed an HIV infection model which incorporated directly cell-to-cell transmission. In Lai and Zou [13, 14], the author considered the effect of cell-to-cell transfer of HIV-1 on the virus dynamics. Wang *et al.* [26] studied age-structured viral infection models with cell-to-cell transmission. In [8], Elaiw and Alshamrani analyzed two nonlinear viral infection models with humoral immune response. Murase *et al.* [18] and Wang and Zou [29] investigated a basic HIV-1 virus model with humoral immunity. In [15], Feng Li and JingLiang Wang considered an HIV-1 infection model with logistic growth. Hu and co-workers [12] studied the dynamics of a delayed viral infection model with logistic growth and immune impairment. Furthermore, time delays (see [7, 22, 23]) have been applied to epidemic models for the sake of having a better understanding of more complicated phenomena for describing several aspects of infectious disease dynamics. On the influence of time delay on model dynamics, scholars mainly discussed the influence of time delay on the stability of system equilibrium point and the existence of Hopf bifurcation [1, 19]. In [17], authors considered an HIV-1 virus model to describe virus-to-cell, cell-to-cell transmissions, intracellular delay and humoral immunity. The model is as

* This work is supported by Natural Science Foundation of Shanxi province (201801D121011).

Keywords and phrases: HIV-1 virus model, delay, stability, Hopf bifurcation, logistic growth.

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follows:

$$\begin{cases} \frac{dx(t)}{dt} = \Lambda - dx(t) - \beta_1 x(t)v(t) - \beta_2 x(t)y(t), \\ \frac{dy(t)}{dt} = \beta_1 e^{-m\tau_1} x(t-\tau)v(t-\tau) + \beta_2 e^{-m\tau_1} x(t-\tau)y(t-\tau) - ay(t), \\ \frac{dv(t)}{dt} = ky(t) - uv(t) - pv(t)z(t), \\ \frac{dz(t)}{dt} = cv(t)z(t) - bz(t), \end{cases} \quad (1.1)$$

denote by $x(t)$, $v(t)$, $v(t)$ and $z(t)$, the uninfected cells (susceptible cells), infected cells, virus and B cells. Uninfected cells (susceptible cells) are produced at rate Λ and died at rate d , β_1 and β_2 are infection rates of virus-to-cell transmission and cell-to-cell transmission, respectively; the delay τ represents the time between viral entry into a cell and the production of new free virus or the time between infected cells spreading virus into uninfected cells and the production of new free virus; m is assumed to be a constant death rate for infected but not yet virus-producing cells. Thus, the feasibility of surviving the time period from $t - \tau$ to t is $e^{-m\tau}$; a , u and b are death rates of infected cells, virus and B cells, respectively; k denotes the number of free virus particles produced by per infected cell. $pv(t)z(t)$ is used to describe the virus killed by B cells and $cv(t)z(t)$ is used to describe the new B cells produced by antigenic stimulation.

However, time delays cannot be ignored in models for immune response as shown in [3, 25, 27]. Besides, we can see that the logistic growth is considered in [14, 15]. Therefore, we propose the following delay and logistic growth model motivated by the works of [17] in the present study,

$$\begin{cases} \frac{dx(t)}{dt} = rx(t)(1 - \frac{x(t)}{x_M}) - \beta_1 x(t)v(t) - \beta_2 x(t)y(t), \\ \frac{dy(t)}{dt} = \beta_1 \alpha x(t - \tau_1)v(t - \tau_1) + \beta_2 \alpha x(t - \tau_1)y(t - \tau_1) - ay(t), \\ \frac{dv(t)}{dt} = ky(t) - uv(t) - pv(t)z(t), \\ \frac{dz(t)}{dt} = cv(t - \tau_2)z(t - \tau_2) - bz(t), \end{cases} \quad (1.2)$$

where the state variables x, y, v, z and all parameters have same biological meanings as in the model (1.0). τ_2 represents the time that HIV-1 virus stimulation needs for generating B cells [3]. Here, target cells grow at a rate r and this growth is limited by a carrying target cells x_M and the probability of surviving the time period from $t - \tau_1$ to t is α . All parameters are assumed to be positive.

Let $\tau = \max\{\tau_1, \tau_2\}$. The initial conditions for system (1.2) take the form

$$\begin{aligned} x(\theta) &= \phi_1(\theta), y(\theta) = \phi_2(\theta), v(\theta) = \phi_3(\theta), z(\theta) = \phi_4(\theta), \\ \phi_i(\theta) &\geq 0, \theta \in [-\tau, 0], \phi_i(0) > 0, i = 1, 2, 3, 4, \end{aligned} \quad (1.3)$$

where $\phi_i(\theta) \in C([-\tau, 0], R_{+0}^4)$, $i = 1, 2, 3, 4$, is the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into R_{+0}^4 , where $R_{+0}^4 = \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1, 2, 3, 4\}$.

It can be proved that system (1.2) has an unique solution $(x(t), y(t), v(t), z(t))$ that satisfying the initial condition (1.3) by the fundamental theory of functional differential equations [9]. It is easy to show that all solutions of system (1.2) with initial condition (1.3) are defined on $[0, +\infty)$ and remain positive for all $t \geq 0$.

The rest of the paper is organized as follows. In Section 2, we investigate and verify the existence of feasible equilibria and the stability of nonnegative equilibria. In Section 3, we determine the stability of positive equilibrium and the existence of Hopf bifurcation. In Section 4, the explicit formulate for determining the direction of Hopf bifurcation and the stability of bifurcating periodic solutions are proved by using the normal form theory and the center manifold theorem. In order to verify our theoretical prediction, some numerical simulations are also included in Section 5. Finally, in Section 6, we give some remarks on the biological interpretation of our results, and some further extensions of the model one can make.

2. EXISTENCE OF EQUILIBRIA AND THE STABILITY OF NONNEGATIVE EQUILIBRIA

2.1. Feasible equilibria

Considering the existence of the three equilibria, we get the following results.

Denote $\mathfrak{R}_0 = \frac{(\alpha\beta_1 k + \alpha\beta_2 u)}{au} x_M$, which is called immune-inactivated reproduction rate of system (1.2), it represents the number of newly infected cells produced by one infected cell during its lifespan.

$$\mathfrak{R}_1 = \frac{\mathfrak{R}_0}{1 + \frac{abu}{ckx_M(\frac{2rx_1}{x_M} - r)\alpha}} = \frac{\beta_1 k + \beta_2 u}{ck(\frac{2rx_1}{x_M} - r + \frac{abu}{x_M}\mathfrak{R}_0)}(cv_1 - b) + 1,$$

which is called immune-activated reproduction rate.

Clearly, system (1.2) always has an infection-free equilibrium $E_0(x_M, 0, 0, 0)$.

If $\mathfrak{R}_0 > 1$, there exists an immunity-inactivated equilibrium $E_1(x_1, y_1, v_1, 0)$, and E_0 , where

$$x_1 = \frac{au}{\alpha\beta_1 k + \alpha\beta_2 u}, \quad y_1 = r\mathfrak{R}_0(\mathfrak{R}_0 - 1)\frac{u}{\beta_1 k + \beta_2 u}, \quad v_1 = r\mathfrak{R}_0(\mathfrak{R}_0 - 1)\frac{k}{\beta_1 k + \beta_2 u}.$$

If $\mathfrak{R}_1 > 1$, there exists an immunity-activated equilibrium $E_2(x_2, y_2, v_2, z_2)$, E_0 and E_1 , where

$$y_2 = \frac{pbz_2 + ub}{ck}, \quad v_2 = \frac{b}{c}, \quad x_2 = \frac{apbz_2 + aub}{\alpha\beta_1 bk + \alpha\beta_2(pbz_2 + ub)},$$

and z_2 is the unique positive real root of the following quadratic equation:

$$p^2 b \alpha \beta_2 z^2(t) + (\alpha r c k p + \alpha \beta_1 p b k x_M - \alpha r p c k x_M + \alpha \beta_2 u b p x_M + \alpha \beta_2 p b u x_M) z(t) + (\alpha \beta_2 u^2 b x_M + \alpha \beta_1 b k u x_M + \alpha c d k u x_M)(1 - \mathfrak{R}_1) = 0.$$

2.2. The stability of the virus-free equilibrium

Theorem 2.1. *For any τ_1, τ_2 , if $\mathfrak{R}_0 < 1$, the infection-free equilibrium E_0 of system (1.2) is locally asymptotically stable; if $\mathfrak{R}_0 > 1$, E_0 is unstable.*

Proof. The characteristic equation of system (1.2) at E_0 is

$$(\lambda + r)(\lambda + b)[(\lambda + a)(\lambda + u) - e^{-\lambda\tau_1} x_M(\alpha\beta_2\lambda + k\alpha\beta_1 + u\alpha\beta_2)] = 0. \quad (2.1)$$

It's clear that equation (2.1) have negative real parts roots $\lambda = -r, \lambda = -b$ and other roots are determined by following equation

$$G(\lambda) \equiv (\lambda + a)(\lambda + u) - e^{-\lambda\tau_1} x_M(\alpha\beta_2\lambda + k\alpha\beta_1 + u\alpha\beta_2) = 0. \quad (2.2)$$

Denote $\mathfrak{R}_0 = \mathfrak{R}_{01} + \mathfrak{R}_{02}$, where $\mathfrak{R}_{01} = \frac{\alpha\beta_1 k x_M}{au}$, $\mathfrak{R}_{02} = \frac{\alpha\beta_2 x_M}{a}$. Direct calculation shows that

$$\left(\frac{\lambda}{u} + 1\right)\left(\frac{\lambda}{a} + 1\right) = e^{-\lambda\tau_1} \left(\frac{\lambda}{u}\mathfrak{R}_{02} + \mathfrak{R}_0\right). \quad (2.3)$$

Now, we claim that all roots of (2.3) has negative real parts. Otherwise, there exists a root $\lambda_1 = x_1 + iy_1$ with $x_1 \geq 0$. In this case, if $\Re_0 < 1$, it is easy to see that

$$\left| \frac{\lambda_1}{u} + 1 \right| > \left| \frac{\lambda_1}{u} \Re_{02} + \Re_0 \right|, \quad \left| \frac{\lambda_1}{a} + 1 \right| > e^{-x_1 \tau_1}.$$

It follows that

$$\left| \left(\frac{\lambda_1}{u} + 1 \right) \left(\frac{\lambda_1}{a} + 1 \right) \right| > \left| e^{-\lambda \tau_1} \left(\frac{\lambda_1}{u} \Re_{02} + \Re_0 \right) \right|,$$

which contradicts to (2.3). Therefore, if $\Re_0 < 1$, all roots of (2.1) have negative real parts and E_0 is locally asymptotically stable.

If $\Re_0 > 1$, $G(0) = au(1 - \Re_0) < 0$ and $G(\lambda) \rightarrow +\infty$ as $\lambda \rightarrow +\infty$. So equation (2.2) has a positive real root, i.e. equation (2.1) has a positive real root, Hence, E_0 is unstable. $\square$

Theorem 2.2. *For any τ_1, τ_2 , the virus-free equilibrium E_0 is globally asymptotically stable if $\Re_0 < 1$.*

Proof. Define a Lyapunov functional as follows

$$\begin{aligned} V_1(t) = & x(t) - x_0 - x_0 \ln \frac{x(t)}{x_0} + c_1 y(t) + c_2 v(t) + c_3 z(t) \\ & + \int_{t-\tau_1}^t (\beta_1 x(s)v(s) + \beta_2 x(s)y(s)) ds + c_2 \int_{t-\tau_2}^t p v(s) z(s) ds, \end{aligned}$$

where $x_0 = x_M$ and c_1, c_2 and c_3 will be determined later.

Calculating the derivative of $V_1(t)$ along the solutions of system (1.2), we obtain that

$$\begin{aligned} \frac{dV_1(t)}{dt} = & \left(1 - \frac{x_0}{x(t)}\right) \frac{dx(t)}{dt} + c_1 \frac{dy(t)}{dt} + c_2 \frac{dv(t)}{dt} + c_3 \frac{dz(t)}{dt} \\ & + \beta_1 x(t)v(t) + \beta_2 x(t)y(t) - \beta_1 x(t - \tau_1)v(t - \tau_1) - \beta_2 x(t - \tau_1)y(t - \tau_1) \\ & + c_2 p v(t)z(t) - c_2 p v(t - \tau_2)z(t - \tau_2) \end{aligned}$$

Direct calculation shows that

$$\begin{aligned} \frac{dV_1(t)}{dt} = & -r \frac{(x(t) - x_0)^2}{x_M} + (c_2 k + \beta_2 x_0 - c_1 a) y(t) - c_3 b z(t) \\ & + (c_1 \alpha - 1) [\beta_1 x(t - \tau_1)v(t - \tau_1) + \beta_2 x(t - \tau_1)y(t - \tau_1)] \\ & + (\beta_1 x_0 - c_2 u) v(t) + (c_3 c - p c_2) v(t - \tau_2) z(t - \tau_2). \end{aligned}$$

Let

$$c_1 = \frac{1}{\alpha}, \quad c_2 = \frac{\beta_1}{u} x_M, \quad c_3 = \frac{\beta_1 p}{cu} x_M.$$

Thus,

$$\frac{dV_1(t)}{dt} = -r \frac{(x(t) - x_0)^2}{x_M} + \alpha a (\Re_0 - 1) y(t) - \frac{\beta_1 p b}{cu} x_M z(t). \quad (2.4)$$

It follows from (2.4) that $\frac{dV_1(t)}{dt} \leq 0$ with equality holding if and only if $x = x_0, y = v = z = 0$. It can be certified that $M_0 = \{E_0\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t)) : \frac{dV_1}{dt} = 0\}$. According to Theorem 2.1, E_0 is locally asymptotically stable. From LaSalle's invariance principle, we obtain that E_0 is globally asymptotically stable. $\square$

2.3. The stability of the immunity-inactivated equilibrium

Theorem 2.3. *For any τ_1, τ_2 , the immunity-inactivated equilibrium E_1 of system (1.2) is locally asymptotically stable if $\mathfrak{R}_1 < 1 < \mathfrak{R}_0$.*

Proof. The characteristic equation of system (1.2) at E_1 is

$$(\lambda + b - cv_1 e^{-\lambda\tau_2})[(\lambda + a)(\lambda + u)(\lambda + r - \frac{2rx_1}{x_M} + \beta_1 v_1 + \beta_2 y_1) - e^{-\lambda\tau_1} x_1(\lambda + r - \frac{2rx_1}{x_M})(\alpha\beta_2 \lambda + \alpha\beta_1 k + \alpha\beta_2 u)] = 0. \quad (2.5)$$

It is clear that $(\lambda + b - cv_1 e^{-\lambda\tau_2}) = 0$ has a negative real root when $\mathfrak{R}_1 < 1$, and other roots are determined by the following equation:

$$(\lambda + a)(\lambda + u)(\lambda + r - \frac{2rx_1}{x_M} + \beta_1 v_1 + \beta_2 y_1) - e^{-\lambda\tau_1} x_1(\lambda + r - \frac{2rx_1}{x_M})(\alpha\beta_2 \lambda + \alpha\beta_1 k + \alpha\beta_2 u) = 0. \quad (2.6)$$

Direct calculation shows that

$$(\frac{\lambda}{a} + 1)(\frac{\lambda}{u} + 1)(\frac{\lambda}{r - \frac{2rx_1}{x_M}} + \mathfrak{R}_0) = e^{-\lambda\tau_1}(\frac{\lambda}{r - \frac{2rx_1}{x_M}} + 1)(\frac{\lambda}{u} \frac{\mathfrak{R}_{02}}{\mathfrak{R}_0} + 1). \quad (2.7)$$

Now, we claim that all roots of (2.7) has negative real parts. Otherwise, there exists a root $\lambda_2 = x_2 + iy_2$ with $x_2 \geq 0$. In this case, if $\mathfrak{R}_0 > 1$, it is easy to see that

$$|\frac{\lambda_2}{a} + 1| > e^{-x_1\tau_1}, \quad |\frac{\lambda_2}{r - \frac{2rx_1}{x_M}} + \mathfrak{R}_0| > |\frac{\lambda_2}{r - \frac{2rx_1}{x_M}} + 1|, \quad |\frac{\lambda_2}{u} + 1| > |\frac{\lambda_2}{u} \frac{\mathfrak{R}_{02}}{\mathfrak{R}_0} + 1|.$$

It follows that

$$|(\frac{\lambda_2}{a} + 1)(\frac{\lambda_2}{u} + 1)(\frac{\lambda_2}{r - \frac{2rx_1}{x_M}} + \mathfrak{R}_0)| > |e^{-\lambda_2\tau_1}(\frac{\lambda_2}{r - \frac{2rx_1}{x_M}} + 1)(\frac{\lambda_2}{u} \frac{\mathfrak{R}_{02}}{\mathfrak{R}_0} + 1)|.$$

which leads to a contradiction to (2.7). Thus, all roots of equation (2.6) have negative real parts, and E_1 is locally asymptotically stable. $\square$

Theorem 2.4. *For any τ_1, τ_2 , the immunity-inactivated equilibrium E_1 is globally asymptotically stable if $\mathfrak{R}_1 < 1 < \mathfrak{R}_0$.*

Proof. Consider the following Lyapunov functional

$$\begin{aligned} V_2(t) = & x(t) - x_1 - x_1 \ln \frac{x(t)}{x_1} + k_1(y(t) - y_1 - y_1 \ln \frac{y(t)}{y_1}) + k_2(v(t) - v_1 - v_1 \ln \frac{v(t)}{v_1}) \\ & + k_3 z(t) + \beta_1 x_1 v_1 \int_{t-\tau_1}^t [\frac{x(s)v(s)}{x_1 v_1} - 1 - \ln \frac{x(s)v(s)}{x_1 v_1}] ds \\ & + \beta_2 x_1 y_1 \int_{t-\tau_1}^t [\frac{x(s)y(s)}{x_1 y_1} - 1 - \ln \frac{x(s)y(s)}{x_1 y_1}] ds + k_2 \int_{t-\tau_2}^t p v(s) z(s) ds, \end{aligned}$$

where constants k_1 , k_2 and k_3 will be determined later.

Calculating the derivative of $V_2(t)$ along the solutions of system (1.2), we have

$$\begin{aligned} \frac{dV_2(t)}{dt} = & -r \frac{(x(t) - x_1)^2}{x_M} + \beta_1 x_1 v_1 (1 + k_1 \alpha - \frac{x_1}{x(t)} - \frac{x(t - \tau_1)v(t - \tau_1)y_1}{x_1 v_1 y(t)} k_1 \alpha + \ln \frac{x(t - \tau_1)v(t - \tau_1)}{x(t)v(t)}) \\ & + \beta_2 x_1 y_1 (1 + k_1 \alpha - \frac{x_1}{x(t)} - \frac{x(t - \tau_1)y(t - \tau_1)y_1}{x_1 y_1 y(t)} k_1 \alpha + \ln \frac{x(t - \tau_1)y(t - \tau_1)}{x(t)y(t)}) \\ & + (k_1 \alpha - 1)(\beta_1 x(t - \tau_1)v(t - \tau_1) + \beta_2 x(t - \tau_1)y(t - \tau_1)) \\ & + (\beta_2 x_1 + k_2 k - k_1 \frac{\beta_1 \alpha x_1 v_1 + \beta_2 \alpha x_1 y_1}{y_1}) y(t) \\ & + (\beta_1 x_1 - k_2 \frac{k y_1}{v_1}) v(t) + (k_2 p v_1 - k_3 b) z(t) \\ & - k_2 k v_1 \frac{y(t)}{v(t)} + k_2 k y_1 + (k_3 c - k_2 p) v(t - \tau_2) z(t - \tau_2) \end{aligned}$$

Let $k_1 = \frac{1}{\alpha}$, $k_2 = \frac{\beta_1 x_1}{u}$, $k_3 = \frac{\beta_1 p x_1}{cu}$. It follows that

$$\begin{aligned} \frac{dV_2(t)}{dt} = & -r \frac{(x(t) - x_1)^2}{x_M} + \frac{\beta_1 p x_1}{cu} (c v_1 - b) z(t) - \beta_1 x_1 v_1 (\frac{x_1}{x(t)} - 1 - \ln \frac{x_1}{x(t)}) \\ & - \beta_1 x_1 v_1 (\frac{y(t)v_1}{v(t)y_1} - 1 - \ln \frac{y(t)v_1}{v(t)y_1}) - \beta_1 x_1 v_1 (\frac{x(t - \tau_1)v(t - \tau_1)y_1}{x_1 v_1 y(t)} - 1 - \ln \frac{x(t - \tau_1)v(t - \tau_1)y_1}{x_1 v_1 y(t)}) \\ & - \beta_2 x_1 y_1 (\frac{x_1}{x(t)} - 1 - \ln \frac{x_1}{x(t)}) - \beta_2 x_1 y_1 (\frac{x(t - \tau_1)y(t - \tau_1)}{x_1 y(t)} - 1 - \ln \frac{x(t - \tau_1)y(t - \tau_1)}{x_1 y(t)}) \end{aligned} \quad (2.8)$$

It follows from (2.8) that $\frac{dV_2(t)}{dt} \leq 0$ with equality holding if and only if $x = x_1, y = y_1, v = v_1, z = 0$. It can be certified that $M_1 = \{E_1\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t)) : \frac{dV_2}{dt} = 0\}$. According to Theorem 2.3, E_1 is locally asymptotically stable. From LaSalle's invariance principle, we obtain that E_1 is globally asymptotically stable. $\square$

3. THE STABILITY OF THE IMMUNITY-ACTIVATED EQUILIBRIUM AND HOPF BIFURCATION

Theorem 3.1. *For any τ_1 , if $\tau_2 = 0$ and $\Re_1 > 1$ the immunity-activated equilibrium E_2 of system (1.2) is locally asymptotically stable.*

Proof. Noting that $b - cv_2 = 0$, the characteristic equation of system (1.2) at E_2 is

$$\begin{aligned} & (\lambda + r - \frac{2rx_2}{x_M} + \beta_1 v_2 + \beta_2 y_2)(\lambda + a)[\lambda^2 + (u + pz_2)\lambda + pz_2 cv_2](\beta_1 v_2 + \beta_2 y_2) \\ & - (\lambda + r - \frac{2rx_2}{x_M}) a e^{-\lambda \tau_1} [\beta_2 y_2 (\lambda^3 + (u + pz_2)\lambda + pz_2 cv_2) + k \beta_1 y_2 \lambda] = 0. \end{aligned} \quad (3.1)$$

Similarly, we claim that all roots of (3.1) has negative real parts. Otherwise, there exists a root $\lambda_3 = x_3 + iy_3$ with $x_3 \geq 0$. In this case, if $\Re_1 > 1$, it is easy to see that

$$| \lambda_3 + r - \frac{2rx_2}{x_M} + \beta_1 v_2 + \beta_2 y_2 | > | \lambda_3 + r - \frac{2rx_2}{x_M} |.$$

Since

$$\begin{aligned} & [\lambda_3^2 + (u + pz_2)\lambda_3 + pz_2cv_2](\beta_1v_2 + \beta_2y_2) - [\beta_2y_2(\lambda_3^2 + (u + pz_2)\lambda_3 + pz_2cv_2) + k\beta_1y_2\lambda_3] \\ & = \beta_1v_2\lambda_3^2 + \beta_1pcv_2^2z_2. \end{aligned}$$

We obtain that

$$| [\lambda_3^2 + (u + pz_2)\lambda_3 + pz_2cv_2](\beta_1v_2 + \beta_2y_2) | > | \beta_2y_2(\lambda_3^2 + (u + pz_2)\lambda_3 + pz_2cv_2) + k\beta_1y_2\lambda_3 | .$$

It follows that

$$\begin{aligned} & | (\lambda_3 + r - \frac{2rx_2}{x_M} + \beta_1v_2 + \beta_2y_2)(\lambda_3 + a)[\lambda_3^2 + (u + pz_2)\lambda_3 + pz_2cv_2](\beta_1v_2 + \beta_2y_2) | \\ & > | (\lambda_3 + r - \frac{2rx_2}{x_M})ae^{-\lambda_3\tau_1}[\beta_2y_2(\lambda_3^2 + (u + pz_2)\lambda_3 + pz_2cv_2) + k\beta_1y_2\lambda_3] | . \end{aligned}$$

Which contradicts to (3.1). Therefore, all roots of equation (3.1) have negative real parts, and E_2 is locally asymptotically stable. $\square$

Theorem 3.2. *For any $\tau_1, \tau_2 = 0$, the immunity-activated equilibrium E_2 is globally asymptotically stable if $\Re_1 > 1$.*

Proof. Define a Lyapunov functional

$$\begin{aligned} V_3(t) = & x(t) - x_2 - x_2 \ln \frac{x(t)}{x_2} + p_1(y(t) - y_2 - y_2 \ln \frac{y(t)}{y_2}) + p_2(v(t) - v_2 - v_2 \ln \frac{v(t)}{v_2}) \\ & + p_3(z(t) - z_2 - z_2 \ln \frac{z(t)}{z_2}) + \beta_1x_2v_2 \int_{t-\tau_1}^t [\frac{x(s)v(s)}{x_2v_2} - 1 - \ln \frac{x(s)v(s)}{x_2v_2}]ds \\ & + \beta_2x_2y_2 \int_{t-\tau_1}^t [\frac{x(s)y(s)}{x_2y_2} - 1 - \ln \frac{x(s)y(s)}{x_2y_2}]ds, \end{aligned}$$

here $p_1 = \frac{1}{\alpha}$, $p_2 = \frac{\beta_1x_2}{u+pz_2}$, $p_3 = \frac{\beta_1px_2}{cu+cpz_2}$.

Calculating the derivative of $V(t)$ along the solution of (1.2), we obtain that

$$\begin{aligned} \frac{dV_3(t)}{dt} = & -r \frac{(x(t) - x_2)^2}{x_M} - \beta_1x_2v_2 \left(\frac{x_2}{x(t)} - 1 - \ln \frac{x_2}{x(t)} \right) \\ & - \beta_1x_2v_2 \left(\frac{y(t)v_2}{v(t)y_2} - 1 - \ln \frac{y(t)v_2}{v(t)y_2} \right) - \beta_2x_2y_2 \left(\frac{x_2}{x(t)} - 1 - \ln \frac{x_2}{x(t)} \right) \\ & - \beta_1x_2v_2 \left(\frac{x(t-\tau_1)v(t-\tau_1)y_2}{x_2v_2y(t)} - 1 - \ln \frac{x(t-\tau_1)v(t-\tau_1)y_2}{x_2v_2y(t)} \right) \\ & - \beta_2x_2y_2 \left(\frac{x(t-\tau_1)y(t-\tau_1)}{x_2y(t)} - 1 - \ln \frac{x(t-\tau_1)y(t-\tau_1)}{x_2y(t)} \right). \end{aligned} \tag{3.2}$$

Since function $g(x) = x - 1 - \ln x$ is always positive except for $x = 1$ where $g(x) = 0$. It follows from (3.2) that $\frac{dV_3(t)}{dt} \leq 0$ with equality holding if and only if $x = x_2, y = y_2, v = v_2, z = z_2$. It can be certified that $M_2 = \{E_2\} \subset \Omega$ is the largest invariant subset of $\{(x(t), y(t), v(t), z(t)) : \frac{dV_2}{dt} = 0\}$. According to Theorem 3.1, E_1 is locally asymptotically stable. From LaSalle's invariance principle, we obtain that E_2 is globally asymptotically stable. $\square$

In the following, we suppose $\tau_2 > 0$, and devote to investigating the existence of the Hopf bifurcation. The characteristic equation of system (1.2) at the immunity-activated equilibrium E_2 is

$$\lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 + (B_1\lambda^3 + B_2\lambda^2 + B_3\lambda + B_4)e^{-\lambda\tau_2} + (C_1\lambda^3 + C_2\lambda^2 + C_3\lambda + C_4)e^{-\lambda\tau_1} + (D_1\lambda^2 + D_2\lambda + D_3)e^{-\lambda\tau_2 - \lambda\tau_1} = 0 \quad (3.3)$$

where

$$\begin{aligned} A_1 &= -(a_{22} + a_{33} + a_{11}) & A_2 &= a_{22}a_{33} + a_{11}a_{33} + a_{11}a_{22} \\ A_3 &= -a_{11}a_{22}a_{33} & A_4 &= -a_{11} + a_{22}a_{44}c_{22} \\ B_1 &= -b_{22} & B_2 &= a_{33}b_{22} - a_{32}b_{33} + a_{11}b_{22} - b_{21}a_{12} \\ B_3 &= a_{11}a_{33}b_{23} - a_{11}a_{33}b_{22} - a_{32}a_{13}b_{21} & B_4 &= -(a_{11}a_{33}a_{22}c_{44}) \end{aligned}$$

$$\begin{aligned} C_1 &= -a_{34} & C_2 &= a_{33}a_{34} - a_{34}c_{43} + a_{22}a_{34} + a_{11}a_{34} \\ C_3 &= a_{22}a_{34}c_{43} - a_{22}a_{34}a_{33} - a_{11}a_{33}a_{34} + a_{11}a_{34}c_{43} - a_{11}a_{22}a_{34} \\ C_4 &= a_{11}a_{22}a_{34}a_{33} - a_{11}a_{22}a_{34}c_{43} \\ D_1 &= a_{34}b_{22} & D_2 &= a_{34}a_{43}b_{22} + a_{32}a_{34}b_{23} - a_{33}a_{34}b_{22} - a_{11}a_{34}b_{22} \\ D_3 &= a_{11}a_{33}a_{34}b_{22} - a_{11}a_{34}c_{43}b_{22} - a_{11}a_{32}a_{34}b_{23} + a_{12}a_{34}b_{21} - a_{12}a_{33}a_{34}b_{21} \\ &\quad + a_{12}a_{34}b_{21}c_{43} + a_{32}a_{13}a_{34}b_{21}. \end{aligned}$$

and

$$\begin{aligned} a_{11} &= r - \frac{2rx_2}{x_M} - \beta_1v_2 - \beta_2y_2 & a_{12} &= -\beta_2x_2 & a_{13} &= -\beta_1x_2 & a_{22} &= a \\ a_{32} &= k & a_{33} &= -a - pz_2 & a_{34} &= -pv_2 & a_{44} &= -b \\ b_{21} &= \alpha\beta_1v_2 + \alpha\beta_2y_2 & b_{22} &= \alpha\beta_2x_2 & b_{23} &= \alpha\beta_1x_2 & c_{43} &= cz_2 \\ c_{44} &= cv_2 \end{aligned}$$

We consider (3.3) with τ_1 in its stable interval and τ_2 is considered as a parameter. For simplification, we consider (3.3) with $\tau_1 = 0$ and $\tau_2 > 0$. Then equation (3.3) is reduced to

$$\lambda^4 + E_1\lambda^3 + E_2\lambda^2 + E_3\lambda + E_4 + (F_1\lambda^3 + F_2\lambda^2 + F_3\lambda + F_4)e^{-\lambda\tau_2} = 0, \quad (3.4)$$

where

$$\begin{aligned} E_1 &= A_1 + C_1, & E_2 &= A_2 + C_2, & E_3 &= A_3 + C_3, & E_4 &= A_4 + C_4, \\ F_1 &= B_1, & F_2 &= B_2 + D_1, & F_3 &= B_3 + D_2, & F_4 &= B_4 + D_3. \end{aligned}$$

We consider

$$P(\lambda) + Q(\lambda)e^{-\lambda\tau_2} = 0, \quad (3.5)$$

where

$$\begin{aligned} P(\lambda) &= \lambda^4 + E_1\lambda^3 + E_2\lambda^2 + E_3\lambda + E_4; \\ Q(\lambda) &= F_1\lambda^3 + F_2\lambda^2 + F_3\lambda + F_4. \end{aligned} \quad (3.6)$$

In the following, we investigate the existence of purely imaginary roots $\lambda = i\omega$ ($\omega > 0$) to equation (3.5). Beretta and Kuang [2] established a geometrical criterion which gives the existence of purely imaginary root of a characteristic equation with delay dependent coefficients.

In order to apply the criterion due to Beretta and Kuang [2], we need to verify the following properties for all $\tau_2 \in [0, \tau_{2max})$, where τ_{2max} is the maximum value which E_2 exists.

- (a) $P(0) + Q(0) \neq 0$.
- (b) $P(i\omega) + Q(i\omega) \neq 0$.
- (c) $\limsup\{|\frac{Q(\lambda)}{P(\lambda)}| : |\lambda| \rightarrow \infty, \text{Re}\lambda \geq 0\} < 1$.
- (d) $F(\omega) = |P(i\omega)|^2 - |Q(i\omega)|^2$ has a finite number of zeros.
- (e) Each positive root ω of $F(\omega) = 0$ is continuous and differentiable in τ_2 whenever it exists.

Here, $P(\lambda)$ and $Q(\lambda)$ are defined as in (3.6).

Let's $\tau \in [0, \tau_{2max})$. It is easy to see that $P(0) + Q(0) = E_4 + F_4 \neq 0$. This implies that (a) is satisfied. And (b) is obviously true because

$$P(i\omega) + Q(i\omega) = [\omega^4 - (E_2 + F_2)\omega^2 + E_4 + F_4] + i\omega[-(E_1 + F_3)\omega^2 + E_3 - F_3] \neq 0.$$

From (3.6) we know that

$$\begin{aligned} \lim_{|\lambda| \rightarrow \infty} \left| \frac{Q(\lambda)}{P(\lambda)} \right| &= \lim_{|\lambda| \rightarrow \infty} \left| \frac{F_1\lambda^3 + F_2\lambda^2 + F_3\lambda + F_4}{\lambda^4 + E_1\lambda^3 + E_2\lambda^2 + E_3\lambda + E_4} \right| \\ &= \lim_{|\lambda| \rightarrow \infty} \left| \frac{3F_1\lambda^2 + 2F_2\lambda + F_3}{4\lambda^3 + 3E_1\lambda^2 + 2E_2\lambda + E_3} \right| \\ &= \lim_{|\lambda| \rightarrow \infty} \left| \frac{6F_1\lambda + 2F_2}{12\lambda^2 + 6E_1\lambda + 2E_2} \right| = 0. \end{aligned}$$

Therefore (c) follows.

Let G be defined as in (d). From

$$\begin{aligned} |P(i\omega)|^2 &= \omega^8 + (E_1 - 2E_2)\omega^6 + (E_2^2 + 2E_4 - 2E_3E_1)\omega^4 \\ &\quad + (E_3^2 - 2E_4E_2)\omega^2 + E_4^2, \\ |Q(i\omega)|^2 &= F_1^2\omega^6 + (F_2^2 - 2F_3F_1)\omega^4 + (F_3^2 - 2F_4F_2)\omega^2 + F_4^2. \end{aligned}$$

we have

$$F(\omega) = \omega^8 + P_1\omega^6 + P_2\omega^4 + P_3\omega^2 + P_4,$$

$$\begin{aligned} \text{where } P_1 &= E_1 - 2E_2 - F_1^2, & P_2 &= E_2^2 + 2E_4 - 2E_3E_1 - F_2^2 + 2F_3F_1, \\ P_3 &= E_3^2 - 2E_4E_2 - F_3^2 + 2F_4F_2, & P_4 &= E_4^2 - F_4^2. \end{aligned}$$

Let $\omega^2 = h$, then we have

$$G(h) = h^4 + P_1h^3 + P_2h^2 + P_3h + P_4 = 0. \quad (3.7)$$

Theorem 3.3. *Suppose that (3.7) has no positive roots, then when $\Re_1 > 1$, E_2 is locally asymptotically stable for all $\tau_2 \geq 0$.*

Suppose that (3.7) has positive roots, then (d) is satisfied. Let ω_0 be a point of its domain of definition such that $F(\omega_0) = 0$. We know the partial derivatives F_ω and F_{τ_2} exist and are continuous in a certain neighborhood of ω_0 , and $F(\omega_0) \neq 0$. By Implicit Function Theorem, (e) is also satisfied.

Now let $\lambda = i\omega$ ($\omega > 0$) be a root of equation (3.11), and from which we have that

$$\omega^4 - iE_1\omega^3 - E_2\omega^2 + iE_3\omega + E_4 + [-iF_1\omega^3 - F_2\omega^2 + iF_3\omega + F_4]e^{-i\omega\tau_2} = 0.$$

Hence, we have

$$\begin{aligned} F_1\omega^3 - F_3(\omega) \sin \omega\tau_2 + (F_2\omega^2 - F_4) \cos \omega\tau_2 &= \omega^4 - E_2\omega^2 + E_4; \\ F_1\omega^3 - F_3(\omega) \cos \omega\tau_2 - (F_2\omega^2 - F_4) \sin \omega\tau_2 &= -E_1\omega^3 + E_3\omega. \end{aligned} \quad (3.8)$$

From (3.8) it follows that

$$\begin{aligned} \sin \omega\tau_2 &= \frac{(\omega^4 - E_2\omega^2 + E_4)(F_1\omega^3 - F_3) - (-E_1\omega^3 + E_3\omega)(F_2\omega^2 - F_4)}{(F_1\omega^3 - F_3\omega)^2 + (F_2\omega^2 - F_4)^2}, \\ \cos \omega\tau_2 &= \frac{(\omega^4 - E_2\omega^2 + E_4)(F_2\omega^2 - F_4) + (-E_1\omega^3 + E_3\omega)(F_1\omega^3 - F_3\omega)}{(F_1\omega^3 - F_3\omega)^2 + (F_2\omega^2 - F_4)^2}. \end{aligned} \quad (3.9)$$

By the definitions of $P(\lambda)$, $Q(\lambda)$ as in (3.6), and applying the property (a), (3.9) can be written as

$$\sin \omega\tau_2 = \operatorname{Im} \frac{P(i\omega)}{Q(i\omega)}, \quad \cos \omega\tau_2 = -\operatorname{Re} \frac{P(i\omega)}{Q(i\omega)}, \quad (3.10)$$

which yields

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

Assume that $I \in \mathbb{R}_{+0}$ is the set where ω is a positive root of

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

and for $\tau_2 \cap I$, ω is not defined. Then for all τ_2 in I , ω satisfied

$$F(\omega) = 0. \quad (3.11)$$

Assume that equation (3.7) has only one positive real root, we denote by h_+ this positive real root. Thus, equation (3.11) has only one positive real root $\omega = \sqrt{h_+}$. And the critical values of τ_2 and ω are impossible to solve explicitly, so we shall use the procedure described in Beretta and Kuang [2]. According to this procedure, we define such that $\sin$ and $\cos$ are given by (3.10).

And the relation between the argument θ and $\omega\tau_2$ in (3.9) for $\tau_2 > 0$ must be

$$\omega\tau_2 = \theta + 2n\pi, \quad n = 0, 1, 2, \dots \quad (3.12)$$

Hence we can define the maps given by

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

where a positive root $\theta(\tau_2)$ of (3.7) exists in I .

Let us introduce the functions $S_n(\tau_2) : I \rightarrow \mathbb{R}$,

$$S_n(\tau_2) = \tau_2 - \frac{\theta(\tau_2) + 2n\pi}{\omega(\tau_2)}, \quad \tau_n > 0, \quad n = 0, 1, 2, \dots$$

that are continuous and differentiable in τ_2 . Thus, we give the following theorem which is due to Beretta and Kuang [2].

Theorem 3.4. *Assume that $\omega(\tau_2)$ is a positive root of (3.11) defined for $\tau_2^* \in I, I \subseteq \mathbb{R}_{+0}$, and at some $\tau_2^* \in I, S_n(\tau_2^*)$ for some $n \in N_0$. Then a pair of simple conjugate pure imaginary roots $\lambda = i\omega$ exists at $\tau_2 = \tau_2^*$ which crosses the imaginary axis from left to right if $\delta(\tau_0) > 0$ and crosses the imaginary axis from right to left if $\delta(\tau_0) < 0$, where*

$$\delta(\tau_2^*) = \text{sign}\{f'_\omega(\omega\tau_2^*, \tau_2^*)\} \text{sign}\left\{\frac{dS_n(\tau_2)}{d\tau_2}\bigg|_{\tau_2=\tau_2^*}\right\}.$$

Applying Theorems 3.3, Theorems 3.4 and the Hopf bifurcation theorem for functional differential equation [9], we can obtain the existence of a Hopf bifurcation as stated in Theorem 3.5.

Theorem 3.5. *For system (1.2), then there exists τ_2 in I , such that the equilibrium E_2 is asymptotically stable for $0 \leq \tau_2 < \tau_2^*$, and becomes unstable for τ_2 staying in some right neighborhood of τ_2^* , with a Hopf bifurcation occurring when $\tau_2 = \tau_2^*$.*

4. DIRECTION AND STABILITY OF HOPF BIFURCATION

In this section, we discuss that the direction of the Hopf bifurcation and stability of bifurcating periodic solution at the positive equilibrium $E_2 = (x_2, y_2, v_2, z_2)$ for $\tau_2 = \tau_2^*$ by applying the normal form and the center manifold theorem introduced by [9, 10]. We assume that $\tau_1^* \geq 0$.

Let $\tau_2 = \tau_2^* + \mu, t = s\tau_2, u_1 = x - x_2, u_2 = y - y_2, u_3 = v - v_2, u_4 = z - z_2$. Still denoting $s = t$, then system (1.2) can be transformed into the following form

$$\frac{du(t)}{dt} = L_\mu(u_t) + f(\mu, u_t), \quad (4.1)$$

where $u(t) = (u_1, u_2, u_3, u_4)^T \in \mathbb{C} = \mathbb{C}([-1, 0], \mathbb{R}^4)$, and $L_\mu : \mathbb{C} \rightarrow \mathbb{R}^4, f : \mathbb{R} \times \mathbb{C} \rightarrow \mathbb{R}^4$, are given, respectively, by

$$L_\mu(\phi) = (\tau_2^* + \mu)[M_1\phi(0) + M_2\phi(\frac{-\tau_1^*}{\tau_2^*}) + M_3\phi(-1)], \quad (4.2)$$

and

$$f(\mu, \phi) = (\tau_2^* + \mu)(f_1, f_2, f_3, f_4)^T = (\tau_2^* + \mu) \begin{pmatrix} -\frac{r}{x_M}\phi_1^2(0) - \beta_1\phi_1(0)\phi_3(0) - \beta_2\phi_1(0)\phi_2(0) \\ \beta_1\alpha\phi_1(0)\phi_3(0) + \beta_2\alpha\phi_1(0)\phi_3(0) \\ -p\phi_3(0)\phi_4(0) \\ c\phi_3(-1)\phi_4(-1) \end{pmatrix},$$

with

$$M_1 = \begin{pmatrix} r - \frac{2rx_2}{x_M} - \beta_1v_2 - \beta_2y_2 & -\beta_2x_2 & -\beta_1x_2 & 0 \\ 0 & -a & 0 & 0 \\ 0 & k & -u - px_2 & -pv_2 \\ 0 & 0 & 0 & -b \end{pmatrix},$$

$$M_2 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ \beta_1\alpha v_2 + \beta_2\alpha y_2 & \beta_2\alpha x_2 & \beta_1\alpha x_2 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, \quad M_3 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & cz_2 & cv_2 \end{pmatrix}.$$

Therefore, according to the Riesz representation theorem, there exists a 4×4 matrix function $\eta(\theta, \mu) : [-1, 0] \rightarrow \mathbb{R}^4$ whose elements are of bounded variations such that

$$L_\mu(\phi) = \int_{-1}^0 d\eta(\theta, \mu)\phi(\theta), \quad \text{for } \phi \in \mathbb{C}. \quad (4.3)$$

Here, we can choose

$$\eta(\theta, \mu) = \begin{cases} (\tau_2^* + \mu)(M_1 + M_2 + M_3), & \theta = 0, \\ (\tau_2^* + \mu)(M_2 + M_3), & \theta \in [\frac{-\tau_1^*}{\tau_2^*}, 0), \\ (\tau_2^* + \mu)M_3, & \theta \in (-1, \frac{-\tau_1^*}{\tau_2^*}), \\ 0 & \theta = -1. \end{cases} \quad (4.4)$$

For any $\phi \in \mathbb{C}$, we define that

$$(A_\mu\phi)(\theta) = \begin{cases} -\frac{d\phi(\theta)}{d\theta}, & \theta \in [-1, 0), \\ \int_{-1}^0 d\eta(\theta, \mu)\phi(\theta), & \theta = 0. \end{cases}$$

and

$$(R_\mu\phi)(\theta) = \begin{cases} 0, & \theta \in [-1, 0), \\ F(\phi, \theta), & \theta = 0. \end{cases} \quad (4.5)$$

Next, system (4.1) is equivalent to the following operator equation

$$\frac{du_t\theta}{dt} = A_u u_t + R(\mu)u_t,$$

with $u_t(\theta) = u(t + \theta)$, $\theta \in [-1, 0]$. The adjoint operator A^* of $A(0)$ is defined by for $\varphi \in \mathbb{C}([0, 1], (\mathbb{R}^4)^*)$, define

$$(A^*\varphi)(s) = \begin{cases} -\frac{d\varphi(s)}{ds}, & s \in (0, 1], \\ \int_{-1}^0 d\eta^T(s, 0)\varphi(-s), & s = 0, \end{cases}$$

and a bilinear inner product

$$\langle \varphi(s), \phi(\theta) \rangle = \bar{\varphi}(0)\phi(0) - \int_{\theta=-1}^0 \int_{\xi=0}^\theta \bar{\varphi}(\xi - \theta)d\eta(\theta)\phi(\xi)d\xi, \quad (4.6)$$

where $\eta(\theta) = \eta(\theta, 0)$, A_0 and A^* are adjoint operators. We know that $\pm i\omega_0\tau_0$ are the eigenvalue of A_0 . Then are also the eigenvalue of A^* .

Let $q(\theta) = (1, q_2, q_3, q_4)^T e^{i\omega_2^*\tau_2^*\theta}$ be the eigenvector of A_0 corresponding to $i\omega_2^*\tau_2^*$, thus $A_0q(\theta) = i\omega_2^*\tau_2^*q(\theta)$, then on the basis of the definition of A_0 and (4.2)–(4.4), when $\theta = 0$, we have

$$\begin{pmatrix} d_{11} & -\beta_2 x_2 & -\beta_1 x_2 & 0 \\ d_{21} & d_{22} & d_{23} & 0 \\ 0 & k & d_{33} & -pv_2 \\ 0 & 0 & d_{43} & d_{44} \end{pmatrix} \begin{pmatrix} 1 \\ q_2 \\ q_3 \\ q_4 \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \end{pmatrix},$$

where

$$\begin{aligned} d_{11} &= r - \frac{2rx_2}{x_M} - \beta_1 v_2 - \beta_2 y_2 - iw_2^*, & d_{21} &= \alpha e^{-i\omega_2^*} (\beta_1 v_2 + \beta_2 y_2), \\ d_{22} &= \beta_2 \alpha e^{-i\omega_2^*} x_2 - a - iw_2^*, & d_{23} &= \beta_1 \alpha e^{-i\omega_2^*} x_2, \\ d_{33} &= -u - pz_2 - iw_2^*, & d_{43} &= cz_2 e^{-i\omega_2^* \tau_2^*}, \\ d_{44} &= cv_2 e^{-i\omega_2^* \tau_2^*} - b - iw_2^*. \end{aligned}$$

Thus, we can obtain from above

$$q_2 = \frac{d_{11} - \beta_1 x_2 q_3(0)}{\beta_2 x_2}, \quad q_3 = \frac{d_{22} \beta_2 x_2 + d_{21} d_{11}}{d_{21} \beta_1 x_2 - \beta_2 x_2 d_{23}}, \quad q_4 = \frac{d_{43} d_{22} \beta_2 x_2 + d_{43} d_{21} d_{11}}{\beta_2 x_2 d_{23} d_{44} - \beta_1 x_2 d_{22} d_{44}}.$$

Similarly, we suppose that $q^*(s) = D(1, q_2^*, q_3^*, q_4^*)^T e^{i\omega_2^* \tau_2^* s}$ be the eigenvector of A^* corresponding to $-i\omega_2^* \tau_2^*$, and $A^* q^*(s) = -i\omega_2^* \tau_2^* q^*(s)$, we can calculate that

$$q_2^* = \frac{d_{21}}{d_{11}}, \quad q_3^* = \frac{d_{11} \beta_2 x_2 - d_{22} d_{21}}{d_{11} k}, \quad q_4^* = \frac{d_{11} \beta_2 p v_2 x_2 - d_{22} d_{21} p v_2}{d_{44} d_{11} k}.$$

Here $\langle q^*, q \rangle = 1$ and $\langle q^*, \bar{q} \rangle = 0$. From (4.6), we can choose that

$$\bar{D} = \frac{1}{1 + q_2 \bar{q}_2^* + q_3 \bar{q}_3^* + q_4 \bar{q}_4^* + \alpha e^{-i\omega_2^*} \bar{q}_2^* (\beta_1 v_2 + \beta_2 y_2 + \beta_2 x_2 q_2 + \beta_1 x_2 q_3) + e^{-i\omega_2^* \tau_2^*} \bar{q}_4^* (cz_2 q_3 + cv_2 q_4)}.$$

Following the algorithms given in Hassard *et al.* [10] and using similar computation process in [12], we can get the coefficients which can be used to determine the direction of Hopf bifurcation and the stability of bifurcating periodic solutions denoted by

$$\begin{aligned} g_{20} &= 2\tau_2^* \bar{D} [(-\beta_1 q_3 - \beta_2 q_2) + (\beta_1 e^{-m\tau_1^*} q_3 + \beta_2 e^{-m\tau_1^*} q_2) \bar{q}_2^* - p q_3 q_4 \bar{q}_3^* + c q_3 q_4 \bar{q}_4^* e^{-2i\tau_2^* \omega_2^*}], \\ g_{11} &= \tau_2^* \bar{D} [-\beta_1 (q_3 + \bar{q}_3) - \beta_2 (q_2 + \bar{q}_2) + (\beta_1 e^{-m\tau_1^*} (q_3 + \bar{q}_3) + \beta_2 e^{-m\tau_1^*} (q_2 + \bar{q}_2)) \bar{q}_2^* \\ &\quad - p (q_3 \bar{q}_4 + q_4 \bar{q}_3) \bar{q}_3^* + c (q_3 \bar{q}_4 + q_4 \bar{q}_3) \bar{q}_4^*], \\ g_{02} &= 2\tau_2^* \bar{D} [(-\beta_1 \bar{q}_3 - \beta_2 \bar{q}_2) + (\beta_1 e^{-m\tau_1^*} \bar{q}_3 + \beta_2 e^{-m\tau_1^*} \bar{q}_2) \bar{q}_2^* - p \bar{q}_3 \bar{q}_4 \bar{q}_3^* + c \bar{q}_3 \bar{q}_4 \bar{q}_4^* e^{-2i\tau_2^* \omega_2^*}], \\ g_{21} &= 2\tau_2^* \bar{D} \left\{ -\frac{r}{x_M} 2W_{11}^1(0) - \beta_1 W_{11}^3(0) + q_3 W_{11}^1(0) + \frac{1}{2} W_{20}^3(0) + \frac{1}{2} \bar{q}_3 W_{20}^1(0) \right. \\ &\quad - \beta_2 W_{11}^2(0) + q_2 W_{11}^1(0) + \frac{1}{2} W_{20}^2(0) + \frac{1}{2} \bar{q}_2 W_{20}^1(0) \\ &\quad + \bar{q}_2^* [\beta_1 e^{-m\tau_1^*} W_{11}^3(0) + q_3 W_{11}^1(0) + \frac{1}{2} W_{20}^3(0) + \frac{1}{2} \bar{q}_3 W_{20}^1(0) \beta_2 e^{-m\tau_1^*} W_{11}^2(0) \\ &\quad + q_2 W_{11}^1(0) + \frac{1}{2} W_{20}^2(0) + \frac{1}{2} \bar{q}_2 W_{20}^1(0)] \\ &\quad - p \bar{q}_3^* [q_3 W_{11}^4(0) + q_4 W_{11}^3(0) + \frac{1}{2} \bar{q}_3 W_{20}^4(0) + \frac{1}{2} \bar{q}_4 W_{20}^3(0)] \\ &\quad \left. - c \bar{q}_4^* [(q_3 W_{11}^4(-1) + q_4 W_{11}^3(-1)) e^{-i\tau_2^*} + (\bar{q}_3 W_{20}^4(-1) + \bar{q}_4 W_{20}^3(-1)) \frac{e^{-i\tau_2^* \omega_2^*}}{2}] \right\}, \end{aligned}$$

with

$$W_{20}(\theta) = \frac{i g_{20}}{\omega_2^* \tau_2^*} q(0) e^{i\omega_2^* \tau_2^* \theta} + \frac{i \bar{g}_{02}}{3\omega_2^* \tau_2^*} \bar{q}(0) e^{-i\omega_2^* \tau_2^* \theta} + G_1 e^{2i\omega_2^* \tau_2^* \theta},$$

$$W_{11}(\theta) = -\frac{ig_{11}}{\omega_2^* \tau_2^*} q(0) e^{i\omega_2^* \tau_2^* \theta} \frac{i\bar{g}_{11}}{\omega_2^* \tau_2^*} \bar{q}^*(0) e^{-i\omega_2^* \tau_2^* \theta} + G_2,$$

where G_1 and G_2 can be computed by the following equations, respectively

$$\begin{pmatrix} b_{11} + 2i\omega_2^* & \beta_2 x^* & \beta_1 x^* & 0 \\ -a_{21} & b_{22} + 2i\omega_2^* & -a_{23} & 0 \\ 0 & -k & u + pz_2 + 2i\omega_2^* & pv_2 \\ 0 & 0 & -a_{43} & b_{44} + 2i\omega_2^* \end{pmatrix} G_1 = 2 \begin{pmatrix} -\beta_1 q_3 - \beta_2 q_2 \\ \beta_1 e^{-m\tau_1^*} q_3 + \beta_2 e^{-m\tau_1^*} q_2 \\ -pq_3 q_4 \\ cq_3 q_4 e^{-2i\tau_2^* \omega_2^*} \end{pmatrix},$$

and

$$\begin{pmatrix} b_{11} & \beta_2 x^* & \beta_1 x^* & 0 \\ -a_{21} & b_{22} & -a_{23} & 0 \\ 0 & -k & u + pz_2 & pv_2 \\ 0 & 0 & -a_{43} & b_{44} \end{pmatrix} G_2 = 2 \begin{pmatrix} -\beta_1(q_3 + \bar{q}_3) \\ \beta_1 e^{-m\tau_1^*}(q_3 + \bar{q}_3) + \beta_2 e^{-m\tau_1^*}(q_2 + \bar{q}_2) \\ -p(q_3 \bar{q}_4 + q_4 \bar{q}_3) \\ -p(q_3 \bar{q}_4 + q_4 \bar{q}_3) \end{pmatrix},$$

where $b_{11} = d + \beta_1 v_2 + \beta_2 y_2$, $b_{22} = -\beta_2 e^{-\tau_1^*(m+i\omega_2^*)} x_2 + a$, $b_{44} = -cv_2 e^{-i\omega_2^* \tau_2^*} + b$. Then we can compute the following values:

$$\begin{aligned} c_1(0) &= \frac{i}{2\omega_2^* \tau_2^*} (g_{20}g_{11} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}) + \frac{g_{21}}{2}, & \mu_2 &= -\frac{\text{Re}\{c_1(0)\}}{\text{Re}\{\lambda'(\tau_2^*)\}}, \\ \alpha_2 &= 2\text{Re}\{c_1(0)\}, & T_2 &= -\frac{\text{Im}\{c_1(0)\} + \mu_2 \text{Im}\{\lambda'(\tau_2^*)\}}{\omega_2^* \tau_2^*}. \end{aligned} \quad (4.7)$$

Which determine the qualities of bifurcating periodic solutions in the center manifold at the critical value τ_2^* .

Theorem 4.1. *For the delayed model (1.2), when $\tau_2 = \tau_2^*$, the direction and the stability of periodic solution of Hopf bifurcation is determined by (4.7). Then,*

- (i) *the sign of μ_2 determines the directions of the Hopf bifurcation: if $\mu_2 > 0$ ($\mu_2 < 0$), then the Hopf bifurcation is supercritical (subcritical) and the bifurcation periodic solutions exist for $\tau > \tau_2^*$ ($\tau < \tau_2^*$);*
- (ii) *the sign of α_2 determines the stability of the bifurcation periodic solutions: the bifurcation periodic solutions are stable (unstable) if $\alpha_2 < 0$ ($\alpha_2 > 0$);*
- (iii) *the sign of T_2 determines the period of the bifurcation periodic solutions: the period increases (decreases) if $T_2 > 0$ ($T_2 < 0$).*

5. NUMERICAL SIMULATIONS

In this section, we will give some numerical simulations in order to illustrate the theoretical results obtained in this paper.

We chose the parameter values set as $x_M = 100000$; $\beta_1 = 4.8 \times 10^{-7} \text{ ml}^{-1} \text{ day}^{-1}$; $\beta_2 = 4.7 \times 10^{-7} \text{ ml}^{-1} \text{ day}^{-1}$; $\alpha = 0.9 \text{ day}^{-1}$; $a = 0.9 \text{ day}^{-1}$; $p = 0.06 \text{ day}^{-1}$; $b = 1 \text{ day}^{-1}$; $u = 13 \text{ day}^{-1}$; $c = 0.00001 \text{ day}^{-1}$ (See Tab. 1).

- (1) We consider parameter $r = 0.01 \text{ day}^{-1}$; $k = 70 \text{ day}^{-1}$ and the initial value is $(500, 600, 2000, 50)$. By a simple computation, we get $\mathcal{R}_0 = 0.5498 < 1$, $E_0 = (100000, 0, 0, 0)$. We consider delay $\tau_1 = 0 \text{ day}^{-1}$, $\tau_2 = 1 \text{ day}^{-1}$ (see Fig. 1), which shows that E_0 is globally asymptotically stable, and this result supports the result of Theorem 2.2.
- (2) We consider parameter $r = 0.99 \text{ day}^{-1}$; $k = 138.44 \text{ day}^{-1}$, and the initial value is $(500, 600, 2000, 50)$. By a simple computation, we get $\mathcal{R}_0 = 1.0047 > 1 > \mathcal{R}_1 = 0.9537$, $E_1 = (98935, 837.23, 8927.51, 0)$.

TABLE 1. The values and sources of parameters in the model.

Parameters	Values	Source
x_M	1 00 000	[17]
β_1	$4.8 \times 10^{-7} \text{ ml}^{-1} \text{ day}^{-1}$	[17]
β_2	$4.7 \times 10^{-7} \text{ ml}^{-1} \text{ day}^{-1}$	[17]
α	0.9 day^{-1}	Assumed
a	0.9 day^{-1}	Assumed
p	0.06 day^{-1}	[17]
b	1 day^{-1}	[17]
u	13 day^{-1}	[17]
c	0.00001 day^{-1}	[17]
r	0.1	Assumed
k	70	[17]

FIGURE 1. The infection-free equilibrium E_0 is asymptotically stable for $\tau_1 = 0, \tau_2 = 1$.

FIGURE 2. The immunity-inactivated equilibrium E_1 is asymptotically stable for $\tau_1 = 0, \tau_2 = 1$.

We consider delay $\tau_1 = 0 \text{ day}^{-1}$, $\tau_2 = 1 \text{ day}^{-1}$, from Figure 2, we can see that the immunity-inactivated equilibrium E_1 is globally asymptotically stable, which supports the result of Theorem 2.4.

- (3) We consider parameter $r = 60 \text{ day}^{-1}$; $k = 170 \text{ day}^{-1}$, and the initial value is $(500, 600, 2000, 50)$. By a simple computation, we get $\mathfrak{R}_1 = 1.2128 > 1$, $E_2 = (98253, 10623.71, 9852.58, 117.53)$, and $\tau_1 = 4.5 \text{ day}^{-1}$, $\tau_2 = 0 \text{ day}^{-1}$. From Figure 3, we can see that the immunity-activated equilibrium E_2 is globally asymptotically stable, which supports the result of Theorem 3.2.
- (4) We consider parameter $r = 60 \text{ day}^{-1}$; $k = 170 \text{ day}^{-1}$, and the initial value is $(500, 600, 2000, 50)$. By a simple computation, we get $\mathfrak{R}_1 = 1.2128 > 1$, $E_2 = (98253, 10623.71, 9852.58, 117.53)$, and the critical value of delay $\tau_2^* \approx 3.412 \text{ day}^{-1}$. According to Theorem 3.5, system (1.2) undergoes a Hopf bifurcation at the equilibrium E_2 when $\tau_2 = \tau_2^*$. We chose $\tau_1 = 0 \text{ day}^{-1}$, $\tau_2 = 3 < \tau_2^*$, then the immune-activated equilibrium E_2 is asymptotically stable (see Fig. 4), we chose $\tau_1 = 0 \text{ day}^{-1}$, $\tau_2 = 4.5 > \tau_2^* = 3.412 \text{ day}^{-1}$, then the equilibrium E_2 becomes unstable (see Fig. 5). Hence the results obtained in Theorem 3.4 are verified.

FIGURE 3. The immunity-activated equilibrium E_2 is asymptotically stable for $\tau_1 = 4.5, \tau_2 = 0$.

6. CONCLUSIONS

In this paper, we have considered two delay HIV-1 virus system to describe both virus-to-cell and cell-to-cell transmissions. Compared with the model mentioned in [17], our model accounts for not only the intracellular delay but also the time delay due to humoral immunity. At the same time, we have considered a HIV-1 infection model with logistic growth for target cells. By a rigorous mathematical analysis, we found that for any τ_1, τ_2 the local stability of feasible equilibria is established, it is verified that global stability of the infection-free equilibrium E_0 and immunity-inactivated equilibrium E_1 . Notice that when $\tau_2 = 0$, the immunity-activated equilibrium E_2 is global stable which shows that the intracellular delay and logistic growth does not affect the global stability of feasible equilibria. Furthermore, we can see that the humoral immunity delay τ_2 plays an important role in the dynamics of model (1.2). The time delay τ_2 can change the stability of E_2 and lead to the existence of Hopf bifurcations when the time delay τ_2 exceeds the critical value τ_2^* . The direction and stability of bifurcating periodic solutions are deduced in explicit formula by using center manifold and normal form method. Clearly, compares to the earlier studies, our analysis combining many aspects is to the actual conditions. This is valuable in the perspectives of biology. Finally, numerical simulations vividly illustrate our main results of model (1.2). Time delays are not the only factors affecting the spread of infectious diseases.

For example, to optimize the control of diseases by means of vaccine prevention and treatment, and establish models, which will be our future research content.

FIGURE 4. The immune-activated equilibrium E_2 is asymptotically stable when $\tau_1 = 0$, $\tau_2 = 3 < \tau_2^*$.

FIGURE 5. The immune-activated equilibrium E_2 is unstable when $\tau_1 = 0, \tau_2 = 4.5 > \tau_2^*$.

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