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Research article

Viral dynamics of a latent HIV infection model with Beddington-DeAngelis incidence function, B-cell immune response and multiple delays

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Abstract: In this paper, an HIV infection model with latent infection, Beddington-DeAngelis infection function, B-cell immune response and four time delays is formulated. The well-posedness of the model solution is rigorously derived, and the basic reproduction number $\mathcal{R}_0$ and the B-cell immune response reproduction number $\mathcal{R}_1$ are also obtained. By analyzing the modulus of the characteristic equation and constructing suitable Lyapunov functions, we establish the global asymptotic stability of the uninfected and the B-cell-inactivated equilibria for the four time delays, respectively. Hopf bifurcation occurs at the B-cell-activated equilibrium when the model includes the immune delay, and the B-cell-activated equilibrium is globally asymptotically stable if the model does not include it. Numerical simulations indicate that the increase of the latency delay, the cell infection delay and the virus maturation delay can cause the B-cell-activated equilibrium stabilize, while the increase of the immune delay can cause it destabilize.

Keywords: latent infection; B-cell immune response; delay; Beddington-DeAngelis function; stability; Hopf bifurcation

1. Introduction

Human immunodeficiency virus (HIV) mainly infects $CD4^+$ T-cells in human body and destroys the immune system gradually, which leads to the occurrence of various opportunistic infections. HIV can persist in a latent form in resting $CD4^+$ T-cells, and it can give rise to infectious virus upon stimulation *in vitro*, which becomes an obstacle to the eradication of virus [1, 2]. The mathematical model of HIV infection has attracted more and more scholars' attention, and the classical virus dynamics model is

composed of three populations: healthy T-cells, infected T-cells and virus [3, 4]. Recently, the four-dimensional mathematical models incorporating latent infection have been developed to describe the mechanism of the latency [5, 6].

When HIV invades the human body, the human body makes two modes of immune responses: one is the humoral immune response mediated by B-cell, and the other is the cellular immune response mediated by cytotoxic T lymphocyte (CTL). It is not clear which immune response mode is more effective. Previous studies have established that the humoral immune response is more effective than the cellular immune reponse in malaria infection [7]. Therefore, we focus on the humoral immune response mediated by B-cell here.

In the process of virus infection, we are more concerned about the number of new infectious virions in unit time, that is, the incidence rate. The incidence rate function of virus infection model is mostly bilinear βTV, and then gradually develops to saturation function $\frac{\beta TV}{1+aT}$ [8], Holling type II function $\frac{\beta TV}{1+bV}$ [9] and Beddington-DeAngelis function $\frac{\beta TV}{1+aT+bV}$ [10–12] (β is the infection rate, and $a, b \geq 0$ are the inhibition constants). The Beddington-DeAngelis function is firstly proposed by Beddington [14] and DeAngelis et al. [15], and it is a generalized infection function, which includes the cases of bilinear, saturation and Holling type II functions. Hence, we will consider the Beddington-DeAngelis incidence rate.

In the process of HIV infection, it takes time for the virus to infect healthy T-cells and then release infectious virus particles. Herz et al. first introduced an intracellular delay to reflect this time period and showed that the model with time delay could shorten the half-life of free virus [16]. Since then, many researchers have analyzed the effect of intracellular delay on the stability of the equilibrium of the virus infection models. Their results showed that the intracellular delay could prolong the progress of the virus, but did not affect the stability of the equilibrium essentially [9, 11–13, 17–28]. In addition, it also takes time for antigenic stimulation to generate an immune response [29]. It shows that the immune delay makes the positive equilibrium unstable and leads to Hopf bifurcation. So, both the intracellular delay and the immune delay will be included in our model, which can reflect the progress of virus more practically.

Motivated by the works of [17–19], we propose an HIV virus infection model incorporating the latent infection, the Beddington-DeAngelis function infection rate, the humoral immunity and mutiple time delays, which can be described as

$$\begin{aligned}
\dot{T}(t) &= \lambda - d_1 T(t) - \frac{\beta T(t)V(t)}{1 + aT(t) + bV(t)},\\
\dot{L}(t) &= \frac{\eta e^{-m\tau_1}\beta T(t-\tau_1)V(t-\tau_1)}{1 + aT(t-\tau_1) + bV(t-\tau_1)} - \alpha L(t) - d_2 L(t),\\
\dot{I}(t) &= \frac{(1-\eta) e^{-m\tau_2}\beta T(t-\tau_2)V(t-\tau_2)}{1 + aT(t-\tau_2) + bV(t-\tau_2)} + \alpha L(t) - d_3 I(t),\\
\dot{V}(t) &= kI(t-\tau_3) - d_4 V(t) - pV(t)B(t),\\
\dot{B}(t) &= qV(t-\tau_4)B(t-\tau_4) - d_5 B(t).
\end{aligned} \tag{1.1}$$

Here, $T(t)$, $L(t)$, $I(t)$, $V(t)$ and $B(t)$ denote the number of healthy T-cells, latently infected T-cells, actively infected T-cells, virions and B-cells at time t, respectively. The healthy T-cells are assumed to be input with a constant rate λ, and it can be infected by the virus with the Beddington-DeAngelis functional response $\frac{\beta T(t)V(t)}{1+aT(t)+bV(t)}$. The constant η is the fraction of the infected T-cells leading to latency.

Latently infected T-cells can be activated and then becomes the productively infected T-cells with a constant α. Parameter k is the production rate of each infected T-cell, and d_i ($i = 1, 2, 3, 4, 5$) is the death rate of each population. p and q are the B-cell effectiveness and responsiveness, respectively. Here, we consider four time delays: (i) τ_1 represents a time delay between the initial virus entering into the cell and the subsequent viral latency; (ii) τ_2 represents a time delay between the cell infection and the subsequent viral generation; (iii) τ_3 is the time it takes from the newly produced virus to be mature and then infectious; (iv) τ_4 is the time for the B-cell immune system to be activated. Factors $e^{-m\tau_1}$ and $e^{-m\tau_2}$ denote the probability that an infected T-cell survives the interval τ_1 and τ_2, respectively.

The rest of this paper is arranged as follows. In section 2, we analyze the well-posedness of the model solution, and obtain the basic reproduction number, the immune response reproduction number and three equilibria. In section 3, by analyzing the characteristic equation at each equilibrium and employing appropriate Lyapunov functions, the global asymptotic stability of uninfected, B-cell-inactivated and B-cell-activated equilibria is obtained, respectively. Furthermore, Hopf bifurcation occurs at the B-cell-activated equilibrium if the system including the immune response delay. In section 4, numerical simulations are given to further investigate the delays and their effects on the stability of the B-cell-activated equilibrium. Finally, we conclude our work in section 5.

2. Preliminary results

2.1. Well-posedness

Assuming that system (1.1) satisfies the following initial value:

$$T(\theta) = \psi_1(\theta),\ L(0) = \psi_2,\ I(\theta) = \psi_3(\theta),\ V(\theta) = \psi_4(\theta),\ B(\theta) = \psi_5(\theta) \quad \text{for } \theta \in [-\tau, 0], \tag{2.1}$$

$\tau = \max\{\tau_1, \tau_2, \tau_3, \tau_4\}$. Here, ψ_2 is a given non-negative constant, $\psi_1(\theta), \psi_3(\theta), \psi_4(\theta), \psi_5(\theta) \in C([-\tau, 0], \mathbb{R}_+)$ with $\mathbb{R}_+ = [0, +\infty)$, and $\psi = (\psi_1, \psi_2, \psi_3, \psi_4, \psi_5) \in C \times \mathbb{R}_+ \times C \times C \times C$.

Theorem 2.1. *For system (1.1), there exists a unique non-negative solution with initial value (2.1), and the solution is ultimately bounded for all $t \geq 0$.*

Proof. By the basic theory of the functional differential equations [30], there exists a unique solution satisfying the initial condition (2.1). According to the proof process in Theorem 3.1 of reference [20], we can obtain the nonnegativity of the solution and we omit the proof process here. In the following, we prove the boundedness of the solution.

By the first equation of system (1.1), we calculate that $\lim\limits_{t\to+\infty} \sup\ T(t) \leq T_0$, and see Eq (2.2) for the expression of T_0.

Define

$$P(t) = \eta e^{-m\tau_1} T(t-\tau_1) + (1-\eta) e^{-m\tau_2} T(t-\tau_2) + L(t) + I(t) + \frac{d_3}{2k} V(t+\tau_3) + \frac{pd_3}{2kq} B(t+\tau_3+\tau_4).$$

Calculating the derivative of $P(t)$ along the solution of system (1.1), we obtain

$$\begin{aligned}
\dot{P} &= \left[\eta e^{-m\tau_1} + (1-\eta) e^{-m\tau_2}\right] \lambda - d_1 \eta e^{-m\tau_1} T(t-\tau_1) - d_1 (1-\eta) e^{-m\tau_2} T(t-\tau_2) - d_2 L(t) \\
&\quad - \frac{d_3}{2} I(t) - \frac{d_3 d_4}{2k} V(t+\tau_3) - \frac{p d_3 d_5}{2kq} B(t+\tau_3+\tau_4) \\
&\leq \left[\eta e^{-m\tau_1} + (1-\eta) e^{-m\tau_2}\right] \lambda - dP(t),
\end{aligned}$$

where $d = \min\{d_1, d_2, \frac{d_3}{2}, d_4, d_5\}$. Therefore,

$$\limsup_{t\to+\infty} P(t) \le \frac{\lambda}{d}\left[\eta e^{-m\tau_1} + (1-\eta)e^{-m\tau_2}\right],$$

which indicates that $T(t)$, $L(t)$, $I(t)$, $V(t)$ and $B(t)$ are all ultimately bounded. This completes the proof. □

Suppose that there exists a positive constant $M > 0$ such that $T \le T_0$, L, I, V, $B \le M$ for large t. We will analyze the dynamics of system (1.1) in the following bounded feasible region

$$\Gamma = \{X = (T, L, I, V, B) \in C \times \mathbb{R}_+ \times C \times C \times C : T \le T_0, L, I, V, B \le M\}.$$

2.2. Reproduction numbers and equilibria

System (1.1) always has one uninfected equilibrium E_0 $(T_0, 0, 0, 0, 0)$, where

$$T_0 = \frac{\lambda}{d_1}. \tag{2.2}$$

For convenience, we define

$$\rho(\tau_1, \tau_2) = \frac{\alpha\eta e^{-m\tau_1}}{\alpha + d_2} + (1-\eta)e^{-m\tau_2}, \quad F(T, V) = \frac{\beta TV}{1 + aT + bV}.$$

Following the derivation method [31,32], we obtain the basic reproduction number of model (1.1),

$$\mathcal{R}_0 = \frac{k\beta T_0}{d_3 d_4(1 + aT_0)}\left[\frac{\alpha\eta e^{-m\tau_1}}{\alpha + d_2} + (1-\eta)e^{-m\tau_2}\right] = \frac{k\beta T_0\rho(\tau_1, \tau_2)}{d_3 d_4(1 + aT_0)}. \tag{2.3}$$

We also define the B-cell immune response reproduction number,

$$\mathcal{R}_1 = \frac{k\beta T_2\rho(\tau_1, \tau_2)}{d_3 d_4(1 + aT_2 + bV_2)},$$

and see Eq (2.6) for the expressions of T_2 and V_2.

System (1.1) has a B-cell-inactivated equilibrium E_1 $(T_1, L_1, I_1, V_1, 0)$ if $\mathcal{R}_0 > 1$, where,

$$\begin{aligned}
T_1 &= \frac{kb\rho(\tau_1, \tau_2)\lambda + d_3 d_4}{kbd_1\rho(\tau_1, \tau_2) + k\beta\rho(\tau_1, \tau_2) - ad_3 d_4} \\
&= \frac{[kb\rho(\tau_1, \tau_2)\lambda + d_3 d_4]\lambda}{kbd_1\rho(\tau_1, \tau_2)\lambda + d_1 d_3 d_4\mathcal{R}_0 + ad_3 d_4\lambda(\mathcal{R}_0 - 1)}, \\
L_1 &= \frac{\eta e^{-m\tau_1}}{\alpha + d_2}F(T_1, V_1), \quad I_1 = \frac{d_4 V_1}{k}, \\
V_1 &= \frac{1}{b}\left[\frac{k\beta T_1\rho(\tau_1, \tau_2)}{d_3 d_4} - (1 + aT_1)\right] \\
&= \frac{k\lambda\rho(\tau_1, \tau_2)d_3 d_4(\mathcal{R}_0 - 1)(d_1 + a\lambda)}{bkd_1\lambda\rho(\tau_1, \tau_2) + \mathcal{R}_0 d_1 d_3 d_4 + ad_3 d_4\lambda(\mathcal{R}_0 - 1)},
\end{aligned}$$

and

$$F(T_1, V_1) = \frac{\beta T_1 V_1}{1 + aT_1 + bV_1}. \tag{2.4}$$

Let

$$\mathcal{R}^* = \frac{k\beta T_1 \rho(\tau_1, \tau_2)}{d_3 d_4 (1 + aT_1)}.$$

Since $T \leq T_0$ in the bounded region Γ, from the expressions of $\mathcal{R}_0$ and $\mathcal{R}^*$, we can derive that

$$\mathcal{R}_0 > 1 \Longleftrightarrow \mathcal{R}^* > 1. \tag{2.5}$$

System (1.1) also has a B-cell-activated equilibrium E_2 (T_2, L_2, I_2, V_2, B_2) if $\mathcal{R}_1 > 1$, where,

$$\begin{aligned}
&T_2 = \frac{a\lambda - \beta V_2 - d_1(1 + bV_2) + \sqrt{\Delta}}{2ad_1}, \quad L_2 = \frac{\eta e^{-m\tau_1}}{\alpha + d_2} F(T_2, V_2),\\
&I_2 = \frac{\rho(\tau_1, \tau_2)}{d_3} F(T_2, V_2), \quad V_2 = \frac{d_5}{q}, \quad B_2 = \frac{1}{p}\left[\frac{k\beta T_2 \rho(\tau_1, \tau_2)}{(1 + aT_2 + bV_2)d_3} - d_4\right],\\
&\Delta = \left[a\lambda - \beta V_2 - d_1(1 + bV_2)\right]^2 + 4ad_1\lambda(1 + bV_2),
\end{aligned} \tag{2.6}$$

and

$$F(T_2, V_2) = \frac{\beta T_2 V_2}{1 + aT_2 + bV_2}.$$

3. Stability analysis

To study the stability at equilibrium $\bar{E}$ ($\bar{T}$, $\bar{L}$, $\bar{I}$, $\bar{V}$, $\bar{B}$), we let $Y_1(t) = T(t) - \bar{T}$, $Y_2(t) = L(t) - \bar{L}$, $Y_3(t) = I(t) - \bar{I}$, $Y_4(t) = V(t) - \bar{V}$, $Y_5(t) = B(t) - \bar{B}$, and $Y(t) = (Y_1(t), Y_2(t), Y_3(t), Y_4(t), Y_5(t))$. The linearization of system (1.1) at $\bar{E}$ ($\bar{T}$, $\bar{L}$, $\bar{I}$, $\bar{V}$, $\bar{B}$) becomes

$$\begin{aligned}
\dot{Y}_1(t) &= -(d_1 + A)Y_1(t) - NY_4(t),\\
\dot{Y}_2(t) &= \eta e^{-m\tau_1} AY_1(t - \tau_1) - (\alpha + d_2)Y_2(t) + \eta e^{-m\tau_1} NY_4(t - \tau_1),\\
\dot{Y}_3(t) &= (1 - \eta)e^{-m\tau_2} AY_1(t - \tau_2) + \alpha Y_2(t) - d_3 Y_3(t) + (1 - \eta)e^{-m\tau_2} NY_4(t - \tau_2),\\
\dot{Y}_4(t) &= kY_3(t - \tau_3) - (d_4 + p\bar{B})Y_4(t) - p\bar{V}Y_5(t),\\
\dot{Y}_5(t) &= q\bar{B}Y_4(t - \tau_4) - q\bar{V}Y_5(t - \tau_4) - d_5 Y_5(t),
\end{aligned} \tag{3.1}$$

where,

$$A = \frac{\beta\bar{V}(1 + b\bar{V})}{(1 + a\bar{T} + b\bar{V})^2}, \quad N = \frac{\beta\bar{T}(1 + a\bar{T})}{(1 + a\bar{T} + b\bar{V})^2}.$$

The characteristic equation of linearized system (3.1) at the equilibrium $\bar{E}$ can be written as

$$\begin{vmatrix}
-(d_1 + A + \xi) & 0 & 0 & -N & 0\\
\eta e^{-m\tau_1} A e^{-\xi\tau_1} & -(\alpha + d_2 + \xi) & 0 & \eta e^{-m\tau_1} N e^{-\xi\tau_1} & 0\\
(1 - \eta)e^{-m\tau_2} A e^{-\xi\tau_2} & \alpha & -(d_3 + \xi) & (1 - \eta)e^{-m\tau_2} N e^{-\xi\tau_2} & 0\\
0 & 0 & ke^{-\xi\tau_3} & -(d_4 + p\bar{B} + \xi) & -p\bar{V}\\
0 & 0 & 0 & q\bar{B}e^{-\xi\tau_4} & q\bar{V}e^{-\xi\tau_4} - d_5 - \xi
\end{vmatrix} = 0.$$

3.1. Global asymptotic stability of the uninfected equilibrium E_0

Theorem 3.1. *If $\mathcal{R}_0 < 1$, the uninfected equilibrium E_0 is locally asymptotically stable for $\tau_i \geq 0$, $i = 1, 2, 3, 4$, and it is unstable if $\mathcal{R}_0 > 1$.*

Proof. The characteristic equation of the linearized system (3.1) at the uninfected equilibrium E_0 is

$$(\xi + d_1)(\xi + d_5)g_1(\xi) = 0, \tag{3.2}$$

where,

$$g_1(\xi) = (\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4) - k\alpha\eta N_0 e^{-(m+\xi)\tau_1 - \xi\tau_3} - (\xi + \alpha + d_2)k(1-\eta)N_0 e^{-(m+\xi)\tau_2 - \xi\tau_3},$$
$$N_0 = \frac{\beta T_0}{1 + aT_0}.$$

It is clear that $\xi = -d_1 < 0$ and $\xi = -d_5 < 0$. The remaining roots of Eq (3.2) can be determined by the following equation

$$g_1(\xi) = 0. \tag{3.3}$$

It is equivalent to the following equation

$$1 = \frac{k\alpha\eta N_0 e^{-(m+\xi)\tau_1 - \xi\tau_3}}{(\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4)} + \frac{k(1-\eta)N_0 e^{-(m+\xi)\tau_2 - \xi\tau_3}}{(\xi + d_3)(\xi + d_4)}. \tag{3.4}$$

It is assumed that $\xi = x + iy$ $(x \geq 0)$ is a solution of Eq (3.4), and we take the modulus on both sides,

$$\begin{aligned} 1 &= \left| \frac{k\alpha\eta N_0 e^{-(m+\xi)\tau_1 - \xi\tau_3}}{(\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4)} + \frac{k(1-\eta)N_0 e^{-(m+\xi)\tau_2 - \xi\tau_3}}{(\xi + d_3)(\xi + d_4)} \right| \\ &\leq k\alpha\eta N_0 e^{-m\tau_1} \left| \frac{e^{-\xi(\tau_1+\tau_3)}}{(\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4)} \right| + k(1-\eta)N_0 e^{-m\tau_2} \left| \frac{e^{-\xi(\tau_2+\tau_3)}}{(\xi + d_3)(\xi + d_4)} \right| \\ &\leq \frac{k\alpha\eta N_0 e^{-m\tau_1}}{(\alpha + d_2)d_3 d_4} + \frac{k(1-\eta)N_0 e^{-m\tau_2}}{d_3 d_4} = \mathcal{R}_0. \end{aligned}$$

If $\mathcal{R}_0 < 1$, the above inequality does not hold. Therefore, Eq (3.3) has only negative real part roots. Hence, E_0 is locally asymptotically stable if $\mathcal{R}_0 < 1$ for all $\tau_i \geq 0$, $i = 1, 2, 3, 4$.

If $\mathcal{R}_0 > 1$, $g_1(0) = d_3 d_4(\alpha + d_2) - kN_0\rho(\tau_1, \tau_2)(\alpha + d_2) = d_3 d_4(\alpha + d_2)(1 - \mathcal{R}_0) < 0$, and $\lim_{\xi \to +\infty} g_1(\xi) = +\infty$. So, Eq (3.3) has at least one positive real root. Therefore, the uninfected equilibrium E_0 is unstable for all time delays. □

Theorem 3.2. *If $\mathcal{R}_0 < 1$, the uninfected equilibrium E_0 is globally asymptotically stable for $\tau_i \geq 0$, $i = 1, 2, 3, 4$.*

Proof. We employ a particular function

$$G(x) = x - 1 - \ln x,$$

and it was first proposed in literature [33]. The function $G(x) > 0$ for $x > 0$, and $G(x) = 0$ when and only when $x = 1$. We define a Lyapunov function W: $C \times \mathbb{R}_+ \times C \times C \times C \to \mathbb{R}$

$$
\begin{aligned}
W &= W_1 + W_2,\\
W_1 &= \frac{T_0\rho(\tau_1,\tau_2)}{1+aT_0}G\left(\frac{T(t)}{T_0}\right) + \frac{\alpha}{\alpha+d_2}L(t) + I(t) + \frac{d_3}{k}V(t) + \frac{d_3p}{kq}B(t),\\
W_2 &= \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}\int_{-\tau_1}^{0} F(\psi_1(t+s),\psi_4(t+s))ds + (1-\eta)e^{-m\tau_2}\int_{-\tau_2}^{0} F(\psi_1(t+s),\psi_4(t+s))ds\\
&\quad + d_3\int_{-\tau_3}^{0}\psi_3(t+s)ds + \frac{d_3p}{k}\int_{-\tau_4}^{0}\psi_4(t+s)\psi_5(t+s)ds.
\end{aligned}
$$

The derivative of W_1 and W_2 along the solution of system (1.1) is

$$
\begin{aligned}
\dot{W}_1 =& \frac{\rho(\tau_1,\tau_2)}{1+aT_0}\left(1-\frac{T_0}{T}\right)[\lambda - d_1T(t) - F(T(t),V(t))] + \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T(t-\tau_1),V(t-\tau_1))\\
&+ (1-\eta)e^{-m\tau_2}F(T(t-\tau_2),V(t-\tau_2)) - d_3I(t) + \frac{d_3}{k}\left[kI(t-\tau_3) - d_4V(t) - pV(t)B(t)\right]\\
&+ \frac{d_3p}{kq}[qV(t-\tau_4)B(t-\tau_4) - d_5B(t)],\\
\dot{W}_2 =& \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}\left[F(T(t),V(t)) - F(T(t-\tau_1),V(t-\tau_1))\right] + d_3\left[I(t) - I(t-\tau_3)\right]\\
&+ (1-\eta)e^{-m\tau_2}\left[F(T(t),V(t)) - F(T(t-\tau_2),V(t-\tau_2))\right]\\
&+ \frac{d_3p}{k}[V(t)B(t) - V(t-\tau_4)B(t-\tau_4)].
\end{aligned}
$$

Using the equality $\lambda = d_1T_0$ at the uninfected equilibrium and Eq (2.3), we calculate that

$$
\begin{aligned}
\dot{W} =& \dot{W}_1 + \dot{W}_2\\
=& -\frac{\rho(\tau_1,\tau_2)}{(1+aT_0)T(t)}\left(1-\frac{T_0}{T(t)}\right)(d_1T_0 - d_1T(t)) - \frac{\rho(\tau_1,\tau_2)}{1+aT_0}\left(1-\frac{T_0}{T(t)}\right)F(T(t),V(t))\\
&+ \rho(\tau_1,\tau_2)F(T(t),V(t)) - \frac{d_3d_4}{k}V(t) - \frac{pd_3d_5B(t)}{kq}\\
\le& -\frac{\rho(\tau_1,\tau_2)d_1(T(t)-T_0)^2}{(1+aT_0)T(t)} + \frac{\rho(\tau_1,\tau_2)\beta T_0V(t)(1+aT(t))}{(1+aT_0)(1+aT(t)+bV(t))} - \frac{d_3d_4}{k}V(t) - \frac{pd_3d_5}{kq}B(t)\\
=& -\frac{\rho(\tau_1,\tau_2)d_1(T(t)-T_0)^2}{(1+aT_0)T(t)} - \frac{d_3d_4V(t)}{k}\left[1 - \frac{\mathcal{R}_0(1+aT(t))}{1+aT(t)+bV(t)}\right] - \frac{pd_3d_5}{kq}B(t)\\
=& -\frac{\rho(\tau_1,\tau_2)d_1(T(t)-T_0)^2}{(1+aT_0)T(t)} - \frac{d_3d_4(1-\mathcal{R}_0)(1+aT(t))}{k\,(1+aT(t)+bV(t))}V(t)\\
&- \frac{bd_3d_4}{k(1+aT(t)+bV(t))}V^2(t) - \frac{pd_3d_5}{kq}B(t).
\end{aligned}
$$

If $\mathcal{R}_0 < 1$, then $\dot{W} \le 0$. Clearly, the singleton E_0 is the largest invariant set in $\{X \in \Gamma | \dot{W} = 0\}$. By the LaSalle's invariance principle [34], we obtain the global attractivity of E_0. Combining with Theorem 3.1, we derive the global asymptotic stability of E_0. □

3.2. Global asymptotic stability of B-cell-inactivated equilibrium E_1

Define a critical condition

$$\mathcal{R}_2 = \frac{qV_1}{d_5}.$$

Theorem 3.3. *If $\mathcal{R}_2 < 1 < \mathcal{R}_0$, then the B-cell-inactivated equilibrium E_1 is locally asymptotically stable for $\tau_i \geq 0$, $i = 1, 2, 3, 4$, and it is unstable if $\mathcal{R}_2 > 1$.*

Proof. The characteristic equation of the linearized system (3.1) at the B-cell-inactivated equilibrium E_1 is

$$(\xi + d_5 - qV_1 e^{-\xi\tau_4}) g_2(\xi) = 0,$$

where,

$$\begin{aligned} g_2(\xi) &= (\xi + d_1 + A_1)(\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4) \\ &\quad -(\xi + d_1)\left[k\alpha\eta N_1 e^{-(\xi+m)\tau_1 - \xi\tau_3} + (\xi + \alpha + d_2)k(1-\eta)N_1 e^{-(\xi+m)\tau_2 - \xi\tau_3}\right] \\ A_1 &= \frac{\beta V_1(1 + bV_1)}{(1 + aT_1 + bV_1)^2} \quad N_1 = \frac{\beta T_1(1 + aT_1)}{(1 + aT_1 + bV_1)^2}. \end{aligned} \tag{3.5}$$

(I) Transcendental equation

$$\xi + d_5 - qV_1 e^{-\xi\tau_4} = 0. \tag{3.6}$$

If $\tau_4 = 0$, then $\xi = qV_1 - d_5$. Under the condition $\mathcal{R}_2 < 1$, that is $qV_1 - d_5 < 0$. If $\tau_4 > 0$, suppose $\xi = i\omega$ ($\omega > 0$), then Eq (3.6) can be written as

$$\begin{cases} d_5 = qV_1 \cos\xi\omega, \\ \omega = -qV_1 \sin\xi\omega. \end{cases}$$

That is to say,

$$\omega^2 = (qV_1)^2 - d_5^2 = (qV_1 + d_5)(qV_1 - d_5).$$

Under the condition $\mathcal{R}_2 < 1$, there is no positive ω such that the above equation holds. Therefore, Eq (3.6) only has negative real roots. If $\mathcal{R}_2 > 1$, then Eq (3.6) has positive real roots.

(II) Equation

$$g_2(\xi) = 0, \tag{3.7}$$

and it is equivalent to the following equation

$$\frac{\xi + d_1 + A_1}{\xi + d_1} = \frac{k\alpha\eta N_1 e^{-(\xi+m)\tau_1 - \xi\tau_3}}{(\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4)} + \frac{k(1-\eta)N_1 e^{-(\xi+m)\tau_2 - \xi\tau_3}}{(\xi + d_3)(\xi + d_4)}. \tag{3.8}$$

Assume $\xi = x + iy$ ($x \geq 0$) is a solution of Eq (3.8), and we take the modulus on both sides. Clearly, the modulus of the left hand side of Eq (3.8) is greater than one. Suppose that the modulus of the right hand side of Eq (3.8) is Λ_1, use Eq (3.5) and equation

$$1 + aT_1 + bV_1 = \frac{k\beta T_1 \rho(\tau_1, \tau_2)}{d_3 d_4}$$

at the B-cell-inactivated equilibrium E_1, we have

$$\begin{aligned}\Lambda_1 &\leq \frac{k\alpha\eta N_1 e^{-m\tau_1}}{(\alpha+d_2)d_3d_4} + \frac{k(1-\eta)N_1e^{-m\tau_2}}{d_3d_4} = \frac{kN_1}{d_3d_4}\left[\frac{\alpha\eta}{\alpha+d_2}e^{-m\tau_1} + (1-\eta)e^{-m\tau_2}\right] \\ &= \frac{k\beta T_1\rho(\tau_1,\tau_2)(1+aT_1)}{d_3d_4(1+aT_1+bV_1)^2} = \frac{d_3d_4(1+aT_1)}{k\beta_1T_1\rho(\tau_1,\tau_2)} = \frac{1}{\mathcal{R}^*}.\end{aligned}$$

If $\mathcal{R}^* > 1$, that is $\mathcal{R}_0 > 1$ (see Eq (2.5)), then $\Lambda_1 < 1$, which leads to a contradiction. Therefore, Eq (3.7) has only negative real part roots.

Combined with the above two steps, we conclude that, under the condition $\mathcal{R}_2 < 1 < \mathcal{R}_0$, E_1 is locally asymptotically stable for all time delays, and it is unstable if $\mathcal{R}_2 > 1$. □

Theorem 3.4. *If $\mathcal{R}_2 < 1 < \mathcal{R}_0$, then the B-cell-inactivated equilibrium E_1 is globally asymptotically stable for $\tau_i \geq 0$, $i = 1, 2, 3, 4$.*

Proof. Define a Lyapunov function $U : C \times \mathbb{R}_+ \times C \times C \times C \to \mathbb{R}$

$$\begin{aligned}U &= U_1 + U_2, \\ U_1 &= \rho(\tau_1,\tau_2)\left(T(t) - T_1 - \int_{T_1}^{T(t)} \frac{(1+as+bV_1)T_1}{(1+aT_1+bV_1)s}ds\right) + \frac{\alpha L_1}{\alpha+d_2}G\left(\frac{L(t)}{L_1}\right) \\ &\quad + I_1G\left(\frac{I(t)}{I_1}\right) + \frac{d_3V_1}{k}G\left(\frac{V(t)}{V_1}\right) + \frac{d_3p}{kq}B(t) \\ U_2 &= \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_1,V_1)\int_{-\tau_1}^{0} G\left(\frac{F(\psi_1(t+s),\psi_4(t+s))}{F(T_1,V_1)}\right)ds \\ &\quad + (1-\eta)e^{-m\tau_2}F(T_1,V_1)\int_{-\tau_2}^{0} G\left(\frac{F(\psi_1(t+s),\psi_4(t+s))}{F(T_1,V_1)}\right)ds \\ &\quad + d_3I_1\int_{-\tau_3}^{0} G\left(\frac{\psi_3(t+s)}{I_1}\right)ds + \frac{d_3p}{k}\int_{-\tau_4}^{0}\psi_4(t+s)\psi_5(t+s)ds\end{aligned}$$

where, the expression of $F(T_1, V_1)$ can be found in Eq (2.4). Computing the derivative of U_1 and U_2 along the solution of system (1.1), we obtain

$$\begin{aligned}\dot{U}_1 &= \rho(\tau_1,\tau_2)D_1D_2 + \frac{\alpha}{\alpha+d_2}\left(1-\frac{L_1}{L(t)}\right)\left[\eta e^{-m\tau_1}F(T(t-\tau_1),V(t-\tau_1)) - \alpha L(t) - d_2L(t)\right] \\ &\quad + \left(1-\frac{I_1}{I(t)}\right)\left[(1-\eta)e^{-m\tau_2}F(T(t-\tau_2),V(t-\tau_2)) + \alpha L(t) - d_3I(t)\right] \\ &\quad + \frac{d_3}{k}\left(1-\frac{V_1}{V(t)}\right)\left[kI(t-\tau_3) - d_4V(t)\right] + \frac{d_3p}{kq}\left[qV(t-\tau_4)B(t-\tau_4) - d_5B(t)\right],\end{aligned}$$

where,

$$\begin{aligned}D_1 &= 1 - \frac{(1+aT(t)+bV_1)T_1}{(1+aT_1+bV_1)T(t)} = \frac{(1+bV_1)(T(t)-T_1)}{(1+aT_1+bV_1)T(t)}, \\ D_2 &= \lambda - d_1T(t) - F(T(t),V(t)) \\ &= d_1T_1 + F(T_1,V_1) - d_1T(t) - F(T(t),V(t)) \\ &= d_1(T_1 - T(t)) + F(T_1,V_1) - F(T(t),V(t)).\end{aligned}$$

Thus,

$$D_1D_2 = -d_1\frac{(1+bV_1)(T(t)-T_1)^2}{(1+aT_1+bV_1)T(t)} + \left[1-\frac{(1+aT(t)+bV_1)T_1}{(1+aT_1+bV_1)T(t)}\right][F(T_1,V_1)-F(T(t),V(t))]$$
$$= -D_3 + \left[1-\frac{(1+aT(t)+bV_1)T_1}{(1+aT_1+bV_1)T(t)}\right][F(T_1,V_1)-F(T(t),V(t))],$$

where,

$$D_3 = d_1\frac{(1+bV_1)(T(t)-T_1)^2}{(1+aT_1+bV_1)T(t)}.$$

It follows that,

$$\begin{aligned}\dot{U}_1 =& -\rho(\tau_1,\tau_2)D_3 + \rho(\tau_1,\tau_2)\left[1-\frac{(1+aT(t)+bV_1)T_1}{(1+aT_1+bV_1)T(t)}\right][F(T_1,V_1)-F(T(t),V(t))]\\ &+\frac{\alpha}{\alpha+d_2}\left(1-\frac{L_1}{L(t)}\right)[\eta e^{-m\tau_1}F(T(t-\tau_1),V(t-\tau_1))-(\alpha+d_2)L(t)]\\ &+\left(1-\frac{I_1}{I(t)}\right)[(1-\eta)e^{-m\tau_2}F(T(t-\tau_2),V(t-\tau_2))+\alpha L(t)-d_3I(t)]\\ &+\frac{d_3}{k}\left(1-\frac{V_1(t)}{V(t)}\right)[kI(t-\tau_3)-d_4V(t)-pV(t)B(t)]\\ &+\frac{d_3p}{kq}[qV(t-\tau_4)B(t-\tau_4)-d_5B(t)].\end{aligned}$$

Thereafter,

$$\begin{aligned}\dot{U} =& \dot{U}_1+\dot{U}_2\\ \le& -\rho(\tau_1,\tau_2)D_3+\rho(\tau_1,\tau_2)F(T_1,V_1)-F(T(t-\tau_1),V(t-\tau_1))\frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}\frac{L_1}{L(t)}\\ &-\rho(\tau_1,\tau_2)F(T_1,V_1)\left[\frac{(1+aT(t)+bV_1)T_1}{(1+aT_1+bV_1)T(t)}-\frac{(1+aT(t)+bV_1)V(t)}{(1+aT(t)+bV(t))V_1}\right]+\alpha L_1\\ &+d_3I_1+\frac{d_3d_4V_1}{k}-(1-\eta)e^{-m\tau_2}F(T(t-\tau_2),V(t-\tau_2))\frac{I_1}{I(t)}-\alpha I_1\frac{L(t)}{I(t)}\\ &-\frac{d_3d_4}{k}V(t)-d_3V_1\frac{I(t-\tau_3)}{V(t)}+\frac{d_3p}{k}B(t)\left(V_1-\frac{d_5}{q}\right)+E_1+E_2+E_3,\end{aligned}$$

where,

$$\begin{aligned}E_1 &= \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_1,V_1)\ln\frac{F(T(t-\tau_1),V(t-\tau_1))}{F(T(t),V(t))},\\ E_2 &= (1-\eta)e^{-m\tau_2}F(T_1,V_1)\ln\frac{F(T(t-\tau_2),V(t-\tau_2))}{F(T(t),V(t))},\\ E_3 &= d_3I_1\ln\frac{I(t-\tau_3)}{I(t)}.\end{aligned}$$

Note that

$$d_3I_1 = \rho(\tau_1,\tau_2)F(T_1,V_1) = \frac{d_3d_4}{k}V_1, \quad \alpha L_1 = \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_1,V_1).$$

Then, we have

$$\begin{aligned}\dot{U} \leq & -\rho(\tau_1,\tau_2)D_3 - \rho(\tau_1,\tau_2)F(T_1,V_1)\left[G\left(\frac{(1+aT(t)+bV_1)T_1}{(1+aT_1+bV_1)T(t)}\right)+G\left(\frac{I(t-\tau_3)V_1}{I_1V(t)}\right)\right]\\ & -\frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_1,V_1)\left[G\left(\frac{F(T(t-\tau_1),V(t-\tau_1))L_1}{F(T_1,V_1)L(t)}\right)+G\left(\frac{I_1L(t)}{I(t)L_1}\right)\right]\\ & -(1-\eta)e^{-m\tau_2}F(T_1,V_1)G\left(\frac{F(T(t-\tau_2),V(t-\tau_2))I_1}{F(T_1,V_1)I(t)}\right)\\ & -\frac{d_3d_5p}{kq}(1-\mathcal{R}_2)B(t)+\rho(\tau_1,\tau_2)F(T_1,V_1)E_4,\end{aligned}$$

where

$$\begin{aligned}E_4 =& \frac{(1+aT(t)+bV_1)V(t)}{(1+aT(t)+bV(t))V_1}-\frac{V(t)}{V_1}+\ln\left(\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_1}\right)\\ =& -G\left(\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_1}\right)+\frac{(1+aT(t)+bV_1)V(t)}{(1+aT(t)+bV(t))V_1}-\frac{V(t)}{V_1}+\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_1}-1\\ =& -G\left(\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_1}\right)-\frac{b(1+aT(t))(V(t)-V_1)^2}{(1+aT(t)+bV_1)(1+aT(t)+bV(t))V_1}.\end{aligned}$$

Therefore,

$$\begin{aligned}\dot{U} \leq & -\rho(\tau_1,\tau_2)D_3-\frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_1,V_1)\left[G\left(\frac{F(T(t-\tau_1),V(t-\tau_1))L_1}{F(T_1,V_1)L(t)}\right)+G\left(\frac{I_1L(t)}{I(t)L_1}\right)\right]\\ & -\rho(\tau_1,\tau_2)F(T_1,V_1)\left[G\left(\frac{(1+aT(t)+bV_1)T_1}{(1+aT_1+bV_1)T(t)}\right)+G\left(\frac{I(t-\tau_3)V_1}{I_1V(t)}\right)+G\left(\frac{(1+aT(t)+bV_1)V(t)}{(1+aT(t)+bV(t))V_1}\right)\right]\\ & -(1-\eta)e^{-m\tau_2}F(T_1,V_1)G\left(\frac{F(T(t-\tau_2),V(t-\tau_2))I_1}{F(T_1,V_1)I(t)}\right)\\ & -\frac{b\rho(\tau_1,\tau_2)F(T_1,V_1)(1+aT(t))(V(t)-V_1)^2}{(1+aT(t)+bV_1)(1+aT(t)+bV(t))V_1}-\frac{d_3d_5p}{kq}(1-\mathcal{R}_2)B(t).\end{aligned}$$

If $\mathcal{R}_2 < 1$, we obtain $\dot{U} \leq 0$. When $\dot{U} = 0$ if and only if

$$\begin{aligned}&T(t)=T_1,\quad V(t)=V_1,\quad B(t)=0,\\ &\frac{F(T(t-\tau_1),V(t-\tau_1))L_1}{F(T_1,V_1)L(t)}=\frac{I_1L(t)}{I(t)L_1}=\frac{F(T(t-\tau_2),V(t-\tau_2))I_1}{F(T_1,V_1)I(t)}=1,\\ &\frac{(1+aT(t)+bV_1)T_1}{(1+aT_1+bV_1)T(t)}=\frac{I(t-\tau_3)V_1}{I_1V(t)}=\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_1}=1.\end{aligned}$$

That is, $T(t) = T_1$, $L(t) = L_1$, $I(t) = I_1$, $V(t) = V_1$ and $B(t) = 0$. It is obvious that the singleton E_1 is the largest invariant set in $\{X \in \Gamma | \dot{U} = 0\}$. By the LaSalle's invariance principle [34], we obtain the global attractivity of E_1. Combining with Theorem 3.3, if $\mathcal{R}_2 < 1 < \mathcal{R}_0$, we conclude the global asymptotic stability of E_1 for $\tau_i \geq 0$, $i = 1, 2, 3, 4$. □

3.3. Global asymptotic stability of the B-cell-activated equilibrium E_2 if $\tau_4 = 0$

Theorem 3.5. *If $\mathcal{R}_1 > 1$, the B-cell-activated equilibrium E_2 is locally asymptotically stable for $\tau_i \geq 0$, $i = 1, 2, 3$ and $\tau_4 = 0$.*

Proof. The characteristic equation of the linearized system (3.1) at the infected state E_2 is

$$\begin{aligned}&(\xi + d_5 - d_5 e^{-\xi\tau_4})(\xi + d_1 + A_2)(\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4 + pB_2)\\ &+ d_5 pB_2 e^{-\xi\tau_4}(\xi + d_1 + A_2)(\xi + \alpha + d_2)(\xi + d_3) - (\xi + d_5 - d_5 e^{-\xi\tau_4})(\xi + d_1)\\ &\times \left[k\alpha\eta N_2 e^{-\xi\tau_3} e^{-(m+\xi)\tau_1} + (\xi + \alpha + d_2)kN_2(1-\eta)e^{-\xi\tau_3} e^{-(m+\xi)\tau_2}\right] = 0,\end{aligned} \tag{3.9}$$

where,

$$A_2 = \frac{\beta V_2(1 + bV_2)}{(1 + aT_2 + bV_2)^2}, \quad N_2 = \frac{\beta T_2(1 + aT_2)}{(1 + aT_2 + bV_2)^2}.$$

If $\tau_4 = 0$, then

$$\begin{aligned}&(\xi + d_1 + A_2)(\xi + \alpha + d_2)(\xi + d_3)\left[\xi(\xi + d_4 + pB_2) + d_5 pB_2\right]\\ =&\xi(\xi + d_1)\left[k\alpha\eta N_2 e^{-\xi\tau_3} e^{-(m+\xi)\tau_1} + (\xi + \alpha + d_2)kN_2(1-\eta)e^{-\xi\tau_3} e^{-(m+\xi)\tau_2}\right].\end{aligned}$$

Divide both sides by $\xi + \alpha + d_2$, and the equation simplifies to

$$\begin{aligned}&(\xi + d_1 + A_2)(\xi + d_3)\left[\xi(\xi + d_4 + pB_2) + d_5 pB_2\right]\\ =&\xi(\xi + d_1)\left[\frac{k\alpha\eta N_2 e^{-\xi\tau_3} e^{-(m+\xi)\tau_1}}{\xi + \alpha + d_2} + kN_2(1-\eta)e^{-\xi\tau_3} e^{-(m+\xi)\tau_2}\right].\end{aligned} \tag{3.10}$$

Let $\xi = x + iy$ $(x \geq 0)$ is a solution of Eq (3.10), then

$$\begin{aligned}&(x + iy + d_1 + A_2)(x + iy + d_3)\left[(x + iy)(x + iy + d_4 + pB_2) + d_5 pB_2\right]\\ =&(x + iy)(x + iy + d_1)kN_2\left[\frac{\alpha\eta e^{-m\tau_1} e^{-(x+iy)(\tau_1+\tau_3)}}{x + iy + \alpha + d_2} + (1-\eta)e^{-m\tau_2} e^{-(x+iy)(\tau_2+\tau_3)}\right].\end{aligned}$$

Take the modulus on both sides, and it is easy to see that

$$\begin{aligned}&|x + iy + d_1 + A_2| > |x + iy + d_1|, \quad |x + iy + d_3| > d_3,\\ &|(x + iy)(x + iy + d_4 + pB_2) + d_5 pB_2|\\ =&\left|(x + iy)^2 + (x + iy)(d_4 + pB_2) + d_5 pB_2\right| > |(x + iy)(d_4 + pB_2)|.\end{aligned}$$

Assume that Λ_2 and Λ_3 are the modulus of the left-hand side and the right-hand side for above equation, respectively. Then,

$$\begin{aligned}&\Lambda_2 > |x + iy + d_1| \cdot |(x + iy)| \cdot d_3(d_4 + pB_2),\\ &\Lambda_3 \leq |x + iy| \cdot |x + iy + d_1| \cdot \frac{k\beta T_2(1 + aT_2)}{(1 + aT_2 + bV_2)^2}\left[\frac{\alpha\eta e^{-m\tau_1}}{\alpha + d_2} + (1-\eta)e^{-m\tau_2}\right].\end{aligned}$$

At the B-cell-activated equilibrium E_2, we have

$$\frac{\beta T_2 V_2}{1 + aT_2 + bV_2}\left[\frac{\alpha\eta e^{-m\tau_1}}{\alpha + d_2} + (1-\eta)e^{-m\tau_2}\right] = d_3 I_2 = \frac{d_3(d_4 + pB_2)}{k}V_2.$$

So,

$$\Lambda_3 \leq |x+iy| \cdot |x+iy+d_1| \cdot d_3(d_4+pB_2).$$

Obviously, this leads to a contradiction. Therefore, under the condition $\mathcal{R}_1 > 1$, E_2 is locally asymptotically stable for $\tau_i \geq 0$, $i = 1, 2, 3$ and $\tau_4 = 0$. □

Theorem 3.6. *If $\mathcal{R}_1 > 1$, the B-cell-activated equilibrium E_2 is globally asymptotically stable for $\tau_i \geq 0$, $i = 1, 2, 3$ and $\tau_4 = 0$.*

Proof. Define a Lyapunov function $Q : C \times \mathbb{R}_+ \times C \times C \times C \to \mathbb{R}$

$$\begin{aligned}
Q &= Q_1 + Q_2,\\
Q_1 &= \rho(\tau_1,\tau_2)\left(T(t) - T_2 - \int_{T_2}^{T(t)} \frac{(1+as+bV_2)T_2}{(1+aT_2+bV_2)s}ds\right) + \frac{\alpha L_2}{\alpha+d_2}G\left(\frac{L(t)}{L_2}\right) + I_2 G\left(\frac{I(t)}{I_2}\right)\\
&\quad + \frac{\rho(\tau_1,\tau_2)F(T_2,V_2)V_2}{kI_2}G\left(\frac{V(t)}{V_2}\right) + \frac{p\rho(\tau_1,\tau_2)F(T_2,V_2)B_2}{kqI_2}G\left(\frac{B(t)}{B_2}\right)\\
Q_2 &= \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_2,V_2)\int_{-\tau_1}^{0} G\left(\frac{F(\psi_1(t+s),\psi_4(t+s))}{F(T_2,V_2)}\right)ds\\
&\quad + (1-\eta)e^{-m\tau_2}F(T_2,V_2)\int_{-\tau_2}^{0} G\left(\frac{F(\psi_1(t+s),\psi_4(t+s))}{F(T_2,V_2)}\right)ds\\
&\quad + \frac{\rho(\tau_1,\tau_2)F(T_2,V_2)}{I_2}\int_{-\tau_3}^{0} G\left(\frac{\psi_3(t+s)}{I_2}\right)ds
\end{aligned}$$

Take the derivative of Q_1 along the solution of system (1.1), and we obtain

$$\begin{aligned}
\dot{Q}_1 =& \rho(\tau_1,\tau_2)\left[1 - \frac{(1+aT(t)+bV_2)T_2}{(1+aT_2+bV_2)T(t)}\right][\lambda - d_1T(t) - F(T(t),V(t))]\\
&+ \frac{\alpha}{\alpha+d_2}\left(1-\frac{L_2}{L(t)}\right)[\eta e^{-m\tau_1}F(T(t-\tau_1),V(t-\tau_1)) - \alpha L(t) - d_2L(t)]\\
&+ \left(1-\frac{I_2}{I(t)}\right)[(1-\eta)e^{-m\tau_2}F(T(t-\tau_2),V(t-\tau_2)) + \alpha L(t) - d_3I(t)]\\
&+ \frac{\rho(\tau_1,\tau_2)F(T_2,V_2)}{kI_2}\left(1-\frac{V_2}{V(t)}\right)[kI(t-\tau_3) - d_4V(t) - pV(t)B(t)]\\
&+ \frac{p\rho(\tau_1,\tau_2)F(T_2,V_2)}{kqI_2}\left(1-\frac{B_2}{B(t)}\right)[qV(t)B(t) - d_5B(t)].
\end{aligned}$$

Use the equalities at the B-cell-activated equilibrium E_2,

$$\begin{aligned}
&\lambda = d_1T_2 + F(T_2,V_2),\\
&\eta e^{-m\tau_1}F(T_2,V_2) = (\alpha+d_2)L_2,\\
&(1-\eta)e^{-m\tau_2}F(T_2,V_2) + \alpha L_2 = d_3I_2,\\
&kI_2 = (d_4+pB_2)V_2, \quad qV_2 = d_5,
\end{aligned}$$

and we have

$$\begin{aligned}\dot{Q}_1 =&\rho(\tau_1,\tau_2)D_4D_5+\frac{\alpha}{\alpha+d_2}\left(1-\frac{L_2}{L(t)}\right)\left[\eta e^{-m\tau_1}F(T(t-\tau_1),V(t-\tau_1))-\frac{\eta e^{-m\tau_1}F(T_2,V_2)}{L_2}L(t)\right]\\&+\left(1-\frac{I_2}{I(t)}\right)\left[(1-\eta)e^{-m\tau_2}F(T(t-\tau_2),V(t-\tau_2))+\alpha L-\frac{(1-\eta)e^{-m\tau_2}F(T_2,V_2)}{I_2}I(t)-\frac{\alpha L_2}{I_2}I(t)\right]\\&+\frac{\rho(\tau_1,\tau_2)F(T_2,V_2)}{kI_2}\left(1-\frac{V_2}{V(t)}\right)[kI(t-\tau_3)-d_4V(t)-pV(t)B(t)]\\&+\frac{p\rho(\tau_1,\tau_2)F(T_2,V_2)}{kqI_2}\left(1-\frac{B_2}{B(t)}\right)[qV(t)B(t)-qV_2B(t)],\end{aligned}$$

where,

$$\begin{aligned}D_4 &= 1-\frac{(1+aT(t)+bV_2)T_2}{(1+aT_2+bV_2)T(t)}=\frac{(1+bV_2)(T(t)-T_2)}{(1+aT_2+bV_2)T(t)},\\D_5 &= \lambda-d_1T(t)-F(T(t),V(t))\\&= d_1T_2+F(T_2,V_2)-d_1T(t)-F(T(t),V(t))\\&= d_1(T_2-T(t))+F(T_2,V_2)-F(T(t),V(t)).\end{aligned}$$

Thus,

$$\begin{aligned}D_4D_5 =&-d_1\frac{(1+bV_2)(T(t)-T_2)^2}{(1+aT_2+bV_2)T(t)}+\left[1-\frac{(1+aT(t)+bV_2)T_2}{(1+aT_2+bV_2)T(t)}\right]\\&\times[F(T_2,V_2)-F(T(t),V(t))]\\=&-D_6+F(T_2,V_2)\left(1-\frac{(1+aT(t)+bV_2)T_2}{(1+aT_2+bV_2)T(t)}\right)-F(T(t),V(t)\\&+F(T_2,V_2)\frac{(1+aT(t)+bV_2)V(t)}{(1+aT_2+bV_2)V_2},\end{aligned}$$

where,

$$D_6=d_1\frac{(1+bV_2)(T(t)-T_2)^2}{(1+aT_2+bV_2)T(t)}.$$

Take the derivative of Q_2 along the solution of system (1.1), and we obtain

$$\begin{aligned}\dot{Q}_2 =&\frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}[F(T(t),V(t))-F(T(t-\tau_1),V(t-\tau_1))]\\&+(1-\eta)e^{-m\tau_2}[F(T(t),V(t))-F(T(t-\tau_2),V(t-\tau_2))]\\&+\frac{\rho(\tau_1,\tau_2)F(T_2,V_2)}{I_2}[I(t)-I(t-\tau_3)]+F_1+F_2+F_3,\end{aligned}$$

where,

$$\begin{aligned}F_1 &= \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_2,V_2)\ln\frac{F(T(t-\tau_1),V(t-\tau_1))}{F(T(t),V(t))},\\F_2 &= (1-\eta)e^{-m\tau_2}F(T_2,V_2)\ln\frac{F(T(t-\tau_2),V(t-\tau_2))}{F(T(t),V(t))},\\F_3 &= \frac{\rho(\tau_1,\tau_2)F(T_2,V_2)}{I_2}\ln\frac{I(t-\tau_3)}{I(t)}.\end{aligned}$$

Then, we have

$$\begin{aligned}
\dot{Q} =&\dot{Q}_1 + \dot{Q}_2\\
=& -\rho(\tau_1,\tau_2)D_6 - \rho(\tau_1,\tau_2)F(T_2,V_2)\left[\frac{(1+aT(t)+bV_2)T_2}{(1+aT_2+bV_2)T(t)} - \frac{(1+aT(t)+bV_2)V(t)}{(1+aT(t)+bV(t))V_2}\right]\\
&-\rho(\tau_1,\tau_2)F(T_2,V_2)\frac{V(t)}{V_2} - \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}\left[\frac{L_2}{L(t)}F(T(t-\tau_1),V(t-\tau_1)) + \frac{I_2L(t)}{I(t)L_2}F(T_2,V_2)\right]\\
&-(1-\eta)e^{-m\tau_2}\frac{I_2}{I(t)}F(T(t-\tau_2),V(t-\tau_2)) - \rho(\tau_1,\tau_2)F(T_2,V_2)\frac{V_2I(t-\tau_3)}{V(t)I_2}\\
&+3\rho(\tau_1,\tau_2)F(T_2,V_2) + \frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_2,V_2) + F_1 + F_2 + F_3\\
=& -\rho(\tau_1,\tau_2)D_6 - \rho(\tau_1,\tau_2)F(T_2,V_2)\left[G\left(\frac{(1+aT(t)+bV_2)T_2}{(1+aT_2+bV_2)T(t)}\right) + G\left(\frac{V_2I(t-\tau_3)}{V(t)I_2}\right)\right]\\
&-\frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_2,V_2)\left[G\left(\frac{F(T(t-\tau_1),V(t-\tau_1))L_2}{F(T_2,V_2)L(t)}\right) + G\left(\frac{I_2L(t)}{I(t)L_2}\right)\right]\\
&-(1-\eta)e^{-m\tau_2}F(T_2,V_2)G\left(\frac{F(T(t-\tau_2),V(t-\tau_2))I_2}{F(T_2,V_2)I(t)}\right) + \rho(\tau_1,\tau_2)F(T_2,V_2)F_4,
\end{aligned}$$

where,

$$\begin{aligned}
F_4 =&\frac{(1+aT(t)+bV_2)V(t)}{(1+aT(t)+bV(t))V_2} - \frac{V(t)}{V_2} + \ln\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_2}\\
=& -G\left(\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_2}\right) + \frac{(1+aT(t)+bV_2)V(t)}{(1+aT(t)+bV(t))V_2} - \frac{V(t)}{V_2} + \frac{1+aT(t)+bV(t)}{1+aT(t)+bV_2} - 1\\
=& -G\left(\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_2}\right) - \frac{b(1+aT(t))(V(t)-V_2)^2}{(1+aT(t)+bV(t))(1+aT(t)+bV_2)V_2}.
\end{aligned}$$

Then,

$$\begin{aligned}
\dot{Q} =& -\rho(\tau_1,\tau_2)F(T_2,V_2)\left[G\left(\frac{(1+aT(t)+bV_2)T_2}{(1+aT_2+bV_2)T(t)}\right) + G\left(\frac{V_2I(t-\tau_3)}{V(t)I_2}\right) + G\left(\frac{1+aT(t)+bV(t)}{1+aT(t)+bV_2}\right)\right]\\
&-\frac{\alpha\eta e^{-m\tau_1}}{\alpha+d_2}F(T_2,V_2)\left[G\left(\frac{F(T(t-\tau_1),V(t-\tau_1))L_2}{F(T_2,V_2)L(t)}\right) + G\left(\frac{I_2L(t)}{I(t)L_2}\right)\right]\\
&-(1-\eta)e^{-m\tau_2}F(T_2,V_2)G\left(\frac{F(T(t-\tau_2),V(t-\tau_2))I_2}{F(T_2,V_2)I(t)}\right) - \rho(\tau_1,\tau_2)D_6\\
&-\frac{b(1+aT(t))(V(t)-V_2)^2}{(1+aT(t)+bV(t))(1+aT(t)+bV_2)V_2}.
\end{aligned}$$

If $\mathcal{R}_1 > 1$, we obtain $\dot{Q} \le 0$. When $\dot{Q} = 0$ if and only if

$$\begin{aligned}
&T(t) = T_2, \quad V(t) = V_2,\\
&\frac{(1+aT(t)+bV_2)T_2}{(1+aT_2+bV_2)T(t)} = \frac{I(t-\tau_3)V_2}{I_2V(t)} = \frac{1+aT(t)+bV(t)}{1+aT(t)+bV_2} = 1,\\
&\frac{F(T(t-\tau_1),V(t-\tau_1))L_2}{F(T_2,V_2)L(t)} = \frac{I_2L(t)}{I(t)L_2} = \frac{F(T(t-\tau_2),V(t-\tau_2))I_2}{F(T_2,V_2)I(t)} = 1,
\end{aligned}$$

That is, $T(t) = T_2$, $L(t) = L_2$, $I(t) = I_2$, $V(t) = V_2$ and $B(t) = B_2$. Clearly, the singleton E_2 is the largest invariant set in $\{X \in \Gamma | \dot{Q} = 0\}$. By the LaSalle's invariance principle [34], we obtain the global attractivity of E_2. Combining with Theorem 3.5, under the condition $\mathcal{R}_1 > 1$, we derive the global asymptotic stability of E_2 for $\tau_i \geq 0$, $i = 1, 2, 3$ and $\tau_4 = 0$. □

3.4. Stability of the B-cell-activated equilibrium E_2 if $\tau_4 > 0$

For the characteristic Eq (3.9) at the B-cell-activated equilibrium E_2, let $\tau_1 = \tau_2 = \tau_3 = 0$, then it yields

$$\begin{aligned}
&(\xi + d_5)(\xi + d_1 + A_2)(\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4 + pB_2)\\
&- (\xi + d_5)(\xi + d_1)kN_2\left[\alpha\eta + (\xi + \alpha + d_2)(1 - \eta)\right]\\
&- d_5e^{-\xi\tau_4}(\xi + d_1 + A_2)(\xi + \alpha + d_2)(\xi + d_3)(\xi + d_4)\\
&+ d_5e^{-\xi\tau_4}(\xi + d_1)kN_2[\alpha\eta + (\xi + \alpha + d_2)(1 - \eta)] = 0.
\end{aligned}$$

For convenience, let $h_1 = d_1 + A_2$, $h_2 = \alpha + d_2$, $h_3 = d_3$, $h_4 = d_4 + pB_2$ and $h_5 = d_5$, the above equation can be rewritten as the following,

$$\xi^5 + p_4\xi^4 + p_3\xi^3 + p_2\xi^2 + p_1\xi + p_0 + e^{-\xi\tau_4}(q_4\xi^4 + q_3\xi^3 + q_2\xi^2 + q_1\xi + q_0) = 0, \tag{3.11}$$

where,

$$\begin{aligned}
p_4 =& h_1 + h_2 + h_3 + h_4 + h_5,\\
p_3 =& h_5(h_1 + h_2 + h_3 + h_4) + h_1h_2 + h_3h_4 + (h_1 + h_2)(h_3 + h_4) - kN_2(1 - \eta),\\
p_2 =& h_5[h_1h_2 + h_3h_4 + (h_1 + h_2)(h_3 + h_4)] + h_3h_4(h_1 + h_2) + h_1h_2(h_3 + h_4)\\
&- kN_2\alpha\eta - kN_2(1 - \eta)(d_1 + h_2 + h_5),\\
p_1 =& h_5[h_1h_2(h_3 + h_4) + h_3h_4(h_1 + h_2)] + h_1h_2h_3h_4 - kN_2\alpha\eta(d_1 + h_5)\\
&- kN_2(1 - \eta)(d_1h_2 + h_2h_5 + d_1h_5),\\
p_0 =& h_1h_2h_3h_4h_5 - kN_2\alpha\eta d_1h_5 - kN_2(1 - \eta)d_1h_2h_5,\\
q_4 =& - h_5,\\
q_3 =& - h_5(h_1 + h_2 + h_3 + d_4),\\
q_2 =& h_5[kN_2(1 - \eta) - h_1h_2 - h_3d_4 - (h_1 + h_2)(h_3 + d_4)],\\
q_1 =& h_5[kN_2\alpha\eta + kN_2(1 - \eta)(d_1 + h_2) - h_3d_4(h_1 + h_2) - h_1h_2(h_3 + d_4)],\\
q_0 =& h_5[d_1kN_2\alpha\eta + kN_2(1 - \eta)d_1h_2 - h_1h_2h_3d_4].
\end{aligned}$$

From Theorem 3.5, we know that the B-cell-activated equilibrium E_2 is locally asymptotically stable when $\tau_i = 0$, $i = 1, 2, 3, 4$.

Now, assume that $\tau_4 > 0$ and let $\xi = i\omega$, $\omega > 0$ of Eq (3.11). Separating real and imaginary parts yields

$$\begin{cases}
p_4\omega^4 - p_2\omega^2 + p_0 = \sin\omega\tau_4(q_3\omega^2 - q_1)\omega - \cos\omega\tau_4(q_4\omega^4 - q_2\omega^2 + q_0),\\
(\omega^4 - p_3\omega^2 + p_1)\omega = \sin\omega\tau_4(q_4\omega^4 - q_2\omega^2 + q_0) + \cos\omega\tau_4(q_3\omega^2 - q_1)\omega.
\end{cases} \tag{3.12}$$

Squaring and adding these equation, we obtain

$$\omega^{10} + m_4\omega^8 + m_3\omega^6 + m_2\omega^4 + m_1\omega^2 + m_0 = 0, \tag{3.13}$$

where,

$$\begin{aligned}
m_4 =&p_4^2 - q_4^2 - 2p_3\\
=&(h_1+h_2+h_3+h_4)(h_1+h_2+h_3+h_4+2h_5) - 2h_5(h_1+h_2+h_3+h_4)\\
&- 2h_1h_2 - 2h_3h_4 - 2(h_1+h_2)(h_3+h_4) + 2kN_2(1-\eta) > 0,\\
m_3 =&p_3^2 + 2p_1 + 2q_2q_4 - 2p_2p_4 - q_3^2,\\
m_2 =&p_2^2 + 2p_0p_4 + 2q_1q_3 - 2p_1p_3 - q_2^2 - 2q_0q_4,\\
m_1 =&p_1^2 + 2q_0q_2 - 2p_0p_2 - q_1^2,\\
m_0 =&p_0^2 - q_0^2 = (p_0+q_0)(p_0-q_0)\\
=&h_1h_2h_3h_5^2pB_2[h_1h_2h_3(2d_4+pB_2) - 2kN_2\alpha\eta d_1 - 2kN_2(1-\eta)d_1h_2]\\
=&h_1h_2h_3h_5^2pB_2J_1,
\end{aligned} \tag{3.14}$$

and

$$\begin{aligned}
J_1 =&(d_1+A_2)(\alpha+d_2)d_3(2d_4+pB_2) - 2kN_2d_1[\alpha+(1-\eta)d_2]\\
=&(d_1+A_2)(\alpha+d_2)d_3(2d_4+pB_2) - 2d_1\mathcal{R}_1d_3d_4(\alpha+d_2)\frac{1+aT_2}{1+aT_2+bV_2}\\
=&A_2(\alpha+d_2)d_3(2d_4+pB_2) + d_1(\alpha+d_2)d_3pB_2 + 2d_1d_3d_4(\alpha+d_2)\frac{(1+aT_2)(1-\mathcal{R}_1)+bV_2}{1+aT_2+bV_2}.
\end{aligned}$$

Let $z = \omega^2 > 0$, then Eq (3.13) becomes

$$H(z) := z^5 + m_4z^4 + m_3z^3 + m_2z^2 + m_1z + m_0 = 0. \tag{3.15}$$

and the derivative of $H(z)$ with respect to z is

$$H'(z) = 5z^4 + 4m_4z^3 + 3m_3z^2 + 2m_2z + m_1.$$

From the expressions of m_0 in Eq (3.14), we know that we could not determine the sign of m_0, and it depends on the size of $\mathcal{R}_1$. According to the relationship between root and coefficient, from the expressions of m_4 in Eq (3.14), we derive that Eq (3.15) has at most four positive real roots.

Theorem 3.7. *Assume $\mathcal{R}_1 > 1$ and $\tau_1 = \tau_2 = \tau_3 = 0$, then the B-cell-activated equilibrium E_2 is locally asymptotically stable when $\tau_4 \in [0, \tau_{40})$ and unstable when $\tau_4 > \tau_{40}$. Furthermore, if $H'(\omega_0^2) \neq 0$, system (1.1) undergoes a Hopf bifurcation to periodic solutions at E_2 when $\tau_4 = \tau_{40}$.*

Proof. Without loss of generality, suppose that Eq (3.15) has four positive real roots z_1, z_2, z_3 and z_4. Then Eq (3.13) has positive roots $\omega_i = \sqrt{z_i}$ $(i = 1, 2, 3, 4)$, and thus $\pm i\omega_i$ is a pair of purely imaginary roots of Eq (3.11). From Eq (3.12), the corresponding τ_{4i} are

$$\begin{aligned}
\tau_{4i}^{(n)} =&\frac{1}{\omega_i}\arccos\left\{\frac{\omega^2(\omega^4 - p_3\omega^2 + p_1)(q_3\omega^2 - q_1) - (q_4\omega^4 - q_2\omega^2 + q_0)(p_4\omega^4 - p_2\omega^2 + p_0)}{(q_4\omega^4 - q_2\omega^2 + q_0)^2 + \omega^2(q_3\omega^2 - q_1)^2}\right\}\\
&+ \frac{2n\pi}{\omega_i}, \quad i = 1, 2, 3, 4;\ n = 0, 1, 2, \ldots.
\end{aligned}$$

It is clear to see that

$$\lim_{n\to+\infty}\tau_{4i}^{(n)} = +\infty,\ i = 1, 2, 3, 4.$$

Define

$$\tau_{40} = \min\{\tau_{4i}^{(n)}; i = 1, 2, 3, 4, n = 0, 1, 2, \ldots.\}, \ \omega_0 = \omega(\tau_{40}). \tag{3.16}$$

Now, differentiating Eq (3.11) with respect to τ_4, we obtain

$$\begin{aligned}
&\Big[5\xi^4 + 4p_4\xi^3 + 3p_3\xi^2 + 2p_2\xi + p_1 + e^{-\xi\tau_4}(4q_4\xi^3 + 3q_3\xi^2 + 2q_2\xi + q_1)\\
&- \tau_4 e^{-\xi\tau_4}(q_4\xi^4 + q_3\xi^3 + q_2\xi^2 + q_1\xi + q_0)\Big]\frac{\mathrm{d}\xi}{\mathrm{d}\tau_4}\\
&= \xi e^{-\xi\tau_4}(q_4\xi^4 + q_3\xi^3 + q_2\xi^2 + q_1\xi + q_0).
\end{aligned}$$

Then,

$$\begin{aligned}
\left(\frac{\mathrm{d}\xi}{\mathrm{d}\tau_4}\right)^{-1} =& \frac{(5\xi^4 + 4p_4\xi^3 + 3p_3\xi^2 + 2p_2\xi + p_1)e^{\xi\tau_4}}{\xi(q_4\xi^4 + q_3\xi^3 + q_2\xi^2 + q_1\xi + q_0)}\\
&+ \frac{4q_4\xi^3 + 3q_3\xi^2 + 2q_2\xi + q_1}{\xi(q_4\xi^4 + q_3\xi^3 + q_2\xi^2 + q_1\xi + q_0)} - \frac{\tau_4}{\xi}.
\end{aligned}$$

Using Eqs (3.12) and (3.16), we get

$$\begin{aligned}
\left[\frac{\mathrm{d}(\mathrm{Re}\xi)}{\mathrm{d}\tau_4}\right]^{-1}_{\tau_4=\tau_{40}} =& \mathrm{Re}\left[\frac{(5\xi^4 + 4p_4\xi^3 + 3p_3\xi^2 + 2p_2\xi + p_1)e^{\xi\tau_4}}{\xi(q_4\xi^4 + q_3\xi^3 + q_2\xi^2 + q_1\xi + q_0)}\right]_{\tau_4=\tau_{40}}\\
&+ \mathrm{Re}\left[\frac{4q_4\xi^3 + 3q_3\xi^2 + 2q_2\xi + q_1}{\xi(q_4\xi^4 + q_3\xi^3 + q_2\xi^2 + q_1\xi + q_0)}\right]_{\tau_4=\tau_{40}}\\
=& \frac{J_2 + J_3}{\omega_0^2\left[(q_3\omega_0^2 - q_1)^2\omega_0^2 + (q_4\omega_0^4 - q_2\omega_0^2 + q_0)^2\right]},
\end{aligned}$$

where,

$$\begin{aligned}
J_2 =& (5\omega_0^4 - 3p_3\omega_0^2 + p_1)\omega_0\left[\sin\omega_0\tau_4(q_4\omega_0^4 - q_2\omega_0^2 + q_0) + \cos\omega_0\tau_4(q_3\omega_0^2 - q_1)\omega_0\right]\\
&+ (2p_2 - 4p_4\omega_0^2)\omega_0^2\left[\cos\omega_0\tau_4(q_4\omega_0^4 - q_2\omega_0^2 + q_0) - \sin\omega_0\tau_4(q_3\omega_0^2 - q_1)\omega_0\right]\\
=& \omega_0^2[5\omega_0^8 + (4p_4^2 - 8p_3)\omega_0^6 + 3(p_3^2 + 2p_1 - 2p_2p_4)\omega_0^4\\
&+ 2(p_2^2 + 2p_1p_3 + 2p_0p_4)\omega_0^2 + p_1^2 - 2p_0p_2],\\
J_3 =& \left[-4q_4^2\omega_0^6 + 3(2q_2q_4 - q_3^2)\omega_0^4 + 2(2q_1q_3 - q_2^2 - 2q_0q_4)\omega_0^2 - q_1^2 + 2q_1q_2\right]\omega_0^2.
\end{aligned}$$

Thus,

$$\begin{aligned}
J_2 + J_3 =& \omega_0^2[5\omega_0^8 + 4(p_4^2 - 2p_3 - q_4^2)\omega_0^6 + 3(p_3^2 + 2p_1 + 2q_2q_4 - q_3^2 - 2p_2p_4)\omega_0^4\\
&+ 2(p_2^2 + 2p_0p_4 + 2q_1q_3 - 2p_0p_3 - q_2^2 - 2q_0q_4)\omega_0^2 + p_1^2 - q_1^2 - 2p_0p_2 + 2q_0q_2],\\
=& \omega_0^2H'(\omega_0^2).
\end{aligned}$$

Thereafter,

$$\left(\frac{\mathrm{Re}\xi}{\mathrm{d}\tau_4}\right)^{-1} = \frac{H'(\omega_0^2)}{(q_3\omega_0^2 - q_1)^2\omega_0^2 + (q_4\omega_0^4 - q_2\omega_0^2 + q_0)^2}.$$

Since $(q_3\omega_0^2 - q_1)^2\omega_0^2 + (q_4\omega_0^4 - q_2\omega_0^2 + q_0)^2 > 0$, then

$$\text{sign}\left[\frac{\text{d}(\text{Re}\xi)}{\text{d}\tau_4}\right]_{\tau_4=\tau_{40}} = \text{sign}\left\{\left[\frac{\text{d}(\text{Re}\xi)}{\text{d}\tau_4}\right]^{-1}\right\}_{\tau_4=\tau_{40}} = \text{sign}H'(\omega_0^2).$$

Therefore, a Hopf bifurcation occurs at $\tau_4 = \tau_{40}$ under the condition $H'(\omega_0^2) \neq 0$. Furthermore, a family of periodic solutions occurs for system (1.1) when $\tau_4 > \tau_{40}$ and $\tau_i = 0$, $i = 1, 2, 3$. □

4. Numerical simulations

In this section, we perform numerical simulations to show the dynamical behaviour at the B-cell-activated equilibrium E_2 of system (1.1), for different values of the cell infection delay τ_2 and the immune system delay τ_4. We choose parameter values from the modelling literature (see Table 1), and let $a = b = 0.015$ in the following numerical simulations.

Table 1. List of Parameters.

Parameters	Definition	Unit	Data	Source
λ	T-cells source term	$\mu l^{-1}\text{day}^{-1}$	100	[35,36]
d_1	Death rate of healthy T-cells	day^{-1}	0.10	[36]
β	Viral infectivity rate	$\mu l\,\text{day}^{-1}$	0.007	[36]
m	The death rate of infected but not yet productive cells	$\mu l\,\text{day}^{-1}$	0.10	
η	Fraction of infections that leading to latency		0.001	[5,6]
α	Activation rate of latently infected T-cells	day^{-1}	0.001	[5,6]
k	Production virions rate	$\text{virions}\,\text{day}^{-1}\text{cell}^{-1}$	10	[36]
p	B-cell effectiveness	$\mu l\,\text{day}^{-1}$	0.001	[36,37]
q	B-cell responsiveness	$\mu l\,\text{day}^{-1}day^{-1}$	0.004	[36,37]
d_2	Death rate of latently infected T-cells	day^{-1}	0.001	[5,6]
d_3	Death rate of actively infected T-cells	day^{-1}	0.5	[36]
d_4	Clearance rate of virus	day^{-1}	3	[36]
d_5	Death rate of B-cells	day^{-1}	0.15	[36,37]

In order to study the effect of cell infection delay on the dynamical behaviour of system (1.1), we fix $\tau_1 = \tau_3 = 1$, $\tau_4 = 0$ and choose $\tau_2 = 0$, $\tau_2 = 2$, $\tau_2 = 6$ and $\tau_2 = 12$, respectively. Using Data values in Table 1, we calculate that $\mathcal{R}_0 > 1$ and $\mathcal{R}_1 > 1$ when $\tau_2 = 0, \tau_2 = 2$ and $\tau_2 = 6$, while $\mathcal{R}_0 < 1$ when $\tau_2 = 12$. From Figure 1, we can see that, the B-cell activated equilibrium E_2 is globally asymptotically stable for τ_2 equals 0, 2 and 6, respectively, which is consistent with Theorem 3.6; the uninfected equilibrium E_0 is globally asymptotically stable for $\tau_2 = 12$, which is consistent with Theorem 3.2. Moreover, as the cell infection delay τ_2 increases, both the number of actively infected T-cells (I) and B-cells (B) decrease, while the number of healthy T-cells (T) and virus (V) remain unchanged. It is also observed that the cell infection delay τ_2 can cause the T-cell, virus and B-cell populations to oscillate in the early stage of infection, and prolong the time for system to reach the B-cell-activated equilibrium. In fact, for the immune delay $\tau_4 = 0$, when system (1.1) has only the latency delay τ_1 or the virus

maturation delay τ_3 and the remaining delay values are fixed, we can obtain graphs similar to Figure 1 (not shown here).

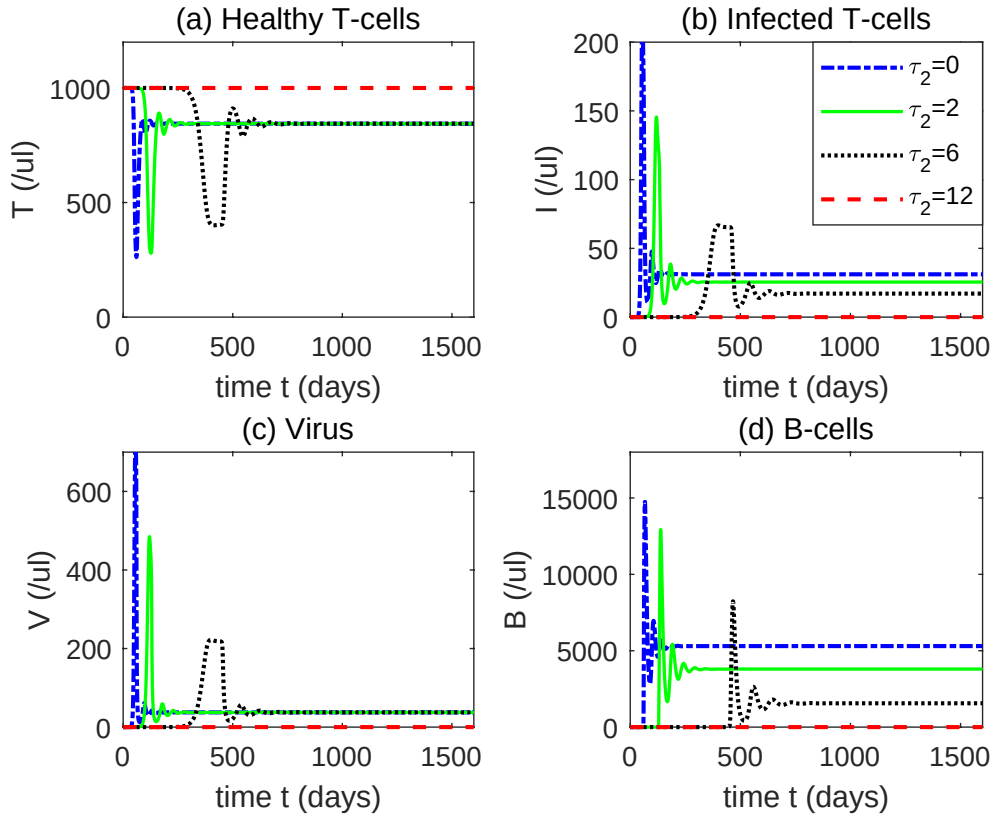

Figure 1. System (1.1) with $\tau_1 = \tau_3 = 1$ and $\tau_4 = 0$, $\mathcal{R}_1 > 1$ when $\tau_2 = 0, 2, 6$, while $\mathcal{R}_0 < 1$ when τ_2=12. Populations T, I, V and B are shown when τ_2 =0, 2, 6, 12, respectively.

Next, we investigate the system behaviour at the B-cell-activated equilibrium E_2 when the immune delay $\tau_4 > 0$ and $\tau_1 = \tau_2 = \tau_3 = 0$. Choose $\beta = 0.0032$ and all the other parameter values can be seen in Table 1. By calculating, we obtain that $\mathcal{R}_1 = 1.2781 > 1$, Eq (3.13) has only one positive real root $\omega \approx 0.0925$, and $\tau_{40} \approx 4.9066$. In this situation, Theorem 3.7 is satisfied. Figure 2 shows that the B-cell-activated equilibrium is locally asymptotically stable when the immune time delay $\tau_4 = 4 < \tau_{40}$, while Figure 3 demonstrates that Hopf bifurcation and period solutions occur at the B-cell-activated equilibrium when $\tau_4 = 7 > \tau_{40}$.

Now, we examine the dynamics of system (1.1) when all time delays $\tau_i > 0$, $i = 1, 2, 3, 4$. The two delays $\tau_1 = 1$ and $\tau_3 = 1$ are fixed, and all the other parameter values are from Table 1 in the following numerical simulations. Let $\tau_4 = 6$ be fixed, and $\tau_2 \in (0, 12]$ varies. With the increase of the cell infection delay τ_2, from the left panel of Figure 4, we observe that, (i) the system firstly undergoes the Hopf bifurcation at the B-cell-activated equilibrium E_2, and the amplitude of the periodic solution decreases gradually; (ii) then the system experiences the local asymptotic stability of the B-cell-inactivated equilibrium E_1, and finally reaches the local asymptotic stability of the uninfected equilibrium E_0. Similar figures can be obtained when τ_1 or τ_3 varies and the other delays are fixed (not shown here). Moreover, let $\tau_2 = 2$ be fixed, and $\tau_4 \in (0, 20]$ varies. With the increase of the

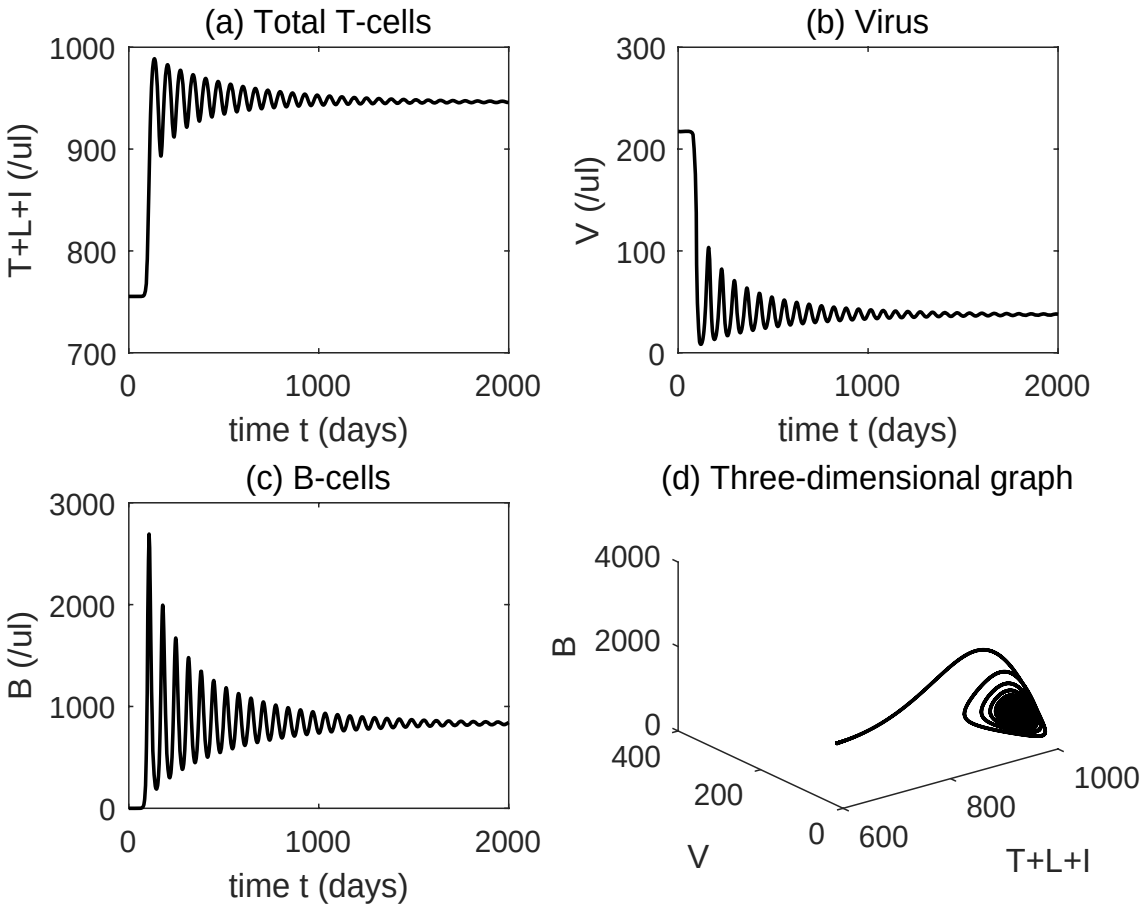

Figure 2. B-cell-activated equilibrium E_2 is locally asymptotically stable if $\tau_4 = 4 < \tau_{40}$ and $\mathcal{R}_1 > 1$.

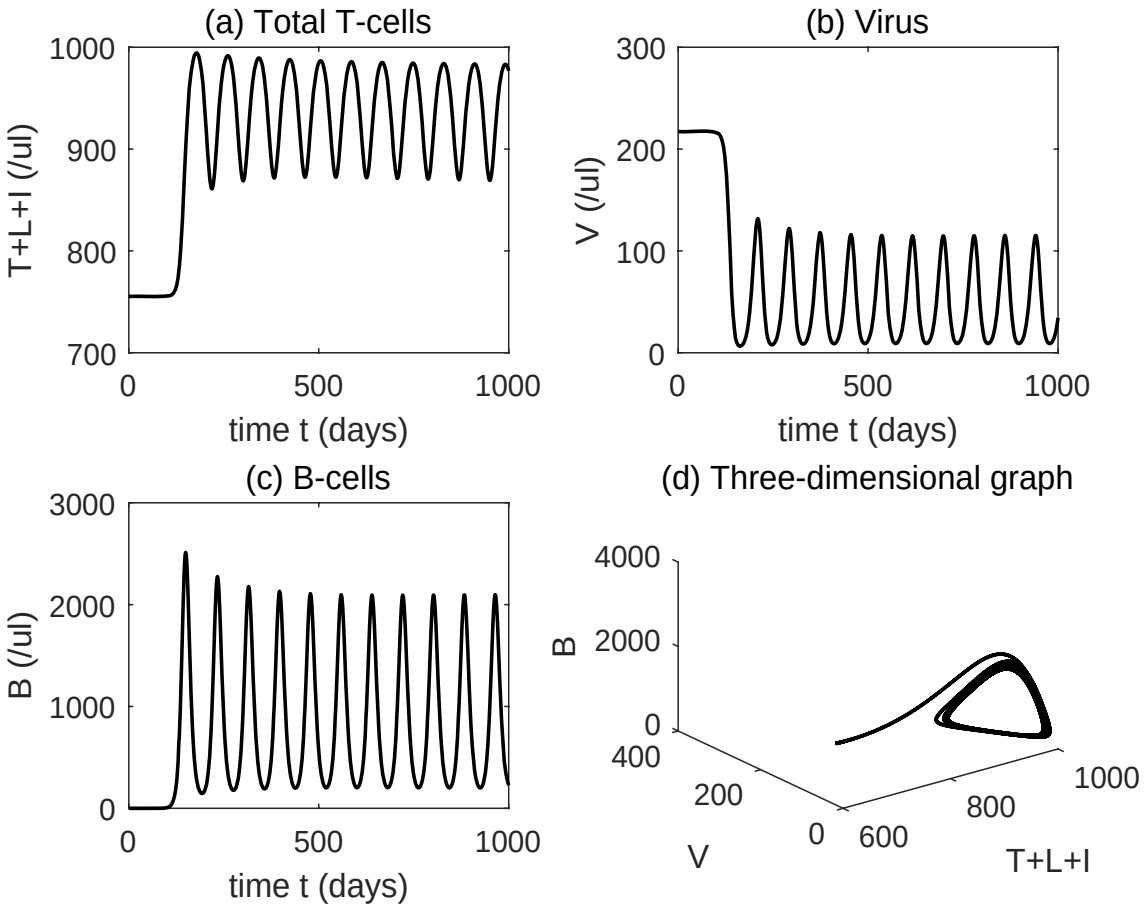

Figure 3. Hopf bifurcation and periodic solutions occur at the B-cell-activated equilibrium E_2 if $\tau_4 = 7 > \tau_{40}$ and $\mathcal{R}_1 > 1$.

immune delay τ_4, from the right panel of Figure 4, we find that, the system firstly reaches the local asymptotic stability of the B-cell-activated equilibrium E_2, then undergoes the Hopf bifurcation at the B-cell-activated equilibrium. In fact, the periodic solutions still exist when τ_4 is greater than 20 (not shown here).

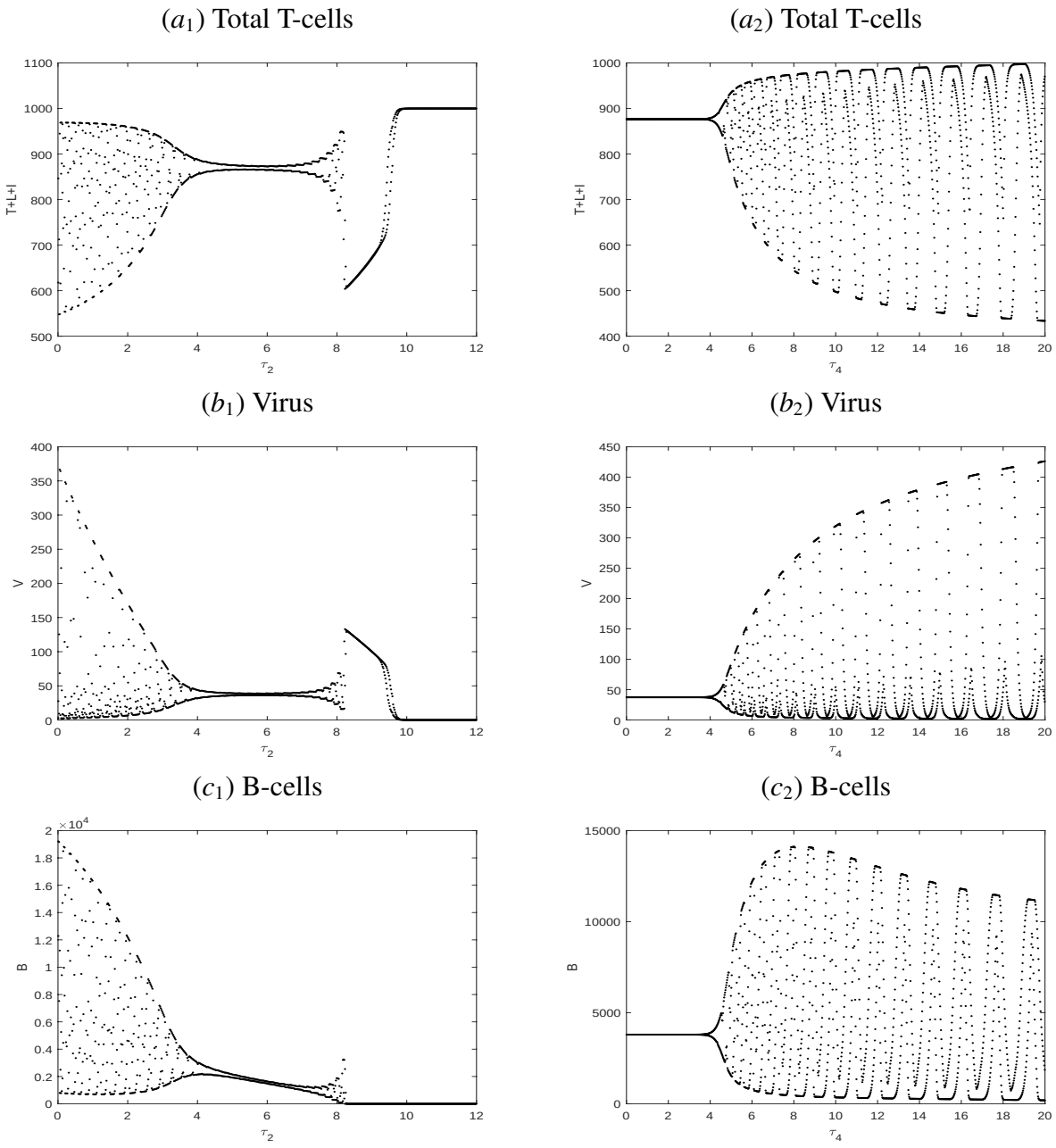

Figure 4. Bifurcation diagrams when τ_2 and τ_4 are varied. (Left) τ_2 increases from 0 to 12 days, and $\tau_4 = 6$. (Right) τ_4 increases from 0 to 20 days, and $\tau_2 = 2$. $\tau_1 = 1$, $\tau_3 = 1$, and all the other parameter values are given by Table 1.

5. Conclusions

In this paper, we have formulated an HIV infection model including the latently infected cell, the Beddington-DeAngelis infection function, the B-cell immune response and multiple delays. The latency delay, the cell infection delay, the virus maturation delay and the immune delay of B-cell activation are considered in our model. Two basic reproduction numbers and three equilibria are obtained. Theoretically, by constructing the appropriate Lyapunov function, we obtain that both the uninfected and B-cell-inactivated equilibria are globally asymptotically stable for the four time delays. The B-cell-activated equilibrium is globally asymptotically stable for the first three delays, while the immune delay may destabilize the stability of the B-cell-activated equilibrium and lead to Hopf bifurcation.

It is a challenging problem to analyze system (1.1) for the joint effect of four time delays theoretically. So, numerical simulations are performed to investigate the dynamical behaviour at the B-cell-activated equilibrium E_2 for $\tau_i > 0$ $i = 1, 2, 3, 4$. It was discovered that, the latency delay τ_1, the cell infection delay τ_2, and the virus maturation delay τ_3 can stabilize the B-cell-activated equilibrium, and the bifurcation disappears gradually; while the immune response delay τ_4 can lead to its instability, and bifurcation occurs.

As far as we know, HIV infection model considering the latent infection, the Beddington-DeAngelis incidence function and the B-cell immune response is rare, and the theoretical study on the analysis of multiple time delay models is also rare. In this paper, we analyze the global stability of the equilibrium through constructing suitable Lyapunov functions, which is a generalization of the existing models.

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Conflict of interest

The authors declare that they have no conflict of interest.

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