

DYNAMICS ANALYSIS OF HIV-1 INFECTION MODEL WITH CTL IMMUNE RESPONSE AND DELAYS

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Abstract. In this paper, we rigorously analyze an HIV-1 infection model with CTL immune response and three time delays which represent the latent period, virus production period and immune response delay, respectively. We begin this model with proving the positivity and boundedness of the solution. For this model, the basic reproduction number R_0 and the immune reproduction number R_1 are identified. Moreover, we have shown that the model has three equilibria, namely the infection-free equilibrium E_0 , the infectious equilibrium without immune response E_1 and the infectious equilibrium with immune response E_2 . By applying fluctuation lemma and Lyapunov functionals, we have demonstrated that the global stability of E_0 and E_1 are only related to R_0 and R_1 . The local stability of the third equilibrium is obtained under four situations. Further, we give the conditions for the existence of Hopf bifurcation. Finally, some numerical simulations are carried out for illustrating the theoretical results.

Key words. HIV-1, Delays, Stability, Hopf bifurcation, Lyapunov functionals.

1. Introduction

In the past few decades, many researchers and scientists focus on the study of simulating the interactions between pathogens and the host immune system. There is a convincing evidence that cytotoxic T lymphocyte (CTL) cells which attack infected cells are the main host immune factor that determines virus load [1–4]. Moreover, the Human Immunodeficiency Virus (HIV) models are crucial among the disease models since the Acquired Immune Deficiency Syndrome (AIDS) is mainly due to HIV and is still not curable today. Therefore, it makes sense to spend some time researching HIV-1 infection model with CTL immune response.

Based on some biological background in cellular immunology, Perelson and Nelson [5] established a four-dimensional ordinary differential system to study the dynamical behavior with cellular immune responses in 1999. The model is as follows:

$$(1) \quad \begin{cases} \dot{x} = s - dx(t) - \beta x(t)v(t), \\ \dot{y} = \beta x(t)v(t) - ay(t) - py(t)z(t), \\ \dot{v} = ky(t) - uv(t), \\ \dot{z} = f(x, y, z) - hz(t), \end{cases}$$

where a dot denotes the differentiation with respect to time t , variables x, y, v and z represent the density of the healthy cells, the infected cells, the virus and CTL cells, respectively. Healthy cells are produced at rate s and they died out naturally at rate dx . These cells may come into contact with the virus and become infected cells at rate βxv . Infected cells died out naturally at rate ay and are removed by z at rate pyz . From the infected cells, the viruses are replicated at rate ky and they are cleared naturally at rate uv . CTL cells decay at a rate hz and $f(x, y, z)$ has some different expressions according to the different assumptions. For example, the authors of [6, 7] supposed that the generation of CTL only depend on the infected

cells, the researchers of [8] think that the emergence of CTL not only depend on the infected cells but also is related to the CTL cells. Based above analysis, the authors of [9] considered the formation of the CTL is also related to the healthy cells.

Most of the models discussed so far capture the CTL in a single population, z . However, when CTLs are stimulated by antigen, the population of CTL precursors (CTLp) expands. Upon contact with the virus during a subsequent infection, CTLp becomes CTL effectors (CTLe) which is again responsible for clearing away the invading virus [10–12]. Therefore, in order to describes the dynamics of CTL immune response more accurately, Wodarz [13] modified model (1) by assuming that the virus population is at a quasi-steady state, i.e. $v = (k/u)y$, and introduced w (represents CTLp) and z (represents CTLe) according to the action principle of CTL. Then, model (1) reduces to

$$(2) \quad \begin{cases} \dot{x} = s - dx(t) - \beta x(t)y(t), \\ \dot{y} = \beta x(t)y(t) - ay(t) - py(t)z(t), \\ \dot{w} = cy(t)w(t) - cqy(t)w(t) - bw(t), \\ \dot{z} = cqy(t)w(t) - hz(t). \end{cases}$$

Compared to model (1), healthy cells in this model become infected cells at rate βxy . CTLp emerges at rate cyw , becomes CTLe at rate $cqyw$ and decays at rate bw . Similarly, CTLe are created at rate $cqyw$ and cleared at rate hz . Chan and Yu [12] analyzed the stability of equilibria and bifurcation dynamics of model (2).

In order to model the immune system more precisely, Yu et al. [14] combined model (2) and the viruses to have the following 5-dimensional system :

$$(3) \quad \begin{cases} \dot{x} = s - dx(t) - \beta x(t)v(t), \\ \dot{y} = \beta x(t)v(t) - ay(t) - py(t)z(t), \\ \dot{v} = ky(t) - uv(t), \\ \dot{w} = cy(t)w(t) - cqy(t)w(t) - bw(t), \\ \dot{z} = cqy(t)w(t) - hz(t). \end{cases}$$

The dynamical properties of model (3) (Fig. 1) have also been studied in [14].

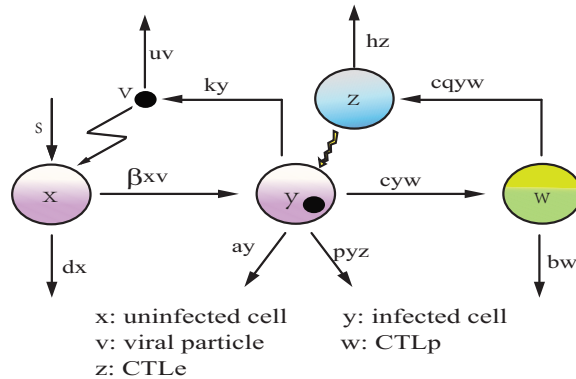


FIGURE 1. Model (3) with viral infection and immune response. Uninfected cell (healthy cell) x is infected with viral particle v , becomes infected cell y ; in order to clear away the infected cell, the immune system generates CTLp w which has receptors specifically for detecting the virus form the previous infection. During a subsequent infection, CTLp differentiates CTLe z which is again responsible for clearing away the invading virus.

The interplay between virus and the host immune system is a more complicated process [15], which includes viral attachment, viral replication, virus clearance and so on. In the real situation, there may be a lag between the time the virus particles attach target cells and the time the host cell contains the infectious viral particles in its cytoplasm [16]. Time is also necessary for a newly infected virus to become mature and then infectious [17]. There is also a period between the time of infection and the recognition of the infected cells by CTLs [18]. In this paper, we introduce three time delays into the model (3) to further describe the real process of HIV-1 infection with CTL immune response. τ_1 , τ_2 and τ_3 denote the eclipse phase, virus production period and the response time delay of CTLp, respectively. Moreover, we assume that the probability density that a cell still remains infected for τ_1 time units after being contacted by the virus obeys an exponentially decay function [19]. Similarly, the probability density of infected cells and CTLp are also exponentially decay functions. Therefore, model (3) can be modified into

$$(4) \quad \begin{cases} \dot{x} = s - dx(t) - \beta x(t)v(t), \\ \dot{y} = \beta e^{-a_1 \tau_1} x(t - \tau_1)v(t - \tau_1) - ay(t) - py(t)z(t), \\ \dot{v} = ke^{-a_2 \tau_2} y(t - \tau_2) - uv(t), \\ \dot{w} = ce^{-a_3 \tau_3} y(t - \tau_3)w(t - \tau_3) - cqy(t)w(t) - bw(t), \\ \dot{z} = cqy(t)w(t) - hz(t). \end{cases}$$

All of the coefficient are positive and $0 < q < 1$ [14]. Because model (4) contains multi-time delays and the dimension of the model is higher than two, it may exhibit more interesting dynamic behaviors. Therefore, we are interested in the study of dynamical properties of model (4).

The rest of the paper is organized as follows. In section 2, the well-posedness of the solution is discussed and equilibria of model (4) is given. Also, in order to properly define biologically meaningful equilibrium, the basic reproduction number R_0 and the immune reproduction number R_1 are define. In section 3, we analyze the stability of the infection-free equilibrium E_0 . It is shown that when $R_0 < 1$, E_0 is globally asymptotically stable which implying that no virus can invade. In section 4, we show that if $R_1 < 1 < R_0$ holds, the infectious equilibrium without immune response E_1 is globally asymptotically stable which implying that CTL immune response has not be successfully activated. In section 5, by analyzing the characteristic equation of the linearized system of model (4) at the infectious equilibrium with immune response E_2 , we establish locally asymptotical stability of equilibrium E_2 under four cases. Meanwhile, according to the Hopf bifurcation theorem for functional differential equations (FDEs), we find that the system can undergo Hopf bifurcation of nonconstant periodic solution at the equilibrium E_2 when the delays cross through a sequence of critical values. Numerical simulations are provided in section 6 to confirm the theoretical results. Finally, discussion and conclusion are given in section 7.

2. Well-posedness, equilibria and the reproduction numbers

For the model (4), positivity implies that the cell population survives and boundedness shows that cell growth is constrained under limited resources. Thus, it is of vital importance to indicate the positivity and the boundedness of solution of model (4).

Let $X = C([-τ, 0], R_+^5)$ be the Banach space of continuous functions from $[-τ, 0]$ to R_+^5 equipped with the sup-norm, where $τ = \max\{\tau_1, \tau_2, \tau_3\}$. The initial conditions are given by

$$(5) \quad \begin{cases} (x(\theta), y(\theta), v(\theta), w(\theta), z(\theta)) \in X, \\ x(\theta) \geq 0, y(\theta) \geq 0, v(\theta) \geq 0, w(\theta) \geq 0, z(\theta) \geq 0, \theta \in [-\tau, 0], \\ x(0) > 0, y(0) > 0, v(0) > 0, w(0) > 0, z(0) > 0. \end{cases}$$

By the standard theory of functional differential equation [20, 21], we know that there exists a unique solution $(x(t), y(t), v(t), w(t), z(t))$ to model (4). Moreover, we establish the positivity and boundedness of solutions to model (4) according to the following theorem.

Theorem 2.1. *Let $(x(t), y(t), v(t), w(t), z(t))$ be the solution of model (4) with the initial conditions (5). Then, we have*

- (i) $x(t) > 0, y(t) > 0, v(t) > 0, w(t) > 0$ and $z(t) > 0$ for $t > 0$,
- (ii) There exists an $M > 0$ such that $x(t) \leq M, y(t) \leq M, v(t) \leq M, w(t) \leq M$ and $z(t) \leq M$ for sufficiently large time t .

Proof. From the first equation of (4), we have

$$(6) \quad x(t) = x(0)e^{-\int_0^t (d+\beta v(\eta))d\eta} + s \int_0^t e^{-\int_n^t (d+\beta v(\xi))d\xi} d\eta.$$

Clearly, $x(t) > 0$ for $t > 0$. We claim that $y(t)$ and $v(t)$ are also positive. Assuming the contrary, let $t_1 > 0$ be the first time such that $y(t_1) = 0$ and $\dot{y}(t_1) \leq 0$. Solving the third equation of system (4), we obtain $v(t_1 - \tau_1) = v(0)e^{-u(t_1 - \tau_1)} + \int_0^{t_1 - \tau_1} ke^{-a_2\tau_2 - u(t_1 - \tau_1)} y(\eta - \tau_2)e^{u\eta} d\eta > 0$. Together with the second equation of (4), we have $\dot{y}(t_1) = \beta e^{-a_1\tau_1} x(t_1 - \tau_1)v(t_1 - \tau_1) > 0$. It is a contradiction with the assumption $\dot{y}(t_1) \leq 0$. Thus, we conclude that $y(t) > 0$, and then $v(t) > 0$. Using the same argument as in the above proof, we can show that $w(t) > 0, z(t) > 0$ for all $t > 0$. Thus, (i) holds.

Next, we prove that (ii) is tenable. From (6), we can get the following inequality:

$$\begin{aligned} x(t) &< e^{-\int_0^t d \, d\eta} x(0) + s \int_0^t e^{-\int_n^t d \, d\xi} d\eta \\ &= e^{-dt} x(0) + s \int_0^t e^{-d(t-\eta)} d\eta \\ &= e^{-dt} x(0) + \frac{s}{d}(1 - e^{-dt}). \end{aligned}$$

Given that the exponential functions have negative exponents, one can see that $x(t)$ is bounded. To show that $y(t)$ must also be bounded, we define

$$G(t) = e^{-a_1\tau_1} x(t) + y(t + \tau_1)$$

and let $n = \min\{a, d\}$. By calculating the time derivative of $G(t)$ along the solution of model (4), we obtain

$$\begin{aligned} \frac{dG(t)}{dt} &= e^{-a_1\tau_1} (s - dx(t) - \beta x(t)v(t)) + \beta e^{-a_1\tau_1} x(t)v(t) \\ &\quad - ay(t + \tau_1) - py(t + \tau_1)z(t + \tau_1) \\ &= se^{-a_1\tau_1} - de^{-a_1\tau_1} x(t) - ay(t + \tau_1) - py(t + \tau_1)z(t + \tau_1) \\ &\leq se^{-a_1\tau_1} - de^{-a_1\tau_1} x(t) - ay(t + \tau_1) \\ &\leq se^{-a_1\tau_1} - nG(t), \end{aligned}$$

which shows that $G(t)$ is bounded, and thus $y(t)$ is also bounded. For $v(t) = v(0)e^{-ut} + \int_0^t ke^{-a_2\tau_2-ut}y(\eta - \tau_2)e^{u\eta}d\eta$, we know that $v(0)e^{-ut}$ is bounded. However, other parts of the solution may be unbounded as $t \rightarrow \infty$. We apply rule of L'hospital to get

$$\lim_{t \rightarrow \infty} \int_0^t ky(\eta - \tau_2)e^{-a_2\tau_2-ut+u\eta}d\eta = \lim_{t \rightarrow \infty} \frac{ky(t - \tau_2)e^{-a_2\tau_2+ut}}{ue^{ut}} = \frac{ky(\infty)e^{-a_2\tau_2}}{u}.$$

Since $y(t)$ is bounded, $v(t)$ is also bounded.

By contradiction, we can prove that w and z are bounded. Firstly, we assume that z is unbounded. From the second equation in (4), we have $\lim_{t \rightarrow \infty} y(t) = 0$. From the fourth equation in (4), the equality $\lim_{t \rightarrow \infty} w(t) = 0$ is also obtained. It thus follows from the fifth equation in (4) that $\lim_{t \rightarrow \infty} z(t) = 0$, which contradicts the assumption. Thus, z must be bounded. Similarly, we assume that w is unbounded. According to the boundedness of z and the fifth equation of (4), we again have $\lim_{t \rightarrow \infty} y(t) = 0$. In this case, we know from the fourth equation of (4) that $\lim_{t \rightarrow \infty} w(t) = 0$ when $\lim_{t \rightarrow \infty} y(t) = 0$, which gives another contradiction, thus w is also bounded. In the other words, there must be a positive constant M such that $x(t) \leq M$, $y(t) \leq M$, $v(t) \leq M$, $w(t) \leq M$ and $z(t) \leq M$ for sufficiently large time t , finishing the proof of Theorem 2.1. \square

Model (4) has three possible equilibria: the infection-free equilibrium E_0 , the infectious equilibrium without immune response E_1 and the infectious equilibrium with immune response E_2 given by:

$$\begin{aligned} E_0 &= (x_0, y_0, v_0, w_0, z_0) = \left(\frac{s}{d}, 0, 0, 0, 0\right), \\ E_1 &= (x_1, y_1, v_1, w_1, z_1) \\ &= \left(\frac{aue^{a_1\tau_1+a_2\tau_2}}{k\beta}, \frac{-adue^{a_2\tau_2} + sk\beta e^{-a_1\tau_1}}{ak\beta}, \frac{sk\beta e^{-a_1\tau_1-a_2\tau_2} - adu}{au\beta}, 0, 0\right), \\ E_2 &= (x_2, y_2, v_2, w_2, z_2), \end{aligned}$$

where

$$\begin{aligned} x_2 &= \frac{suc(e^{-a_3\tau_3} - q)}{duc(e^{-a_3\tau_3} - q) + \beta bke^{-a_2\tau_2}}, \\ y_2 &= \frac{b}{c(e^{-a_3\tau_3} - q)}, \\ v_2 &= \frac{kbe^{-a_2\tau_2}}{uc(e^{-a_3\tau_3} - q)}, \\ w_2 &= \frac{h(e^{-a_3\tau_3} - q)(c(e^{-a_3\tau_3} - q)(ks\beta e^{-a_1\tau_1-a_2\tau_2} - adu) - ab\beta ke^{-a_2\tau_2})}{qbp(duc(e^{-a_3\tau_3} - q) + kb\beta e^{-a_2\tau_2})}, \\ z_2 &= \frac{c(e^{-a_3\tau_3} - q)(ks\beta e^{-a_1\tau_1-a_2\tau_2} - adu) - ab\beta ke^{-a_2\tau_2}}{p(duc(e^{-a_3\tau_3} - q) + kb\beta e^{-a_2\tau_2})}. \end{aligned}$$

Obviously, there always exists an infection-free equilibrium E_0 , which represents the state that the viruses are absent. By applying the general mathematical theory of basic reproduction number of disease model [22], we define the basic reproduction number R_0 as

$$(7) \quad R_0 = \frac{ke^{-a_2\tau_2}}{u} \cdot \frac{\beta e^{-a_1\tau_1}}{a} \cdot \frac{s}{d} = \frac{ks\beta e^{-a_1\tau_1-a_2\tau_2}}{adu}.$$

It follows from the expression of the E_1 that E_1 exists if and only if $R_0 > 1$. The equilibrium E_1 represents the state that the viruses are present while the CTL cells are absent. According to the method in [23], we introduce an immune reproduction number

$$R_1 = \frac{cu(e^{-a_3\tau_3} - q)}{bke^{-a_2\tau_2}} \cdot \frac{ks\beta e^{-a_1\tau_1 - a_2\tau_2} - adu}{a\beta u} = \frac{c(e^{-a_3\tau_3} - q)(ks\beta e^{-a_1\tau_1 - a_2\tau_2} - adu)}{a\beta bke^{-a_2\tau_2}}.$$

Thus, the equilibrium E_2 (the state in which both the viruses and CTL cells are present) exists if and only if $R_1 > 1$ and $0 \leq \tau_3 < -\frac{\ln q}{a_3}$. If $\tau_1 = \tau_2 = \tau_3 = 0$, model (4) and model (3) are equivalent.

In order to determine the local stability of model (4) at the equilibrium $E = (\hat{x}, \hat{y}, \hat{v}, \hat{w}, \hat{z})$ (where E represents any of the equilibria E_0, E_1 and E_2), we need to linearize the model. The Jacobian matrix of model (4) is given by

$$A = \begin{bmatrix} -d - \beta\hat{v} & 0 & -\beta\hat{x} & 0 & 0 \\ \beta\hat{v}e^{-(\lambda+a_1)\tau_1} & -a - p\hat{z} & \beta\hat{x}e^{-(\lambda+a_1)\tau_1} & 0 & -p\hat{y} \\ 0 & ke^{-(\lambda+a_2)\tau_2} & -u & 0 & 0 \\ 0 & c\hat{w}e^{-(\lambda+a_3)\tau_3} - cq\hat{w} & 0 & c\hat{y}e^{-(\lambda+a_3)\tau_3} - cq\hat{y} - b & 0 \\ 0 & cq\hat{w} & 0 & cq\hat{y} & -h \end{bmatrix}.$$

The characteristic equation of model (4) at E is

$$(8) \quad \Delta(\lambda) = |\lambda I - A|,$$

where λ is an eigenvalue of model (4). The roots of (8) determine the local stability of E .

3. Stability of the infection-free equilibrium E_0

First, we consider the local stability of the infection-free equilibrium E_0 and have the following theorem.

Theorem 3.1. *When $R_0 < 1$, the infection-free equilibrium E_0 is locally asymptotically stable for any time delays $\tau_1, \tau_2, \tau_3 \geq 0$; when $R_0 > 1$, E_0 becomes unstable and the infectious equilibrium without immune response E_1 occurs.*

Proof. From (8), we can obtain the characteristic equation at the equilibrium E_0 as follows:

$$(9) \quad (\lambda + h)(\lambda + b)(\lambda + d)[\lambda^2 + (a + u)\lambda + au - \frac{sk\beta}{d}e^{-a_1\tau_1 - a_2\tau_2 - \lambda(\tau_1 + \tau_2)}] = 0.$$

Thus the eigenvalues of model (4) are $-h, -b, -d$, the remaining eigenvalues are determined from the following transcendental equation which is obtained from (9)

$$(10) \quad \lambda^2 + (a + u)\lambda + au - \frac{sk\beta}{d}e^{-a_1\tau_1 - a_2\tau_2 - \lambda(\tau_1 + \tau_2)} = 0.$$

If $R_0 > 1$, we define a function

$$f(\lambda) = \lambda^2 + (a + u)\lambda + au - \frac{sk\beta}{d}e^{-a_1\tau_1 - a_2\tau_2 - \lambda(\tau_1 + \tau_2)}.$$

It is clear that $f(0) = au - \frac{sk\beta}{d}e^{-a_1\tau_1 - a_2\tau_2} < 0$, $\lim_{\lambda \rightarrow +\infty} f(\lambda) = +\infty$. Therefore, there exists at least one positive root when $R_0 > 1$.

If $R_0 < 1$, when $\tau_1 = \tau_2 = \tau_3 = 0$, equation (10) becomes

$$(11) \quad \lambda^2 + (a + u)\lambda + au - \frac{sk\beta}{d} = 0.$$

Obviously, all the roots of (11) have negative real parts when $R_0 < 1$. For any $\tau = (\tau_1, \tau_2, \tau_3)$, where $\tau_1, \tau_2, \tau_3 > 0$, the roots of equation (10) $\lambda(\tau) = r(\tau) + i\omega(\tau)$ must have negative real part. Otherwise, there has $\bar{\tau}$ which satisfies the inequality $r(\bar{\tau}) > 0$. Because $r(0) < 0$ by simple calculation, there must exist $\hat{\tau} = (\hat{\tau}_1, \hat{\tau}_2, \hat{\tau}_3)$ such that $r(\hat{\tau}) = 0$. Thus, we define $\lambda(\hat{\tau}) = i\varpi$ ($\varpi > 0$) to be a purely imaginary root of (10). Then we get

$$(12) \quad -\varpi^2 + i(a + u)\varpi + au - \frac{sk\beta e^{-a_1\hat{\tau}_1 - a_2\hat{\tau}_2}}{d} [\cos \varpi(\hat{\tau}_1 + \hat{\tau}_2) - i \sin \varpi(\hat{\tau}_1 + \hat{\tau}_2)] = 0.$$

Separating the real and imaginary parts of equation (12), we have

$$\begin{cases} -\varpi^2 + au = \frac{sk\beta}{d} e^{-a_1\hat{\tau}_1 - a_2\hat{\tau}_2} \cos[\varpi(\hat{\tau}_1 + \hat{\tau}_2)], \\ -a\varpi - u\varpi = \frac{sk\beta}{d} e^{-a_1\hat{\tau}_1 - a_2\hat{\tau}_2} \sin[\varpi(\hat{\tau}_1 + \hat{\tau}_2)], \end{cases}$$

which lead to

$$\varpi^4 + (a^2 + u^2)\varpi^2 + a^2u^2 - \frac{\beta^2 s^2 k^2}{d^2} e^{-2a_1\hat{\tau}_1 - 2a_2\hat{\tau}_2} = 0.$$

The above equation has a unique positive solution if and only if $au - \frac{sk\beta}{d} e^{-a_1\hat{\tau}_1 - a_2\hat{\tau}_2} < 0$, which is equivalent to $R_0 > 1$. This contradicts to the condition $R_0 < 1$. Therefore, for any $\tau_1, \tau_2, \tau_3 \geq 0$ and $R_0 < 1$, all the roots of equation (10) have negative real parts, which means that the infection-free equilibrium E_0 is locally asymptotically stable. \square

For the global stability of E_0 , we employ the method of fluctuation lemma [24] and have the following theorem.

Theorem 3.2. *If $R_0 < 1$, the infection-free equilibrium E_0 is globally asymptotically stable, implying that no virus can invade.*

Proof. For convenience, we first introduce the following notations

$$f^\infty = \limsup_{t \rightarrow \infty} f(t), \quad f_\infty = \liminf_{t \rightarrow \infty} f(t),$$

where $f(t)$ is a bounded and continuously differentiable function defined on $[0, \infty)$. In section 2, we have shown that the solution of model (4) are positive and bounded for the initial condition (5). Therefore, $\lim_{t \rightarrow \infty} \sup$ and $\lim_{t \rightarrow \infty} \inf$ are meaningful for the solution in model (4). By the fluctuation lemma, there exists a sequence t_n with $t_n \rightarrow \infty$ as $n \rightarrow \infty$ such that

$$(13) \quad \lim_{n \rightarrow \infty} x(t_n) = x^\infty, \quad \lim_{n \rightarrow \infty} \dot{x}(t_n) = 0.$$

Substituting $t = t_n$ into the first equation of (4) and taking limit, using the equations in (13), we obtain

$$(14) \quad dx^\infty \leq (d + \beta v_\infty)x^\infty \leq s.$$

Apply similar technique to the other equations in model (4), we have

$$(15) \quad ay^\infty \leq (a + pz_\infty)y^\infty \leq \beta e^{-a_1\tau_1} x^\infty v^\infty,$$

$$(16) \quad uv^\infty = ke^{-a_2\tau_2} y^\infty,$$

$$(17) \quad bw^\infty = ce^{-a_3\tau_3} y^\infty w^\infty - cqy^\infty w^\infty = c(e^{-a_3\tau_3} - q)y^\infty w^\infty,$$

$$(18) \quad hz^\infty = cqy^\infty w^\infty.$$

Combining with (14), (15) and (16), we obtain

$$ay^\infty \leq \beta e^{-a_1\tau_1} x^\infty v^\infty \leq \frac{sk\beta}{du} e^{-a_1\tau_1 - a_2\tau_2} y^\infty.$$

If $y^\infty > 0$, the above inequality leads to $a \leq \frac{sk\beta}{du} e^{-a_1\tau_1 - a_2\tau_2}$, this implies $R_0 = \frac{sk\beta}{adu} e^{-a_1\tau_1 - a_2\tau_2} \geq 1$ which contradicts $R_0 < 1$, thus $y^\infty = 0$. By applying $y^\infty = 0$ and (16), (17) and (18), we know that $v^\infty = 0$, $w^\infty = 0$ and $z^\infty = 0$. Since $0 \leq f_\infty \leq f^\infty$, we must have $y(t)$, $v(t)$, $w(t)$ and $z(t)$ approach 0 as $t \rightarrow \infty$. Thus, the first equation in model (4) becomes $\dot{x} = s - dx$ with $v(t) \rightarrow 0$. Finally, we apply the theory of asymptotically autonomous system [25] and conclude that $\lim_{t \rightarrow \infty} x(t) = \frac{s}{d}$. This completes the proof of the theorem. \square

4. stability of the infectious equilibrium without immune response E_1

From the analysis given in the section 3, we know that when R_0 crosses the critical value 1, the infection-free equilibrium E_0 changes its stability and the infectious equilibrium without immune response E_1 existences. Thus, in order to study the stability of equilibrium E_1 , we always assume $R_0 > 1$ in this section. We have the following theorem for the local stability of infectious equilibrium without immune response E_1 .

Theorem 4.1. *When $R_1 < 1 < R_0$ holds, the infectious equilibrium without immune response E_1 is locally asymptotically stable for any time delay $\tau_1, \tau_2, \tau_3 \geq 0$, E_1 becomes unstable and the infectious equilibrium with immune response E_2 emerges if $R_1 > 1$ and $0 \leq \tau_3 < -\frac{\ln q}{a_3}$.*

Proof. From (8), we obtain the characteristic equation at E_1 given by $f_1(\lambda) f_2(\lambda) f_3(\lambda) = 0$, where

$$(19) \quad \begin{cases} f_1(\lambda) = \lambda + b + \frac{cqdu e^{a_2\tau_2}(R_0-1)}{k\beta} - \frac{cdu e^{a_2\tau_2} e^{-(\lambda+a_3)\tau_3}(R_0-1)}{k\beta}, \\ f_2(\lambda) = \lambda + h, \\ f_3(\lambda) = \lambda^3 + (a + u + dR_0)\lambda^2 + (duR_0 + au + dR_0a - aue^{-\lambda(\tau_1+\tau_2)})\lambda + aduR_0 - adue^{-\lambda(\tau_1+\tau_2)}. \end{cases}$$

Obviously, for the local stability of E_1 , we only need to consider the equations $f_1(\lambda) = 0$ and $f_3(\lambda) = 0$.

Similar to theorem 3.1, we analyze the above equation when $\tau_1, \tau_2, \tau_3 > 0$. First, for $f_1(\lambda) = 0$, we assume that $\lambda = i\varpi$ ($\varpi > 0$) is a solution of equation, then separating the real and imaginary parts yields

$$(20) \quad \begin{cases} b + \frac{cqdu e^{a_2\tau_2} R_0}{\beta k} - \frac{cqdu e^{a_2\tau_2}}{k\beta} = \frac{cdu e^{-a_3\tau_3} e^{a_2\tau_2}(R_0-1)}{k\beta} \cos(\varpi\tau_3), \\ \varpi = -\frac{cdu e^{-a_3\tau_3} e^{a_2\tau_2}(R_0-1)}{k\beta} \sin(\varpi\tau_3). \end{cases}$$

Squaring and adding the two equations of (20), we have

$$(21) \quad \varpi^2 + f_4 = 0,$$

where

$$f_4 = b^2 + \frac{c^2 q^2 d^2 u^2 e^{2a_2\tau_2}}{k^2 \beta^2} (R_0 - 1)^2 + \frac{2bcqdu e^{a_2\tau_2}}{k\beta} (R_0 - 1) - \frac{c^2 d^2 u^2 e^{2a_2\tau_2 - 2a_3\tau_3}}{k^2 \beta^2} (R_0 - 1)^2.$$

For convenience, we introduce f_5 and f_6 , then f_4 can be rewritten as

$$f_4 = f_5 \cdot f_6,$$

where

$$\begin{cases} f_5 = b + \frac{cqdue^{a_2\tau_2}(R_0-1)}{k\beta} + \frac{cdue^{a_2\tau_2-a_3\tau_3}(R_0-1)}{k\beta}, \\ f_6 = b + \frac{cqdue^{a_2\tau_2}(R_0-1)}{k\beta} - \frac{cdue^{a_2\tau_2-a_3\tau_3}(R_0-1)}{k\beta} = b(1-R_1). \end{cases}$$

Given that $R_0 > 1$ and all the parameters are positive, thus $f_5 > 0$. Clearly, $f_6 > 0$ if and only if $R_1 < 1$. Therefore, the all the roots of the equation $f_1(\lambda) = 0$ have negative real parts when $R_1 < 1 < R_0$, or the roots with positive real parts if $R_1 > 1$. When $\tau_1 = \tau_2 = \tau_3 = 0$, the first equality in (19) becomes $f_1(\lambda) = \lambda + b - \frac{c(1-q)du(R_0-1)}{k\beta}$. It is easy to see that if $R_1 < 1$, the root of the equation $f_1(\lambda) = 0$ has negative real part. Thus, the same conclusion is given in this case.

We rewrite $f_3(\lambda) = 0$ as

$$(22) \quad \lambda^3 + d_1\lambda^2 + d_2\lambda + d_3 - (au\lambda + adu)e^{-\lambda(\tau_1+\tau_2)} = 0,$$

where

$$d_1 = a + u + dR_0, \quad d_2 = duR_0 + au + adR_0, \quad d_3 = aduR_0.$$

When $\tau_1, \tau_2, \tau_3 = 0$, (22) becomes

$$(23) \quad \lambda^3 + b_1\lambda^2 + b_2\lambda + b_3 = 0$$

and denotes

$$b_1 = a + u + dR_0, \quad b_2 = duR_0 + adR_0, \quad b_3 = adu(R_0 - 1).$$

It is clear that $b_1, b_2, b_3 > 0$ due to all the parameters are positive and $R_0 > 1$. According to the Routh-Hurwitz criterion [26], the equilibrium is locally asymptotically stable if and only if the coefficients of characteristic polynomial satisfy $\Delta_i > 0$, ($i = 1, 2, 3$), where

$$\Delta_1 = b_1, \quad \Delta_2 = b_1b_2 - b_3, \quad \Delta_3 = b_3\Delta_2.$$

Since $b_1, b_2, b_3 > 0$, we only need to verify the sign of Δ_2 . The straightforward calculation shows that

$$\Delta_2 = (a + u)d^2R_0^2 + (a^2 + u^2)dR_0 + adu(R_0 + 1) > 0.$$

Thus, all roots of (23) have negative real parts when $\tau_1 = \tau_2 = \tau_3 = 0$.

For $\tau_1, \tau_2, \tau_3 > 0$, we still employ the method of theorem 3.1. By defining $\lambda = i\omega$ ($\omega > 0$) to be a purely imaginary root of $f_3(\lambda) = 0$, we can obtain

$$f_7 + f_8 = 0,$$

where

$$\begin{cases} f_7 = (a + u + dR_0)\omega^2 + au\omega \sin(\omega\tau_1 + \omega\tau_2) - aduR_0 + adu \cos(\omega\tau_1 + \omega\tau_2), \\ f_8 = i(\omega^3 + (-duR_0 - au + \cos(\omega\tau_1 + \omega\tau_2)au - adR_0)\omega - adu \sin(\omega\tau_1 + \omega\tau_2)). \end{cases}$$

Taking moduli of the above equation results in

$$(24) \quad \omega^6 + (a^2 + u^2 + d^2R_0^2)\omega^4 + (a^2d^2R_0^2 + u^2d^2R_0^2)\omega^2 + a^2d^2u^2(R_0^2 - 1) = 0.$$

Let

$$z = \omega^2, \quad c_1 = a^2 + u^2 + d^2R_0^2, \quad c_2 = (d^2u^2R_0^2 + a^2d^2R_0^2), \quad c_3 = a^2d^2u^2(R_0^2 - 1),$$

then (22) becomes

$$(25) \quad z^3 + c_1z^2 + c_2z + c_3 = 0.$$

Since $R_0 > 1$, all the coefficients of the equation (25) are positive, and thus all roots of $f_3 = 0$ have negative real parts. Therefore, we conclude that E_1 is locally asymptotically stable for any time delay $\tau_1, \tau_2, \tau_3 \geq 0$ when $R_1 < 1 < R_0$, completing the proof. \square

Furthermore, we can also show the global stability of the equilibrium E_1 in the following theorem.

Theorem 4.2. *If $R_1 < 1 < R_0$, the infectious equilibrium without immune response E_1 is globally asymptotically stable, implying that CTL immune response has not been established.*

Proof. To construct the Lyapunov functional of model (4), we first consider the following equations:

$$(26) \quad \begin{cases} \dot{x} = s - dx(t) - \beta x(t)v(t), \\ \dot{y} = \beta e^{-a_1\tau_1}x(t)v(t) - ay(t) - py(t)z(t), \\ \dot{v} = ke^{-a_2\tau_2}y(t) - uv(t), \\ \dot{w} = ce^{-a_3\tau_3}y(t)w(t) - cqy(t)w(t) - bw(t), \\ \dot{z} = cqy(t)w(t) - hz(t). \end{cases}$$

Note that E_1 is also the equilibrium of (26). Define a Lyapunov function V_0 for E_1 ,

$$V_0 = \tilde{m}[e^{-a_1\tau_1}(x - x_1 - x_1 \ln \frac{x}{x_1}) + (y - y_1 - y_1 \ln \frac{y}{y_1}) + \frac{a + pz_1}{ke^{-a_2\tau_2}}(v - v_1 - v_1 \ln \frac{v}{v_1})] + m(w + z),$$

where \tilde{m} and m are positive coefficients yet to be determined. Due to the positivity of the solutions of model (4), and the following inequality

$$x - 1 - \ln x \geq 0$$

for any $x > 0$, we have $V_0 \geq 0$. The equality $V_0 = 0$ holds if and only if $x = x_1, y = y_1, v = v_1, w_1 = z_1 = 0$, showing that E_1 is the unique global minimum of the Lyapunov function. Differentiating V_0 along the solution of model (26), we obtain

$$\begin{aligned} \frac{dV_0}{dt} \Big|_{(4.8)} &= \tilde{m}[e^{-a_1\tau_1}(1 - \frac{x_1}{x})\dot{x} + (1 - \frac{y_1}{y})\dot{y} + \frac{a + pz_1}{ke^{-a_2\tau_2}}(1 - \frac{v_1}{v})\dot{v}] + m(\dot{w} + \dot{z}) \\ &= \tilde{m}[e^{-a_1\tau_1}(1 - \frac{x_1}{x})(s - dx - \beta xv) + (1 - \frac{y_1}{y})(\beta e^{-a_1\tau_1}xv - ay - pyz) \\ &\quad + \frac{a + pz_1}{ke^{-a_2\tau_2}}(1 - \frac{v_1}{v})(ke^{-a_2\tau_2}y - uv)] + m(ce^{-a_3\tau_3}yw - bw - hz) \\ &= \tilde{m}[e^{-a_1\tau_1}(1 - \frac{x_1}{x})(-d(x - x_1) + \beta x_1 v_1 - \beta xv) + (1 - \frac{y_1}{y})(\beta e^{-a_1\tau_1}xv \\ &\quad - (a + pz_1)y + py(z_1 - z)) + \frac{a + pz_1}{ke^{-a_2\tau_2}}(1 - \frac{v_1}{v})(ke^{-a_2\tau_2}y - uv)] \\ &\quad + m(ce^{-a_3\tau_3}yw - bw - hz) \\ &= \tilde{m}[-de^{-a_1\tau_1} \frac{(x - x_1)^2}{x} + \beta e^{-a_1\tau_1}x_1 v_1 - \beta e^{-a_1\tau_1}xv - \beta e^{-a_1\tau_1}x_1 v_1 \frac{x_1}{x} \\ &\quad + \beta e^{-a_1\tau_1}x_1 v + \beta e^{-a_1\tau_1}xv - (a + pz_1)y + py(z_1 - z) - \beta e^{-a_1\tau_1}xv \frac{y_1}{y} \\ &\quad + (a + pz_1)y_1 - py_1(z_1 - z) + (a + pz_1)y - \frac{(a + pz_1)uv}{ke^{-a_2\tau_2}} - (a + pz_1)y \frac{v_1}{v} \\ &\quad + \frac{(a + pz_1)uv_1}{ke^{-a_2\tau_2}}] + m(ce^{-a_3\tau_3}yw - bw - hz) \end{aligned}$$

$$\begin{aligned}
&= \tilde{m}[-de^{-a_1\tau_1} \frac{(x-x_1)^2}{x} + \beta e^{-a_1\tau_1} x_1 v_1 (3 - \frac{x_1}{x} - \frac{xyy_1}{x_1 v_1 y} - \frac{yv_1}{y_1 v}) \\
&\quad + p(y_1 - y)z + p(y - y_1)z_1] + m(ce^{-a_3\tau_3} yw - bw - hz),
\end{aligned}$$

where

$$s - dx_1 - \beta x_1 v_1 = 0, \quad \beta e^{-a_1\tau_1} x_1 v_1 - (a + pz_1)y_1 = 0, \quad ke^{-a_2\tau_2} y_1 - uv_1 = 0, \quad z_1 = 0$$

and the inequality $f_1 + f_2 + f_3 \geq 3\sqrt[3]{f_1 f_2 f_3}$, ($f_1 > 0, f_2 > 0, f_3 > 0$) have been used.

Next, according to the method in [27], we can calculate the derivative of V_0 along (4) using the result for (26). We have

$$\begin{aligned}
\frac{dV_0}{dt} \Big|_{(1.4)} &= \frac{dV_0}{dt} \Big|_{(4.8)} + \tilde{m}(1 - \frac{y_1}{y})[\beta e^{-a_1\tau_1} x(t - \tau_1)v(t - \tau_1) - \beta e^{-a_1\tau_1} xv] \\
&\quad + \tilde{m} \frac{a + pz_1}{ke^{-a_2\tau_2}} (1 - \frac{v_1}{v})[ke^{-a_2\tau_2} y(t - \tau_2) - ke^{-a_2\tau_2} y] \\
&\quad + m[ce^{-a_3\tau_3} y(t - \tau_3)w(t - \tau_3) - ce^{-a_3\tau_3} yw] \\
&= \frac{dV_0}{dt} \Big|_{(4.8)} + \tilde{m}\beta e^{-a_1\tau_1} (1 - \frac{y_1}{y})[x(t - \tau_1)v(t - \tau_1) - xv] + \tilde{m}(a + pz_1) \\
&\quad \cdot (1 - \frac{v_1}{v})[y(t - \tau_2) - y] + mce^{-a_3\tau_3} [y(t - \tau_3)w(t - \tau_3) - yw] \\
&= -d\tilde{m}e^{-a_1\tau_1} \frac{(x-x_1)^2}{x} + \tilde{m}\beta e^{-a_1\tau_1} x_1 v_1 (3 - \frac{x_1}{x} - \frac{x(t - \tau_1)v(t - \tau_1)y_1}{x_1 v_1 y} \\
&\quad - \frac{y(t - \tau_2)v_1}{y_1 v} + \ln \frac{x(t - \tau_1)v(t - \tau_1)y(t - \tau_2)}{xyv}) + \tilde{m}p(y_1 - y)z \\
&\quad + m(ce^{-a_3\tau_3} y(t - \tau_3)w(t - \tau_3) - bw - hz) \\
&\quad + \tilde{m}\beta e^{-a_1\tau_1} x_1 v_1 (\frac{x(t - \tau_1)v(t - \tau_1)}{x_1 v_1} - \frac{xv}{x_1 v_1} - \ln \frac{x(t - \tau_1)v(t - \tau_1)}{xv} \\
&\quad + \frac{y(t - \tau_2)}{y_1} - \frac{y}{y_1} - \ln \frac{y(t - \tau_2)}{y}) \\
&= -d\tilde{m}e^{-a_1\tau_1} \frac{(x-x_1)^2}{x} + \tilde{m}\beta e^{-a_1\tau_1} x_1 v_1 (4 - \frac{x_1}{x} - \frac{x(t - \tau_1)v(t - \tau_1)y_1}{x_1 v_1 y} \\
&\quad - \frac{y(t - \tau_2)v_1}{y_1 v} - \frac{xvv_1}{xvv_1} + \ln \frac{x(t - \tau_1)v(t - \tau_1)y(t - \tau_2)}{xyv}) + \tilde{m}p(y_1 - y)z \\
&\quad + m(ce^{-a_3\tau_3} y(t - \tau_3)w(t - \tau_3) - bw - hz) \\
&\quad + \tilde{m}\beta e^{-a_1\tau_1} x_1 v_1 (\frac{x(t - \tau_1)v(t - \tau_1)}{x_1 v_1} - \frac{xv}{x_1 v_1} - \ln \frac{x(t - \tau_1)v(t - \tau_1)}{xv} \\
&\quad + \frac{y(t - \tau_2)}{y_1} - \frac{y}{y_1} - \ln \frac{y(t - \tau_2)}{y}).
\end{aligned}$$

(27)

To eliminate the last term of (27), we use the technique in [28] and define V_1 and V_2 as follows:

$$V_1 = \int_0^{\tau_1} H(\frac{x(t-\eta)v(t-\eta)}{x_1 v_1}) d\eta, \quad V_2 = \int_0^{\tau_2} H(\frac{y(t-\eta)}{y_1}) d\eta,$$

where $H(t) = t - 1 - \ln t$. $V_1 \geq 0, V_2 \geq 0$ and $V_1 = V_2 = 0$ if and only if $x(t)v(t) = x_1 v_1$ and $y = y_1$. It will be useful to digress here and give a brief outline of the property of $H(t)$. We introduce $U = \int_0^\tau H(\frac{\psi(t-\eta)}{\delta}) d\eta$, ψ stands for a positive

and continuous function, δ is a positive constant. Thus, we have

$$\begin{aligned}
 \frac{dU}{dt} &= \int_0^\tau \frac{d}{dt} H\left(\frac{\psi(t-\eta)}{\delta}\right) d\eta = - \int_0^\tau \frac{d}{d\eta} H\left(\frac{\psi(t-\eta)}{\delta}\right) d\eta \\
 &= H\left(\frac{\psi(t)}{\delta}\right) - H\left(\frac{\psi(t-\tau)}{\delta}\right) \\
 (29) \quad &= \frac{\psi(t)}{\delta} - \frac{\psi(t-\tau)}{\delta} + \ln \frac{\psi(t-\tau)}{\psi(t)}.
 \end{aligned}$$

From (29), we have

$$\begin{aligned}
 (30) \quad \frac{dV_1}{dt} &= \frac{xv}{x_1v_1} - \frac{x(t-\tau_1)v(t-\tau_1)}{x_1v_1} + \ln \frac{x(t-\tau_1)v(t-\tau_1)}{xv}, \\
 \frac{dV_2}{dt} &= \frac{y}{y_1} - \frac{y(t-\tau_2)}{y_1} + \ln \frac{y(t-\tau_2)}{y}.
 \end{aligned}$$

Finally, we construct the Lyapunov function $V = V_0 + \tilde{m}\beta e^{-a_1\tau_1} x_1v_1(V_1 + V_2)$. From (27) and (30), we have

$$\begin{aligned}
 \frac{dV}{dt} \Big|_{(1.4)} &= -d\tilde{m}e^{-a_1\tau_1} \frac{(x-x_1)^2}{x} + \tilde{m}\beta e^{-a_1\tau_1} x_1v_1 \left(4 - \frac{x_1}{x} - \frac{x(t-\tau_1)v(t-\tau_1)y_1}{x_1v_1y}\right. \\
 &\quad \left. - \frac{y(t-\tau_2)v_1}{y_1v} - \frac{xvv_1}{xvv_1} + \ln \frac{x(t-\tau_1)v(t-\tau_1)y(t-\tau_2)}{xyv}\right) \\
 &\quad - [mh + \tilde{m}p(y-y_1)]z + m[ce^{-a_3\tau_3}y(t-\tau_3)w(t-\tau_3) - bw].
 \end{aligned}$$

The second term is non-positive comes from the inequality

$$4 - \frac{x_1}{x} - \frac{y_1x(t-\tau_1)v(t-\tau_1)}{yx_1v_1} - \frac{v_1y(t-\tau_2)}{vy_1} - \frac{xvv_1}{xvv_1} + \ln \frac{x(t-\tau_1)v(t-\tau_1)y(t-\tau_2)}{xyv} \leq 0,$$

which can be obtained by (7) in [27] with $a_1 = x$, $a_2 = xvv_1$, $a_3 = x_1v_1y$, $a_4 = vy_1$, $b_1 = x_1$, $b_2 = xvv_1$, $b_3 = xvy_1$, $b_4 = v_1y$, $b'_3 = y_1x(t-\tau_1)v(t-\tau_1)$, $b'_4 = v_1y(t-\tau_2)$. Thus, the following inequality

$$\frac{dV}{dt} \Big|_{(1.4)} \leq -[mh + \tilde{m}p(y(t) - y_1)]z(t) + m[ce^{-a_3\tau_3}y(t-\tau_3)w(t-\tau_3) - bw(t)]$$

holds.

We assume $y > y_1$ and choose $\tilde{m} \gg m$ such that $\frac{dV}{dt} \Big|_{(1.4)} < 0$. Thus, the trajectory enters and stays in the region bounded by $y < y_1 + \varepsilon$ for $t \in [T_1, \infty)$ (finite time $T_1 > 0$). The inequality

$$\frac{b}{c(e^{-a_3\tau_3} - q)} - y_1 = \frac{b}{c(e^{-a_3\tau_3} - q)} - \frac{du(R_0 - 1)}{ke^{-a_2\tau_2}\beta} = \frac{b(1 - R_1)}{c(e^{-a_3\tau_3} - q)} > 0$$

when $R_1 < 1 < R_0$, implying that we can choose appropriate \tilde{m} and m to ensure that $y - \varepsilon < y_1 < \frac{b}{c(e^{-a_3\tau_3} - q)}$, i.e., $y < \frac{b}{c(e^{-a_3\tau_3} - q)} + \varepsilon$ for arbitrary small ε . Thus, the solution must enter and stay in the region bounded by $y \leq \frac{b}{c(e^{-a_3\tau_3} - q)}$ for $t \in [T_2, \infty)$ (finite time $T_2 > T_1$).

Next, we prove that the solution trajectory asymptotically tends to E_1 . From (17), we have

$$\left(\frac{b}{c(e^{-a_3\tau_3} - q)} - y^\infty\right)w^\infty = 0.$$

Since $y < \frac{b}{c(e^{-a_3\tau_3} - q)} + \varepsilon$, the above equation holds if and only if $w^\infty = 0$ (for $t \in [T_2, \infty)$), which generates $z^\infty = 0$ on the basis of (18). Hence, model (4) has

the same dynamics as

$$(31) \quad \begin{cases} \dot{x} = s - dx(t) - \beta x(t)v(t), \\ \dot{y} = \beta e^{-a_1\tau_1} x(t - \tau_1)v(t - \tau_1) - ay(t) - py(t)z(t), \\ \dot{v} = ke^{-a_2\tau_2} y(t - \tau_2) - uv(t). \end{cases}$$

By simple calculation, we obtain two equilibria of model (31) as follows:

$$\begin{aligned} \tilde{E}_0 &= (x_0, y_0, v_0) = \left(\frac{s}{d}, 0, 0\right), \\ \tilde{E}_1 &= (x_1, y_1, v_1) = \left(\frac{aue^{a_1\tau_1+a_2\tau_2}}{k\beta}, \frac{-adue^{a_2\tau_2} + sk\beta e^{-a_1\tau_1}}{ak\beta}, \frac{sk\beta e^{-a_1\tau_1-a_2\tau_2} - adu}{au\beta}\right). \end{aligned}$$

It is easy to verify that \tilde{E}_0 is unstable and \tilde{E}_1 is asymptotically stable if $R_1 < 1 < R_0$. To show the model (31) is globally asymptotically stable at \tilde{E}_1 , we define the Lyapunov function as

$$\begin{aligned} \tilde{V} &= e^{-a_1\tau_1} \left(x - x_1 - x_1 \ln \frac{x}{x_1}\right) + (y - y_1 - y_1 \ln \frac{y}{y_1}) + \frac{a + pz_1}{ke^{-a_2\tau_2}} (v - v_1 - v_1 \ln \frac{v}{v_1}) \\ &\quad + \beta e^{-a_1\tau_1} x_1 v_1 \left(\int_0^{\tau_1} H\left(\frac{x(t-\eta)v(t-\eta)}{x_1 v_1}\right) d\eta + \int_0^{\tau_2} H\left(\frac{y(t-\eta)}{y_1}\right) d\eta\right). \end{aligned}$$

Clearly,

$$\left.\frac{d\tilde{V}}{dt}\right|_{(4.12)} \leq -d\tilde{m}e^{-a_1\tau_1} \frac{(x - x_1)^2}{x} < 0.$$

Thus, when $R_1 < 1 < R_0$, the equilibrium \tilde{E}_1 of model (31) is globally asymptotically stable, which indicates that the equilibrium E_1 of model (4) is globally asymptotically stable. \square

As shown in Theorems 3.1-4.2, the infection-free equilibrium E_0 is globally asymptotically stable if $R_0 < 1$; when $R_0 > 1$, E_0 becomes unstable and the infectious equilibrium without immune response E_1 exists; when $R_1 < 1 < R_0$, the equilibrium E_1 is globally asymptotically stable. From which, we know that the time delays τ_1 , τ_2 and τ_3 do not affect the global stability of the equilibria E_0 and E_1 . Moreover, the forward transcritical bifurcation occurs as R_0 crosses the threshold value 1. Because this bifurcation is straightforward compared with Hopf bifurcation, we only plot it in Fig. 4. From Fig. 4, it is clear that model (1.4) exhibit a forward bifurcation at $R_0 = 1$.

5. Local stability of the infectious equilibrium with immune response E_2 and Hopf bifurcation from E_2

From the previous section, we show that the characteristic equations of equilibria E_0 and E_1 can be factored into lower degree polynomials, but it is difficult to factor the characteristic equation at E_2 . Thus, we determine the stability of E_2 by the different method in sections 3 and 4. We also show that Hopf bifurcation can occur from E_2 when the parameters satisfy certain condition in this section. Because we mainly focus on the local stability of E_2 , we always assume that $R_1 > 1$ and $0 \leq \tau_3 < -\frac{\ln q}{a_3}$.

To simplify the analysis for E_2 , let $\mu_1(t) = x(t) - x_2(t)$, $\mu_2(t) = y(t) - y_2(t)$, $\mu_3(t) = v(t) - v_2(t)$, $\mu_4(t) = w(t) - w_2(t)$, $\mu_5(t) = z(t) - z_2(t)$, then model (4)

becomes

$$(32) \quad \begin{cases} \dot{\mu}_1(t) = A\mu_1(t) + B\mu_3(t) + a_{11}\mu_1(t)\mu_3(t), \\ \dot{\mu}_2(t) = I\mu_2(t) + D\mu_5(t) + E\mu_1(t - \tau_1) + F\mu_3(t - \tau_1) \\ \quad + a_{12}\mu_1(t - \tau_1)\mu_3(t - \tau_1) + a_{13}\mu_2(t)\mu_5(t), \\ \dot{\mu}_3(t) = G\mu_2(t - \tau_2) + H\mu_3(t), \\ \dot{\mu}_4(t) = L\mu_2(t - \tau_3) - Q\mu_2(t) + M\mu_4(t - \tau_3) - N\mu_4(t) \\ \quad + a_{14}\mu_2(t - \tau_3)\mu_4(t - \tau_3) + a_{15}\mu_2(t)\mu_4(t), \\ \dot{\mu}_5(t) = Q\mu_2(t) + R\mu_4(t) + T\mu_5(t) - a_{15}\mu_2(t)\mu_4(t), \end{cases}$$

where

$$\begin{aligned} A &= -d - \beta v_2, & B &= -\beta x_2, & a_{11} &= -\beta, & I &= -a - pz_2, & D &= -py_2, \\ E &= \beta e^{-a_1\tau_1} v_2, & F &= \beta e^{-a_1\tau_1} x_2, & a_{12} &= \beta e^{-a_1\tau_1}, & a_{13} &= -p, & G &= ke^{-a_2\tau_2}, \\ H &= -u, & L &= ce^{-a_3\tau_3} w_2, & M &= ce^{-a_3\tau_3} y_2, & N &= cqy_2 + b, & a_{14} &= ce^{-a_3\tau_3}, \\ a_{15} &= -cq, & Q &= cqw_2, & R &= cqy_2, & T &= -h. \end{aligned}$$

Because the infectious equilibrium with immune response E_2 of model (4) is transformed into the zero equilibrium $(0, 0, 0, 0, 0)$ of model (32), it is sufficient to study the stability of the origin for (32). The linearization of (32) at $(0, 0, 0, 0, 0)$ is

$$(33) \quad \begin{cases} \dot{\mu}_1(t) = A\mu_1(t) + B\mu_3(t), \\ \dot{\mu}_2(t) = I\mu_2(t) + D\mu_5(t) + E\mu_1(t - \tau_1) + F\mu_3(t - \tau_1), \\ \dot{\mu}_3(t) = G\mu_2(t - \tau_2) + H\mu_3(t), \\ \dot{\mu}_4(t) = L\mu_2(t - \tau_3) - Q\mu_2(t) + M\mu_4(t - \tau_3) - N\mu_4(t), \\ \dot{\mu}_5(t) = Q\mu_2(t) + R\mu_4(t) + T\mu_5(t), \end{cases}$$

and the corresponding characteristic equation is

$$(34) \quad \lambda^5 + b_4\lambda^4 + b_3\lambda^3 + b_2\lambda^2 + b_1\lambda + b_0 + (d_4\lambda^4 + d_3\lambda^3 + d_2\lambda^2 + d_1\lambda + d_0)e^{-\lambda\tau_3} \\ + (p_3\lambda^3 + p_2\lambda^2 + p_1\lambda + p_0)e^{-\lambda(\tau_1+\tau_2)} + (s_2\lambda^2 + s_1\lambda + s_0)e^{-\lambda(\tau_1+\tau_2+\tau_3)} = 0,$$

where

$$\begin{aligned} b_4 &= -I - H - T + N - A, \\ b_3 &= -HN + AH - QD - AN + HT + IA + AT - IN + IH + IT - NT, \\ b_2 &= -IAH + IHN + INT - IHT + AHN + AQD - QDN - AHT + IAN \\ &\quad - IAT + QDH + HNT + DRQ + ANT, \\ b_1 &= QDHN - AHNT + AQDN - AQDH - ADRQ - DRQH - IANT \\ &\quad - IAHN - IHNT + IAHT, \\ b_0 &= ADRQH - AQDHN + IAHNT, & d_4 &= -M, \\ d_3 &= AM + IM + HM + MT, \\ d_2 &= -IHM + QDM - AHM - AMT - DRL - IMT - HMT - IAM, \\ d_1 &= IAMT + AHMT + IAHM + DRLH - QDHM \\ &\quad - AQDM + IHMT + ADRL, \\ d_0 &= -IAHMT - ADRLH + AQDHM, \\ p_3 &= -GF, & p_2 &= GFT - GFN + AGF - EGB, \\ p_1 &= GFNT + EGBT - EGBN - AGFT + AGFN, \\ p_0 &= -AGFNT + EGBNT, & s_2 &= GFM, \end{aligned}$$

$$s_1 = -AGFM + EGBM - GFMT, \quad s_0 = -EGBMT + AGFMT.$$

We note that the characteristic equation (34) is a transcendental equation of λ , so the following lemma is useful.

Lemma 5.1. [29] *For the transcendental equation*

$$\begin{aligned} p(\lambda, e^{-\lambda\tau_1}, \dots, e^{-\lambda\tau_m}) &= \lambda^n + p_1^{(0)}\lambda^{n-1} + \dots + p_{n-1}^{(0)}\lambda + p_n^{(0)} \\ &\quad + [p_1^{(1)}\lambda^{n-1} + \dots + p_{n-1}^{(1)}\lambda + p_n^{(1)}]e^{-\lambda\tau_1} \\ &\quad + \dots + [p_1^{(m)}\lambda^{n-1} + \dots + p_{n-1}^{(m)}\lambda + p_n^{(m)}]e^{-\lambda\tau_m} = 0, \end{aligned}$$

where $\tau_i (i = 1, 2, \dots, m)$ and $p_j^{(i)} (i = 0, 1, 2, \dots, m; j = 1, 2, \dots, n)$ are constants. As $(\tau_1, \tau_2, \dots, \tau_m)$ varies, the sum of orders of the zeros of $p(\lambda, e^{-\lambda\tau_1}, \dots, e^{-\lambda\tau_m})$ in the open right half plane can change, and only a zero appears on or crosses the imaginary axis.

It is well known that the zero equilibrium $(0, 0, 0, 0, 0)$ of model (32) is asymptotically stable if all roots of equation (34) locate the left-half complex plane, or it is unstable when equation (34) has a root with positive real part. Thus, we will discuss the distribution of roots of equation (34) when τ_1, τ_2 and τ_3 have following different values.

5.1. Case (I): $\tau_1 = \tau_2 = \tau_3 = 0$. In the absence of three delays, the equation (34) becomes

$$(35) \quad \begin{aligned} &\lambda^5 + (b_4 + d_4)\lambda^4 + (b_3 + d_3 + p_3)\lambda^3 + (b_2 + d_2 + p_2 + s_2)\lambda^2 \\ &\quad + (b_1 + d_1 + p_1 + s_1)\lambda + b_0 + d_0 + p_0 + s_0 = 0. \end{aligned}$$

By employing the Routh-hurwitz criteria for the equation (35), a set of necessary and sufficient conditions which all roots of (35) have negative real parts are given in the following form:

$$\begin{aligned} (T1) \quad \Delta_1 &= b_4 + d_4 > 0, \\ \Delta_2 &= (b_4 + d_4)(b_3 + d_3 + p_3) - (b_2 + d_2 + p_2 + s_2) > 0, \\ \Delta_3 &= -(b_4 + d_4)^2(b_1 + d_1 + p_1 + s_1) + (b_4 + d_4)[(b_3 + d_3 + p_3)(b_2 + d_2 + p_2 + s_2) \\ &\quad + (b_0 + d_0 + p_0 + s_0)] \\ &\quad - (b_2 + d_2 + p_2 + s_2)^2 > 0, \\ \Delta_4 &= -[(b_4 + d_4)(b_1 + d_1 + p_1 + s_1) - (b_0 + d_0 + p_0 + s_0)]^2 + [(b_2 + d_2 + p_2 + s_2)(b_1 + d_1 + p_1 + s_1) \\ &\quad - (b_3 + d_3 + p_3)(b_0 + d_0 + p_0 + s_0)][(b_4 + d_4)(b_3 + d_3 + p_3) - (b_2 + d_2 + p_2 + s_2)] > 0, \\ \Delta_5 &= (b_0 + d_0 + p_0 + s_0)\Delta_4 > 0. \end{aligned}$$

Thus, we have following result for the local stability of the equilibrium E_2 .

Theorem 5.1. *When $R_1 > 1$ and the coefficients of the equation (35) satisfy (T1), the infectious equilibrium with immune response E_2 is locally asymptotically stable.*

5.2. Case (II): $\tau_1 = \tau_2 = 0$ and $0 < \tau_3 < -\frac{\ln q}{a_3}$. When the intracellular delays [18] τ_1, τ_2 are zero and the immune delay $0 < \tau_3 < -\frac{\ln q}{a_3}$, the characteristic equation (34) becomes

$$(36) \quad \lambda^5 + h_9\lambda^4 + h_8\lambda^3 + h_7\lambda^2 + h_6\lambda + h_5 + (h_4\lambda^4 + h_3\lambda^3 + h_2\lambda^2 + h_1\lambda + h_0)e^{-\lambda\tau_3} = 0,$$

where

$$\begin{aligned} h_9 &= b_4, & h_8 &= b_3 + p_3, & h_7 &= b_2 + p_2, & h_6 &= b_1 + p_1, & h_5 &= b_0 + p_0, \\ h_4 &= d_4, & h_3 &= d_3, & h_2 &= s_2 + d_2, & h_1 &= s_1 + d_1, & h_0 &= s_0 + d_0. \end{aligned}$$

Assume that $\lambda = i\omega$ ($\omega > 0$) is a root of the equation (36), then separating the real and imaginary parts, we have

$$(37) \quad \begin{cases} h_9\omega^4 - h_7\omega^2 + h_5 = -(h_4\omega^4 - h_2\omega^2 + h_0) \cos(\omega\tau_3) - (-h_3\omega^3 + h_1\omega) \sin(\omega\tau_3), \\ \omega^5 - h_8\omega^3 + h_6\omega = -(-h_3\omega^3 + h_1\omega) \cos(\omega\tau_3) + (h_4\omega^4 - h_2\omega^2 + h_0) \sin(\omega\tau_3). \end{cases}$$

Squaring and adding the two equations in (37) yields

$$(38) \quad \omega^{10} + c_1\omega^8 + c_2\omega^6 + c_3\omega^4 + c_4\omega^2 + c_5 = 0,$$

where

$$\begin{aligned} c_1 &= h_9^2 - h_4^2 - 2h_8, & c_2 &= 2h_4h_2 - 2h_9h_7 + h_8^2 - h_3^2 + 2h_6, \\ c_3 &= h_7^2 - 2h_4h_0 + 2h_3h_1 - h_2^2 - 2h_8h_6 + 2h_9h_5, \\ c_4 &= -h_1^2 - 2h_7h_5 + h_6^2 + 2h_2h_0, & c_5 &= -h_0^2 + h_5^2. \end{aligned}$$

Denote $\nu = \omega^2$, then (38) becomes

$$(39) \quad \nu^5 + c_1\nu^4 + c_2\nu^3 + c_3\nu^2 + c_4\nu + c_5 = 0.$$

In order to study the local Hopf bifurcation at E_2 of model (4), the equation (39) should have at least a positive real root.

Using $e^{-a_3\tau_3} - q > 0$ and $ce^{-a_3\tau_3}y_2 = cqy_2 + b$ (i.e., $M = N$), we obtain $c_5 > 0$ by simple calculation. It is easy to see that if the condition

$$(T2) \quad c_1 > 0, c_2 > 0, c_3 > 0, c_4 > 0$$

holds, the equation (39) has no positive root. Otherwise, if the condition

$$(T3) \quad (39) \text{ has at least one positive root } \nu_0$$

holds, then the equation (36) has a pair of purely imaginary roots $\pm i\omega_+ = \pm i\sqrt{\nu_0}$. By substituting ω_+ into (37), we obtain

$$\cos(\omega_+\tau_3) = -\frac{(-h_3 + h_4h_9)\omega_+^8 + (h_1 - h_2h_9 + h_3h_8 - h_4h_7)\omega_+^6 + (h_0h_9 - h_1h_8 + h_2h_7 - h_3h_6 + h_4h_5)\omega_+^4 + (-h_0h_7 + h_1h_6 - h_2h_5)\omega_+^2 + h_0h_5}{(h_4\omega_+^4 - h_2\omega_+^2 + h_0)^2 + (-h_3\omega_+^3 + h_1\omega)^2}.$$

Since $\cos x$ is a periodic function with period 2π , the critical value have the following form:

$$\begin{aligned} \tau_{3_j} &= \frac{1}{\omega_+} \left[\arccos\left(-\frac{(-h_3 + h_4h_9)\omega_+^8 + (h_1 - h_2h_9 + h_3h_8 - h_4h_7)\omega_+^6 + h_0h_9\omega_+^4}{(h_4\omega_+^4 - h_2\omega_+^2 + h_0)^2 + (-h_3\omega_+^3 + h_1\omega)^2}\right) \right. \\ &\quad \left. + \frac{(-h_1h_8 + h_2h_7 - h_3h_6 + h_4h_5)\omega_+^4 + (-h_0h_7 + h_1h_6 - h_2h_5)\omega_+^2 + h_0h_5}{(h_4\omega_+^4 - h_2\omega_+^2 + h_0)^2 + (-h_3\omega_+^3 + h_1\omega)^2} \right] + 2j\pi, \end{aligned}$$

($j = 0, 1, 2, 3, \dots$). Let $\lambda(\tau_3) = \alpha(\tau_3) + i\omega(\tau_3)$ be the root of the equation (36) near $\tau_3 = \tau_{3_j}$ satisfying $\alpha(\tau_{3_j}) = 0$ and $\omega(\tau_{3_j}) = \omega_+$. By differentiating the equation (36) with respect to τ_3 , we get

$$\frac{d\lambda}{d\tau_3} = \frac{\lambda(h_4\lambda^4 + h_3\lambda^3 + h_2\lambda^2 + h_1\lambda + h_0)}{(5\lambda^4 + 4h_9\lambda^3 + 3h_8\lambda^2 + 2h_7\lambda + h_6)e^{\lambda\tau_3} + (4h_4\lambda^3 + 3h_3\lambda^2 + 2h_2\lambda + h_1) - \tau_3(h_4\lambda^4 + h_3\lambda^3 + h_2\lambda^2 + h_1\lambda + h_0)}.$$

Substituting $\tau_3 = \tau_{3_j}$ into the above equation yields

$$\left. \frac{d\lambda}{d\tau_3} \right|_{\tau_3=\tau_{3_j}}$$

$$(40) = \frac{(i\omega_+)(h_4\omega_+^4 - ih_3\omega_+^3 - h_2\omega_+^2 + ih_1\omega_+ + h_0)}{(5\omega_+^4 - 4ih_9\omega_+^3 - 3h_8\omega_+^2 + 2ih_7\omega_+ + h_6)e^{i\omega_+(\tau_{3j})} + (-4ih_4\omega_+^3 - 3h_3\omega_+^2 + 2ih_2\omega_+ + h_1) - \tau_{3j}(h_4\omega_+^4 - ih_3\omega_+^3 - h_2\omega_+^2 + ih_1\omega_+ + h_0)}.$$

Notice that

$$\Re\left(\frac{d\lambda}{d\tau_3}\Big|_{\tau_3=\tau_{3j}}\right) \neq 0 \Leftrightarrow \Re\left(\frac{d\lambda}{d\tau_3}\Big|_{\tau_3=\tau_{3j}}\right)^{-1} \neq 0.$$

From (40), we obtain

$$\Re\left(\frac{d\lambda}{d\tau_3}\Big|_{\tau_3=\tau_{3j}}\right)^{-1} \neq 0.$$

According to the above results, we have the following theorem.

Theorem 5.2. *When $R_1 > 1$, $0 < \tau_3 < -\frac{\ln q}{a_3}$ and the condition (T1) is satisfied, then we have the following conclusions,*

- (i) *If (T2) holds, then the equilibrium E_2 of model (4) is asymptotically stable.*
- (ii) *If the condition (T3) holds, then the infectious equilibrium with immune response E_2 of model (4) is locally asymptotically stable for $\tau_3 \in [0, \tau_{3_0})$ and becomes unstable for $\tau_3 > \tau_{3_0}$. Moreover, when $\tau_3 = \tau_{3_0}$, a Hopf bifurcation occurs. That is, a family of periodic solutions bifurcate from E_2 as τ_3 passes through the critical value τ_{3_0} .*

5.3. Case (III): $\tau_1 > 0, \tau_2 > 0$ and $\tau_3 = 0$. When intracellular delays $\tau_1, \tau_2 \neq 0$ and immune delay $\tau_3 = 0$, the characteristic equation (34) becomes

$$(41) \quad \lambda^5 + m_8\lambda^4 + m_7\lambda^3 + m_6\lambda^2 + m_5\lambda + m_4 + (m_3\lambda^3 + m_2\lambda^2 + m_1\lambda + m_0)e^{-\lambda(\tau_1+\tau_2)} = 0,$$

where

$$\begin{aligned} m_8 &= b_4 + d_4, & m_7 &= b_3 + d_3, & m_6 &= b_2 + d_2, & m_5 &= b_1 + d_1, & m_4 &= b_0 + d_0, \\ m_3 &= p_3, & m_2 &= s_2 + p_2, & m_1 &= s_1 + p_1, & m_0 &= s_0 + p_0. \end{aligned}$$

Here, we assume that τ_1 is a parameter and τ_2 is located within a stable interval. Similar to case (II), let $\lambda = i\varpi$ ($\varpi > 0$) is a root of (41), then (41) can be rewritten as

$$(42) \quad h(\varpi) = \varpi^{10} + g_1\varpi^8 + g_2\varpi^6 + g_3\varpi^4 + g_4\varpi^2 + g_5 = 0,$$

where

$$\begin{aligned} g_1 &= m_8^2 - 2m_7, & g_2 &= m_7^2 - m_3^2 - 2m_8m_6 + 2m_5, \\ g_3 &= 2m_8m_4 + m_6^2 - 2m_7m_5 - m_2^2 + 2m_1m_3, \\ g_4 &= m_5^2 - m_1^2 + 2m_2m_0 - 2m_6m_4, & g_5 &= m_4^2 - m_0^2. \end{aligned}$$

By simple calculation, we find that $g_5 > 0$ always holds. We assume that the condition of Hopf bifurcation similars to those in case (II), that is,

(T4) (42) has at least one positive root

holds, and define the positive roots of the equation (42) are $\varpi_1, \varpi_2, \dots, \varpi_{10}$. Since the periodicity of trigonometric function, there exists a sequence $\{\tau_{1_i}^j | j = 1, 2, 3, \dots\}$ for every fixed $\varpi_i (i = 1, 2, 3, \dots, 10)$. Define

$$\tau_{1_0} = \min\{\tau_{1_i}^j | i = 1, 2, \dots, n; j = 1, 2, 3, \dots\}.$$

When $\tau_3 = 0$, $\tau_1 = \tau_{1_0}$ and $\tau_2 \in [0, \tau_{2_0}]$, equation (41) has a pair of purely imaginary roots $\pm(i\varpi)$. If

$$(T5) \Re\left(\frac{d\lambda}{d\tau_1}\Big|_{\lambda=i\omega}\right) \neq 0$$

holds, we have the following theorem.

Theorem 5.3. *When $R_1 > 1$, for $\tau_1 > 0$, $\tau_2 > 0$ and $\tau_3 = 0$, assume that (T1), (T4) and (T5) are satisfied, then the infectious equilibrium with immune response E_2 of model (4) is locally asymptotically stable for $\tau_1 \in [0, \tau_{1_0}]$, and becomes unstable for $\tau_1 > \tau_{1_0}$. Furthermore, when $\tau_1 = \tau_{1_0}$, a Hopf bifurcation occurs. That is, a family of periodic solutions bifurcate from E_2 as τ_1 passes through the critical value τ_{1_0} .*

In [18], the authors divide three time delays into intracellular delay and immune delay. In this paper, we also focus on the effect of intracellular delays (τ_1 and τ_2) and immune delay (τ_3) on HIV-1 infection model. In addition, the research methods and conclusions of the other four cases ($\tau_1 = \tau_3 = 0, \tau_2 > 0$ ’, $\tau_2 = \tau_3 = 0, \tau_1 > 0$ ’, $\tau_2 = 0, \tau_1 > 0, \tau_3 > 0$ ’ and $\tau_1 = 0, \tau_2 > 0, \tau_3 > 0$ ’) are similar to those of cases (II) and (III). Thus, we ignore the other cases to make the presentation more clear.

5.4. Case (IV): $\tau_1 > 0, \tau_2 > 0$ and $0 < \tau_3 < -\frac{\ln q}{a_3}$. For the equation (34), we can regard τ_2 as a parameter and τ_1, τ_3 are located within stable interval. Let $\lambda = i\omega (\omega > 0)$ to be a purely imaginary root of (34), we obtain

$$(43) \omega^{10} + l_1\omega^9 + l_2\omega^8 + l_3\omega^7 + l_4\omega^6 + l_5\omega^5 + l_6\omega^4 + l_7\omega^3 + l_8\omega^2 + l_9\omega + l_{10} = 0,$$

where

$$\begin{aligned} r_1 &= \cos \omega\tau_3, & r_2 &= \sin \omega\tau_3, & l_1 &= -2d_4r_2, \\ l_2 &= b_4^2 - 2d_3r_1 + 2b_4d_4r_1 - 2b_3 + d_4^2, \\ l_3 &= 2d_2r_2 - 2b_4d_3r_2 + 2b_3d_4r_2, \\ l_4 &= 2b_1 + d_3^2 - 2b_2d_4r_1 - 2b_4b_2 - p_3^2 + 2d_1r_1 + 2b_3d_3r_1 - 2d_4d_2 - 2b_4d_2r_1 + b_3^2, \\ l_5 &= 2p_3r_2s_2 + 2b_4d_1r_2 + 2b_2d_3r_2 - 2d_0r_2 - 2b_3d_2r_2 - 2b_1d_4r_2, \\ l_6 &= b_2^2 - 2b_3b_1 + 2d_4d_0 - 2b_3d_1r_1 + 2b_4b_0 + 2p_3r_1s_1 + 2b_2d_2r_1 - 2d_3d_1 + d_2^2 \\ &\quad - p_2^2 - s_2^2 + 2b_4d_0r_1 + 2p_3p_1 + 2b_0d_4r_1 - 2p_2r_1s_2 - 2b_1d_3r_1, \\ l_7 &= 2p_2r_2s_1 - 2p_3r_2s_0 + 2b_3d_0r_2 - 2p_1r_2s_2 - 2b_0d_3r_2 - 2b_2d_1r_2, \\ l_8 &= d_1^2 - s_1^2 - 2p_1r_1s_1 + 2p_2r_1s_0 + 2p_0p_2 + 2s_0s_2 - 2b_2d_0r_1 + 2p_0r_1s_2 + b_1^2 - p_1^2 \\ &\quad - 2b_0d_2r_1 + 2b_1d_1r_1 - 2b_0b_2 - 2d_0d_2, \\ l_9 &= -2b_1d_0r_2 - 2p_0r_2s_1 + 2b_0d_1r_2 + 2p_1r_2s_0, \\ l_{10} &= 2b_0d_0r_1 + b_0^2 - s_0^2 - p_0^2 - 2p_0s_0r_1 + d_0^2. \end{aligned}$$

Denote

$$(44) h(\omega) = \omega^{10} + l_1\omega^9 + l_2\omega^8 + l_3\omega^7 + l_4\omega^6 + l_5\omega^5 + l_6\omega^4 + l_7\omega^3 + l_8\omega^2 + l_9\omega + l_{10}.$$

We assume that

$$(T6) l_{10} < 0$$

holds, and thus $h(0) < 0$ holds. Because $h(\omega) \rightarrow +\infty$ as $\omega \rightarrow +\infty$, the equation (43) has finite positive roots $\omega_1, \omega_2, \dots, \omega_{10}$. Since the periodicity of trigonometric function, there exists a sequence $\{\tau_{2_i}^j | j = 1, 2, 3, \dots\}$ for every fixed $\omega_i (i = 1, 2, 3, \dots, 10)$. Define

$$\tau_{2_0} = \min\{\tau_{2_i}^j | i = 1, 2, \dots, k; j = 1, 2, 3, \dots\}.$$

When $\tau_2 = \tau_{2_0}$ and $\tau_1 \in [0, \tau_{1_0}]$, $\tau_3 \in [0, \tau_{3_0}]$, the equation (43) has a pair of purely imaginary roots $\pm(i\omega)$. Let condition

$$(T7) \Re\left(\frac{d\lambda}{d\tau_2}\Big|_{\lambda=i\omega}\right) \neq 0$$

hold, we have the following theorem.

Theorem 5.4. *When $R_1 > 1$, for $\tau_1 > 0, \tau_2 > 0$ and $0 < \tau_3 < -\frac{\ln q}{a_3}$, assume that (T1), (T3), (T4), (T5), (T6) and (T7) are satisfied, then the infectious equilibrium with immune response E_2 of model (4) is locally asymptotically stable for $\tau_2 \in [0, \tau_{2_0}]$ and becomes unstable for $\tau_2 > \tau_{2_0}$. Furthermore, when $\tau_2 = \tau_{2_0}$, a Hopf bifurcation occurs. That is, a family of periodic solutions bifurcate from E_2 as τ_2 passes through the critical value τ_{2_0} .*

6. Numerical simulations

In this section, we demonstrate the theoretical results obtained in the sections 3, 4 and 5 through numerical simulations. We have shown that the basic reproduction number R_0 and the immune reproduction number R_1 play a decisive role in determining the dynamics in sections 3 and 4. Thus, for convenience, we vary R_0 and R_1 by changing s and fixing the rest of the parameter values in model (4). Next, when $R_1 > 1$ and $0 \leq \tau_3 < -\frac{\ln q}{a_3}$, we choose τ_1, τ_2 or τ_3 as a bifurcation parameter and fix all other parameter values in model (4) for the simulations of the section 5.

Let

$$(45) \quad \begin{aligned} d = c = h = q = \frac{1}{10}, \beta = \frac{3}{400}, p = 1, b = 0.6, a = 0.02, k = 27, \\ u = 5.2, a_1 = 0.02, a_2 = 0.28, a_3 = 0.08, \tau_1 = 0, \tau_2 = 13, \tau_3 = 24. \end{aligned}$$

With these parameter values, we have

$$R_0 = \frac{19.47115384}{e^{3.64}} s$$

and

$$R_1 = 41.15226337 \left(\frac{1}{e^{1.92}} - 0.1 \right) (0.2025s - 0.0104).$$

6.1. Infection-free equilibrium E_0 . Straightforward calculation shows that when $0 < s < 1.95$, the inequality $0 < R_0 < 1$ holds. If $s = 1.4$, we get the infection-free equilibrium $E_0 : (x, y, v, w, z) = (14, 0, 0, 0, 0)$. Numerical simulation for the infection-free equilibrium E_0 are shown in Fig. 2 which shows that E_0 is asymptotically stable. This confirms the result in Theorem 3.2.

6.2. Infectious equilibrium without immune response E_1 . Increasing s to pass through the critical value 1.95 causes E_0 loses its stability and the equilibrium E_1 exists. According to Theorem 4.2, E_1 is asymptotically stable when $R_1 < 1 < R_0$, i.e., $1.95 < s < 2.63$. We choose $s = 2.6$, with the parameter values given in (45), the infectious equilibrium without immune response E_1 becomes $E_1 : (x, y, v, w, z) = (19.5632, 32.1839, 4.387, 0, 0)$. Numerical simulation for the infectious equilibrium without immune response E_1 are shown in Fig. 3 which shows that E_1 is asymptotically stable. This confirms the result in Theorem 4.2.

6.3. Infectious equilibrium with immune response E_2 . In this section, we consider model (4) with the coefficients:

$$(46) \quad \begin{aligned} d = c = h = q = \frac{1}{10}, \beta = \frac{3}{400}, p = 1, b = 0.6, a = 0.02, \\ k = 27, u = 5.2, s = 7, a_1 = 0.02, a_2 = 0.28, a_3 = 0.08. \end{aligned}$$

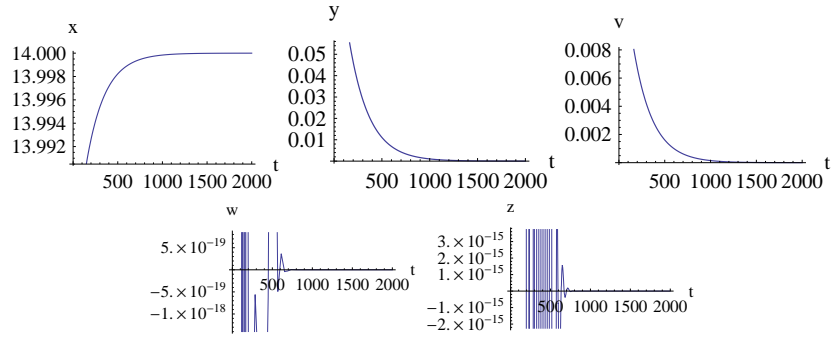


FIGURE 2. The numerical approximations of system (4) for the parameter values given in (45) and $s = 1.4$, which shows that solution trajectories converge to the infection-free equilibrium $E_0 : (x, y, v, w, z) = (14, 0, 0, 0, 0)$.

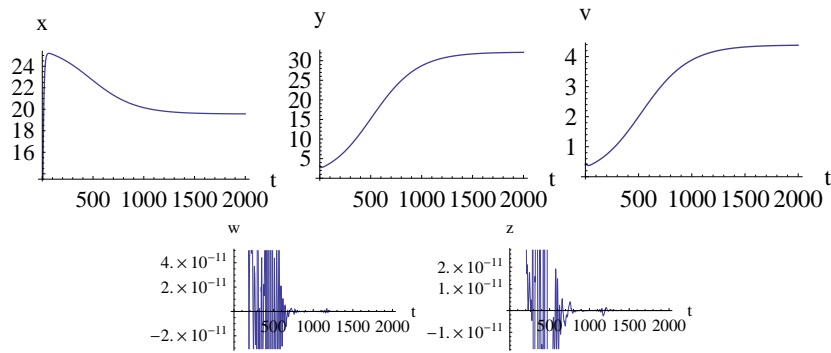


FIGURE 3. The numerical approximations of system (4) for the parameter values given in (45) and $s = 2.6$, which shows that solution trajectories converge to the infectious equilibrium without immune response $E_1 : (x, y, v, w, z) = (19.5632, 32.1839, 4.387, 0, 0)$.

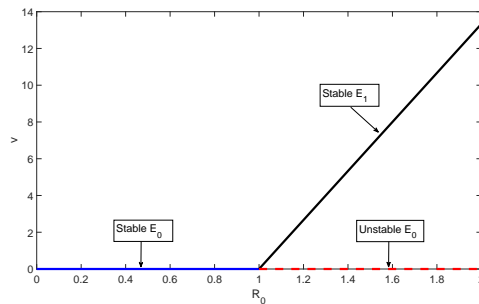


FIGURE 4. The figure of the virus versus the basic reproduction number R_0

Based on the analysis in the section 5, the four cases will be simulated.

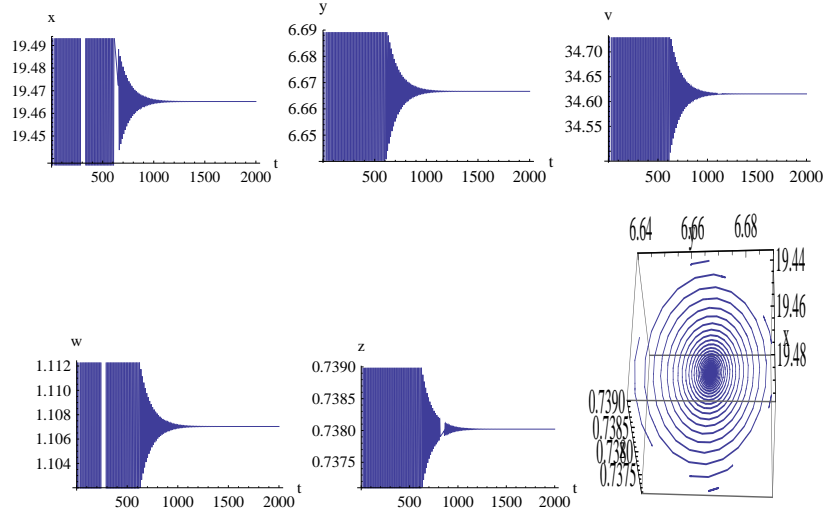


FIGURE 5. The numerical approximations of system (4) for the parameter values given in (46) and $\tau_1 = \tau_2 = \tau_3 = 0$, showing that the infectious equilibrium with immune response $E_2 : (x, y, v, w, z) = (19.4652, 6.66667, 34.6154, 1.10703, 0.738021)$ is asymptotically stable.

Case (I): In the absence of delays (i.e., $\tau_1 = \tau_2 = \tau_3 = 0$), we choose the parameter values in (46). In this case, $R_1 = 52.1148 > 1$ and $0 \leq \tau_3 < -\frac{\ln q}{a_3} \approx 28.78$, i.e., the conditions for existence of the infectious equilibrium with immune response E_2 are satisfied. Note that we always choose $\tau_3 < 28.78$ in the following simulation. Substituting the parameter values in (46) into the expressions in (T1), we have $\Delta_1 = 4.32578 > 0$, $\Delta_2 = 25.1694 > 0$, $\Delta_3 = 53.2214 > 0$, $\Delta_4 = 14.0264 > 0$, $\Delta_5 = 2.3608 > 0$. Thus, the equilibrium $E_2 = (19.4652, 6.66667, 34.6154, 1.10703, 0.738021)$ is asymptotically stable (see Fig. 5). This confirms the result in Theorem 5.1.

Case (II): In the absence of intracellular delays and using the parameter values in (46), the conditions (T1) and (T3) hold. In this case, we obtain the critical value of immune delay $\tau_{3_0} = 19.2107$. If $\tau_3 = 11.6 < \tau_{3_0}$, the immune reproduction number $R_1 = 17.1 > 1$, the solution trajectories converge to the infectious equilibrium with immune response $E_2 = (7.85524, 20.3153, 105.483, 0.140732, 0.285901)$ after some initial transient oscillations (see Fig. 6). When $\tau_3 = 24 > \tau_{3_0}$, model (4) undergoes Hopf bifurcation and the periodic solutions are shown in Fig. 7. The results obtained in Theorem 5.2 are verified.

Case (III): In the absence of immune delay ($\tau_3 = 0$), we choose $\tau_2 = 3.6$ and fix all other parameter values in (46). With these values, we know that the conditions (T1), (T4) and (T5) are satisfied. Moreover, the critical value of delay τ_1 is 11.4942. When $\tau_1 = 9 < 11.4942$, the solution trajectories are shown in Fig. 8. From Fig. 8, we observe that the solution trajectories eventually tend to the infectious equilibrium with immune response $E_2 = (35.9442, 6.6667, 12.6328, 0.61003, 0.406687)$. If we choose $\tau_1 = 12.6 > 11.4942$, the model (4) undergoes Hopf bifurcation and the periodic solutions are shown in Fig. 9. This confirms the result in Theorem 5.3.

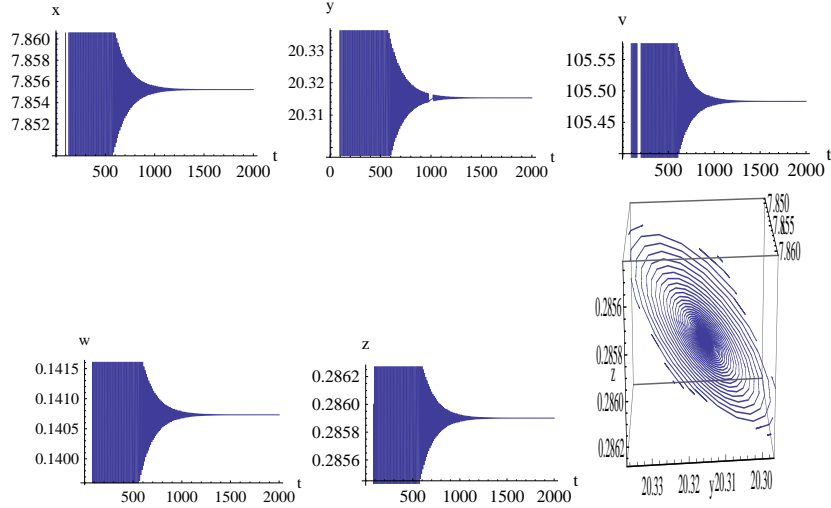


FIGURE 6. The numerical approximations of system (4) for the parameter values given in (46) and $\tau_1 = \tau_2 = 0$, $\tau_3 = 11.6 < 19.2107$, showing that solution trajectories converge to the infectious equilibrium with immune response $E_2 : (x, y, v, w, z) = (7.85524, 20.3153, 105.483, 0.140732, 0.285901)$.

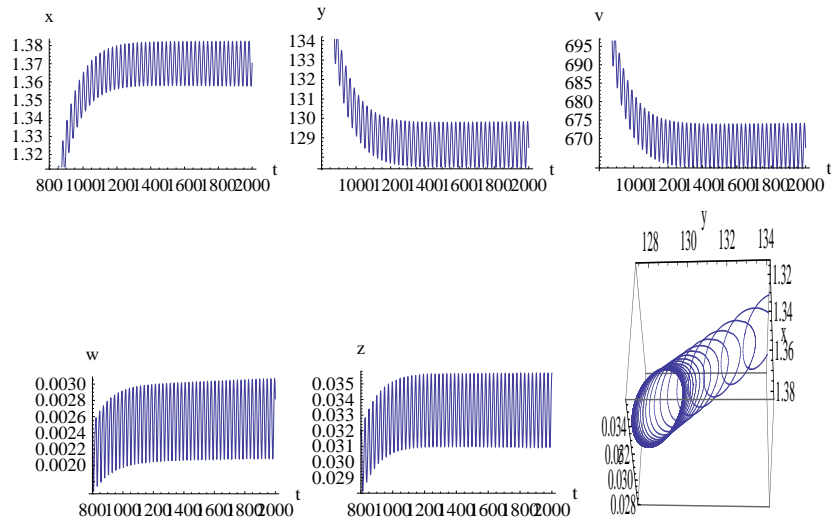


FIGURE 7. The numerical approximations of system (4) for the parameter values given in (46) and $\tau_1 = \tau_2 = 0$, $\tau_3 = 24 > 19.2107$, showing that Hopf bifurcation occurs from the infectious equilibrium with immune response $E_2 : (x, y, v, w, z) = (1.36893, 128.736, 668.438, 0.002587, 0.033314)$.

Case (IV): When $\tau_1 > 0, \tau_2 > 0$ and $0 < \tau_3 < -\frac{\ln q}{a_3}$, we choose $\tau_1 = 1, \tau_3 = 1$ and use the parameter values in (46). In this case, the conditions (T1) and (T3)-(T7) hold, the critical value of delay is $\tau_{2_0} = 5.11681$. For the case $\tau_2 = 0.5 < \tau_{2_0}$, the solution trajectories converge to the infectious equilibrium with immune response

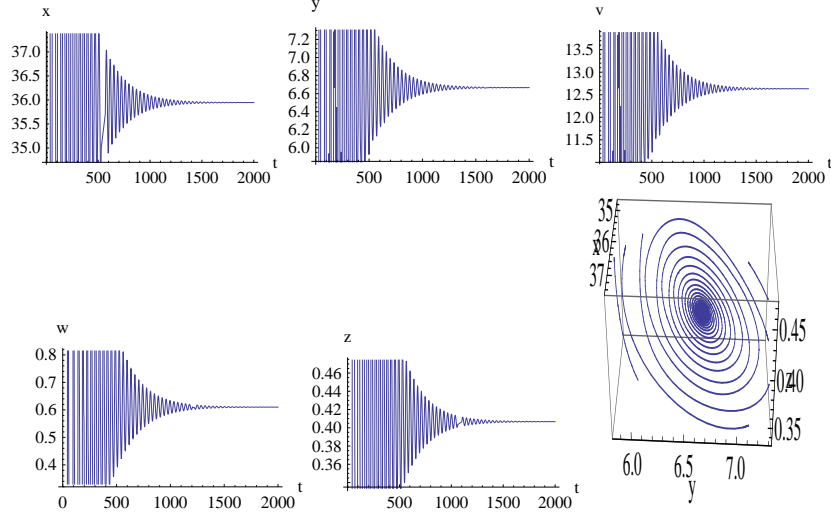


FIGURE 8. The numerical approximations of system (4) for the parameter values given in (46) and $\tau_2 = 3.6$, $\tau_3 = 0$, $\tau_1 = 9 < 11.4942$, showing that solution trajectories converge to the infectious equilibrium with immune response $E_2 : (x, y, v, w, z) = (35.9442, 6.6667, 12.6328, 0.61003, 0.406687)$.

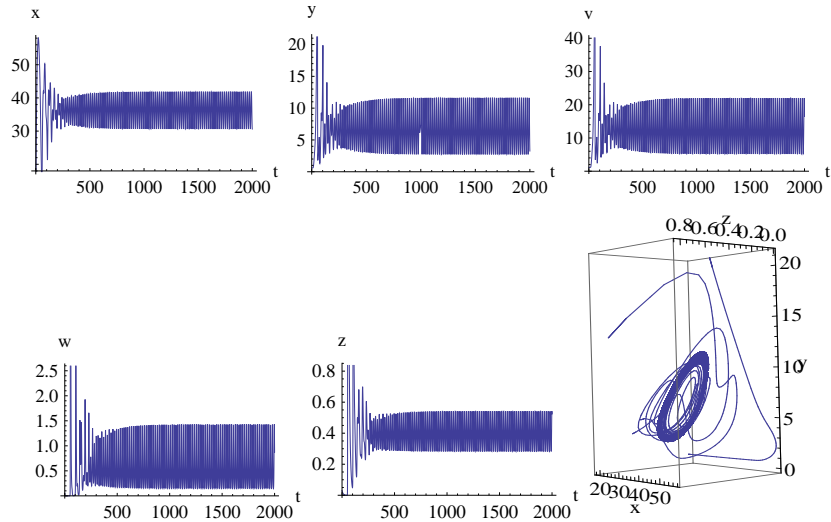


FIGURE 9. The numerical approximations of system (4) for the parameter values given in (46) and $\tau_2 = 3.6$, $\tau_3 = 0$, $\tau_1 = 12.6 > 12.4879$, showing that Hopf bifurcation occurs from the infectious equilibrium with immune response $E_2 : (x, y, v, w, z) = (35.9442, 6.6667, 12.6328, 0.565568, 0.377045)$.

$E_2 = (20.1857, 7.28937, 32.904, 0.891505, 0.649851)$ (see Fig. 10). If $\tau_2 = 5.6 > \tau_{2_0}$, the model (4) undergoes Hopf bifurcation and the periodic solutions are shown in

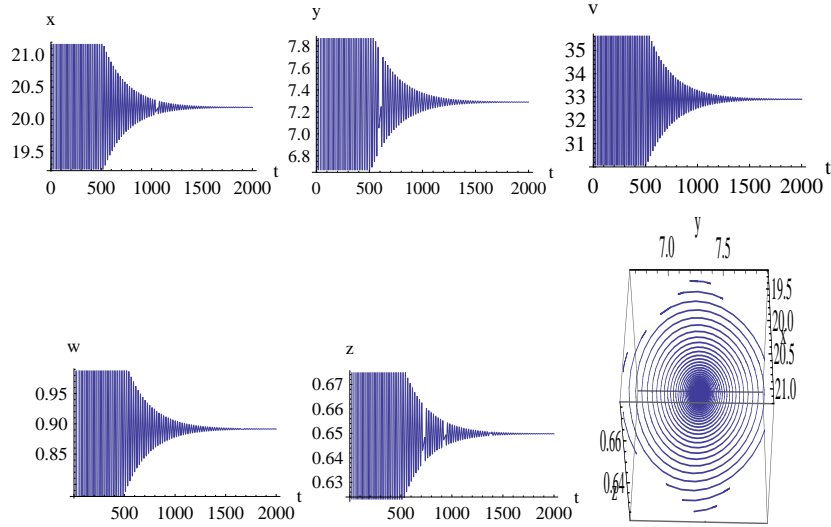


FIGURE 10. The numerical approximations of system (4) for the parameter values given in (46) and $\tau_1 = 1, \tau_3 = 1, \tau_2 = 0.5 < 5.11681$, showing that solution trajectories converge to the infectious equilibrium with immune response $E_2 : (x, y, v, w, z) = (20.1857, 7.28937, 32.904, 0.891505, 0.649851)$.

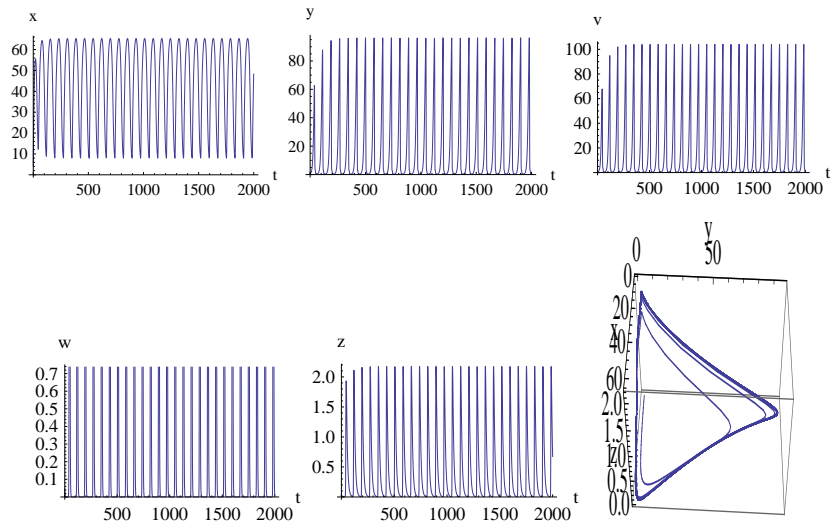


FIGURE 11. The numerical approximations of system (4) for the parameter values given in (46) and $\tau_1 = 1, \tau_3 = 1, \tau_2 = 5.6 > 5.11681$, showing that Hopf bifurcation occurs from the infectious equilibrium with immune response $E_2 : (x, y, v, w, z) = (43.9768, 7.28937, 7.88999, 0.452623, 0.329933)$.

Fig. 11. This supports the results in Theorem 5.4.

7. Conclusion and discussion

In this paper, we analyze a 5-dimensional HIV-1 model with three delays. τ_1, τ_2 are intracellular delays (τ_1, τ_2 represent the latent period and virus production period, respectively) and τ_3 is immune response delay. Because positivity implies that the cell population survives and boundedness can be interpreted as a natural restriction to growth due to limited resources, we prove that the solutions of model (4) are positive and bounded in section 2. The theoretical results show that model (4) has three equilibria: the infection-free equilibrium E_0 , the infectious equilibrium without immune response E_1 and the infectious equilibrium with immune response E_2 . The basic reproduction number R_0 and the immune reproduction number R_1 are identified. We show that if $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable in section 3; if $R_1 < 1 < R_0$, the infectious equilibrium without immune response equilibrium is globally asymptotically stable in section 4; if $R_1 > 1$ and $0 < \tau_3 < -\frac{\ln q}{a_3}$, under suitable conditions of the parameters, the infectious equilibrium with immune response is locally asymptotically stable when τ_2 is less than a certain critical value, and loses its stability and a Hopf bifurcation occurs at the equilibrium E_2 when τ_2 is greater than the critical value in case (IV) of section 5. It follows from the coordinates of E_2 that if τ_3 is too large, all coordinates are negative. Mathematically, the disappearance or appearance of equilibria depends on its own characteristics, i.e., the coordinates of the equilibria. Thus, the equilibrium E_2 does not exist. In this case, the model finally converges to the equilibria E_0 or E_1 under their respective conditions of stability. The reproduction numbers R_0, R_1 and the times delays play an important role in determining the dynamic behavior of model (4). In section 6, some numerical simulations are carried out to illustrate the theoretical results.

In this paper, in order to simulate real situation, we introduce three time delays. Generally speaking, the mathematical analysis of the model with multiple delays is more complicated. Moreover, we introduce the immune reproduction number R_1 , and expound its influence on the stability of equilibria. Because three delays and two classes of CTL immune cells are considered, the current model has rich dynamics. However, the studies [30–32] have shown that distributed delay is more close to biological significance than discrete delay. Thus, we will consider the distributed time delays in future research.

From biological point of view, the basic reproduction number R_0 denotes the average number of infected cells that arise from any one infected cell in the expected life time in the initial infection [33], and the immune reproduction number R_1 represents the average number of the CTL cells produced by one CTL cell (in the survival time) activated by infected cells [34]. Moreover, we conclude that the infected cells can be cleared by decreasing the value of the basic reproduction number to below one from theoretical results. According to the equation (7) for R_0 , we can increase the intracellular delays τ_1 and τ_2 to reduce R_0 . In other words, any drugs that can prolong the latent period or slow down virus production process may help to control the HIV-1 infection. However, HIV-1 still cannot be eradicated thoroughly in terms of the current treatment regiments.

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