Stability and Hopf Bifurcation Analysis of an HIV Infection Model with Saturation Incidence and Two Time Delays

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Abstract—**In this paper, we investigate the dynamical properties for an HIV infection model with saturation incidence and two delays describing time needed for infection of cell and CTL response generation. Moreover, the effect of time delays on stability of the equilibria for the CTL response has been studied. Finally, numerical simulations are carried out to validate our analytical results.**

Index Terms—**Basic reproduction number; Equilibrium; Asymptotically stable; Hopf bifurcation.**

I. Introduction

THE disease of human immunodeficiency virus (HIV) is one of the most destructive pandemic infecting humans. The interactions between HIV and the immune system are more complex. HIV infects $CD4^+$ T cells, which are a central component of the immune system. $CD4^+$ T cells can help to facilitate the body's response to potentially fatal infections. Virus clearance after actue infection is associated with strong and polyclonal $CD4^+$ T cells reponse, as well as sustained CTL responses. While HIV destroys $CD4^+$ T cells, the immune system is impaired and eventually loses its potential to fight other diseases. These prompt many researchers to study mathematical models and model analysis of the interaction between the host cells and viruses. Some HIV models have played a significant role in the development of a better understanding of the disease and the various drug therapy strategies. The basic viral infection model with CTL immune response has been constructed by Nowak et al.[1] as:

$$\begin{cases} \dfrac{dx}{dt} = \lambda - dx(t) - \beta x(t)v(t), \\ \dfrac{dy}{dt} = \beta x(t)v(t) - ay(t) - py(t)z(t), \\ \dfrac{dv}{dt} = ky(t) - uv(t), \\ \dfrac{dz}{dt} = cy(t)z(t) - bz(t), \end{cases} \tag{1.1}$$

where x, y, v and z are the uninfected cells, infected cells, virus and CTL cells, respectively. Parameters d, a, u and b represent the death rates of the uninfected cells, infected cells, virus and CTL cells, respectively. Parameter β is the infection rate. Parameters λ, k and c are the birth rates of the uninfected cells, virus and CTL cells, respectively. Based on the importance of infection rate in models, different forms of infection rate have been incorporated into HIV models. As a matter of fact, Bilinear incidence is not a reasonable assume when the quantity of cells are too large. Thus it is reasonable for us to assume that the infection rate of modeling CTL response is saturation incidence.

In the process of viral infections, many models considered time delays in the variables being modeled (see [2, 6-8, 10, 11, 13, 15-17, 19, 20]). In order to account for the intracellular viral life-cycle process, we assume that virus production occurs after the virus entry by the constant τ_1, the recruitment of virus producing cells at time $t-\tau_1$ and are still alive at time t, the probability of surviving the time period from $t-\tau_1$ to t is $e^{-m\tau_1}$. On the other hand, the immune response plays a critical role in eliminating or controlling the disease. Antigenic stimulation generating CTL cells may need a period of time τ_2, i.e, the CTL cells response at time t may depend on the population of antigen at a period time $t-\tau_2$. Therefore, we consider a HIV infection model with saturation incidence and two time delays as follows:

$$\begin{cases} \dfrac{dx}{dt} = \lambda - dx(t) - \dfrac{\beta x(t)v(t)}{1+\alpha v(t)}, \\ \dfrac{dy}{dt} = \dfrac{\beta e^{-m\tau_1} x(t-\tau_1)v(t-\tau_1)}{1+\alpha v(t-\tau_1)} - ay(t) \\ \qquad -py(t)z(t), \\ \dfrac{dv}{dt} = ky(t) - uv(t), \\ \dfrac{dz}{dt} = cy(t-\tau_2)z(t-\tau_2) - bz(t). \end{cases} \tag{1.2}$$

In this paper, our primary goal is to carry out a complete mathematical analysis of model (1.2) and establish its global dynamics and Hopf bifurcation. The organization of this paper is as follows: In the next section, we deal with some basic properties such as positivity and boundedness of the solutions and existence of equilibria of model (1.2). In Section 3, we prove the local stability of three possible equilibria. we further prove the global asymptotic stability of the infection-free equilibrium, infection equilibrium without CTL response and infection equilibrium with CTL response by using the Lasalle's invariance principle. By bifurcation theory, we also prove that there is a stability switch for another special case for infection equilibrium with CTL response. In Section 4, one example is given to illustrate our main results are applicable. In the final section, we offer

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a brief conclusion.

II. Basic results

Let $\tau = \max\{\tau_1, \tau_2\}$ and $R_+^4 = \{(x_1, x_2, x_3, x_4) : x_i \geq 0, i = 1,2,3,4\}$. $C([-\tau, 0], R_+^4)$ denotes the space of continuous functions mapping the interval $[-\tau, 0]$ into R_+^4 with norm $\|\phi\| = \sup_{-\tau\leq t\leq 0}\{|\phi(t)|\}$ for any $\phi \in C([-\tau, 0], R_+^4)$.

The initial conditions for model (1.2) are given as follows

$$\begin{cases} x(\theta) = \phi_1(\theta), y(\theta) = \phi_2(\theta), \\ v(\theta) = \phi_3(\theta), z(\theta) = \phi_4(\theta), \\ \phi_i(\theta) \geq 0, \theta \in [-\tau, 0], \\ \phi_i(0) \geq 0 \ (i = 1,2,3,4) \end{cases} \tag{2.1}$$

where $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta), \phi_4(\theta)) \in C([-\tau, 0], R_+^4)$. It is well known by the fundamental theory of functional differential equation [12], model (1.2) admits a unique solution $(x(t), y(t), v(t), z(t))$ satisfying initial conditions (2.1).

Theorem 2.1 *Let $(x(t), y(t), v(t), z(t))$ be the solution of (1.2) satisfying initial condition (2.1), then $x(t), y(t), v(t)$ and $z(t)$ are positive and ultimately bounded.*

Proof: It is easy to show that all solutions of model (1.2) with initial conditions (2.1) are defined on $[0, +\infty)$ and remain positive for all $t \geq 0$.

Denote

$$N(t) = e^{-m\tau_1}x(t-\tau_1) + y(t) + \frac{a}{2k}v(t) + \frac{p}{c}z(t+\tau_2),$$

and $s = \min\{d, \frac{a}{2}, u, b\}$. By positivity of solution of model (1.2), we have

$$\begin{aligned} \dot{N}(t) = \ & \lambda e^{-m\tau_1} - de^{-m\tau_1}x(t-\tau_1) - \frac{1}{2}ay(t) \\ & -\frac{au}{2k}v(t) - \frac{pb}{c}z(t+\tau_2) \\ \leq \ & \lambda e^{-m\tau_1} - sN(t). \end{aligned}$$

Therefore, we have

$$\limsup_{t\to\infty} N(t) \leq \frac{\lambda e^{-m\tau_1}}{s}.$$

This implies that $x(t)$, $y(t)$, $v(t)$ and $z(t)$ are ultimately bounded. This completes the proof.

For model (1.2), the basic reproductive ratio of virus which describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process is given by

$$R_0 = \frac{k\beta\lambda e^{-m\tau_1}}{adu},$$

and the immune response reproductive ratio is given by

$$R_1 = \frac{\lambda ck\beta e^{-m\tau_1}}{a[ucd + kb(\beta + \alpha d)]}.$$

By direct calculation we have that model (1.2) has three possible equilibria.

Infection-free equilibrium $E_0 = (x_0, 0, 0, 0) = (\frac{\lambda}{d}, 0, 0, 0)$.

If $R_0 > 1$, then there is a infection equilibrium without CTL response $E_1 = (x_1, y_1, v_1, 0)$, where $x_1 = \frac{aue^{m\tau_1}(1+\alpha v_1)}{\beta k}$, $y_1 = \frac{uv_1}{k}$ and $v_1 = \frac{\beta k\lambda e^{-m\tau_1} - adu}{ua(\beta + \alpha d)}$.

If $R_1 > 1$, then there is a infection equilibrium with CTL response $E_2 = (x_2, y_2, v_2, z_2)$, where $x_2 = \frac{\lambda(uc + \alpha kb)}{ucd + kb(\beta + \alpha d)}$, $y_2 = \frac{b}{c}$, $v_2 = \frac{kb}{uc}$ and $z_2 = \frac{a}{p}(R_1 - 1)$.

III. Stability analysis

In this section, we will analyze local and global asymptotic stability of infection-free equilibrium E_0, infection equilibria without CTL response E_1 and with CTL response E_2.

A. Stability of equilibrium E_0

Theorem 3.1 *For the infection-free equilibrium E_0 of model (1.2), we have*
(i) If $R_0 < 1$, then E_0 is locally asymptotically stable.
(ii) If $R_0 > 1$, then E_0 is unstable.

Proof: At infection-free equilibrium E_0, the characteristic equation for the corresponding linearized system of model (1.2) becomes

$$(s+b)(s+d)[(s+a)(s+u) - \beta k\frac{\lambda}{d}e^{-(m+s)\tau_1}] = 0. \tag{3.1}$$

Two roots of (3.1) are $s_1 = -b$ and $s_2 = -d$. The remaining two roots are obtained by considering the following equation

$$(s+a)(s+u) = \beta k\frac{\lambda}{d}e^{-(m+s)\tau_1}. \tag{3.2}$$

If s has a nonnegative real part, then the modulus of the left-hand side of (3.2) satisfies

$$|\ (s+a)(s+u)\ | \geq au,$$

while the modulus of the right-hand side (3.2) satisfies

$$\beta k\frac{\lambda}{d}e^{-(m+s)\tau_1} = |\ aue^{-s\tau_1}R_0\ | \leq auR_0 < au.$$

This leads to a contradiction. Thus, when $R_0 < 1$, all the eigenvalues have negative real parts, and hence the equilibrium E_0 is locally asymptotically stable.

When $R_0 > 1$, let

$$\begin{aligned} f(s) = \ & (s+a)(s+u) - \beta k\frac{\lambda}{d}e^{-(m+s)\tau_1} \\ = \ & (s+a)(s+u) - aue^{-s\tau_1}R_0. \end{aligned}$$

It is easy to show that

$$f(0) = au - auR_0 < 0, \quad \lim_{s\to+\infty} f(s) = +\infty.$$

Hence, $f(s) = 0$ has at least one positive real root. Therefore, if $R_0 > 1$, then equilibrium E_0 is unstable. This completes the proof.

Theorem 3.2 *If $R_0 \leq 1$, then infection-free equilibrium E_0 of model (1.2) is globally asymptotically stable.*

Proof: Define a Lyapunov functional $V_1(t)$ as follows

$$\begin{aligned} V_1(t) = \ & x(t) - x_0 - x_0\ln\frac{x(t)}{x_0} + e^{m\tau_1}y(t) + \frac{a}{k}v(t) \\ & +\frac{p}{c}z(t) + U(t), \end{aligned}$$

where

$$\begin{aligned} U(t) = \ & \int_{t-\tau_1}^{t} \frac{\beta x(\theta_1)v(\theta_1)}{1+\alpha v(\theta_1)}\,\mathrm{d}\theta_1 \\ & +ae^{m\tau_1}\int_{t-\tau_2}^{t} y(\theta_2)z(\theta_2)\,\mathrm{d}\theta_2. \end{aligned}$$

Calculating the time derivative of $V_1(t)$ along any positive solution of model (1.2) and noticing that $x_0 = \frac{\lambda}{d}$, we can obtain

$$\begin{aligned}\frac{dV_1(t)}{dt} &= -\frac{d(x(t)-x_0)^2}{x(t)}+\frac{\beta x_0 v(t)}{1+\alpha v(t)}-\frac{aue^{m\tau_1}}{k}v(t)\\ &\quad -\frac{pbe^{m\tau_1}}{c}z(t)\\ &= -d\frac{(x(t)-x_0)^2}{x(t)}-\frac{aue^{m\tau_1}}{k(1+\alpha v(t))}(R_0-1)\\ &\quad -\frac{pbe^{m\tau_1}}{c}z(t)-\frac{au\alpha e^{m\tau_1}v(t)}{k(1+\alpha v(t))}.\end{aligned}$$

Obviously, if $R_0 \le 1$, then $\frac{dV_1(t)}{dt} \le 0$ for any $(x(t), y(t), v(t), z(t))$. We have $\frac{dV_1(t)}{dt}=0$ if and only if $x(t)=x_0$, $y(t)=0$, $v(t)=0$ and $z(t)=0$. Let M be the largest invariant set of $\{(x,y,v,z)\in R_+^4 : \frac{dV_1(t)}{dt}=0\}$. From the third equation of model (1.2), we easily obtain $M=\{E_0\}$. It follows from LaSalle's invariance principle [12] that equilibrium E_0 is globally asymptotically stable when $R_0 \le 1$. This completes the proof.

B. Stability of equilibrium E_1

Theorem 3.3 *For infection equilibrium without CTL response E_1 of model (1.2)*
(i) If $R_0 > 1$ and $R_1 < 1$, then E_1 is locally asymptotically stable.
(ii) If $R_1 > 1$, then E_1 is unstable.

Proof: At equilibrium E_1, the characteristic equation for the corresponding linearized system of model (1.2) is

$$(s-cy_1e^{-s\tau_2}+b)[s^3+p_2s^2+p_1s+p_0+(q_1s+q_0)e^{-s\tau_1}]=0, \quad (3.3)$$

where

$$\begin{aligned}p_2 &= d+a+u+\frac{\beta v_1}{1+\alpha v_1},\\ p_1 &= au+(a+u)(d+\frac{\beta v_1}{1+\alpha v_1}),\\ p_0 &= au(d+\frac{\beta v_1}{1+\alpha v_1}),\\ q_1 &= -\frac{k\beta e^{-m\tau_1}x_1}{(1+\alpha v_1)^2}=-\frac{au}{1+\alpha v_1},\\ q_0 &= -\frac{k\beta d e^{-m\tau_1}x_1}{(1+\alpha v_1)^2}=-\frac{aud}{1+\alpha v_1}.\end{aligned}$$

Consider the equation

$$s^3+p_2s^2+p_1s+p_0+(q_1s+q_0)e^{-s\tau_1}=0. \quad (3.4)$$

When $\tau_1=0$, equation (3.4) becomes

$$s^3+p_2s^2+(p_1+q_1)s+(p_0+q_0)=0. \quad (3.5)$$

Since

$$\begin{aligned}&p_2>0,\\ &p_1+q_1=au+(a+u)(d+\frac{\beta v_1}{1+\alpha v_1})-\frac{au}{1+\alpha v_1}>0,\\ &p_0+q_0=au(d+\frac{\beta v_1}{1+\alpha v_1})-\frac{aud}{1+\alpha v_1}>0,\end{aligned}$$

and

$$\begin{aligned}&p_2(p_1+q_1)-(p_0+q_0)\\ =\;&(d+a+u+\frac{\beta v_1}{1+\alpha v_1})[(a+u)(d+\frac{\beta v_1}{1+\alpha v_1})\\ &+\frac{au\alpha v_1}{1+\alpha v_1}]-au(d+\frac{\beta v_1}{1+\alpha v_1})+\frac{aud}{1+\alpha v_1}\\ >\;&0.\end{aligned}$$

By the Routh-Hurwitz criterion, all roots of (3.5) have negative real parts.
If $\tau_1 \neq 0$, $s=i\omega$ with $\omega>0$ is a root of equation (3.4), separating the real from the imaginary parts, it follows that

$$\begin{cases}p_2\omega^2-p_0=q_1\omega\sin\omega\tau_1+q_0\cos\omega\tau_1,\\ \omega^3-p_1\omega=q_1\omega\cos\omega\tau_1-q_0\sin\omega\tau_1.\end{cases} \quad (3.6)$$

Squaring and adding the two equations of (3.6) yields

$$\omega^6+(p_2^2-2p_1)\omega^4+(p_1^2-2p_2p_0-q_1^2)\omega^2+p_0^2-q_0^2=0. \quad (3.7)$$

Let $r=\omega^2$, then (3.7) becomes

$$r^3+(p_2^2-2p_1)r^2+(p_1^2-2p_2p_0-q_1^2)r+p_0^2-q_0^2=0. \quad (3.8)$$

By calculating, we have

$$\begin{aligned}&p_2^2-2p_1=(d+\frac{\beta v_1}{1+\alpha v_1})^2+(a^2+u^2)>0,\\ &p_1^2-2p_2p_0-q_1^2\\ =\;&a^2u^2+(a^2+u^2)(d+\frac{\beta v_1}{1+\alpha v_1})^2\\ &-(\frac{au}{1+\alpha v_1})^2\\ >\;&0,\\ &p_0^2-q_0^2=[au(d+\frac{\beta v_1}{1+\alpha v_1})]^2-(\frac{aud}{1+\alpha v_1})^2>0,\end{aligned}$$

and

$$\begin{aligned}&(p_2^2-2p_1)(p_1^2-2p_2p_0-q_1^2)-(p_0^2-q_0^2)\\ =\;&a^2+u^2(d+\frac{\beta v_1}{1+\alpha v_1})^2[(\frac{(au\alpha v_1)^2+2a^2u^2\alpha v_1}{1+\alpha v_1})^2\\ &+(a^2+u^2)(d+\frac{\beta v_1}{1+\alpha v_1})^2]\\ &-[au(d+\frac{\beta v_1}{1+\alpha v_1})]^2+(\frac{aud}{1+\alpha v_1})^2\\ >\;&0.\end{aligned}$$

By the Routh-Hurwitz criterion, equation (3.8) has no positive roots. This shows that (3.4) can not have a purely imaginary root. Next, we analyze the transcendental equation

$$s-gv_1e^{-s\tau_2}+c=0. \quad (3.9)$$

If $\tau_2=0$, we have

$$s=gv_1-c=\frac{\lambda\beta kge^{-d\tau_1}-a[dug+cu(\beta+\alpha d)]}{au(\beta+\alpha d)}.$$

Clearly, if $R_1<1$, then $s<0$.
If $s=\omega i$ with $\omega>0$ is a root of equation (3.9), separating the real from the imaginary parts, it follows that

$$\begin{cases}\omega=-gv_1\sin\omega\tau_2,\\ c=gv_1\cos\omega\tau_2.\end{cases} \quad (3.10)$$

Which implies that $\omega^2=(gv_1)^2-c^2$. Note that when $R_1<1$, then $\omega^2<0$, which is a contradiction.
Therefore, we conclude that the equation (3.3) does not have any root with nonnegative real part. By the general theory of Delay Differential Equations from Kuang [12], we see that if $R_0>1$ and $R_1<1$, the equilibrium E_1 is locally asymptotically stable. This completes the proof.

Theorem 3.4 *If $R_0>1$ and $R_1<1$, then the infection equilibrium without CTL response E_1 of model (1.2) is globally asymptotically stable.*

Proof: Define a Lyapunov functional $V_2(t)$ as follows

$$\begin{aligned} V_2(t)= \quad & y(t)-y_1-y_1\ln\frac{y(t)}{y_1}+e^{-m\tau_1}(x(t)-x_1 \\ & -x_1\ln\frac{x(t)}{x_1})+\frac{a}{k}(v(t)-v_1-v_1\ln\frac{v(t)}{v_1}) \\ & +\frac{p}{c}z(t)+ay_1U(t)+p\int_{t-\tau_2}^{t}(y(\theta_2)z(\theta_2))\mathrm{d}\theta_2 \end{aligned}$$

and

$$\begin{aligned} U(t)= \quad & \int_0^{\tau_1}(\frac{e^{-m\tau_1}\beta x(t-\theta_1)v(t-\theta_1)}{ay_1(1+\alpha v(t-\theta_1))}-1 \\ & -\ln\frac{\beta x(t-\theta_1)v(t-\theta_1)}{ae^{m\tau_1}y_1(1+\alpha v(t-\theta_1))})\,\mathrm{d}\theta_1. \end{aligned}$$

Calculating the derivative of $V_2(t)$ along the solution of model (1.2), we obtain that

$$\begin{aligned} \frac{dV_2(t)}{dt} = \quad & -\frac{de^{-m\tau_1}(x(t)-x_1)^2}{x(t)} \\ & +\frac{\beta e^{-m\tau_1}x_1v_1}{1+\alpha v_1}(3-\frac{x_1}{x(t)}-\frac{v(t)}{v_1}-\frac{y(t)v_1}{y_1v(t)} \\ & -\frac{x(t-\tau_1)v(t-\tau_1)(1+\alpha v_1)}{x_1v_1(1+\alpha v(t-\tau_1))}\frac{y_1}{y(t)}) \\ & +\frac{\beta e^{-m\tau_1}x_1v(t)}{1+\alpha v(t)}-p(\frac{b}{c}-y_1)z(t) \\ & +ay_1\ln\frac{x(t-\tau_1)v(t-\tau_1)}{(1+\alpha v(t-\tau_1))}\frac{1+\alpha v(t)}{x(t)v(t)} \\ = \quad & -\frac{de^{-m\tau_1}(x(t)-x_1)^2}{x(t)} \\ & +\frac{\beta e^{-m\tau_1}x_1v_1}{1+\alpha v_1}(1-\frac{x_1}{x(t)}-\ln\frac{x_1}{x}) \\ & -p(\frac{b}{c}-y_1z)+\frac{\beta e^{-m\tau_1}x_1v_1}{1+\alpha v_1}(1 \\ & -\frac{x(t-\tau_1)v(t-\tau_1)}{x_1v_1}\frac{1+\alpha v_1}{1+\alpha v(t-\tau_1)}\frac{y_1}{y} \\ & +\ln\frac{x(t-\tau_1)v(t-\tau_1)}{x_1v_1}\frac{1+\alpha v_1}{1+\alpha v(t-\tau_1)}\frac{y_1}{y}) \\ & +\frac{\beta e^{-m\tau_1}x_1v_1}{1+\alpha v_1}(1-\frac{yv_1}{y_1v}-\ln\frac{yv_1}{y_1v}) \\ & +\frac{\beta e^{-m\tau_1}x_1v_1}{1+\alpha v_1}(1-\frac{1+\alpha v}{1+\alpha v_1}-\ln\frac{1+\alpha v}{1+\alpha v_1}) \\ & +\frac{\beta e^{-m\tau_1}x_1v_1}{1+\alpha v_1}(-1+\frac{1+\alpha v}{1+\alpha v_1} \\ & -\frac{v}{v_1}+\frac{1+\alpha v_1}{1+\alpha v}\frac{v}{v_1}), \end{aligned}$$

where

$$\begin{aligned} & -1+\frac{1+\alpha v}{1+\alpha v_1}-\frac{v}{v_1}+\frac{1+\alpha v_1}{1+\alpha v}\frac{v}{v_1} \\ = \quad & \frac{-\alpha(v(t)-v_1)^2}{v_1(1+\alpha v(t))(1+\alpha v_1)}. \end{aligned}$$

Let $H(t)=1-f(t)+\ln f(t)$. Since $H(t)$ is always non-positive for any $f(t)>0$ and $H(t)=0$ if and only if $f(t)=1$. Obviously, we always have $\frac{dV_2(t)}{dt}\leq 0$, and $\frac{dV_2(t)}{dt}=0$ if and only if $(x(t),y(t),v(t),z(t))=(x_1,y_1,v_1,0)$. From LaSalle's invariance principle [12], we finally have that equilibrium E_1 is globally asymptotically stable when $R_0>1$ and $R_1<1$. This completes the proof.

C. *Stability of equilibrium E_2*

On the stability analysis of the infection equilibrium with CTL response E_2, we only consider the two special cases, that is $\tau_2=0,\tau_1\geq 0$ and $\tau_1=0,\tau_2\geq 0$.

Firstly, we consider the local and global stability of E_2 for first case, we have the following results.

Theorem 3.5 *If $\tau_2=0$, $\tau_1\geq 0$ and $R_1>1$, then infection equilibrium with CTL response E_2 is locally asymptotically stable.*

Proof: At equilibrium E_2, the characteristic equation for the corresponding linearized system of model (1.2) is

$$\begin{aligned} & (s+d+\frac{\beta v_2}{1+\alpha v_2})(s+u)[(s+b-cy_2e^{-s\tau_2})(s \\ & +a+pz_2)+cpy_2z_2e^{-s\tau_2}] \\ = \quad & (s+b-cy_2e^{-s\tau_2})(s+d)\frac{\beta ke^{-(s+m)\tau_1}x_2}{(1+\alpha v_2)^2}, \end{aligned} \tag{3.11}$$

where $\tau_2=0$, then (3.11) becomes

$$\begin{aligned} & (s+d+\frac{\beta v_2}{1+\alpha v_2})(s+u)[(s+a+pz_2)s \\ & +pbz_2] \\ = \quad & s(s+d)\frac{u(a+pz_2)e^{-s\tau_1}}{1+\alpha v_2}. \end{aligned} \tag{3.12}$$

Assume that equation (3.12) has a nonnegative real root, where $s=i\omega_0$.

$$\begin{aligned} & (i\omega_0+d+\frac{\beta v_2}{1+\alpha v_2})(i\omega_0+u)[(i\omega_0)(i\omega_0+a) \\ & +pz_2+pbz_2] \\ = \quad & (i\omega_0)(i\omega_0+d)\frac{u(a+pz_2)e^{-(i\omega_0)\tau_1}}{1+\alpha v_2}. \end{aligned} \tag{3.13}$$

Since

$$\begin{aligned} & \mid (i\omega_0)(i\omega_0+a+pz_2)+pbz_2 \mid \\ > \quad & \mid (i\omega_0)(a+pz_2) \mid \\ > \quad & \mid (i\omega_0)\frac{a+pz_2}{1+\alpha v_2} \mid, \end{aligned}$$

and

$$\mid i\omega_0+d+\frac{\beta v_2}{1+\alpha v_2} \mid\geq\mid i\omega_0+d \mid,\ \mid i\omega_0+u \mid\geq u.$$

Therefore, the modulus of the left-hand side of (3.13) is greater than the modulus of the right-hand side. This leads to a contradiction. We conclude that the (3.12) does not have any root with nonnegative real part. Thus, equilibrium E_2 is locally asymptotically stable when $R_1>1$ in the case of $\tau_2=0$ and $\tau_1\geq 0$. This completes the proof.

Theorem 3.6 *If $\tau_2=0$, $\tau_1\geq 0$ and $R_1>1$, then infection equilibrium with CTL response E_2 is globally asymptotically stable.*

Proof: Define a Lyapunov functional $V_3(t)$ as follows

$$\begin{aligned} V_3(t)= \quad & U(t)+(a+pz_2)y_2U^{+}(t) \\ & +p\int_{t-\tau_2}^{t}y(\theta_2)z(\theta_2)\mathrm{d}\theta_2, \end{aligned}$$

where

$$\begin{aligned} U(t)= \quad & e^{-m\tau_1}(x(t)-x_2-x_2\ln\frac{x(t)}{x_2})+(y(t)-y_2 \\ & -y_2\ln\frac{y(t)}{y_2})+\frac{a+pz_2}{k}(v(t)-v_2-v_2\ln\frac{v(t)}{v_2}) \\ & +\frac{p}{c}(z(t)-z_2-z_2\ln\frac{z(t)}{z_2}), \end{aligned}$$

and

$$\begin{aligned} U^{+}(t)= & \int_0^{\tau_1}[\frac{\beta e^{-m\tau_1}x(t-\theta_1)v(t-\theta_1)}{(a+pz_2)y_2(1+\alpha v(t-\theta_1))}-1 \\ & -\ln\frac{\beta e^{-m\tau_1}x(t-\theta_1)v(t-\theta_1)}{(a+pz_2)y_2(1+\alpha v(t-\theta_1))}]\mathrm{d}\theta_1, \end{aligned}$$

where x_2, y_2, v_2, z_2 satisfies the following equations

$$\lambda = dx_2 + \frac{\beta x_2 v_2}{1+\alpha v_2}, \frac{\beta e^{-m\tau_1}x_2v_2}{1+\alpha V_2} = ay_2 - py_2z_2,$$
$$ky_2 = uv_2, cy_2z_2 = bz_2.$$

Calculating the derivative of $V_3(t)$ along the solution of model (1.2), and using the similar method with the proof of Theorem 3.4, we have

$$\begin{aligned} \frac{dV_3(t)}{dt} = & -\frac{de^{-m\tau_1}(x(t)-x_2)^2}{x(t)} \\ & +\frac{\beta e^{-m\tau_1}x_2v_2}{1+\alpha v_2}(1-\frac{x_2}{x(t)}-\ln\frac{x_2}{x(t)}) \\ & +\frac{\beta e^{-m\tau_1}x_2v_2}{1+\alpha v_2}(1 \\ & -\frac{x(t-\tau_1)v(t-\tau_1)(1+\alpha v_2)}{x_2v_2(1+\alpha v(t-\tau_1))}\frac{y_2}{y(t)} \\ & +\ln\frac{x(t-\tau_1)v(t-\tau_1)(1+\alpha v_2)}{x_2v_2(1+\alpha v(t-\tau_1))}\frac{y_2}{y(t)}) \\ & +\frac{\beta e^{-m\tau_1}x_2v_2}{1+\alpha v_2}(1-\frac{y(t)v_2}{y_2v(t)}+\ln\frac{y(t)v_2}{y_2v(t)}) \\ & +\frac{\beta e^{-m\tau_1}x_2v_2}{1+\alpha v_2}(1-\frac{1+\alpha v(t)}{1+\alpha v_2} \\ & +\ln\frac{1+\alpha v(t)}{1+\alpha v_2})+\frac{\beta e^{-m\tau_1}x_2v_2}{1+\alpha v_2}(-1 \\ & +\frac{1+\alpha v(t)}{1+\alpha v_2}-\frac{v(t)}{v_2}+\frac{v(t)(1+\alpha v_2)}{v_2(1+\alpha v(t))}), \end{aligned}$$

where

$$\begin{aligned} & \frac{\beta x_2v_2}{1+\alpha v_2}[-1+\frac{1+\alpha v(t)}{1+\alpha v_2}-\frac{v(t)}{v_2}+\frac{v(t)(1+\alpha v_2)}{v_2(1+\alpha v(t))}] \\ = & \frac{-\alpha\beta x_2(v(t)-v_2)^2}{(1+\alpha v(t))(1+\alpha v_2)^2}. \end{aligned}$$

It follows that $\frac{dV_3(t)}{dt} \le 0$ for all $x, y, v, z > 0$ and $\frac{dV_3(t)}{dt} = 0$ if and only if $(x(t), y(t), v(t), z(t)) = (x_2, y_2, v_2, z_2)$. From Lasalle's Invariance Principle [12], we have that equilibrium E_2 is globally asymptotically stable. This completes the proof. The following discussions focus on the stability of the equilibrium E_2 in the second case. Let $\tau_1 = 0$, $\tau_2 \ge 0$ in the equation (3.11), it follows that

$$s^4+a_1s^3+a_2s^2+a_3s+a_4+(b_1s^3+b_2s^2+b_3s+b_4)e^{-s\tau_2}=0, \tag{3.14}$$

where

$$\begin{aligned} a_1 = & \ b+d+a+u+pz_2+\frac{\beta v_2}{1+\alpha v_2}, \\ a_2 = & \ (a+u+pz_2)(d+\frac{\beta v_2}{1+\alpha v_2})+u(a+pz_2) \\ & +b(d+a+u+pz_2+\frac{\beta v_2}{1+\alpha v_2})-\frac{u(a+pz_2)}{1+\alpha v_2}, \\ a_3 = & \ (d+\frac{\beta v_2}{1+\alpha v_2})u(a+pz_2)+bu(a+pz_2) \\ & +b(a+pz_2-u)\frac{d+\beta v_2}{1+\alpha v_2}-(b+d)\frac{u(a+pz_2)}{1+\alpha v_2}, \\ a_4 = & \ bu(d+\frac{\beta v_2}{1+\alpha v_2})(a+pz_2)-\frac{bdu(a+pz_2)}{1+\alpha v_2}, \end{aligned}$$

$$\begin{aligned} b_1 = & -b_1, \\ b_2 = & -b(d+\frac{\beta v_2}{1+\alpha v_2}+a+pz_2+u)+pbz_2, \\ b_3 = & -bu(a+pz_2)-b(a+pz_2+u)(d+\frac{\beta v_2}{1+\alpha v_2}) \\ & -bu(d+\frac{\beta v_2}{1+\alpha v_2})(a+pz_2)+(d+u \\ & +\frac{\beta v_2}{1+\alpha v_2})pbz_2+\frac{bu(a+pz_2)}{1+\alpha v_2}, \\ b_4 = & \frac{bdu(a+pz_2)}{1+\alpha v_2}-bu(d+\frac{\beta v_2}{1+\alpha v_2})(a+pz_2) \\ & +u(d+\frac{\beta v_2}{1+\alpha v_2})pbz_2. \end{aligned}$$

Let

$$P(s) = s^4 + a_1s^3 + a_2s^2 + a_3s + a_4,$$
$$Q(s) = b_1s^3 + b_2s^2 + b_3s + b_4.$$

Then we can rewrite the equation (3.14) as follows

$$P(s) + Q(s)e^{-s\tau_2} = 0. \tag{3.15}$$

Assume that $P(s)$ and $Q(s)$ are analytic functions in the right half-plane $Res > -\delta$ where $\delta > 0$.

Lemma 3.1 *Consider equation (3.15), $P(s)$ and $Q(s)$ satisfy the following conditions:*
(i) $P(0)+Q(0) \neq 0$,
(ii) $P(i\omega)+Q(i\omega) \neq 0$,
(iii) $\lim\sup\{|\frac{Q(s)}{P(s)}| : |s| \to \infty, Res \ge 0\} < 1$ for any τ_2,
(iv) $F(\omega) \equiv |P(i\omega)|^2 - |Q(i\omega)|^2$ for real ω, has at most a finite number of real zeros.
Under these conditions, the following statements are true. (I) Suppose that the equation $F(\omega) = 0$ has no positive roots. Then if equation (3.15) is stable at $\tau_2 = 0$ it remains stable for all $\tau_2 \ge 0$, whereas if it is unstable at $\tau_2 = 0$ it remains unstable for all $\tau_2 \ge 0$.
(II) Suppose that the equation $F(\omega) = 0$ has at least one positive root and that each positive root is simple. As τ_2 increases, stability switches may occur. There exists a positive number τ_2^* such that equation (3.15) is unstable for all $\tau_2 \ge \tau_2^*$. As τ_2 varies from 0 to τ_2^*, at most a finite number of stability switches may occur.

Proof: (i)

$$\begin{aligned} P(0)+Q(0) = & \ bu(d+\frac{\beta v_2}{1+\alpha v_2})(a+pz_2)+u(d \\ & +\frac{\beta v_2}{1+\alpha v_2})pbz_2 \\ \neq & \ 0. \end{aligned}$$

This means $s = 0$ is not a characteristic root of (3.15).

(ii)

$$\begin{aligned} P(i\omega)+Q(i\omega) = & \ \omega^4-(a_1+b_1)\omega^3i-(a_2+b_2)\omega^2 \\ & +(a_3+b_3)\omega i+a_4+b_4 \\ \neq & \ 0. \end{aligned}$$

(iii) Since

$$\lim_{|s|\to\infty}|\frac{Q(s)}{P(s)}| = \lim_{|s|\to\infty}|\frac{b_1s^3+b_2s^2+b_3s+b_4}{s^4+a_1s^3+a_2s^2+a_3s+a_4}| = 0,$$

we have $\limsup\limits_{|s|\to\infty, Res\ge 0}|\frac{Q(s)}{P(s)}| < 1$ for any $\tau_2 > 0$.

(iv) Since

$$\begin{aligned} F(\omega)= & |P(i\omega)|^2-|Q(i\omega)|^2 \\ = & \omega^8+(-2a_2+a_1^2-b_1^2)\omega^6+(a_2^2+2a_4 \\ & -2a_1a_3-b_2^2+2b_1b_3)\omega^4+(-2a_2a_4 \\ & +a_3^2+2b_2b_4-b_3^2)\omega^2+a_4^2-b_4^2. \end{aligned} \tag{3.16}$$

It is obvious that property (iv) is satisfied. This completes the proof.

When $\tau_2>0$, substituting $s=i\omega$ with $\omega>0$ into equation (3.14) and separating the real from the imaginary parts, one obtains that

$$\begin{cases} \omega^4-a_2\omega^2+a_4=(b_2\omega^2-b_4)\cos\omega\tau_2 \\ \qquad\qquad +(b_1\omega^3-b_3\omega)\sin\omega\tau_2, \\ -a_1\omega^3+a_3\omega=(b_1\omega^3-b_3\omega)\cos\omega\tau_2 \\ \qquad\qquad -(b_2\omega^2-b_4)\sin\omega\tau_2. \end{cases} \tag{3.17}$$

Squaring and adding the two equations of equation (3.17), it follows that

$$\omega^8+p\omega^6+q\omega^4+r\omega^2+u_0=0. \tag{3.18}$$

Let $z=\omega^2$, $p=a_1^2-2a_2-b_1^2$, $q=a_2^2+2a_4-2a_1a_3-b_2^2+2b_1b_3$, $r=a_3^2-2a_4a_2+2b_4b_2-b_3^2$ and $u_0=a_4^2-b_4^2$. Then equation (3.18) becomes

$$F(z)=z^4+pz^3+qz^2+rz+u_0=0. \tag{3.19}$$

Li et al. [18] obtained the following results on the distribution of roots of equation (3.19). Denote

$$\begin{aligned} a_1= & \frac{q}{2}-\frac{3}{16}p^2, \\ b_1= & \frac{1}{32}p^3-\frac{1}{8}pq+r, \\ \Delta= & (\frac{b_1}{2})^2+(\frac{a_1}{3})^3, \\ z_1^*= & -\frac{p}{4}+\sqrt[3]{-\frac{b_1}{2}+\sqrt{\Delta}}+\sqrt[3]{-\frac{b_1}{2}-\sqrt{\Delta}}, \text{if}\Delta>0, \\ z_2^*= & \max\{-\frac{p}{4}-2\sqrt[3]{-\frac{b_1}{2}}, -\frac{p}{4}+2\sqrt[3]{-\frac{b_1}{2}}\}, \text{if}\Delta=0, \\ z_3^*= & \max\{-\frac{p}{4}+2Re\{\delta\}, -\frac{p}{4}+2Re\{\delta\epsilon\}, \\ & -\frac{p}{4}+2Re\{\delta\bar{\epsilon}\}\}, \text{if}\Delta=0, \end{aligned}$$

where δ is one of cube roots of the complex number $-\frac{b_1}{2}+\sqrt{\Delta}$ and $\epsilon=-\frac{1}{2}+\frac{\sqrt{3}}{2}i$.

By a similar argument as that in [18], we have the following results.

Lemma 3.2 *[18]. For the polynomial equation (3.19), the following results hold true:*

(i) If $u_0<0$, then equation (3.19) has at least one positive root,

(ii) If $u_0\geq 0$, then equation (3.19) has no positive root if one of the following conditions holds:

(a) $\Delta>0$ and $z_1^*<0$;

(b) $\Delta=0$ and $z_2^*<0$;

(c) $\Delta<0$ and $z_3^*<0$.

(iii) If $u_0\geq 0$, then equation (3.19) has at least one positive root if one of the following conditions holds:

(a) $\Delta>0$, $z_1^*>0$ and $F(z_1^*)<0$;

(b) $\Delta=0$, $z_2^*>0$ and $F(z_2^*)<0$;

(c) $\Delta<0$, $z_3^*>0$ and $F(z_3^*)<0$.

Without loss of generality, we assume that it has four positive roots, denoted by $z_i^*, i=1,2,3,4$. Then equation (3.19) has four positive roots, say $\omega_i=\sqrt{z_i^*}, i=1,2,3,4$. From (3.17) we have

$$\begin{aligned} \sin\omega\tau_2= & \frac{(\omega_k^4-a_2\omega_k^2+a_4)(b_1\omega_k^3-b_3\omega_k)}{(b_1\omega_k^3-b_3\omega_k)^2+(b_2\omega_k^2-b_4)^2} \\ & +\frac{(a_1\omega_k^3-a_3\omega_k)(b_2\omega_k^2-b_4)}{(b_1\omega_k^3-b_3\omega_k)^2+(b_2\omega_k^2-b_4)^2}. \end{aligned} \tag{3.20}$$

When $\omega=\omega_i$ $(i=1,2,3,4)$, we solve τ_2 from (3.20) to obtain that

$$\begin{aligned} \tau_k^{(j)}= & \frac{1}{\omega_k}\arcsin[\frac{(\omega_k^4-p_2\omega_k^2+p_0)(q_3\omega_k^3-q_1\omega_k)}{(q_3\omega_k^3-q_1\omega_k)^2+(q_2\omega_k^2-q_0)^2} \\ & +\frac{(p_3\omega_k^3-p_1\omega_k)(q_2\omega_k^2-q_0)}{(q_3\omega_k^3-q_1\omega_k)^2+(q_2\omega_k^2-q_0)^2}]+\frac{2\pi j}{\omega_k}, \end{aligned} \tag{3.21}$$

where $k=1,2,3,4,\ j=0,1,\cdots$. Therefore, when $\tau=\tau_k^{(j)}, k=1,2,3,4,\ j=0,1,\cdots$, $\pm i\omega_k$ is a pair of purely imaginary roots of equation (3.16). Clearly, for every $k=1,2,3,4$, $\{\tau_k^{(j)}\}$ is monotonically increasing for $j=0,1,2,\cdots$ and

$$\lim_{j\to+\infty}\tau_k^{(j)}=\infty.$$

Therefore, there is a $k_0\in\{1,2,3,4,\}$ and $j_0\in\{0,1,2,\cdots\}$ such that

$$\tau_{k_0}^{(j_0)}=\min\{\tau_k^{(j)}: k=1,2,3,4,\ j=0,1,2,\cdots\}.$$

Thus, we can define

$$\tau_0=\tau_{k_0}^{(j_0)}, \quad \omega_0=\omega_{k_0}, \quad z_0=z_{k_0}^*. \tag{3.22}$$

Let $s(\tau_2)=\xi(\tau_2)+i\omega(\tau_2)$ be a root of equation (3.15) satisfying

$$\xi(\tau_0)=0, \quad \omega(\tau_0)=\omega_0. \tag{3.23}$$

Differentiating equation (3.15) with respect to τ_2, we get

$$\begin{aligned} & (4s^3+3a_1s^2+2a_2s+a_3)\frac{ds}{d\tau_2}+(3b_1s^2+2b_2s \\ & +b_3)e^{-s\tau_2}\frac{ds}{d\tau_2}+(b_1s^3+b_2s^2+b_3s+b_4)(-s \\ & -\tau_2\frac{ds}{d\tau_2})e^{-s\tau_2}=0. \end{aligned}$$

This gives

$$\begin{aligned} (\frac{ds}{d\tau_2})^{-1}= & -\frac{4s^3+3a_1s^2+2a_2s+a_3}{s(s^4+a_1s^3+a_2s^2+a_3s+a_4)} \\ & +\frac{3b_1s^2+2b_2s+b_3}{s(b_1s^3+b_2s^2+b_3s+b_4)}-\frac{\tau_2}{s}. \end{aligned}$$

Therefore

$$\begin{aligned} & sign\{\frac{dRes(\tau_2)}{d\tau_2}\}|_{\tau_2=\tau_k^{(j)}} \\ = & sign\{Re(\frac{ds}{d\tau_2})^{-1}\}|_{s=i\omega_0} \\ = & sign\{\frac{4\omega_0^6+\omega_0^4(3a_1^2-6a_2)}{\omega_0^2(a_1\omega_0^2-a_3)^2+(\omega_0^4-a_2\omega_0^2+a_4)^2} \\ & \frac{\omega_0^2(-4a_3a_1+4a_4+2a_2^2)}{\omega_0^2(a_1\omega_0^2-a_3)^2+(\omega_0^4-a_2\omega_0^2+a_4)^2} \\ & +\frac{(a_3^2-2a_2a_4)}{\omega_0^2(a_1\omega_0^2-a_3)^2+(\omega_0^4-a_2\omega_0^2+a_4)^2} \\ & +\frac{-3b_1^2\omega_0^4+\omega_0^2(4b_1b_3-2b_2^2)+(-b_3^2+2b_2b_4)}{\omega_0^2(b_1\omega_0^2-b_3)^2+(b_2\omega_0^2-b_4)^2}\}. \end{aligned}$$

From equation (3.18), we get

$$
\begin{aligned}
& \omega_0^2(a_1\omega_0^2 - a_3)^2 + (\omega_0^4 - a_2\omega_0^2 + a_4)^2 \\
= \;& \omega_0^2(b_1\omega_0^2 - b_3)^2 + (b_2\omega_0^2 - b_4)^2.
\end{aligned}
$$

It follows that

$$
\begin{aligned}
& sign\{\frac{dRes(\tau_2)}{d\tau_2}\}|_{\tau_2=\tau_k^{(j)}} \\
= \;& sign[\frac{F'(z_k)}{(a_1\omega_0^2 - a_3)^2\omega_0^2 + (b_4 - b_2\omega_0^2)^2}].
\end{aligned}
$$

Since $z_k > 0$, we obtain that $\frac{dRes(\tau_2)}{d\tau_2}|_{\tau_2=\tau_k^{(j)}}$ and $F'(z_k)$ have the same sign. Therefore, we finally have the following result.

Theorem 3.7 *Let $\tau_k^{(j)}$, ω_0 and τ_0 be defined by (3.22) and (3.23). Then we have*

(a) The equilibrium E_2 is locally asymptotically stable for any $\tau_2 \geq 0$ if equation (3.19) has no positive real root.

(b) If equation (3.19) has some positive real roots, then equilibrium E_2 is locally asymptotically stable for $\tau_2 \in [0, \tau_{k_0}^{(j_0)})$, where $\tau_{k_0}^{(j_0)}$ is defined by (3.22).

(c) Assume $F'(z_{k_0}^{(j_0)}) > 0$, there is a Hopf bifurcation for the model (1.2) from equilibrium E_2 as τ_2 passes through the critical value $\tau_{k_0}^{(j_0)}$.

IV. Numerical simulations

In order to verify the stability switches as shown Theorem 3.7 in above Section 3 and find the complex dynamical behaviors of model (1.2), we perform numerical analysis for different time delays τ_1 and τ_2 by using the software MATLAB.

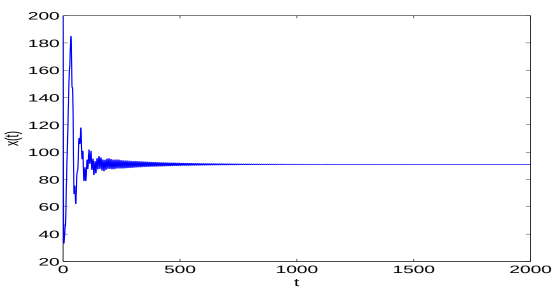
Example. Corresponding to model (1.2), we consider the following model

$$
\begin{cases}
\frac{dx}{dt} = 10 - 0.01x(t) - \frac{0.5x(t)v(t)}{1+0.01v(t)}, \\
\frac{dy}{dt} = \frac{0.5e^{-0.01\tau_1}x(t-\tau_1)v(t-\tau_1)}{1+0.01v(t-\tau_1)} \\
\qquad -0.5y(t) - y(t)z(t), \\
\frac{dv}{dt} = 0.4y(t) - 3v(t), \\
\frac{dz}{dt} = 0.1y(t-\tau_2)z(t-\tau_2) - 0.15z(t),
\end{cases}
\tag{4.1}
$$

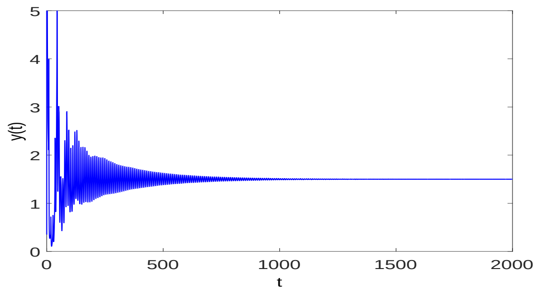
where $\tau_1 = 8.5$.

By direct calculation we can obtain CTL-present infection equilibrium $E_2 = (91.0744, 1.5000, 0.2000, 5.0657)$ for model (4.1).

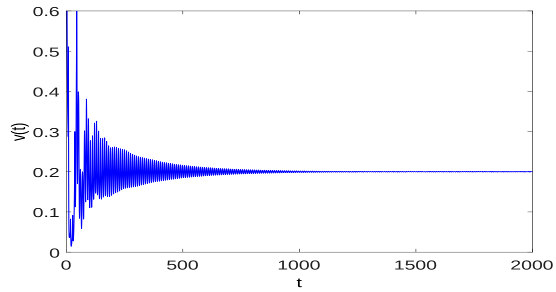
In the following Figs.1-4, we denote figure (a): time-series of $x(t)$, figure (b): time-series of $y(t)$, figure (c): time-series of $v(t)$ and figure (d): time-series of $z(t)$.



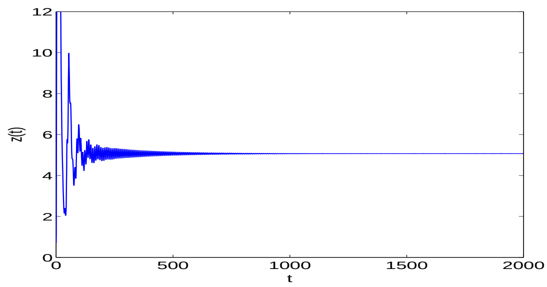
(a)



(b)

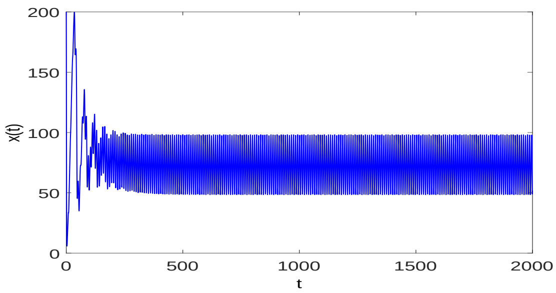


(c)

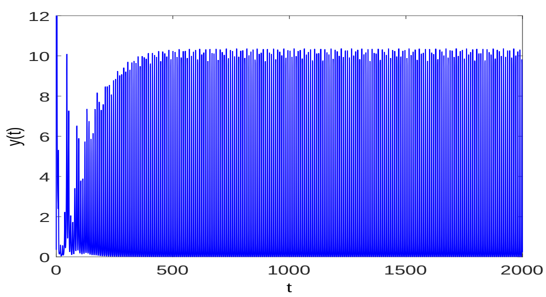


(d)

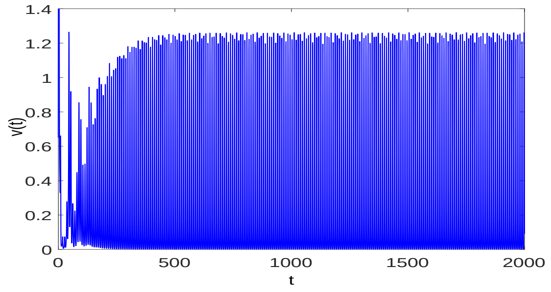
Fig.1. The time-series of model (4.1) for $\tau_2 = 0.02$. It shows that equilibrium E_2 is locally stable.



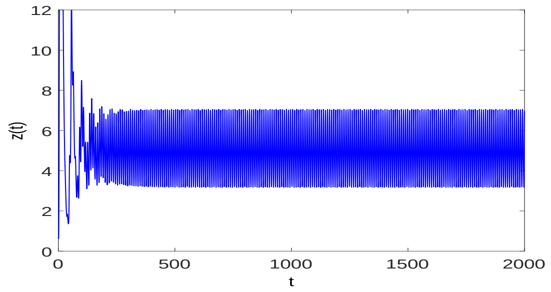
(a)



(b)

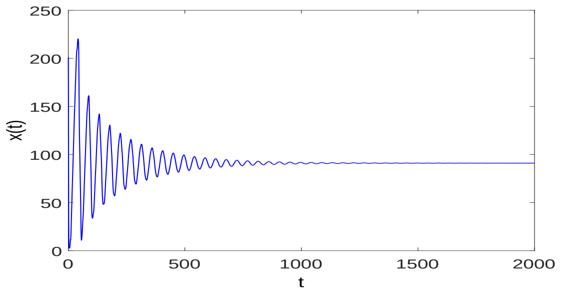


(c)

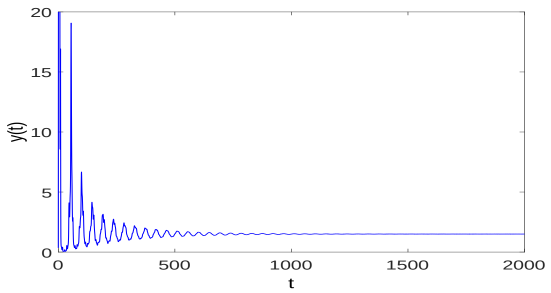


(d)

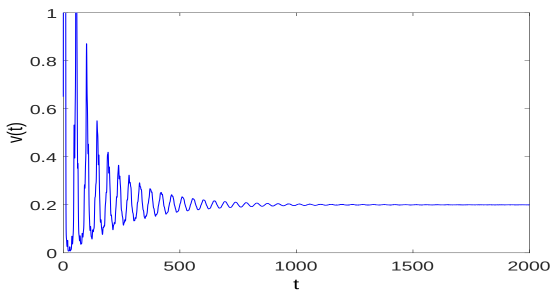
Fig.2. The time-series of model (4.1) with $\tau_2 = 1.2$. It shows that equilibrium E_2 is unstable and the Hopf bifurcation occurs.



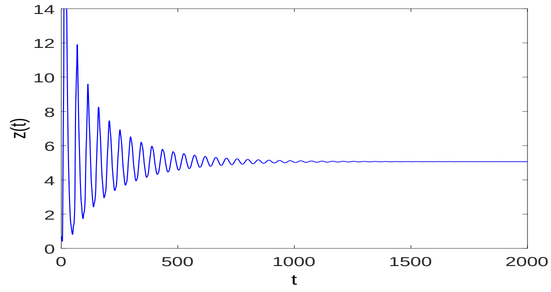
(a)



(b)

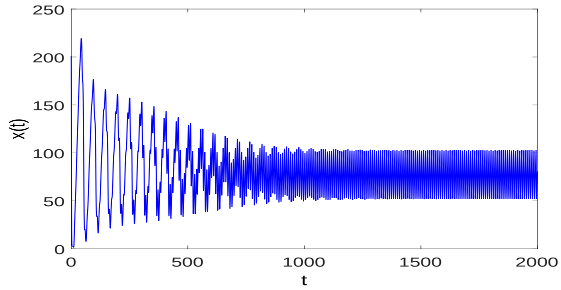


(c)

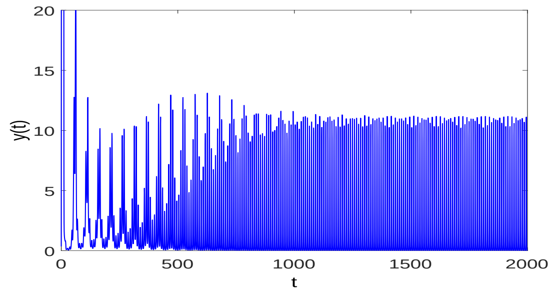


(d)

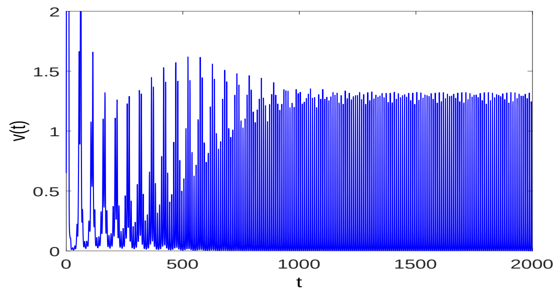
Fig.3. The time-series of model (4.1) for $\tau_2 = 5$. It shows that equilibrium E_2 is locally stable.



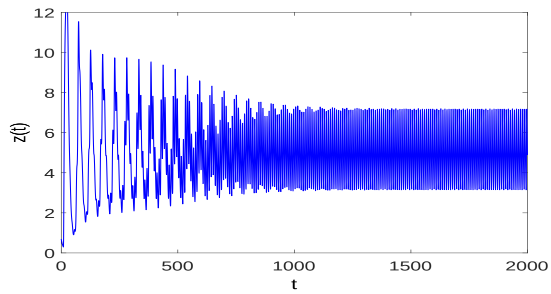
(a)



(b)



(c)



(d)

Fig.4. The time-series of model (4.1) with $\tau_2 = 9.5$. It shows that equilibrium E_2 is unstable and the Hopf bifurcation occurs.

From the parameters given in model (4.1) and the values of τ_2, we can see that there are three critical values of the delay τ_2, denoted by τ_2^*, τ_2^{**} and τ_2^{***}, and $\tau_2^* \approx 0.3244$, $\tau_2^{**} \approx 4.4234$, $\tau_2^{***} \approx 7.1146$. Simple numerical simulations show that infection equilibrium with CTL response of model (4.1) is locally asymptotically stable for $\tau_2 \in [0, \tau_2^*)$ (see Fig.1). In this case, we take $\tau_2 = 0.02 < \tau_2^*$. E_2 is unstable for $\tau_2 \in (\tau_2^*, \tau_2^{**})$ (see Fig.2). In this case, we take $\tau_2 = 1.2 \in (\tau_2^*, \tau_2^{**})$. E_2 is locally asymptotically stable for $\tau_2 \in (\tau_2^{**}, \tau_2^{***})$ (see Fig.3). In this case, we take $\tau_2 = 5 \in (\tau_2^{**}, \tau_2^{***})$. E_2 is unstable for $\tau_2 > \tau_2^{***}$ (see Fig.4). In this case, we take $\tau_2 = 9.5 > \tau_2^{***}$. From the analysis above, we can conclude that Hopf bifurcation occurs at τ_2^* ,τ_2^{**} and τ_2^{***}.

V. Conclusion

In this paper, we have discussed an HIV infection model with intracellular delay and immune response delay. We assume that the production of CTL cells response depends on the infected cells and CTL cells for some important biological meanings. Dynamical analysis of model (1.2) shows that intracellular delay τ_1 and immune delay τ_2 play different roles in the stability of the equilibria. The results show that when $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable, which means that the virus is cleared up and the immune is not active. When $1 < R_0$ and $R_1 < 1$, the infection equilibrium without CTL response exists and globally asymptotically stable, which means that the CTL response would not be activated and viral infection becomes vanished. When $R_1 > 1$ and $\tau_2 = 0$, the infection equilibrium with CTL response is globally asymptotically stable. Actually, the intracellular delay does not affect the stability of the model. When $R_1 > 1$ and $\tau_2 > 0$, by using the theory of bifurcation, we obtain the sufficient conditions on the existence of the Hopf bifurcation at the infection equilibrium with CTL response E_2. Meanwhile, by means of numerical simulations, it is shown that the Hopf bifurcation and stability switches occur at infection equilibrium with CTL response E_2 as τ_2 increases. From Figs.1-4 we see that as $\tau_2 \geq 0$ increases from zero the dynamical behaviors of equilibrium E_2 will occur: locally asymptotically stable $\rightarrow$ unstable and Hopf bifurcation appears $\rightarrow$ locally asymptotically stable $\rightarrow$ unstable and Hopf bifurcation appears. We obtain that model (4.1) may undergo Hopf bifurcation and stability switch. That is, by choosing immune response delay as bifurcation parameter, we have demonstrated that a limit cycle occurs via Hopf bifurcation, when the delay passes through the critical value. This explains the fact that the immune response delay plays negative role in controlling disease progression.

However, when $\tau_1 > 0$ and $\tau_2 > 0$, the theoretical analysis and results for the Hopf bifurcation and stability switches occur at infection equilibrium E_2 with CTL response in model (1.2), up to now, it is a few and also very rough and incompact. Therefore, whether we can establish a systemic and complete theoretical analysis and results will be a very estimable and significative subject.

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