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VIRUS DYNAMICS MODEL WITH INTRACELLULAR DELAYS AND IMMUNE RESPONSE

Haitao Song and Weihua Jiang

Department of Mathematics
Harbin Institute of Technology
Harbin, 150001, China

Shengqiang Liu

The Academy of Fundamental and Interdisciplinary Science
Harbin Institute of Technology
3041#, 2 Yi-Kuang Street, Harbin, 150080, China

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Abstract. In this paper, we incorporate an extra logistic growth term for uninfected $CD4^+$ T-cells into an HIV-1 infection model with both intracellular delay and immune response delay which was studied by Pawelek et al. in [26]. First, we proved that if the basic reproduction number $R_0 < 1$, then the infection-free steady state is globally asymptotically stable. Second, when $R_0 > 1$, then the system is uniformly persistent, suggesting that the clearance or the uniform persistence of the virus is completely determined by R_0. Furthermore, given both the two delays are zero, then the infected steady state is asymptotically stable when the intrinsic growth rate of the extra logistic term is sufficiently small. When the two delays are not zero, we showed that both the immune response delay and the intracellular delay may destabilize the infected steady state by leading to Hopf bifurcation and stable periodic oscillations, on which we analyzed the direction of the Hopf bifurcation as well as the stability of the bifurcating periodic orbits by normal form and center manifold theory introduced by Hassard et al [15]. Third, we engaged numerical simulations to explore the rich dynamics like chaotic oscillations, complicated bifurcation diagram of viral load due to the logistic term of target cells and the two time delays.

1. **Introduction.** Human Immunodeficiency Virus (HIV) has spread to all of mainland China [44] and becomes a serious threat to public health. The dynamics of HIV have three distinct phases which are primary infection, chronic infection and Acquired Immune Deficiency Syndrome (AIDS) or drug therapy [9, 10]. Mathematic modeling of viral dynamics for HIV infection has an important role for understanding the pathogenesis of HIV infection [3, 11, 43, 17, 23, 24, 28, 32, 34, 37].

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Following the basic models of viral dynamics[30, 25], many mathematical models have been used to study the dynamics of HIV infection and immune responses [1, 5, 6, 16, 26, 27, 40, 42, 45]. Ciupe et al. [6] considered the following HIV model

$$\begin{cases} \dfrac{\mathrm{d}T}{\mathrm{d}t} = s - dT - kVT, \\ \dfrac{\mathrm{d}T^*}{\mathrm{d}t} = kVT - \delta T^* - d_x E T^*, \\ \dfrac{\mathrm{d}V}{\mathrm{d}t} = N\delta T^* - cV, \\ \dfrac{\mathrm{d}E}{\mathrm{d}t} = pT^* - d_E E, \end{cases} \tag{1}$$

where $T(t)$, $T^*(t)$, $V(t)$ and $E(t)$ are uninfected T-cells, infected cells, free virus and effector cells. s is the rate at which new T cells are created, d is their natural death rate, k is the infection rate, and δ represents the death rate of the infected cells before viral production commences. d_x is the death rate of T^* due to action of the immune response. N is the number of virus particles produced by each infected cell, c is the viral clearance rate constant, d_E is the death rate of E, and p is the produce rate of the effector cells.

Time delays have also been introduced into HIV mathematical model to study the dynamics. In [17], Herz et al. firstly introduced an intracellular delay, the time between infection of a cell and production of new virus particles, to analyze the clinical data. Nelson and Perelson [23] considered a set of models with intracellular delays, and predicted that frequent early sampling of plasma virus will lead to reliable estimates of the free virus half-life. Li and Shu [19] incorporated a time delay into the immune response in the HTLV-1 infection model, and showed that the time delay can destabilize the endemic equilibrium, leading to Hopf bifurcation. More within-host HIV models with time delays can be found in [2, 8, 12, 20, 21, 38, 41, 46].

In [26], Pawelek et al. incorporated an intracellular delay and an immune response delay into (1) to analyze virus dynamics, where the criteria on local stability of the infection-free and infected steady states, and uniform persistence of the system as well as the global stability of the infected steady states were established. Moreover, it was shown in [26] that introducing the intracellular delay does not change the stability results if there is no immune delay. However, incorporating the immune delay may lead to rich dynamics like Hopf bifurcation even if there is no intracellular delay.

Since the proliferation rate of T-cells is density-dependent with the proliferation slowing as the T-cell count becomes high [4, 8, 29, 30, 39]. Culshaw and Ruan [8] considered a basic HIV model with logistic growth and an intracellular delay, and obtained the stability of the endemic equilibrium. Wang and Li [39] studied a HIV model with a logistic proliferation of all T-cells and showed that the stability of the endemic equilibrium is dependent on the T-cell proliferation rate. In this paper, we incorporate the intracellular delay, immune response delay and logistic growth term for T-cells into the model (1). We additionally consider the intracellular delay by assuming that the generation of virus producing cells at time t is caused by the infection of target cells at time $t - \tau_1$, i.e., τ_1 is the lag between the time virus contacts a target cell and the time cell becomes actively infected. τ_2 is the time of activation for the effector cells. As described in [22], we assume $k_1 = ke^{-\alpha_1\tau_1}$, where α_1 is the death rate of infected cells before viral production commences. The

model is as follows

$$\begin{cases} \dfrac{\mathrm{d}T(t)}{\mathrm{d}t} = s - dT(t) - kV(t)T(t) + rT(t)\left(1 - \dfrac{T(t)}{T_{max}}\right), \\ \dfrac{\mathrm{d}T^*(t)}{\mathrm{d}t} = k_1 V(t-\tau_1)T(t-\tau_1) - \delta T^*(t) - d_x E(t)T^*(t), \\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t} = N\delta T^*(t) - cV(t), \\ \dfrac{\mathrm{d}E(t)}{\mathrm{d}t} = pT^*(t-\tau_2) - d_E E(t), \end{cases} \tag{2}$$

with initial conditions

$$T(\theta) = \varphi_1(\theta), T^*(\theta) = \varphi_2(\theta), V(\theta) = \varphi_3(\theta), E(\theta) = \varphi_4(\theta), \theta \in [-\tau, 0], \tag{3}$$

where $\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4) \in C\left([-\tau, 0], R_+^4\right)$ with $\varphi_i(0) > 0 (\theta \in [-\tau, 0], i = 1, 2, 3, 4)$. Where r is the growth rate of T-cells (thus, $r > d$ in general), T_{max} ($dT_{max} > s$) is the carrying capacity of the T-cells population, and the term $T^*(t - \tau_2)$ accounts for a time delay between the moment of infection and the recognition of the infected cells by the cytotoxic CD8+T cells.

The paper is organized as follows. In section 2, local stability and global stability of the uninfected equilibrium, and uniform persistence of the system are proved by rigorous mathematical analysis. In section 3, we establish local stability of the infected equilibrium and obtain sufficient conditions for the existence of the local Hopf bifurcation, and the direction of Hopf bifurcation and stability of the bifurcating periodic solutions are considered. In section 4, results from numerical simulations are presented. We also study the effect of the immune response delay and the growth rate of T-cells on the stability transition and viral load. Finally, a brief discussion completes the paper.

2. **Threshold dynamics of the steady states.** We denote by $X = C\left([-\tau, 0], R_+^4\right)$, $\tau = max\{\tau_1, \tau_2\}$, here C denotes the Banach space $C\left([-\tau, 0], R_+^4\right)$ of continuous functions mapping the interval $[-\tau, 0]$ into R_+^4 equipped with the sup-norm. Then by the standard theory of functional differential equations [14] we obtain that, for any $\varphi \in C\left([-\tau, 0], R_+^4\right)$, there is a unique solution

$$Y(t, \varphi) = (T(t, \varphi), T^*(t, \varphi), V(t, \varphi), E(t, \varphi))$$

of the system (2) which satisfies $Y_0 = \varphi$.

System (2) has an uninfected equilibrium and an infected (positive) equilibrium. The uninfected equilibrium is $E_0 = (T_0, 0, 0, 0)$, where

$$T_0 = \frac{T_{max}}{2r}\left[r - d + \sqrt{(r-d)^2 + \frac{4rs}{T_{max}}}\right].$$

From the first equation of system (2), we have

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} \le s - dT(t) + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right),$$

then

$$\limsup_{t \to +\infty} T(t) \le T_0. \tag{4}$$

The infected (positive) equilibrium is $E_1 = (T_1, T_1^*, V_1, E_1)$, where

$$\begin{aligned} T_1 &= \frac{r - d + \frac{kd_E N\delta^2}{cpd_x} + \sqrt{(r - d + \frac{kd_E N\delta^2}{cpd_x})^2 + 4s(\frac{r}{T_{max}} + \frac{kk_1 N^2\delta^2 d_E}{Pc^2 d_x})}}{2(\frac{r}{T_{max}} + \frac{kk_1 N^2\delta^2 d_E}{Pc^2 d_x})}, \\ T_1^* &= \frac{d_E(\frac{k_1 N\delta T_1}{c} - \delta)}{pd_x}, \\ V_1 &= \frac{N\delta}{c} T_1^*, \\ E_1 &= \frac{p}{d_E} T_1^*. \end{aligned} \tag{5}$$

The basic reproduction number is defined as

$$R_0 = k_1 N T_0 / c. \tag{6}$$

Following $T_1^* > 0$, we know that the infected equilibrium exists if and only if $k_1 N T_1 / c > 1$, which is equivalent to $k_1 N T_0 / c > 1$.

Theorem 2.1. *Assume that $Y(t, \varphi)$ is the solution of the system (2) with the initial conditions (3). $\{T(t), T^*(t), V(t), E(t)\}$ $(\forall t \geq 0)$ are nonnegative and ultimately bounded. Furthermore, there is an $\epsilon > 0$ such that $\liminf_{t\to\infty} T(t) \geq \varepsilon$.*

Proof. By [35, Theorem 5.2.1], the nonnegativeness of $T(t)$, $T^*(t)$, $V(t)$ and $E(t)$ follows immediately.

From the first equation of (2), we have

$$\frac{\mathrm{d}T}{\mathrm{d}t} \leq s - dT + rT\left(1 - \frac{T}{T_{max}}\right).$$

Then $\limsup_{t\to+\infty} T(t) \leq T_0$, and then $T(t)$ is ultimately bounded. Now we define a Lyapunov functional

$$U(t) = T(t) + \frac{k}{k_1} T^*(t + \tau_1).$$

Obviously, $U(t) \geq 0$ for all $t \geq 0$. Differentiating $U(t)$ along the solution of system (2) yields

$$\begin{aligned} \frac{\mathrm{d}U(t)}{\mathrm{d}t} &\leq s - dT(t) + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right) - \frac{\delta k}{k_1} T^*(t + \tau_1) \\ &= s - dT(t) + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right) + \delta T(t) - \delta U(t) \\ &\leq s + rT(t)\left(1 - \frac{T(t)}{T_{max}}\right) + \delta T(t) - \delta U(t) \end{aligned}$$

Therefore, $\limsup_{t\to+\infty} U(t) \leq C/\delta$, where $C = \max\{s + rT\left(1 - \frac{T}{T_{max}}\right) + \delta T\}, T \in (0, T_0]$. It follows that $\limsup_{t\to+\infty} T(t) \leq C/\delta$ and that $T^*(t)$ is ultimately bounded. From the third and fourth equation of system (2), we know that $V(t)$ and $E(t)$ are also ultimately bounded. In addition, by the first equation of (2), we have

$$\dot{T}(t) \geq s - T\left[d + kV_{upper} - r + \frac{rT_0}{T_{max}}\right], \quad \text{for a large t,}$$

where V_{upper} is the upper bound of $V(t)$. Then we can show that $T(t)$ is uniformly bounded away from zero. The proof is completed. □

2.1. **Local stability of the uninfected equilibrium.** In order to analyze the local stability of the uninfected equilibrium E_0, we denote

$$\alpha = \frac{s}{T_1} + \frac{rT_1}{T_{max}} > 0.$$

Theorem 2.2. *Consider system (2). The uninfected equilibrium E_0 is locally asymptotically stable if $R_0 < 1$, and unstable if $R_0 > 1$, where R_0 is defined by (6).*

Proof. The characteristic equation of the uninfected equilibrium E_0 is

$$(\lambda + \alpha)(\lambda + d_E)\left[\lambda^2 + (c+\delta)\lambda + c\delta - k_1 T_0 N \delta e^{-\lambda\tau_1}\right] = 0. \tag{7}$$

Obviously, $\lambda = -\alpha$ and $\lambda = -d_E$ are negative roots of Eq.(7). The other roots are determined by the solutions of the following equation

$$\lambda^2 + (c+\delta)\lambda + c\delta - k_1 T_0 N \delta e^{-\lambda\tau_1} = 0. \tag{8}$$

Substituting $\tau_1 = 0$ into Eq.(8) leads to

$$\lambda^2 + (c+\delta)\lambda + c\delta - k_1 T_0 N \delta = 0. \tag{9}$$

If $R_0 < 1$, then $c\delta > k_1 N \delta T_0$. Then we obtain that the equation (9) has two negative real roots, and E_0 is locally asymptotically stable for $\tau_1 = 0$.

If $\tau_1 > 0$ and Eq.(8) has a purely imaginary root $\lambda = i\omega(\tau_1)(\omega > 0)$. Separating real and imaginary parts yields

$$\begin{aligned} c\delta R_0 \cos\omega\tau_1 &= c\delta - \omega^2, \\ -c\delta R_0 \sin\omega\tau_1 &= (c+\delta)\omega. \end{aligned}$$

Squaring and adding the two equations give

$$F_1(\omega) = \omega^4 + (c^2+\delta^2)\omega^2 + c^2\delta^2 - c^2\delta^2 R_0^2 = 0. \tag{10}$$

If $R_0 < 1$ then $c^2\delta^2 - c^2\delta^2 R_0^2 > 0$. Thus, Eq.(10) has no positive roots. If $R_0 < 1$, there is no root of Eq.(10) which can cross the imaginary axis when the delay τ_1 increases. Then E_0 is locally asymptotically stable for $\tau_1 \geq 0$.

If $R_0 > 1$, then $c\delta < c\delta R_0$, and the equation (9) has a positive root. Then E_0 is unstable for $\tau_1 = 0$. Moreover, $\frac{\partial F_1(\omega)}{\partial\omega} = 4\omega^3 + 2(c^2+\delta^2)\omega > 0$, and by Cooke and Van den Driessche [7] and Freedman and Kuang [13], E_0 is unstable for $\tau_1 \geq 0$. The proof is completed. □

2.2. **Global stability of the uninfected equilibrium.**

Theorem 2.3. *Consider system (2). If $R_0 < 1$, The uninfected equilibrium E_0 is globally asymptotically stable.*

Proof. Define

$$M = \{\varphi = (\varphi_1, \varphi_2, \varphi_3, \varphi_4) \in C([-\tau, 0], R_+^4), 0 \leq \varphi_1 \leq T_0\}.$$

From (4), it is verified that M attracts all solutions of system (2). Suppose $(T(t), T^*(t), V(t), E(t))$ be a solution of system (2) with initial value in M.

We claim that $T(t) \leq T_0 (\forall t \geq 0)$. Suppose by contradiction that there must exist the first $t_1 > 0$, such that $T(t_1) = T_0$ and $T'(t_1) > 0$. From the first equation of system (2), we have

$$T'(t_1) = s - dT(t_1) + rT(t_1)\left(1 - \frac{T(t_1)}{T_{max}}\right) - kV(t_1)T(t_1) = -kV(t_1)T(t_1) \leq 0,$$

which contradict $T'(t_1) > 0$. Therefore, M is positively invariant set with respect to the system (2). Define a Lyapunov functional on M

$$V(\varphi) = \frac{k}{k_1}\varphi_2(0) + b_1\varphi_3(0) + b_2\varphi_4(0) + k\int_{-\tau_1}^{0}\varphi_3(s)\varphi_1(s)ds + b_2p\int_{-\tau_2}^{0}\varphi_2(s)\mathrm{d}s,$$

where $b_1 = \frac{kT_0}{c}$, $b_2 = -\frac{k\delta}{2pk_1}(R_0 - 1)$. The invariance of M implies that, for any $\varphi \in M$, the solution $(T(t), T^*(t), V(t), E(t))$ of system (2) such that $T(t) \le T_0 (\forall t \ge 0)$. Then the derivative of $V(\varphi)$ along the system (2) is

$$\begin{aligned} V'(\varphi) &= \frac{k}{k_1}\left(k_1\varphi_3(-\tau_1)\varphi_1(-\tau_1) - \delta\varphi_2(0) - d_x\varphi_4(0)\varphi_2(0)\right) \\ &\quad + b_1(N\delta\varphi_2(0) - c\varphi_3(0)) + b_2\left(p\varphi_2(-\tau_2) - d_E\varphi_4(0)\right) \\ &\quad + k\left(\varphi_3(0)\varphi_1(0) - \varphi_3(-\tau_1)\varphi_1(-\tau_1)\right) + b_2p\left(\varphi_2(0) - \varphi_2(-\tau_2)\right) \\ &= k\varphi_3(0)(\varphi_1(0) - T_0) + (b_1N\delta + b_2p - \frac{k\delta}{k_1})\varphi_2(0) - b_2d_E\varphi_4(0) \\ &\quad - \frac{kd_x}{k_1}\varphi_2(0)\varphi_4(0) \\ &= \frac{1}{2}\frac{k}{k_1}\delta(R_0 - 1)\varphi_2(0) - b_2d_E\varphi_4(0) - \frac{kd_x}{k_1}\varphi_2(0)\varphi_4(0) \\ &\quad + k\varphi_3(0)(\varphi_1(0) - T_0). \end{aligned}$$

If $R_0 < 1$, then $V'(\varphi) \le 0$, and $V'(\varphi) = 0$ if and only if $\varphi_2(0) = 0$, $\varphi_4(0) = 0$, $\varphi_1(0) = T_0$ or $\varphi_3(0) = 0$. Then the largest compact invariant set in $\{\varphi \in M \mid V'(\varphi) = 0\}$ is the singleton $\{E_0\}$. By LaSalle's Invariance Principle [18], we obtain that all solutions of system (2) converge to E_0. This result together with the local stability of E_0 established in Theorem 2.2 implies the global stability of E_0. The proof is completed. □

2.3. **Persistence as $R_0 > 1$.**

Theorem 2.4. *Consider system (2). If $R_0 > 1$, then the system (2) is uniformly persistent, and there exists a $\bar{\varepsilon} > 0$, such that $\liminf_{t\to\infty} T(t) \ge \bar{\varepsilon}$, $\liminf_{t\to\infty} T^*(t) \ge \bar{\varepsilon}$, $\liminf_{t\to\infty} V(t) \ge \bar{\varepsilon}$, and $\liminf_{t\to\infty} E(t) \ge \bar{\varepsilon}$.*

Proof.

$$X = \{\varphi = (T, T^*, V, E) \in C([-\tau, 0], R_+^4) : \varphi_2(0) \ge 0, \varphi_3(0) \ge 0\}.$$

Denote

$$X_1 = \{\varphi \in X \mid \varphi_2(0) > 0, \varphi_3(0) > 0\},$$

$$X_2 = \{\varphi \in X \mid \varphi_2(0) = 0 \text{ or } \varphi_3(0) = 0\},$$

which is relatively closed in X.

Next we prove X_1 is positively invariant for $P(t)$, where $P(t)(t \ge 0)$ is the family of solution operators associated to system (2). The ω-limit set $\omega(x)$ of x consists of $y \in X$ such that there is a sequence $t_n \to \infty$ as $n \to \infty$, and $P(t_n)x \to y$ as $n \to \infty$.

The equations of system (2) give

$$\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} \ge -\delta T^*(t), \quad \frac{\mathrm{d}V(t)}{\mathrm{d}t} \ge -cV(t), \forall t \ge 0. \tag{11}$$

Since $T^*(0,\varphi)=\varphi_2(0)>0,\quad V(0,\varphi)=\varphi_3(0)>0$, then

$$T^*(t,\varphi)\geq\varphi_2(0)e^{-\delta t}>0,\quad V(t,\varphi)\geq\varphi_3(0)e^{-ct}>0,\forall t\geq 0,$$

thus, X_1 is positively invariant for $P(t)$.

Denote

$$M_\partial=\{\varphi\in X: Y(t,\varphi)\ \text{ satisfies }\ (2)\ \text{ and }\ Y(t,\varphi)\in X_2,\forall t\geq 0\}.$$

Then we can claim that

$$M_\partial=\{(T,0,0,E)\}. \tag{12}$$

Assume that $Y(t)\in M_\partial(\forall t\geq 0)$. It suffices to prove that $T^*(t)=V(t)=0(\forall t\geq 0)$. Assume, by contradiction, that there exists a $t_0\geq 0$ such that either

(i): $T^*(t_0)>0, V(t_0)=0$; or
(ii): $T^*(t_0)=0, V(t_0)>0$.

Consider (i), from the equations of system (2) we obtain

$$\left.\frac{\mathrm{d}V}{\mathrm{d}t}\right|_{t=t_0}=N\delta T^*(t_0)>0.$$

Therefore, there exists an $\varepsilon_0>0$ such that $V(t)>0,\forall t\in(t_0,t_0+\varepsilon_0)$. Since $T^*(t_0)>0$, then there exists a $0<\varepsilon_1<\varepsilon_0$ such that $T^*(t)>0,\forall t\in(t_0,t_0+\varepsilon_1)$. So we can get $T^*(t)>0, V(t)>0,\forall t\in(t_0,t_0+\varepsilon_1)$, which contradicts our assumption that $(T(t),T^*(t),V(t),E(t))\in M_\partial$. Case (ii) can be treated similarly. Then (12) holds.

Denote $\Omega=\bigcap_{x\in\mathcal{A}}\omega(x)$, where $\mathcal{A}$ is the global attractor of $P(t)$ restricted to X_2. Then we can claim that $\Omega=\{E_0\}$. Since $\Omega\subseteq M_\partial$ and (12), then from the equations of (2), we can obtain that $\lim\limits_{t\to\infty}E(t)=0$, $\lim\limits_{t\to\infty}T(t)=T_0$. Therefore, $\{E_0\}$ is a isolated invariant set in X.

Next we prove that $W^s(E_0)\bigcap X_1=\emptyset$. Suppose by contradiction that there exists a solution $(T(t),T^*(t),V(t),E(t))\in X_1$ such that

$$\lim_{t\to\infty}T(t)=T_0,\quad \lim_{t\to\infty}T^*(t)=0,\quad \lim_{t\to\infty}V(t)=0,\quad \lim_{t\to\infty}E(t)=0.$$

For any small enough constant $\varepsilon>0$, there is a positive constant $t_1=t_1(\varepsilon)$ such that $T(t)>T_0-\varepsilon>0, E(t)<\varepsilon,\ \forall t\geq t_1$.

From the equations of (2), we have

$$\begin{cases}\dfrac{\mathrm{d}T^*(t)}{\mathrm{d}t}\geq k_1(T_0-\varepsilon)V(t-\tau_1)-\delta T^*-d_x\varepsilon T^*,\\ \dfrac{\mathrm{d}V(t)}{\mathrm{d}t}=N\delta T^*-cV,\quad t\geq t_1+\tau.\end{cases}$$

If $T^*(t),V(t)\to 0$, as $t\to\infty$, using the nonnegativity and a standard comparison argument, then the solution $(T_2^*(t),V_2(t))$ of the following monotone system

$$\begin{cases}\dfrac{\mathrm{d}T_2^*(t)}{\mathrm{d}t}=k_1(T_0-\varepsilon)V_2(t-\tau_1)-\delta T_2^*(t)-d_x\varepsilon T_2^*(t),\\ \dfrac{\mathrm{d}V_2(t)}{\mathrm{d}t}=N\delta T_2^*(t)-cV_2(t),\quad t\geq t_1+\tau.\end{cases} \tag{13}$$

with initial value $T_2^*(t)=T^*(t),\quad V_2(t)=V(t),\forall t\in[t_1,t_1+\tau]$ converges to $(0,0)$. Therefore, $\lim\limits_{t\to\infty}U(t)=0$, where $U(t)>0$ is given by

$$U(t)=T_2^*(t)+\frac{k_1(T_0-\varepsilon)}{c}V_2(t)+k_1(T_0-\varepsilon)\int_{t-\tau_1}^{t}V_2(\xi)d\xi.$$

Differentiating $U(t)$ with respect to (13) gives

$$\left.\frac{\mathrm{d}U(t)}{\mathrm{d}t}\right|_{(13)} = \left[\frac{1}{c}N\delta k_1(T_0-\varepsilon)-\delta-d_x\varepsilon\right]T_2^*(t).$$

When $R_0 > 1$, we can get that $N\delta k_1(T_0-\varepsilon)/c-\delta-d_x\varepsilon > 0$ for small enough ε. Then $U(t)$ goes to either infinity or some positive number as $t\to\infty$, which contradicts $\lim\limits_{t\to\infty} U(t)=0$. Therefore, we obtain that $W^s(E_0)\bigcap X_1=\emptyset$.

Define $f: X\to R_+$ by $f(\varphi)=min\{\varphi_2(0),\varphi_3(0)\}$, $\forall\varphi\in X$. It can be verified that $X_1=f^{-1}(0,\infty)$ and $X_2=f^{-1}(0)$. Following the Theorem 3 in [36], we have $\liminf\limits_{t\to\infty}(T^*(t),V(t))\geq(\varepsilon_1,\varepsilon_1)$ for some constant $\varepsilon_1>0$. Following Theorem 2.1, we know that $\liminf\limits_{t\to\infty} T(t)\geq\varepsilon>0$. Furthermore, from the fourth equation of (2), we can get that $\liminf\limits_{t\to\infty} E(t)\geq\varepsilon_2$ for some constant $\varepsilon_2>0$. Define $\bar{\varepsilon}=\min\{\varepsilon,\varepsilon_1,\varepsilon_2\}$, note that $\liminf\limits_{t\to\infty} T(t)\geq\varepsilon>0$, then the proof is completed. □

3. **Local stability and Hopf bifurcation.** Let $x_1=T-T_1$, $x_2=T^*-T_1^*$, $x_3=V-V_1$, $x_4=E-E_1$. Then system (2) becomes

$$\begin{cases}
\dfrac{\mathrm{d}x_1}{\mathrm{d}t} = \left[r(1-\dfrac{2T_1}{T_{max}})-d-kV_1\right]x_1-kT_1x_3-\dfrac{r}{T_{max}}x_1^2-kx_1x_3,\\
\dfrac{\mathrm{d}x_2}{\mathrm{d}t} = -(\delta+d_xE_1)x_2-d_xT_1^*x_4+k_1V_1x_1(t-\tau_1)+k_1T_1x_3(t-\tau_1)\\
\qquad\quad -d_xx_2x_4+k_1x_1(t-\tau_1)x_3(t-\tau_1),\\
\dfrac{\mathrm{d}x_3}{\mathrm{d}t} = N\delta x_2-cx_3,\\
\dfrac{\mathrm{d}x_4}{\mathrm{d}t} = -d_Ex_4+px_2(t-\tau_2).
\end{cases}\tag{14}$$

We linearize the system and obtain the characteristic equation of system (14) at $F(0,0,0,0)$ is

$$\begin{vmatrix}
\lambda+d+kV_1-r+\frac{2rT_1}{T_{max}} & 0 & kT_1 & 0\\
-k_1V_1e^{-\lambda\tau_1} & \lambda+\delta+d_xE_1 & -k_1T_1e^{-\lambda\tau_1} & d_xT_1^*\\
0 & -N\delta & \lambda+c & 0\\
0 & -pe^{-\lambda\tau_2} & 0 & \lambda+d_E
\end{vmatrix}=0,$$

that is,

$$\begin{aligned}
&\lambda^4+a_1\lambda^3+a_2\lambda^2+a_3\lambda+a_4+e^{-\lambda\tau_1}(b_0\lambda^2+b_1\lambda+b_2)\\
&+e^{-\lambda\tau_2}(c_0\lambda^2+c_1\lambda+c_2)=0,
\end{aligned}\tag{15}$$

where

$$\begin{aligned}
a_1&=\alpha+\tfrac{k_1N\delta T_1}{c}+c+d_E,\\
a_2&=\alpha\left(\tfrac{k_1N\delta T_1}{c}+c+d_E\right)+k_1N\delta T_1+cd_E+d_E\tfrac{k_1N\delta T_1}{c},\\
a_3&=\alpha\left(k_1N\delta T_1+cd_E+d_E\tfrac{k_1N\delta T_1}{c}\right)+d_Ek_1N\delta T_1,\\
a_4&=\alpha d_Ek_1N\delta T_1,\\
b_0&=-k_1N\delta T_1,\\
b_1&=k_1N\delta T_1(kV_1-\alpha-d_E),\\
b_2&=k_1N\delta T_1(kV_1d_E-\alpha d_E),\\
c_0&=pd_xT_1^*,\\
c_1&=pd_xT_1^*(\alpha+c),\\
c_2&=pd_xT_1^*\alpha c.
\end{aligned}$$

When $\tau_1 = \tau_2 = 0$, this characteristic equation reduces to

$$\lambda^4 + a_1\lambda^3 + (a_2 + b_0 + c_0)\lambda^2 + (a_3 + b_1 + c_1)\lambda + a_4 + b_2 + c_2 = 0. \quad (16)$$

By Routh-Hurwitz criterion we know that all solutions of Eq.(16) have negative real parts if and only if

$\Delta_1 = a_1 > 0,$
$\Delta_2 = a_1(a_2 + b_0 + c_0) - (a_3 + b_1 + c_1) > 0,$
$\Delta_3 = a_1(a_2 + b_0 + c_0)(a_3 + b_1 + c_1) - a_1^2(a_4 + b_2 + c_2) - (a_3 + b_1 + c_1)^2 > 0$
$\Delta_4 = a_4 + b_2 + c_2 > 0.$

It is easy to show that $\Delta_1 = a_1 = \alpha + \frac{k_1 N\delta T_1}{c} + c + d_E > 0$, and $\Delta_4 = a_4 + b_2 + c_2 = k_1 N\delta T_1 k_1 V_1 d_E + p d_x T_1^* \alpha c > 0$. Then we need $\Delta_2 > 0$ and $\Delta_3 > 0$. If $2\alpha > kV_1$ and $\alpha > d_E$ hold, we have $\Delta_2 > 0$ and $\Delta_3 > 0$. If

$$(H_1) \quad 2\alpha > kV_1 \quad \text{and} \quad \alpha > d_E$$

holds, then all roots of Eq.(16) have negative real parts. Thus, we have

Theorem 3.1. *Assume $R_0 > 1$ and $\tau_1 = \tau_2 = 0$, then the infected equilibrium E_1 is locally asymptotically stable if (H_1) holds.*

When $\tau_1 = 0$ and $\tau_2 > 0$, the characteristic equation (15) reduces to

$$\lambda^4 + a_1\lambda^3 + (a_2 + b_0)\lambda^2 + (a_3 + b_1)\lambda + a_4 + b_2 + e^{-\lambda\tau_2}(c_0\lambda^2 + c_1\lambda + c_2) = 0. \quad (17)$$

Since $c_2 + a_4 + b_2 > 0$, $\lambda = 0$ is not a root of characteristic equation (17).

If $i\omega(\tau_2)(\omega > 0)$ is a purely imaginary root of the characteristic equation (17), separating real and imaginary parts leads to

$$\begin{aligned} &\omega^4 - (a_2 + b_0)\omega^2 + a_4 + b_2 = -(c_2 - c_0\omega^2)\cos\omega\tau_2 - c_1\omega\sin\omega\tau_2, \\ &-a_1\omega^3 + (a_3 + b_1)\omega = (c_2 - c_0\omega^2)\sin\omega\tau_2 - c_1\omega\cos\omega\tau_2. \end{aligned} \quad (18)$$

Squaring and adding the two equations of (18) give

$$\begin{aligned} &f(\omega) = \omega^8 + \omega^6[a_1^2 - 2(a_2 + b_0)] + \omega^4[(a_2 + b_0)^2 + 2(a_4 + b_2) - 2a_1(a_3 + b_1) - c_0^2] \\ &+\omega^2[(a_3 + b_1)^2 - 2(a_2 + b_0)(a_4 + b_2) + 2c_0c_2 - c_1^2] + (a_4 + b_2)^2 - c_2^2 = 0. \end{aligned} \quad (19)$$

Denote

$$\begin{aligned} &f(v) = v^4 + [a_1^2 - 2(a_2 + b_0)]v^3 + [(a_2 + b_0)^2 + 2(a_4 + b_2) - 2a_1(a_3 + b_1) - c_0^2]v^2 \\ &+[(a_3 + b_1)^2 - 2(a_2 + b_0)(a_4 + b_2) + 2c_0c_2 - c_1^2]v + (a_4 + b_2)^2 - c_2^2. \end{aligned}$$

By Routh-Hurwitz criterion we know that if

(H_2): $(a_2 + b_0)^2 + 2(a_4 + b_2) - 2a_1(a_3 + b_1) - c_0^2 > 0$,$(a_3 + b_1)^2 - 2(a_2 + b_0)(a_4 + b_2) + 2c_0c_2 - c_1^2 > 0$ and $a_4 + b_2 - c_2 > 0$

holds, then equation (17) has no positive real roots. Accordingly, by the Theorem 3.1 in [13], we obtain the following result.

Theorem 3.2. *Assume $R_0 > 1$, $\tau_1 = 0$ and $\tau_2 > 0$, then the infected equilibrium E_1 is locally asymptotically stable if (H_1) and (H_2) hold.*

We know that if

(H_3): $(a_2 + b_0)^2 + 2(a_4 + b_2) - 2a_1(a_3 + b_1) - c_0^2 > 0$, $(a_3 + b_1)^2 - 2(a_2 + b_0)(a_4 + b_2) + 2c_0c_2 - c_1^2 > 0$ and $a_4 + b_2 - c_2 < 0$

holds, then Eq.(17) have positive real roots.

If (H_3) holds. Continuity of $f(\omega)$ implies that $f(\omega)=0$ have a solution $\omega>0$ for $\tau_1=0$ and $\tau_2>0$, since $\lim_{\omega\to+\infty} f(\omega)=\infty$. As $\frac{\partial f(\omega)}{\partial\omega}=8\omega^7+6\omega^5[a_1^2-2(a_2+b_0)]+4\omega^3[(a_2+b_0)^2+2(a_4+b_2)-2a_1(a_3+b_1)-c_0^2]+2\omega[(a_3+b_1)^2-2(a_4+b_2)+2c_0c_2-c_1^2]>0$ for $\omega>0$, the Implicit Function Theorem implies that there exists a unique C^1 function $\omega=\omega(\tau_2)$ such that $f(\omega)=0$ for $\tau_1=0$ and $\tau_2>0$. We thus obtain the following result.

Lemma 3.3. *If $\tau_1=0$, $\tau_2>0$ and (H_3) hold, then $f(\omega)=0$ has a unique positive root ω_{20}.*

Since equation (17) has a unique positive root ω_{20}, then equation (15) has a pair of purely imaginary roots of the form $\pm i\omega_{20}$. Denote

$$\tau_2^k=\frac{\theta_1+2k\pi}{\omega_{20}}, k=0,1,2,\cdots. \tag{20}$$

where $\theta_1\in[0,2\pi]$ is defined by

$$\begin{cases}\sin\theta_1=\dfrac{-c_1\omega_{20}[\omega_{20}^4-(a_2+b_0)\omega_{20}^2+a_4+b_2]+(c_2-c_0\omega_{20}^2)[-a_1\omega_{20}^3+(a_3+b_1)\omega_{20}]}{c_1^2\omega_{20}^2+(c_2-c_0\omega_{20}^2)^2},\\ \cos\theta_1=-\dfrac{(c_2-c_0\omega_{20}^2)[\omega_{20}^4-(a_2+b_0)\omega_{20}^2+a_4+b_2]+c_1\omega_{20}[-a_1\omega_{20}^3+(a_3+b_1)\omega_{20}]}{c_1^2\omega_{20}^2+(c_2-c_0\omega_{20}^2)^2}.\end{cases} \tag{21}$$

Now differentiating Eq.(17) with respect to τ_2, we have

$$\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau_2}\right)^{-1}=\frac{4\lambda^3+3a_1\lambda^2+2(a_2+b_0)\lambda+a_3+b_1+e^{-\lambda\tau_2}(2c_0\lambda+c_1)}{\lambda e^{-\lambda\tau_2}(c_0\lambda^2+c_1\lambda+c_2)}-\frac{\tau_2}{\lambda}. \tag{22}$$

Hence, a direct calculation shows that

$$\begin{aligned}&\left\{\frac{(\mathrm{d}Re\lambda)}{\mathrm{d}\tau_2}\right\}^{-1}_{\lambda=i\omega_{20}}\\ &=\left\{Re\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau_2}\right)\right\}^{-1}_{\lambda=i\omega_{20}}\\ &=-\frac{-\omega_{20}[-a_1\omega_{20}^3+(a_3+b_1)\omega_{20}][(a_3+b_1)-3a_1\omega_{20}^2]}{\omega_{20}^2[-a_1\omega_{20}^3+(a_3+b_1)\omega_{20}]^2+\omega_{20}^2[\omega_{20}^4-(a_2+b_0)\omega_{20}^2+a_4+b_2]^2}\\ &\quad-\frac{\omega_{20}[2(a_2+b_0)\omega_{20}-4\omega_{20}^3][\omega_{20}^4-(a_2+b_0)\omega_{20}^2+a_4+b_2]}{\omega_{20}^2[-a_1\omega_{20}^3+(a_3+b_1)\omega_{20}]^2+\omega_{20}^2[\omega_{20}^4-(a_2+b_0)\omega_{20}^2+a_4+b_2]^2}\\ &\quad+\frac{-c_1^2\omega_{20}^2+2c_0\omega_{20}^2(c_2-c_0\omega_{20}^2)}{c_1^2\omega_{20}^4+\omega_{20}^2(c_2-c_0\omega_{20}^2)^2}\\ &=\frac{4\omega_{20}^6+\omega_{20}^4[3a_1^2-6(a_2+b_0)]+\omega_{20}^2[4(a_4+b_2)-4a_1(a_3+b_1)+2(a_2+b_0)^2-2c_0^2]}{c_1^2\omega_{20}^2+(c_2-c_0\omega_{20}^2)^2}\\ &\quad+\frac{(a_3+b_1)^2-2(a_2+b_0)(a_4+b_2)-c_1^2+2c_0c_2}{c_1^2\omega_{20}^2+(c_2-c_0\omega_{20}^2)^2}\\ &=\frac{f'(\omega_{20}^2)}{c_1^2\omega_{20}^2+(c_2-c_0\omega_{20}^2)^2}.\end{aligned} \tag{23}$$

Note that $c_1^2\omega_{20}^2+(c_2-c_0\omega_{20}^2)^2>0$, then we have

$$sign\left\{Re\left(\frac{\mathrm{d}\lambda}{\mathrm{d}\tau_2}\right)^{-1}\right\}_{\lambda=i\omega_{20}}=signf'(\omega_{20}^2). \tag{24}$$

Then we can get the following result.

Theorem 3.4. *If (H_3), $f'(\omega^2) \neq 0$ and $\tau_1 = 0$ hold, then the infected equilibrium E_1 is locally asymptotically stable for $\tau_2 \in [0, \tau_2^0)$, and system (2) undergoes a Hopf bifurcation at the infected equilibrium E_1 when $\tau_2 = \tau_2^k (k = 0, 1, 2, \ldots)$.*

When $\tau_1 > 0$, $\tau_2 = \tau_2^* \in I$, where I is the stability internal such that the infected equilibrium E_1 is locally asymptotically stable when $\tau_1 = 0$ and $\tau_2 \in I$. Then the characteristic equation is Eq.(15). Since $c_2 + a_4 + b_2 > 0$, then $\lambda = 0$ is not a root of characteristic equation (15).

If $i\omega(\tau_1)(\omega > 0)$ is a purely imaginary root of the characteristic equation (15), separating real and imaginary parts gives

$$\begin{aligned} &\omega^4 - a_2\omega^2 + a_4 + (c_2 - c_0\omega^2)\cos\omega\tau_2^* + c_1\omega\sin\omega\tau_2^* = (b_0\omega^2 - b_2)\cos\omega\tau_1 - b_1\omega\sin\omega\tau_1, \\ &-a_1\omega^3 + a_3\omega + (c_0\omega^2 - c_2)\sin\omega\tau_2^* + c_1\omega\cos\omega\tau_2^* = -(b_0\omega^2 - b_2)\sin\omega\tau_1 - b_1\omega\cos\omega\tau_1. \end{aligned} \tag{25}$$

Squaring and adding the two equations of (25) lead to

$$\begin{aligned} &[\omega^4 - a_2\omega^2 + a_4 + (c_2 - c_0\omega^2)\cos\omega\tau_2^* + c_1\omega\sin\omega\tau_2^*]^2 \\ &+[-a_1\omega^3 + a_3\omega + (c_0\omega^2 - c_2)\sin\omega\tau_2^* + c_1\omega\cos\omega\tau_2^*]^2 \\ &-b_1^2\omega^2 - (b_0\omega^2 - b_2)^2 = 0. \end{aligned} \tag{26}$$

Denote

$$\begin{aligned} F(\omega) = &[\omega^4 - a_2\omega^2 + a_4 + (c_2 - c_0\omega^2)\cos\omega\tau_2^* + c_1\omega\sin\omega\tau_2^*]^2 \\ &+[-a_1\omega^3 + a_3\omega + (c_0\omega^2 - c_2)\sin\omega\tau_2^* + c_1\omega\cos\omega\tau_2^*]^2 - b_1^2\omega^2 - (b_0\omega^2 - b_2)^2. \end{aligned}$$

Then we have $\lim\limits_{\omega\to\infty} F(\omega) = \infty$, since

$$\begin{aligned} F(0) &= (a_4 + c_2)^2 - b_2^2 \\ &= (\alpha d_E k_1 N\delta T_1 + p d_x \bar{T}^* \alpha c)^2 - [d_E k_1 N\delta T_1(kV_1 - \alpha)]^2 \\ &= [p d_x T_1^* \alpha c + d_E k_1 N\delta T_1 k V_1][p d_x T_1^* \alpha c + (2\alpha - kV_1) d_E k_1 N\delta T_1]. \end{aligned}$$

We can know that if $a_4 + c_2 - b_2 < 0$ holds, that is, $F(0) < 0$, then Eq.(26) has limited positive real roots $\omega_1, \omega_2, \cdots, \omega_m$.

Denote

$$\tau_{1k}^j = \frac{\theta_2 + 2j\pi}{\omega_k}, j = 1, 2, \cdots, m, \quad k = 0, 1, \cdots,$$

where $\theta_2 \in [0, 2\pi]$ is defined by

$$\begin{cases} \sin\theta_2 = -\dfrac{b_1\omega_k[\omega_k^4 - a_2\omega_k^2 + a_4 + (c_2 - c_0\omega_k^2)\cos\omega_k\tau_2^* + c_1\omega_k\sin\omega_k\tau_2^*]}{b_1^2\omega_k^2 + (b_0\omega_k^2 - b_2)^2} \\ \qquad + \dfrac{(b_0\omega_k^2 - b_2)[-a_1\omega_k^3 + a_3\omega_k + (c_0\omega_k^2 - c_2)\sin\omega_k\tau_2^* + c_1\omega_k\cos\omega_k\tau_2^*]}{b_1^2\omega_k^2 + (b_0\omega_k^2 - b_2)^2}, \\ \cos\theta_2 = \dfrac{(b_0\omega_k^2 - b_2)[\omega_k^4 - a_2\omega_k^2 + a_4 + (c_2 - c_0\omega_k^2)\cos\omega_k\tau_2^* + c_1\omega_k\sin\omega_k\tau_2^*]}{b_1^2\omega_k^2 + (b_0\omega_k^2 - b_2)^2} \\ \qquad - \dfrac{b_1\omega_k[-a_1\omega_k^3 + a_3\omega_k + (c_0\omega_k^2 - c_2)\sin\omega_k\tau_2^* + c_1\omega_k\cos\omega_k\tau_2^*]}{b_1^2\omega_k^2 + (b_0\omega_k^2 - b_2)^2}. \end{cases} \tag{27}$$

Define

$$\tau_1^0 = \min_{1\leq k\leq m} \tau_{1k}^0, \quad \omega_0 = \omega_i, i = 1, 2, \ldots, m, \tag{28}$$

where ω_0 corresponds to τ_1^0.

Let $\lambda(\tau_1) = \alpha(\tau_1) + i\omega(\tau_1)$ be the root of Eq.(15) satisfying $\alpha(\tau_{1k}^j) = 0$ and $\omega(\tau_{1k}^j) = \omega_0$. Differentiating Eq.(15) with respect to τ_2 and a direct calculation give

$$\begin{aligned}(\alpha'(\tau_1^0))^{-1} = &\frac{B_{11}\sin\omega_0\tau_1^0 + B_{12}\cos\omega_0\tau_1^0 + B_{13}\cos\omega_0(\tau_1^0-\tau_2^*) + B_{14}\sin\omega_0(\tau_1^0-\tau_2^*)}{b_2^2\omega_0^4 + (b_2 - b_0\omega_0^2)^2\omega_0^2} \\ &+ \frac{-b_1^2 + 2b_0(b_2 - b_0\omega_0^2)}{b_1^2\omega_0^2 + (b_2 - b_0\omega_0^2)^2} - \cos\omega_0\tau_1^0\end{aligned} \tag{29}$$

where

$$\begin{aligned}B_{11} &= \omega_0(b_2 - b_0\omega_0^2)(a_3 - 3a_1\omega_0^2) + b_1\omega_0^2(2a_2\omega_0 - 4\omega_0^3), \\ B_{12} &= [(b_2 - b_0\omega_0^2)(2a_2 - 4\omega_0^2) - b_1(a_3 - 3a_1\omega_0^2)]\omega_0^2, \\ B_{13} &= [(b_2 - b_0\omega_0^2)(2a_2 - 4\omega_0^2) - b_1c_1]\omega_0^2, \\ B_{14} &= c_1\omega_0(b_2 - b_0\omega_0^2) + 2b_1c_0\omega_0^3,\end{aligned}$$

From the above discussions, we can get the following result.

Theorem 3.5. *Assume that Eq.(26) has positive roots, and that $\tau_2 = \tau_2^* \in I$ and (H_1) hold. Then we have that all roots of Eq.(15) have negative real parts for $\tau_1 \in [0, \tau_1^0)$ and the infected equilibrium E_1 is locally asymptotically stable for $\tau_1 \in [0, \tau_1^0)$. In addition, if $(\alpha'(\tau_1^0))^{-1} \neq 0$, then system (2) undergoes a Hopf bifurcation at the infected equilibrium E_1 when $\tau_1 = \tau_1^0$.*

From the previous discussions, sufficient conditions are given for Hopf bifurcation to occur when $\tau_1 = \tau_1^0$. Next we analyze the direction of the Hopf bifurcation and the stability of the bifurcating periodic orbits when $\tau_1 = \tau_1^0$ by normal form and center manifold theory (see e.g. Hassard et al. [15]). As the details are given in the Appendix, from (29), (34) and (35), we can compute the following quantities:

$$\begin{aligned}C_1(0) &= \frac{i}{2\omega_0}\left(g_{11}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right) + \frac{g_{21}}{2}, \\ \mu_2 &= -\frac{Re(C_1(0))}{Re(\lambda'(\tau_1^0))}, \\ \beta_2 &= 2Re(C_1(0)), \\ T_2 &= -\frac{Im(C_1(0)) + \mu_2 Im(\lambda'(\tau_1^0))}{\omega_0}.\end{aligned} \tag{30}$$

Theorem 3.6. *Assume that conditions of Theorem 3.5 hold. Then μ_2 determines the direction of the Hopf bifurcation: if $\mu_2 > 0 (\mu_2 < 0)$, then the Hopf bifurcation is forward (backward) and the bifurcating periodic orbits exist for $\tau_1 > \tau_1^0 (\tau_1 < \tau_1^0)$; β_2 determines the stability of bifurcating periodic orbits: the bifurcating orbits are asymptotically stable(unstable) if $\beta_2 < 0 (\beta_2 > 0)$; and T_2 determines the period of the bifurcating periodic orbits: the period increases(decreases) if $T_2 > 0 (T_2 < 0)$.*

4. Numerical simulations.

In this section, we carry out numerical simulations to illustrate our results on the variation of stability of E_1 and the occurrence of Hopf bifurcation for several values of the time delays. Throughout this section, we refer the parameter values of system (2.1) to Table 1. The parameter values given in Table 1 refer to [6, 29, 31, 33, 37, 41].

Fig. 1 shows the relationship between the basic reproduction number R_0 and growth rate of T-cells. The basic reproduction number R_0 can be less than unity when growth rate of T-cells r is reduced to 0.015 (day^{-1}). The growth rate of T-cells has an effect on the basic reproduction number, and then impacts on the dynamics of the system.

Variables		Values
$T(0)$	Uninfected T-cells	10 μl^{-1} [37]
$T^*(0)$	Productively infected T-cells	10^{-6} μl^{-1} [6]
$V(0)$	Virus	10^{-6} μl^{-1} [6]
$E(0)$	CTLs	10^{-6} μl^{-1} [37]
Parameters		Values
s	Source term for uninfected T-cells	0.103 μl^{-1} $(day)^{-1}$ [6]
d	Natural death rate of healthy T-cells	0.01 $(day)^{-1}$ [6]
r	Growth rate of T-cells	0.95 $(day)^{-1}$ [41, 29]
k	Viral infectively rate	0.00065 μl day^{-1} [6]
k_1	Activation rate	0.00065 μl day^{-1} [6]
T_{max}	Carrying capacity of T-cells	1000 μl^{-1} [37]
δ	Death rate of infected T-cells	0.514 day^{-1} [37]
d_x	Death rate of infected T-cells due to action of immune response	0.812 μl day^{-1} [37]
d_E	Death rate of effector cells	1.618 day^{-1} [37]
N	Number of virus particles produced by each infected T-cells	1861 cells [37]
c	Clearance rate of virus	0.517 day^{-1} [31, 33]
p	Produce rate of effector cells	1.473 μl day^{-1} [37]

TABLE 1. Variables and parameters for viral spread

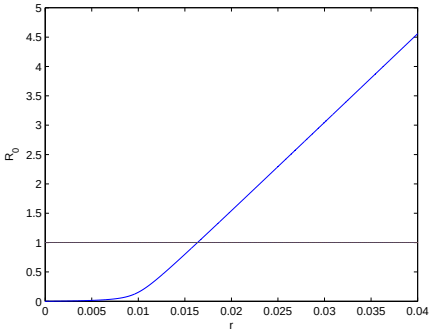


FIGURE 1. The relationship between the basic reproduction number and the growth rate of T-cells. The parameter values in Table 1.

According to [31, 33], set $0 < c \leq 36$ (day^{-1}). Following the estimates of the intracellular time delay τ_1 and the immune delay τ_2 in [22, 31], we assume that $\tau_1 \leq 2$ (days) and $\tau_2 \leq 32$ (days). From Wang et al. [41] and Perelson et al. [29], we suppose $0.03 \leq r \leq 3$ (day^{-1}). We choose that the initial values are $T(0) = 10$ cells μl^{-1}, $T^*(0) = 10^{-6}$ cells μl^{-1}, $V(0) = 10^{-6}$ cells μl^{-1} and $E(0) = 10^{-6}$ cells μl^{-1}. Other parameter values of system (2.1) to Table 1. Correspondingly, $R_0 = 2.3154e + 003 > 1$, and $E_1 = (0.9621, 0.8699, 1609.5, 0.7919)$. We can get (H_1) and (H_2) hold. When $\tau_1 = 0$, by direct computation we get $\omega_{20} = 0.7415$ and $\tau_2^{(j)} = 1.6558 + 8.4736j (j = 0, 1, 2, \ldots)$. By Theorem 3.4 we know that the stability of the infected equilibrium E_1 varies when τ_2 increases, and the infected equilibrium E_1 is asymptotically stable for $\tau_2 \in [0, 1.6558)$. Fig. 2 illustrates the results. Fig. 3 illustrates the bifurcating periodic orbits are asymptotically stable.

Let $\tau_2 = 1.2 \in [0, 1.6558)$, we can obtain $\tau_1^0 = 0.5300$. By Theorem 3.5 we can get that the infected equilibrium E_1 is asymptotically stable when $\tau_1 \in [0, 0.5300)$. By a direct computation, we can get $C_1(0) = -15.9427 - 46.2952i$, $\beta_2 = -31.8854 < 0$ and $\mu_2 = 15.0233 > 0$. By Theorem 3.6, when $\tau_1^0 = 0.5300$, the direction of the Hopf bifurcation is forward and the bifurcating periodic orbits are asymptotically stable. Fig. 4 and Fig. 5 illustrate the results.

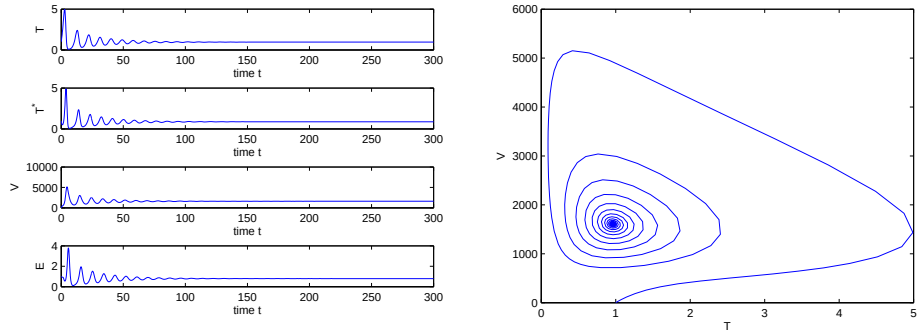


FIGURE 2. Behavior and phase portrait of system (2) with $\tau_1 = 0$, $\tau_2 = 1.5$. The infected equilibrium is stable. The parameter values in Table 1.

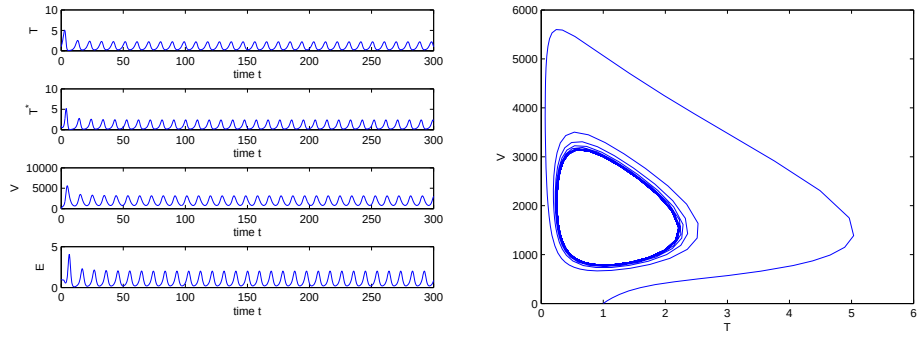


FIGURE 3. Behavior and phase portrait of system (2) with $\tau_1 = 0$, $\tau_2 = 2$. Hopf bifurcation occurs from the infected equilibrium. The parameter values in Table 1.

We not only concern the local behaviors near the critical point, but we also concern the dynamics when τ_2 away from the critical point. Therefore, we give a bifurcation diagram for $\tau_2 \in [0.001, 16]$ (see Fig. 6). It is plotted by using Matlab software, which depicts the change of periodic solutions in the V-axis as τ_2 increases. In the case of $\tau_1 = 0$, by the rigorous mathematical analysis we know that the endemic equilibrium is asymptotically stable for $\tau_2 \in [0, 1.6558)$, and the delay τ_2 destabilize the endemic equilibrium by leading to stable periodic oscillations when $\tau_2 > 1.6558$, and the fluctuation of viral load increases. The amplitude of periodic solutions quickly drops near $\tau_2 = 1.6558 + 8.4736 \times 1 = 10.1294$, and the fluctuation of viral load is small at $\tau_2 = 10.13$. When $\tau_2 > 10.13$, the delay τ_2 can destabilize the infected state leading to Hopf bifurcation and stable periodic oscillations, and the amplitude of periodic solutions goes up gradually as τ_2 increases. Fig. 7-9 illustrate the results. When r, τ_1 and τ_2 are very large, we give the time history and phase portraits to show that system (2) has chaotic motions (see Fig. 10-11). Fig. 12 shows that system (2) has stable periodic, quasi periodic and chaotic motions. Thus, immune response delay has an effect on the control of HIV.

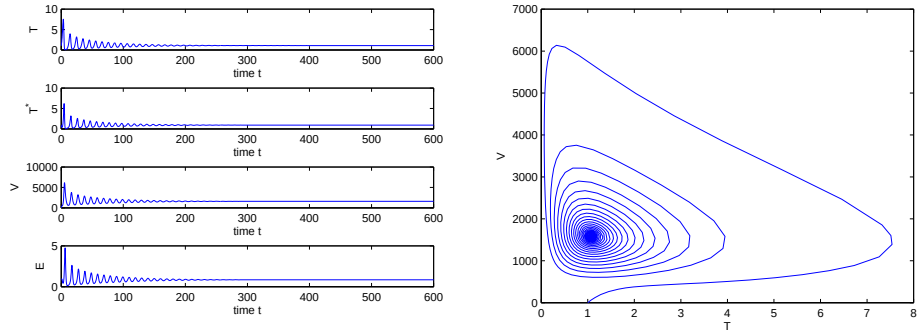


FIGURE 4. Behavior and phase portrait of system (2) with $\tau_1 = 0.4$, $\tau_2 = 1.2$. The infected equilibrium is stable. The parameter values in Table 1.

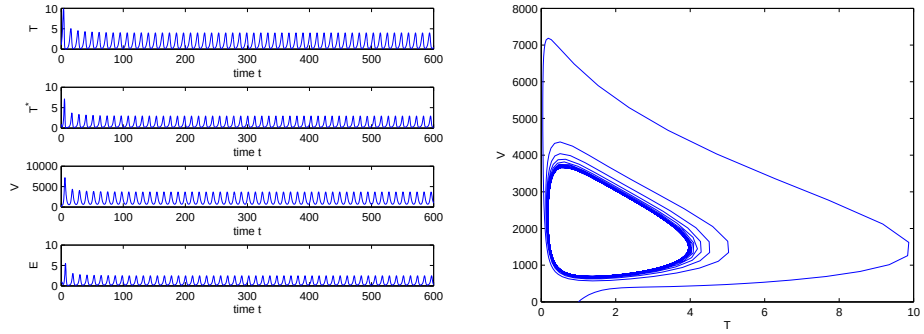


FIGURE 5. Behavior and phase portrait of system (2) when $\tau_1 = 0.7$, $\tau_2 = 1.2$. Hopf bifurcation occurs from the infected equilibrium. The parameter values in Table 1.

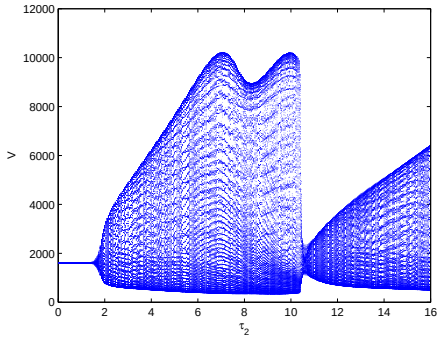


FIGURE 6. Bifurcation diagram of V versus τ_2 when $\tau_1 = 0$ and $\tau_2 \in [0.001, 16]$. The parameter values in Table 1.

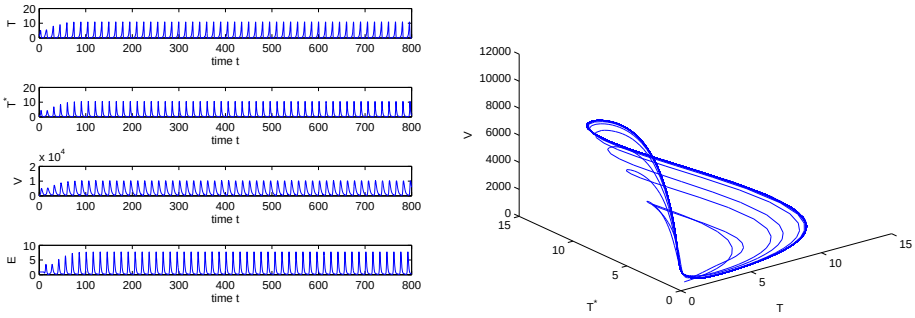


FIGURE 7. Behavior and phase portrait of system (2) when $\tau_1 = 0$, $\tau_2 = 10$. Hopf bifurcation occurs from the infected equilibrium. The parameter values in Table 1.

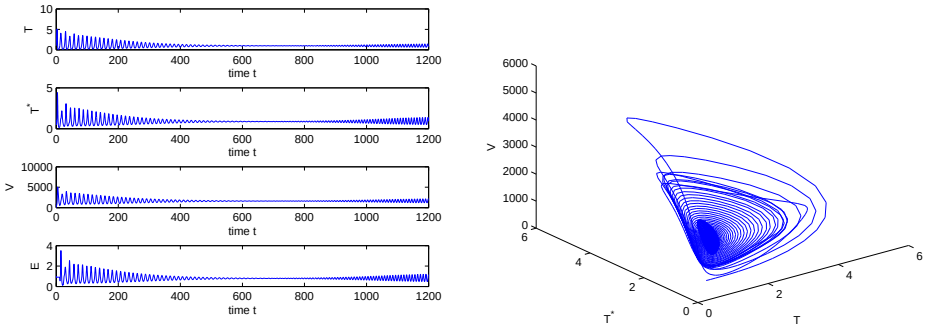


FIGURE 8. Behavior and phase portrait of system (2) when $\tau_1 = 0$, $\tau_2 = 10.13$. Hopf bifurcation occurs from the infected equilibrium. The parameter values in Table 1.

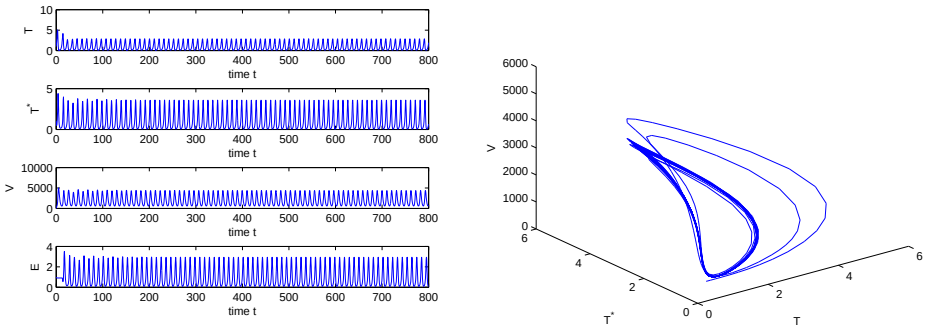
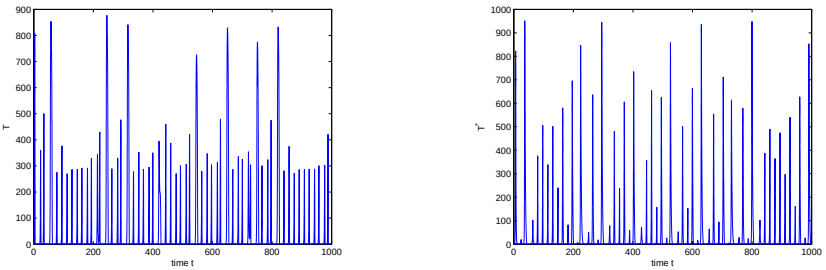
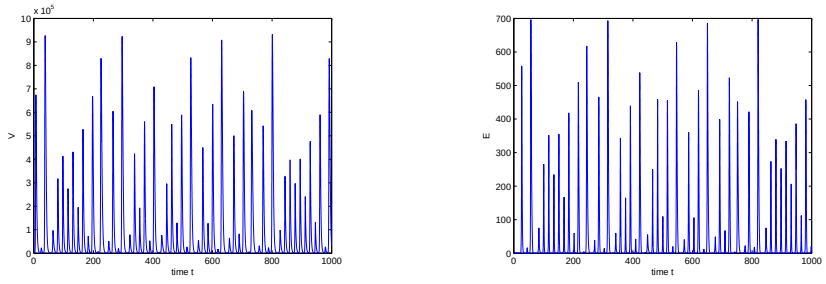


FIGURE 9. Behavior and phase portrait of system (2) when $\tau_1 = 0$, $\tau_2 = 13$. Hopf bifurcation occurs from the infected equilibrium. The parameter values in Table 1.



(a) Uninfected cells (b) Infected cells



(c) Infectious virus (d) CTLs

FIGURE 10. When τ_1, τ_2 and r are very large, system (2) shows chaotic phenomenon. $\tau_1 = 2$, $\tau_2 = 20$ and $r = 3$, and other parameters are given in Table 1.

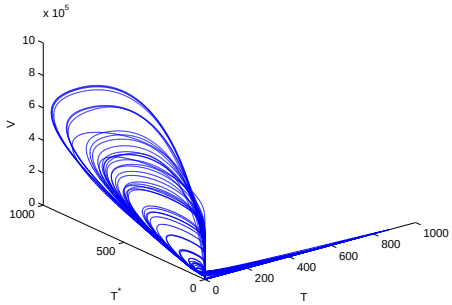
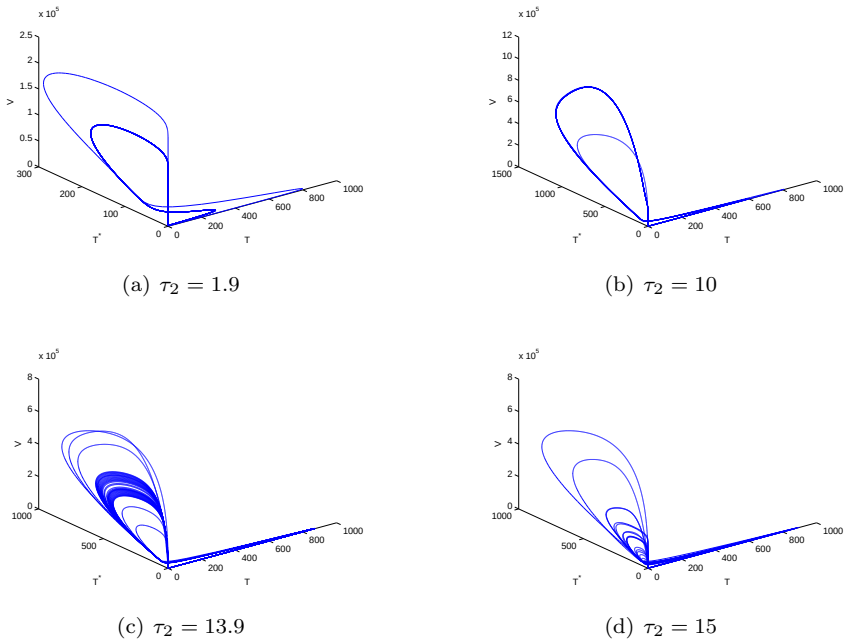


FIGURE 11. Simulating solution of system (2) when $r = 3$, $\tau_1 = 2$ and $\tau_2 = 20$, showing a chaotic attractor. Other parameter values in Table 1.

The bifurcation diagram of V versus r in the range $0.01 \leq r \leq 3$ is shown in Fig. 13, and is realized by varying r in steps of 0.01. At the left end of the r range, up to 2.1, the infected steady state is asymptotically stable, but the viral load increases. As r increases, r destabilize the infected steady state and leading to stable periodic oscillations. Fig. 14 illustrates the results. These results imply that the growth rate of T-cells have an effect on the dynamics of the HIV model.



(a) $\tau_2 = 1.9$ (b) $\tau_2 = 10$

(c) $\tau_2 = 13.9$ (d) $\tau_2 = 15$

FIGURE 12. Phase portraits of system (2) at: (a)$\tau_2 = 1.9$; (b)$\tau_2 = 10$; (c)$\tau_2 = 13.9$; (d)$\tau_2 = 15$, showing the evolution of dynamics types with increasing τ_2. Where $\tau_1 = 2$ and $r = 3$, and other parameters are given in Table 1.

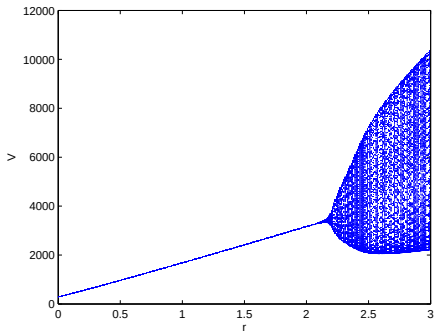
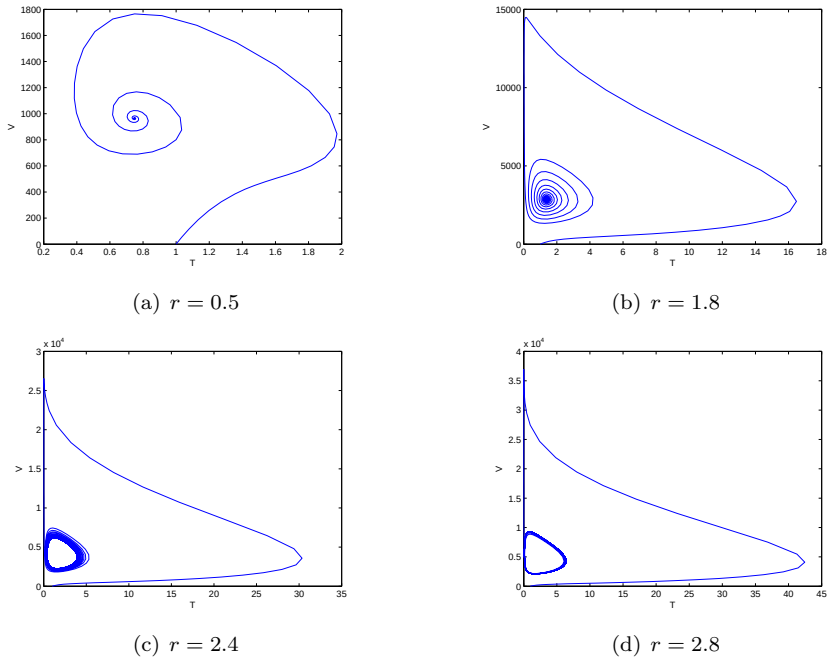


FIGURE 13. Bifurcation diagram of V versus r when $\tau_1 = 0$, $\tau_2 = 1$ and $r \in [0.01, 3]$. Other parameter values in Table 1.

5. **Discussion.** In this paper, we incorporate an extra logistic term for target cells into a model of HIV-1 infection with two time delays studied in [26]. We define a basic reproduction number R_0 which plays a major role in determining the uniform persistence or clearance of viral load. When $R_0 < 1$, the uninfected steady state is globally asymptotically stable. When $R_0 > 1$, the system is uniform persistent. For the case of $R_0 > 1$, given both the two delays are zero, then we show that the infected steady state is asymptotically stable when the intrinsic growth rate of the



(a) $r = 0.5$ (b) $r = 1.8$

(c) $r = 2.4$ (d) $r = 2.8$

FIGURE 14. Phase portraits of system (2) at: (a)$r = 0.5$; (b)$r = 1.8$; (c)$r = 2.4$; (d)$r = 2.8$, showing the evolution of dynamics types with increasing r. Where $\tau_1 = 0$ and $\tau_2 = 1$, and other parameters are given in Table 1.

logistic term r is sufficiently small. In the case of the intracellular delay τ_1 that is zero, by analyzing the distribution of the roots of the corresponding characteristic equation, stability varies for the infected equilibrium when the immune delay τ_2 increases. Fixing τ_2, we get that there exists a first critical value of τ_1 at which the infected equilibrium loses its stability and the Hopf bifurcation occurs. The direction of the Hopf bifurcation and the stability of the bifurcating periodic solution are investigated.

Comparing our results with those established in [26] without logistic growth, we show some new results in our paper. First, we prove that the intracellular delay τ_1 may also destabilize the infected equilibrium by leading to a Hopf bifurcation and stable periodic oscillations for some fixed immune delay τ_2, while in [26] it was shown that τ_1 is unable to destabilize the infected steady state provided that $\tau_2 = 0$. Second, we prove that, with the increase of the intrinsic rate for target cells r, the behaviors of viral load may be destabilized into oscillations, moreover by simulation we show that the oscillation interval will be enlarged as r increases. Third, our simulations suggest that richer dynamics chaotic oscillations as observed in Figs. 10-11 will occur in the system. Therefore, our results suggest that the logistic growth for T-cells, the intracellular delay τ_1 or the immune delay τ_2 may be responsible for the rich virus dynamics.

Determining the stability switching regions for a model with two positive delays and logistic term, it is worth of further study on the combined effects of these three elements, which we leave for future work.

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Appendix. In this section, by normal form and center manifold theory [15], we analyze the direction of the Hopf bifurcation and the stability of the bifurcating periodic orbits under the conditions of Theorem 3.5.

Assume that $\tau_2^* > \tau_1^0$. Let $\tau_1 = \tau_1^0 + \mu$, then system (14) is transformed into an FDE in $C = C([-\tau_2^*, 0], R^4)$ as

$$\dot{x}(t) = L_\mu(x_t) + f(\mu, x_t), \tag{31}$$

where $x_t(\theta) = x(t+\theta)$ and $L_\mu : C \to R^4$ is defined by

$$L_\mu\varphi = A_1\varphi(0) + B_1\varphi(-\tau_1^0) + B_2\varphi(-\tau_2^*) \tag{32}$$

where

$$A_1 = \begin{pmatrix} r(1-\frac{2T_1}{T_{max}}) - kV_1 - d & 0 & -kT_1 & 0 \\ 0 & -(\delta + d_x E_1) & 0 & -d_x T_1^* \\ 0 & N\delta & -c & 0 \\ 0 & 0 & 0 & -d_E \end{pmatrix}$$

$$B_1 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ k_1 V_1 & 0 & k_1 T_1 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$B_2 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & p & 0 & 0 \end{pmatrix}$$

$$\varphi(t) = (\varphi_1(t), \varphi_2(t), \varphi_3(t), \varphi_4(t))^T$$

and

$$f(\mu, \varphi) = (\tau_1^0 + \mu) \begin{pmatrix} -\frac{r}{T_{max}}\varphi_1(0)^2 - k\varphi_1(0)\varphi_3(0) \\ -d_x\varphi_2(0)\varphi_4(0) + k_1\varphi_1(-\tau_1^0)\varphi_3(-\tau_1^0) \\ 0 \\ 0 \end{pmatrix}$$

From the discussions in Section 3, we obtain that system (14) undergoes a Hopf bifurcation at $(0,0,0,0)$ when $\mu = 0$, and the corresponding characteristic equation of system (14) with $\mu = 0$ has a pair of purely imaginary roots $\pm i\omega_0$.

Using the Riesz representation theorem, there is a function $\eta(\theta, \mu)(\theta \in [-\tau_2^*, 0)$ such that

$$L_\mu\varphi = \int_{-\tau_2^*}^{0} \mathrm{d}\eta(\theta, \mu)\varphi(\theta), \quad \forall\varphi \in C. \tag{33}$$

Denote

$$\eta(\theta, \mu) = \begin{cases} A_1 + B_2, & \theta = 0, \\ B_1, & \theta \in [-\tau_1^0, 0), \\ -B_2\delta(\theta + \tau_2^*), & \theta \in [-\tau_2^*, -\tau_1^0), \end{cases}$$

where

$$\delta(\theta) = \begin{cases} 0, & \theta \neq 0, \\ 1, & \theta = 0. \end{cases}$$

For $\varphi \in C^1([-\tau_2^*, 0], R^4)$, define

$$A(\mu)\varphi = \begin{cases} \frac{\mathrm{d}\varphi(\theta)}{\mathrm{d}\theta}, & \theta \in [-\tau_2^*, 0), \\ \int_{-\tau_2^*}^{0} \mathrm{d}\eta(s,\mu)\varphi(s), & \theta = 0. \end{cases}$$

and

$$R(\mu)\varphi = \begin{cases} 0, & \theta \in [-\tau_2^*, 0), \\ f(\mu,\varphi), & \theta = 0. \end{cases}$$

Then system (14) becomes

$$\dot{x_t} = A(\mu)x_t + R(\mu)x_t,$$

where $x_t(\theta) = x(t+\theta)$ for $\theta \in [-\tau_2^*, 0)$. For $\psi \in ([0, \tau_2^*], (R^4)^*)$, define an operator

$$A^*\psi = \begin{cases} -\frac{\mathrm{d}\varphi(s)}{\mathrm{d}s}, & s \in [0, \tau_2^*), \\ \int_{-\tau_2^*}^{0} \mathrm{d}\eta^T(t,0)\psi(-t), & s = 0. \end{cases}$$

and a bilinear form

$$\langle \psi(s), \varphi(\theta) \rangle = \bar{\psi}(0)\varphi(0) - \int_{-\tau_2^*}^{0} \int_{\xi=0}^{\theta} \bar{\psi}(\xi - \theta)\mathrm{d}\eta(\theta)\varphi(\xi)\mathrm{d}\xi,$$

Therefore, $A(0)$ and A^* are adjoint operators. From the above discussions, we know that $\pm i\omega_0$ are eigenvalues of $A(0)$ and so they are also eigenvalues of A^*.

Denote

$$\begin{aligned}
q_2 &= \frac{(i\omega_0 + c)(r(1 - \frac{2T_1}{T_{max}}) - kV_1 - d - i\omega_0)}{N\delta k T_1}, \\
q_3 &= \frac{r(1 - \frac{2T_1}{T_{max}}) - kV_1 - d - i\omega_0}{kT_1}, \\
q_4 &= \frac{(i\omega_0 + c)(r(1 - \frac{2T_1}{T_{max}}) - kV_1 - d - i\omega_0)pe^{-i\omega_0\tau_2^*}}{(N\delta k T_1)(i\omega_0 + d_E)}, \\
q_2^* &= \frac{i\omega_0 - r(1 - \frac{2T_1}{T_{max}}) + kV_1 + d}{k_1 V_1 e^{-i\omega_0\tau_1^0}}, \\
q_3^* &= \frac{(i\omega_0 - r(1 - \frac{2T_1}{T_{max}}) + kV_1 + d)T_1 - kV_1 T_1}{(i\omega_0 + c)V_1}, \\
q_4^* &= \frac{-d_x T_1^*(i\omega_0 - r(1 - \frac{2T_1}{T_{max}}) + kV_1 + d)}{k_1 V_1 e^{-i\omega_0\tau_1^0}(i\omega_0 + d_E)}, \\
D &= \left(1 + \bar{q_2}q_2^* + \bar{q_3}q_3^* + \bar{q_4}q_4^* + k_1 V \tau_1^0 e^{i\omega_0\tau_1^0} q_2^* + p\tau_2^* e^{i\omega_0\tau_2^*} q_4^* + k_1 T_1 \tau_1^0 e^{-i\omega_0\tau_1^0} q_2{}^* \bar{q_3}\right)^{-1}.
\end{aligned} \tag{34}$$

We can show that the vectors $q(\theta) = (1, q_2, q_3, q_4)^T e^{i\omega_0\theta}, \theta \in [-\tau_2^*, 0)$, and $q^*(s) = D(1, q_2^*, q_3^*, q_4^*)e^{i\omega_0 s}, s \in (0, \tau_2^*]$, are the eigenvectors of $A(0)$ and A^* associated with the eigenvalue $i\omega_0$ and $-i\omega_0$. Moreover, $\langle q^*(s), q(\theta) \rangle = 1$, $\langle q^*(s), \bar{q}(\theta) \rangle = 0$.

Following the procedure in [15], we can obtain the coefficients:

$$
\begin{aligned}
g_{20} &= 2\bar{D}\left[-\tfrac{r}{T_{max}} - kq_3 + \bar{q_2}^*(-d_x q_2 q_4 + k_1 q_3 e^{-2i\omega_0\tau_1^0})\right],\\
g_{11} &= \bar{D}\left[-\tfrac{2r}{T_{max}} - k(q_3+\bar{q_3}) + d_x\bar{q_2}^*(q_2\bar{q_4}+\bar{q_2}q_4) + k_1\bar{q_2}^*(q_3+\bar{q_3})\right],\\
g_{02} &= 2\bar{D}\left[-\tfrac{r}{T_{max}} - k\bar{q_3} + \bar{q_2}^*(-d_x\bar{q_2}\bar{q_4} + k_1\bar{q_3}e^{2i\omega_0\tau_1^0})\right],\\
g_{21} &= \bar{D}\{-\tfrac{2r}{T_{max}}[4W_{11}^{(1)}(0) + 2W_{20}^{(1)}(0)]\\
&-k[2W_{11}^{(3)}(0) + W_{20}^{(3)}(0) + \bar{q_3}W_{20}^{(1)}(0) + 2q_3W_{11}^{(1)}(0)]\\
&-d_x\bar{q_2}^*[2q_2W_{11}^{(4)}(0) + \bar{q_2}W_{20}^{(4)}(0) + \bar{q_4}W_{20}^{(2)}(0) + 2q_4W_{11}^{(2)}(0)]\\
&+k_1\bar{q_2}^*[2W_{11}^{(3)}(-\tau_1^0)e^{-i\omega_0\tau_1^0} + W_{20}^{(3)}(-\tau_1^0)e^{i\omega_0\tau_1^0}]\\
&+k_1\bar{q_2}^*[\bar{q_3}W_{20}^{(1)}(-\tau_1^0)e^{i\omega_0\tau_1^0} + 2q_3W_{11}^{(1)}(-\tau_1^0)e^{-i\omega_0\tau_1^0}]\},
\end{aligned}
\tag{35}
$$

where for $\theta \in [-\tau_2^*, 0)$,

$$
\begin{aligned}
W_{20}(\theta) &= \frac{ig_{20}}{\omega_0}q(0)e^{i\omega_0\theta} + \frac{i\bar{g}_{02}}{3\omega_0}\bar{q}(0)e^{-i\omega_0\theta} + H_1 e^{2i\omega_0\theta},\\
W_{11}(\theta) &= -\frac{ig_{11}}{\omega_0}q(0)e^{i\omega_0\theta} + \frac{i\bar{g}_{11}}{\omega_0}\bar{q}(0)e^{-i\omega_0\theta} + H_2,
\end{aligned}
$$

$$
H_1 = 2G_1^{-1}\begin{pmatrix} -\frac{r}{T_{max}} - kq_3 \\ -d_x q_2 q_4 + k_1 q_3 e^{-2i\omega_0\tau_1^0} \\ 0 \\ 0 \end{pmatrix},
$$

where

$$
G_1 = \begin{pmatrix} 2i\omega_0 - r(1-\frac{2T_1}{T_{max}}) + kV_1 + d & 0 & kT_1 & 0 \\ -k_1V_1e^{-2i\omega_0\tau_1^0} & 2i\omega_0 + \delta + d_xE_1 & -k_1T_1e^{-2i\omega_0\tau_1^0} & d_xT_1^* \\ 0 & -N\delta & 2i\omega_0 + c & 0 \\ 0 & -pe^{-2i\omega_0\tau_2^*} & 0 & 2i\omega_0 + d_E \end{pmatrix},
$$

and

$$
H_2 = G_2^{-1}\begin{pmatrix} -\frac{2r}{T_{max}} - k(q_3+\bar{q_3}) \\ -d_x(q_2\bar{q_4} + \bar{q_2}q_4) + k_1(q_3+\bar{q_3}) \\ 0 \\ 0 \end{pmatrix},
$$

where

$$
G_2 = \begin{pmatrix} kV_1 + d - r(1-\frac{2T_1}{T_{max}}) & 0 & kT_1 & 0 \\ -k_1V_1 & \delta + d_xE_1 & -k_1T_1 & d_xT_1^* \\ 0 & -N\delta & c & 0 \\ 0 & -p & 0 & d_E \end{pmatrix}.
$$

Consequently, g_{21} can be expressed definitely.

REFERENCES

[1] R. Arnaout, M. A. Nowak and D. Wodarz, HIV-1 dynamics revisited: Biphasic decay by cytotoxic lymphocyte killing?, *Proc. R. Soc. Lond. B*, **267** (2000), 1347–1354.

[2] H. T. Banks and D. M. Bortz, A parameter sensitivity methodology in the context of HIV delay equation models, *J. Math. Biol.*, **50** (2005), 607–625.

[3] S. Bonhoeffer, J. M. Coffin and M. A. Nowak, Human immunodeficiency virus drug therapy and virus load, *J. Virol.*, **71** (1997), 3275–3278.

[4] L. M. Cai and X. Z. Li, Stability and Hopf bifurcation in a delayed model for HIV infection of CD4$^+$ T-cells, *Chaos, Solitons and Fractals*, **42** (2009), 1–11.

[5] D. S. Callaway and A. S. Perelson, HIV-1 infection and low steady state viral loads, *Bull. Math. Biol.*, **64** (2002), 29–64.

[6] M. S. Ciupe, B. L. Bivort, D. M. Bortz and P. W. Nelson, Estimating kinetic parameters from HIV primary infection data through the eyes of three different mathmatical models, *Math. Biosci.*, **200** (2006), 1–27.
[7] K. L. Cooke and P. van den Driessche, On zeros of some transcendental equations, *Funkcialaj Ekvacioj*, **29** (1986), 77–90.
[8] R. V. Culshaw and S. Ruan, A delay-differential equation model of HIV infection of CD4+ T-cells, *Math. Biosci.*, **165** (2000), 27–39.
[9] E. S. Daar, T. Moudgil, R. D. Meyer and D. D. Ho, Transient high levels of viremia in patients with primary human immunodefiniency virus type 1 infection, *N. Engl. J. Med.*, **324** (1991), 961–964.
[10] R. J. De Boer and A. S. Perelson, Towards a general function describing T cell proliferation, *J. Theor. Biol.*, **175** (1995), 567–576.
[11] R. J. De Boer and A. S. Perelson, Target cell limited and immune control models of HIV infection: A comparison, *J. Theor. Biol.*, **190** (1998), 201–214.
[12] N. M. Dixit and A. S. Perelson, Complex patterns of viral load decay under antiretroviral therapy: influence of pharmacokinetics and intracellur delay, *J. Theor. Biol.*, **226** (2004), 95–109.
[13] H. I. Freedman and Y. Kuang, Stability switches in linear scalar neutral delay equations, *Funkcialaj Ekvacioj*, **34** (1991), 187–209.
[14] J. K. Hale and S. M. Verduyn Lunel, *Introduction to Functional Differential Equations*, Springer-Verlag, New York, 1993.
[15] B. D. Hassard, N. D. Kazarinoff and Y. H. Wan, *Theory and Application of Hopf Bifurcation*, Cambrige University Press, Cambrige, 1981.
[16] J. M. Heffernan and L. M. Wahl, Natural variation in HIV infection: Monte carlo estimates that include CD8 effector cells, *J. Theor. Biol.*, **243** (2006), 191–204.
[17] A. V. Herz, S. Bonhoeffer, R. M. Anderson, R. M. May and M. A. Nowak, Viral dynamics in vivo: limitations on estimates of intracellular delay and virus decay, *Proc. Natl. Acad. Sci. USA*, **93** (1996), 7247–7251.
[18] J. P. Lasalle, The stability of dynamical systems, in *Regional Conference Series in Applied Mathematics*, SIAM, Philadelphia, PA, 1976.
[19] M. Y. Li and H. Y. Shu, Global dynamics of a mathematical model for HTLV-I infection of CD4+ T cells with delayed CTL response, *Nonlinear Analysis: Real World Applications*, **13** (2012), 1080–1092.
[20] M. Y. Li and H. Shu, Impact of intracelluar delays and target-cell dynamics on in vivo viral infections, *SIAM J. Appl. Math.*, **70** (2010), 2434–2448.
[21] S. Q. Liu and L. Wang, Global stability of an HIV-1 model with distributed intracellular delays and a combination therapy, *Math. Biosci. Eng.*, **7** (2010), 675–685.
[22] P .W. Nelson, J. D. Murray and A. S. Perelson, A model of HIV-1 pathogenesis that includes an intracellular delay, *Math. Biosci.*, **163** (2000), 201–215.
[23] P. W. Nelson and A. S. Perelson, Mathematical analysis of delay differential equation models of HIV-1 infection, *Math. Biosci.*, **179** (2002), 73–94.
[24] M. A. Nowak and C. R. Bangham, Population dynamics of immune responses to persistent virus, *Science*, **272** (1996), 74–79.
[25] M. A. Nowak and R. M. May, *Virus dynamics: Mathematical principles of immunology and virology*, Oxford University, Oxford, 2000.
[26] K. A. Pawelek, S. Liu, F. Pahlevani and L. Rong, A model of HIV-1 infection with two time delays: Mathematical analysis and comparison with patient data, *Math. Biosci.*, **235** (2012), 98–109.
[27] A. S. Perelson, Modelling viral and immune system dynamics, *Nat. Rev. Immunol.*, **2** (2002), 28–36.
[28] A. S. Perelson, P. Essunger, Y. Cao, M. Vesanen, A. Hurley, K. Saksela, M. Markowitz and D. D. Ho, Decay characteristics of HIV-1 infected compartments during combination therepy, *Nature*, **387** (1997), 188–191.
[29] A. S. Perelson, D. E. Kirschner and R. De Boer, Dynamics of HIV infection of CD4+ T cells, *Math. Biosci.*, **114** (1993), 81–125.
[30] A. S. Perelson and P. W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, *SIAM Rev.*, **41** (1999), 3–44.

[31] A. S. Perelson, A. U. Neumann, M. Markowitz, J. M. Leonard and D. D. Ho, HIV-1 dynamics in vivo: Virion clearance rate, infected cell life-span, and viral generation time, *Science*, **271** (1996), 1582–1586.
[32] A. N. Phillips, Reduction of HIV concentration during acute infection: Independence from a specific immune response, *Science*, **271** (1996), 497–499.
[33] B. Ramratnam, S. Bonhoeffer, J. Binley, A. Hurley, L. Zhang, J. E. Mittler, M. Minarkowitz, J. P. Moore, A. S. Perelson and D. D. Ho, Rapid production and clearance of HIV-1 and hepatitis C virus assessed by large volume plasma apheresis, *Lancet*, **354** (1999), 1782–1785.
[34] L. Rong, Z. Feng and A. S. Perelson, Emergence of HIV-1 drug resistence during antiretroviral treatment, *Bull. Math. Biol.*, **69** (2007), 2027–2060.
[35] H. L. Smith, *Monotone Dynamical Systems: An Introduction to the Theory of Competitive and Cooperative Systems*, in *Mathematical Surveys and Monographs*, **41**. American Mathematical Society, Providence, RI, 1995.
[36] H. Smith and X. Zhao, Robust persistence for semidynamical systems, *Nonlinear Anal.*, **47** (2001), 6169–6179.
[37] M. A. Stafford, L. Corey, Y. Z. Cao, E. S. Daar, D. D. Ho and A. S. Perelson, Modeling Plasma Virus Concentration during Primary HIV Infection, *J. Theor. Biol.*, **203** (2000), 285–301.
[38] J. Wang, G. Huang and Y. Takeuchi, Global asymptotic stability for HIV-1 dynamics with two distributed delays, *Mathematical Medicine and Biology*, **29** (2012), 283–300.
[39] L. Wang and M. Y. Li, Mathematical analysis of the global dynamics of a model for HIV infection of CD4+ T cells, *Math. Biosci.*, **200** (2006), 44–57.
[40] K. Wang, W. Wang and X. Liu, Global stability in a viral infection model with lytic and nonlytic immune response, *Comput. Math. Appl.*, **51** (2006), 1593–1610.
[41] Y. Wang, Y. Zhou, J. Wu and J. Heffernan, Oscillatory viral dynamics in a delayed HIV pathogenesis model, *Math, Biosci.*, **219** (2009), 104–112.
[42] D. Wodarz, J. P. Christensen and A. R. Thomsen, The importance of lytic and nonlytic immune responses viral infections, *Trends. Immunol.*, **23** (2002), 194–200.
[43] D. Wodarz, K. Page, R. Arnaout, A. Thomsen, J. Lifson and M. A. Nowak, A new theiry of cytotoxic T-lymphocyte memory: Implications for HIV treatment, *Philosophical Transactions of the Royal Society B: Biological Sciences*, **355** (2000), 329–343.
[44] Z. Wu, Z. Y. Liu and R. Detels, HIV-1 infection in commercial plasma donors in China, *Lancet*, **346** (1995), 61–62.
[45] H. Zhu and X. Zou, Dynamics of an HIV-1 infection model with cell-mediated immune response and intracellular delay, *Discrete Contin. Dyn. Syst. B*, **12** (2009), 511–524.
[46] H. Zhu and X. Zou, Impact of delays in cell infection and virus production on HIV-1 dynamics, *Math. Med. Biol.*, **25** (2008), 99–112.

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E-mail address: htsong@hit.edu.cn
E-mail address: jiangwh@hit.edu.cn, author for correspondence
E-mail address: sqliu@hit.edu.cn