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Oscillatory viral dynamics in a delayed HIV pathogenesis model ☆

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ABSTRACT

We consider an HIV pathogenesis model incorporating antiretroviral therapy and HIV replication time. We investigate the existence and stability of equilibria, as well as Hopf bifurcations to sustained oscillations when drug efficacy is less than 100%. We derive sufficient conditions for the global asymptotic stability of the uninfected steady state. We show that time delay has no effect on the local asymptotic stability of the uninfected steady state, but can destabilize the infected steady state, leading to a Hopf bifurcation to periodic solutions in the realistic parameter ranges.

1. Introduction

Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS) have spread in successive waves in various regions around the globe thus becoming a serious threat to public health. When HIV enters the body, it targets cells with CD4 receptors, including the $CD4^+$ T-cells, the main driver of the immune response. Through infection and eventual killing of these cells, HIV damages the body's immune system, leading to humoral and cellular immune function loss (the marker of the onset of AIDS), making the body susceptible to opportunistic infections.

The fact that HIV replicates rapidly, producing on average 10^{10} viral particles per day [23], led to the realization that HIV evolves so rapidly that treatment with a single drug is bound to fail [23]. The best current therapy for HIV involves the simultaneous administration of two or more anti-viral drugs, potential inhibitors of HIV replication *in vivo*. These drug cocktails generally consist of reverse transcriptase inhibitors (RTIs) that block the infection of target T-cells by infection virus and protease inhibitors (PIs) that prevent HIV protease from cleaving HIV polyprotein into functional units, causing infected cells to produce virus particles that are non-infectious.

The basic mathematical model of HIV pathogenesis in-host describes interactions of the immune system and the virus by including healthy and infected $CD4^+$ T-cells and HIV virions [1,20,21,24,26]. Much has been learned regarding the pathogenesis of HIV in-host using this basic model (i.e. infected cell lifespan, viral clearance rate, bud rate of virions from infected cells); however, extensions are needed to further our understanding of this pathogen.

One such extension includes the addition of drug therapy [7,18–20,23], usually included using constant terms describing drug efficacy. Studies including drug therapy have proven the important of antiretroviral drugs in disrupting the infection process [7,8,18–20,23].

Another extension of the basic model is to include a logistic growth term that describes the growth rate of health $CD4^+$ T-cells [3,5,7,14,22,23,28,29], since the proliferation rate of T-cells is density-dependent with the rate of proliferation slowing as the T-cell count gets high [12,25]. The inclusion of logistic growth in models of HIV pathogenesis has aided in the understanding of the latent stage of infection. For example, the inclusion of logistic growth enabled Wang and Li [29] to obtain the global stability of the infected equilibrium. Furthermore, in [28], Wang and Ellermeyer presented a model that considered a logistic proliferation of all T-cells (uninfected and infected), and obtained the stability of the infected steady state depending on the T-cell proliferation rate.

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Perelson et al. [24] built on the biology of the HIV life cycle, including an intracellular delay. The delay describes the amount of time needed for a newly infected cell to start producing HIV virions. This work inspired several modeling studies (see [5,8,11,17–19]). Herz et al. [11] demonstrated that the half-life of free virus is reduced considerably if a discrete intracellular delay is included in the model. In another study, Nelson et al. [18] found that the predicted rate of decline in plasma virus concentration depends on three factors: the death rate of virus producing cells, the efficacy of therapy, and the length of the delay if an intracellular delay and drug therapy are included.

In a study by Culshaw and Ruan [5], the basic model of HIV infection in-host was extended to incorporate logistic growth and an intracellular delay. They demonstrated that the stability of the infected steady state is not affected by these realistic modifications, using realistic parameter values. However, they did find conditions that lead to a Hopf bifurcation lying outside realistic parameter space. Cai and Li [3] and Jiang et al. [14] also studied models incorporating logistic growth and intracellular delay and found conditions for the existence of Hopf bifurcations. However, none of these models have incorporated the effects of drug therapy.

Here, we build on the basic model of HIV pathogenesis in-host, adding the effects of drug therapy (reverse transcriptase and protease inhibitors), an intracellular delay and logistic growth. We use this new model to determine whether the infected or uninfected steady states can be destabilized, leading to either transient or sustained oscillations.

In the sections that follow we formulate a mathematical model including combination antiretroviral therapy, intracellular delay and logistic growth of CD4$^+$ T-cells. We establish the local asymptotic stability of the uninfected and the infected equilibria, construct a Lyapunov function to establish the global asymptotic stability of the uninfected equilibrium and find sufficient conditions for the occurrence of a Hopf bifurcation. In addition, numerical simulations are used to demonstrate transient and sustained oscillations using realistic parameter values of HIV pathogenesis as well as investigate the joint impact of the time delay and treatment efficacy on healthy and infected CD4$^+$ T-cells. Finally, a modified model, including full logistic proliferation and a varying bud rate is introduced. Stability of the uninfected and infected equilibria of this model and the occurrence of a Hopf bifurcation are studied through numerical simulations.

2. Model

We consider a model of HIV pathogenesis in-host which describes the interactions of uninfected ($T(t)$) and infected ($T^*(t)$) CD4$^+$ T-cells and infectious ($V_I(t)$) and non-infectious ($V_{NI}(t)$) virus. The model includes antiretroviral therapy, logistic growth of the CD4$^+$ T-cells and a time delay. The model is as follows:

$$\begin{aligned}
\frac{d}{dt}T(t) &= \lambda - dT(t) + rT(t)\left(1-\frac{T(t)}{T_{\max}}\right) - k_I(1-n_{rt})V_I(t)T(t),\\
\frac{d}{dt}T^*(t) &= k_A(1-n_{rt})V_I(t-\tau)T(t-\tau) - \delta T^*(t),\\
\frac{d}{dt}V_I(t) &= (1-n_p)N\delta T^*(t) - cV_I(t),\\
\frac{d}{dt}V_{NI}(t) &= n_pN\delta T^*(t) - cV_{NI}(t).
\end{aligned} \tag{1}$$

And the initial values are

$$\begin{aligned}
T(\theta) = \varphi_1(\theta) \geqslant 0, \quad T^*(0) = \varphi_2 \geqslant 0, \quad V_I(\theta) = \psi_1(\theta)\\
\geqslant 0, \ V_{NI}(\theta) = \psi_2 \geqslant 0 \text{ for } \theta \in [-\tau, 0],
\end{aligned} \tag{2}$$

where φ_2, ψ_2 are given constants, and φ_1, $\psi_1 \in C([-\tau,0],R_+)$ with $R_+ = [0,+\infty)$.

Here, λ is the source of CD4$^+$ T-cells from precursors, d is the natural death rate of CD4$^+$ T-cells, r is the growth rate (thus, $r > d$ in general) and $T_{\max}$, where $dT_{\max} > \lambda$, is the carrying capacity of the T-cell population. The parameter k_I represents the rate of infection of T-cells with free virus, k_A is the rate at which infected cells become actively infected (the ratio k_A/k_I is the proportion of T-cells, which become actively infected (proportion of infected cells surviving incubation)), δ is the death rate of infected cells, N (burst size) is the total number of virus particles released by a productively infected cell over its lifespan with mean $1/\delta$, and c is the viral clearance rate constant. τ represents a time delay between initial viral entry into a cell and subsequent viral production. Protease inhibitors, with efficacy $0 \leqslant n_p < 1$, cause infected cells to produce non-infectious virus with rate n_pN. Reverse transcriptase inhibitors prevent the production of infected cells with efficacy $0 \leqslant n_{rt} < 1$. Table 1 gives brief definitions and reference values of the above parameters.

Note that the non-infectious HIV virus V_{NI} does not appear in the first three equations. Thus, we can consider the following subsystem of system (1):

$$\begin{aligned}
\frac{d}{dt}T(t) &= \lambda - dT(t) + rT(t)\left(1-\frac{T(t)}{T_{\max}}\right) - k_I(1-n_{rt})V_I(t)T(t),\\
\frac{d}{dt}T^*(t) &= k_A(1-n_{rt})V_I(t-\tau)T(t-\tau) - \delta T^*(t),\\
\frac{d}{dt}V_I(t) &= (1-n_p)N\delta T^*(t) - cV_I(t),
\end{aligned} \tag{3}$$

with initial conditions

$$\begin{aligned}
T(\theta) = \varphi_1(\theta) \geqslant 0, \quad T^*(0) = \varphi_2 \geqslant 0, \quad V_I(\theta) = \psi_1(\theta)\\
\geqslant 0 \text{ for } \theta \in [-\tau, 0],
\end{aligned} \tag{4}$$

where φ_2 is a given constant, and φ_1, $\psi_1 \in C([-\tau,0],R_+)$ with $R_+ = [0,+\infty)$.

System (3) has an uninfected steady state and an infected (positive) steady state. The uninfected steady state is $E_0 = (T_0, 0, 0)$, where

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

From the first equation of system (1), we find that

$$\frac{d}{dt}T(t) \leqslant \lambda - dT(t) + rT(t)\left(1-\frac{T(t)}{T_{\max}}\right),$$

therefore,

$$\limsup_{t\to+\infty} T(t) \leqslant T_0. \tag{5}$$

The infected (positive) steady state is $\overline{E} = (\overline{T}, \overline{T}^*, \overline{V}_I)$, where,

$$\begin{aligned}
\overline{T} &= \frac{c}{k_AN(1-\eta_c)},\\
\overline{T}^* &= \frac{c\overline{V}_I}{N\delta(1-n_p)},\\
\overline{V}_I &= \frac{\lambda - d\overline{T} + r\overline{T}\left(1-\frac{\overline{T}}{T_{\max}}\right)}{k_I(1-n_{rt})\overline{T}},\\
\eta_c &= 1-(1-n_{rt})(1-n_p).
\end{aligned} \tag{6}$$

Suppose that

$$\eta_{\text{crit}} := 1 - \frac{c}{k_ANT_0}. \tag{7}$$

Then $\eta_c < \eta_{\text{crit}}$ ensures the existence of the infected (positive) steady state $\overline{E}$.

Table 1
List of parameters.

Parameters	Definition	Range of the parameters	Source	Data1 values	Data2 values
T	Uninfected T-cells concentration		[2,5]	1000 cells mm^{-3}	408 cells mm^{-3}
T^*	Productively infected T-cells concentration		[2,5]	0 cells mm^{-3}	0.1626 cells mm^{-3}
V_I	Infectious virus concentration		[2,5]	10^{-3} virions mm^{-3}	28.5 virions mm^{-3}
V_{NI}	Non-infectious virus concentration				
λ	T-cells source term	0–10 cells mm^{-3} day^{-1}	[5,7,8,18]	10 cells mm^{-3} day^{-1}	10 cells mm^{-3} day^{-1}
d	Death rate of healthy T-cells	0.007–0.1 day^{-1}	[6,18]	0.007 day^{-1}	0.03 day^{-1}
r	Growth rate of T-cells	0.03–3 day^{-1}	[5,7,28]	0.03 day^{-1}	0.95 day^{-1}
k_I	Viral infectivity rate	0.00025–0.5 virions mm^3 day^{-1}	[5,7,8,29] [6,15]	2.4 × 10^{-5} virions mm^3 day^{-1}	0.0027 virions mm ^{3} day^{-1}
k_A	Rate infected cells becomes active	$k_A/k_I \approx 1$	[5,6]	2.0 × 10^{-5} virions mm^3 day^{-1}	0.0020 virions mm^3 day^{-1}
δ	Death rate of infected T-cells	0.2–0.5 day^{-1}	[5,6,15,24]	0.26 day^{-1}	0.26 day^{-1}
$T_{\max}$	Carrying capacity of T-cells	1500 mm^{-3}	[5,29]	1500 mm^{-3}	1500 mm^{-3}
N	Bursting term for viral production after lysis	10–2500 virions/cell	[7,8]	2500 virions/cell	50 virions/cell
c	Clearance rate of virus	2.4–3 day^{-1}	[5,18,24]	2.4 day^{-1}	3 day^{-1}
τ	Virus replication time	0–2 days	[2,5,8]	1.5 days	1, 1.5 days
n_{rt}	Reverse transcriptase inhibitor efficacy	(0,1)	Variable	0.4, 0.5, 0.6	0.6
n_p	Protease inhibitor efficacy	(0,1)	Variable	0.3, 0.55, 0.8	0.7

2.1. Global stability of the uninfected steady state (E_0)

To discuss the local stability of the uninfected steady state E_0, we let

$$\alpha = \frac{\lambda}{T_0} + \frac{rT_0}{T_{\max}} > 0.$$

Theorem 2.1. *The uninfected steady state E_0 is locally asymptotically stable if $\eta_c > \eta_{crit}$, and unstable if $\eta_c < \eta_{crit}$.*

Proof. The characteristic equation of the uninfected steady state E_0 is

$$(\xi + \alpha)[\xi^2 + (\delta + c)\xi + c\delta - Ae^{-\xi\tau}] = 0, \tag{8}$$

where $A = k_A N \delta T_0(1 - \eta_c)$. Clearly, $\xi = -\alpha$ is a negative root of Eq. (8). The remaining roots are given by the solutions of the following transcendental equation:

$$\xi^2 + (\delta + c)\xi + c\delta - Ae^{-\xi\tau} = 0. \tag{9}$$

Substituting $\tau = 0$ into Eq. (9) we obtain the following quadratic equation:

$$\xi^2 + (\delta + c)\xi + c\delta - A = 0. \tag{10}$$

In this case, if $\eta_c > \eta_{\text{crit}}$ then $c\delta > A$. Thus, the quadratic equation (10) has two negative real roots, and hence E_0 is locally asymptotically stable for $\tau = 0$.

If $\tau > 0$ and Eq. (9) has a purely imaginary root $\xi = i\omega(\tau)$ with $\omega(\tau) > 0$, then separating real and imaginary parts yields

$$\begin{cases} c\delta - \omega^2 = A\cos(\omega\tau), \\ (\delta + c)\omega = -A\sin(\omega\tau). \end{cases}$$

Squaring and adding the above equations, we obtain

$$F_1(\omega) = \omega^4 + (\delta^2 + c^2)\omega^2 + c^2\delta^2 - A^2 = 0. \tag{11}$$

Here, if $\eta_c > \eta_{\text{crit}}$ then $c^2\delta^2 - A^2 > 0$. Thus, Eq. (11) has no positive roots. If, however, $\eta_c > \eta_{\text{crit}}$, when the delay τ is increased, no root of Eq. (9) can cross the imaginary axis. Therefore, E_0 remains locally asymptotically stable for $\tau \geqslant 0$.

Finally, if $\eta_c < \eta_{\text{crit}}$ (i.e. $c\delta < A$), then the quadratic equation (10) has a positive root. Therefore, E_0 is unstable for $\tau = 0$. Furthermore, $\frac{\partial F_1(\omega)}{\partial \omega} = 4\omega^3 + 2(\delta^2 + c^2)\omega > 0$, and thus from Cooke and van den Driessche [4] and Freedman and Kuang [9], E_0 is unstable for $\tau \geqslant 0$. This completes the proof. □

Theorem 2.2. *If $\eta_c > \eta_{crit}$, the uninfected steady state E_0 is globally asymptotically stable for every given $\tau \geqslant 0$.*

Proof. Define

$$M = \{\phi = (\varphi_1, \varphi_2, \psi_1) \in C([-\tau, 0], R_+) \times R_+ \times C([-\tau, 0], R_+); \\ 0 \leqslant \varphi_1 \leqslant T_0\}.$$

From (5), it is evident that M attracts all solutions of system (3). Let $(T(t), T^*(t), V_I(t))$ be a solution of system (3) with initial value in M. We claim that for any $t \geqslant 0$, $T(t) \leqslant T_0$. Otherwise, there must exist the first $t_1 > 0$ such that $T(t_1) > T_0$ and $\dot{T}(t_1) > 0$. From the first equation of system (3), we find that

$$T'(t_1) = \lambda - dT(t_1) + rT(t_1)(1 - T(t_1)/T_{\max}) - k_I(1 - n_{rt})V_I(t_1)T(t_1) \\ \leqslant -k_I(1 - n_{rt})V_I(t_1)T(t_1) \leqslant 0,$$

a contradiction. Hence, M is positively invariant with respect to system (3). Consider now a Lyapunov functional on M given by

$$V(\phi) = N(1 - n_p)\varphi_2(0) + \psi_1(0) + k_A N(1 - \eta_c)\int_{-\tau}^{0} \psi_1(s)\varphi_1(s)\,ds.$$

From the invariance of M, for any $\phi \in M$, the solution $(T(t), T^*(t), V_I(t))$ of (3) with the initial condition (2) satisfies $T(t) \leqslant T_0$ for all $t \geqslant 0$. In region M the derivative of $V(\phi)$ along system (3) is

$$V'(\phi) = (k_A N(1 - \eta_c)\varphi_1(0) - c)\psi_1(0) \\ = k_A N\psi_1(0)[(1 - \eta_c)\varphi_1(0) - (1 - \eta_{\text{crit}})T_0].$$

If $\eta_c > \eta_{\text{crit}}$, then $1 - \eta_c < 1 - \eta_{\text{crit}}$. Thus with $\varphi_1(0) \leqslant T_0$, we find that $(1 - \eta_c)\varphi_1(0) - (1 - \eta_{\text{crit}})T_0 \leqslant 0$. Hence, $V'(\phi) \leqslant 0$. $V'(\phi) = 0$ if and only if $\psi_1(0) = 0$ or $\varphi_1(0) = T_0$. The maximum invariant set in $\{\phi \in M | V'(\phi) = 0\}$ is the singleton E_0. LaSalle's Invariance Principle [16] implies that all solutions converge to E_0. This and the local stability of E_0 established in Theorem 2.1 imply the globally asymptotical stability of E_0. This completes the proof. □

It is interesting to note that η_{crit} is independent of the time delay, the infected rate of T-cells with free virus k_I and the death rate of infected cells δ. Theorem 2.2 implies that all solutions of system (3) converge to E_0 when $\eta_c > \eta_{\text{crit}}$, and the final outcome is independent of the time delay. Biologically, it implies that, when the combinated efficacy of RTIs and PIs is larger than η_{crit}, the infected T-cells and virus particles are eventually cleared from the T-cells population.

2.2. Local stability and Hopf bifurcation of $\overline{E}$

To discuss the stability of $\overline{E}$, we let

$$\bar{\alpha} = \frac{\lambda}{\overline{T}} + \frac{r\overline{T}}{T_{\max}} > 0.$$

Time delay has been shown to be a main source of fluctuations in population size due to the generation of instabilities [27]. Here, under some conditions, we will show that the delay affects the stability of the infected steady state for a wide range of realistic parameter values, leading to either transient or sustained oscillations in the T-cells on the viral load. For simplicity, we set

$$\begin{aligned}
a_1 &= \bar{\alpha} + \delta + c > 0,\\
a_2 &= c\bar{\alpha} + c\delta + \bar{\alpha}\delta > 0,\\
a_3 &= c\bar{\alpha}\delta > 0,\\
b_1 &= -c\delta < 0,\\
b_2 &= ck_I\delta(1-n_{rt})\overline{V}_I - c\bar{\alpha}\delta.
\end{aligned}$$

Theorem 2.3. *Assume $\eta_c < \eta_{crit}$.*

(i) *If $\frac{\lambda}{\overline{T}} + d - r\left(1 - \frac{3\overline{T}}{T_{\max}}\right) > 0$, then the infected steady state $\overline{E}$ is locally asymptotically stable for every given $\tau \geqslant 0$.*

(ii) *If*

$$\frac{\lambda}{\overline{T}} + d - r\left(1 - \frac{3\overline{T}}{T_{\max}}\right) < 0,$$

$$\bar{\alpha}(\delta + c)(\bar{\alpha} + \delta + c) > c\delta\left(\frac{\lambda}{\overline{T}} - d + r\left(1 - \frac{\overline{T}}{T_{\max}}\right)\right),$$

$$a_2^2 b_2^2 - 2a_1 a_3 b_2^2 - a_3^2 b_1^2 > 0,$$

then there is a value $\tau_0 > 0$ such that the unique positive equilibrium $\overline{E}$ is locally asymptotically stable when $\tau \in [0, \tau_0)$ and unstable when $\tau > \tau_0$. Furthermore, system (3) undergoes a Hopf bifurcation to periodic solutions at $\overline{E}$ when $\tau = \tau_0$.

Proof. The characteristic equation of the linearized system of Eq. (2) at the infected steady state $\overline{E}$ is

$$\xi^3 + a_1\xi^2 + a_2\xi + a_3 + e^{-\xi\tau}(b_1\xi + b_2) = 0. \tag{12}$$

(1) When $\tau = 0$, this characteristic equation reduces to a cubic equation

$$\xi^3 + a_1\xi^2 + (a_2 + b_1)\xi + a_3 + b_2 = 0. \tag{13}$$

The Routh–Hurwitz criterion for all solutions of Eq. (13) to have negative real parts is $a_1(a_2 + b_1) - (a_3 + b_2) > 0$. Since

$$\begin{aligned}
a_1(a_2 + b_1) - (a_3 + b_2) &= \bar{\alpha}(\delta + c)(\bar{\alpha} + \delta + c) - ck_I\delta(1 - n_{rt})\overline{V}_I\\
&= \left(\frac{\lambda}{\overline{T}} + \frac{r\overline{T}}{T_{\max}}\right)(\delta + c)\left(\frac{\lambda}{\overline{T}} + \frac{r\overline{T}}{T_{\max}} + \delta + c\right)\\
&\quad - c\delta\left(\frac{\lambda}{\overline{T}} - d + r\left(1 - \frac{\overline{T}}{T_{\max}}\right)\right)\\
&= \left(\frac{\lambda}{\overline{T}} + \frac{r\overline{T}}{T_{\max}}\right)^2(\delta + c) + \left(\frac{\lambda}{\overline{T}} + \frac{r\overline{T}}{T_{\max}}\right)(\delta + c)^2\\
&\quad - c\delta\left(\frac{\lambda}{\overline{T}} - d + r\left(1 - \frac{\overline{T}}{T_{\max}}\right)\right)\\
&= \left(\frac{\lambda}{\overline{T}} + \frac{r\overline{T}}{T_{\max}}\right)^2(\delta + c) + \left(\frac{\lambda}{\overline{T}} + \frac{r\overline{T}}{T_{\max}}\right)(\delta^2\\
&\quad + c^2) + c\delta\left(\frac{\lambda}{\overline{T}} + d - r\left(1 - \frac{3\overline{T}}{T_{\max}}\right)\right),
\end{aligned}$$

we conclude that if the condition $\frac{\lambda}{\overline{T}} + d - r\left(1 - \frac{3\overline{T}}{T_{\max}}\right) > 0$ holds, then roots of Eq. (13) have negative real parts, therefore the positive equilibrium $\overline{E}$ is locally asymptotically stable for $\tau = 0$.

If $\tau > 0$ and $\xi = i\omega(\tau)$ with $\omega(\tau) > 0$ is a solution of Eq. (12), then separating the real and imaginary part gives

$$\begin{cases}
-a_1\omega^2 + a_3 = -b_2\cos(\omega\tau) - b_1\omega\sin(\omega\tau),\\
-\omega^3 + a_2\omega = -b_1\omega\cos(\omega\tau) + b_2\sin(\omega\tau).
\end{cases} \tag{14}$$

Squaring and adding both equations of (14) yields

$$F_2(\omega) = \omega^6 + (a_1^2 - 2a_2)\omega^4 + \left(a_2^2 - 2a_1a_3 - b_1^2\right)\omega^2 + a_3^2 - b_2^2 = 0. \tag{15}$$

However, from condition $\frac{\lambda}{\overline{T}} + d - r\left(1 - \frac{3\overline{T}}{T_{\max}}\right) > 0$ it follows that

$$\begin{aligned}
a_3^2 - b_2^2 &= k_I c^2\delta^2(1 - n_{rt})\overline{V}_I(2\bar{\alpha} - k_I(1 - n_{rt})\overline{V}_I)\\
&= k_I c^2\delta^2(1 - n_{rt})\overline{V}_I\left(\frac{\lambda}{\overline{T}} + d - r\left(1 - \frac{3\overline{T}}{T_{\max}}\right)\right) > 0,
\end{aligned}$$

$$\begin{aligned}
a_2^2 - 2a_1a_3 - b_1^2 &= (a_2 + b_1)(a_2 - b_1) - 2a_1a_3\\
&= \bar{\alpha}(c + \delta)(c(\bar{\alpha} + 2\delta) + \bar{\alpha}\delta) - 2(\bar{\alpha} + \delta + c)\bar{\alpha}\delta c\\
&= \bar{\alpha}^2(c^2 + \delta^2) > 0,
\end{aligned}$$

$$a_1^2 - 2a_2 = (\bar{\alpha} + \delta + c)^2 - 2(c\bar{\alpha} + c\delta + \bar{\alpha}\delta) = \bar{\alpha}^2 + \delta^2 + c^2 > 0.$$

Therefore, by Claim 1 of [5], it is evident that Eq. (15) has no positive real roots. This shows that equation (12) cannot have a purely imaginary root for any $\tau > 0$. Therefore, the infected steady state $\overline{E}$ is locally asymptotically stable, for any $\tau \geqslant 0$, provided that $\frac{\lambda}{\overline{T}} + d - r\left(1 - \frac{3\overline{T}}{T_{\max}}\right) > 0$.

Next, we consider the occurrence of a Hopf bifurcation at the positive equilibrium $\overline{E}$. Note that if

$$\bar{\alpha}(\delta + c)(\bar{\alpha} + \delta + c) > c\delta\left(\frac{\lambda}{\overline{T}} - d + r\left(1 - \frac{\overline{T}}{T_{\max}}\right)\right)$$

is satisfied, then $a_1(a_2 + b_1) - (a_3 + b_2) > 0$, and thus Eq. (13) has only roots with negative real parts. Therefore, $\overline{E}$ is locally asymptotically stable when $\tau = 0$. If, in addition, we assume that

$$\frac{\lambda}{\overline{T}} + d - r\left(1 - \frac{3\overline{T}}{T_{\max}}\right) < 0,$$

then $a_3^2 - b_2^2 < 0$, that is, $F_2(0) < 0$. As $F_2'(\omega) = 6\omega^5 + 4(a_1^2 - 2a_2)\omega^3 + 2(a_2^2 - 2a_1a_3 - b_1^2)\omega > 0$ and $\lim_{\omega\to+\infty} F_2(\omega) = +\infty$, we conclude that there is a unique positive root ω_0 satisfying Eq. (15). Therefore, the characteristic equation (12) has a pair of purely imaginary roots $\pm i\omega_0$. From Eqs. (14) it follows that the corresponding τ_n are

$$\tau_n = \frac{1}{\omega_0}\arccos\left\{\frac{b_1\omega_0^4 + (a_1b_2 - a_2b_1)\omega_0^2 - a_3b_2}{b_1^2\omega_0^2 + b_2^2}\right\} + \frac{2n\pi}{\omega_0},$$
$$n = 0, 1, 2, \ldots.$$

For $\tau = 0$, $\overline{E}$ is stable. Hence by Butler's Lemma [10], $\overline{E}$ remains stable for $\tau < \tau_0 = \min\{\tau_n;\ n = 0, 1, 2, \ldots\}$.

Now differentiating Eq. (12) with respect τ, we get

$$\left(3\xi^2 + 2a_1\xi + a_2 - \tau(b_1\xi + b_2)e^{-\xi\tau} + b_1e^{-\xi\tau}\right)\frac{d\xi}{d\tau} = \xi(b_1\xi + b_2)e^{-\xi\tau}.$$

That is,

$$\left(\frac{d\xi}{d\tau}\right)^{-1} = \frac{3\xi^2 + 2a_1\xi + a_2 - \tau(b_1\xi + b_2)e^{-\xi\tau} + b_1 e^{-\xi\tau}}{\xi(b_1\xi + b_2)e^{-\xi\tau}}$$
$$= \frac{3\xi^2 + 2a_1\xi + a_2}{\xi(b_1\xi + b_2)e^{-\xi\tau}} + \frac{b_1}{\xi(b_1\xi + b_2)} - \frac{\tau}{\xi}$$
$$= -\frac{2\xi^3 + a_1\xi^2 - a_3}{\xi^2(\xi^3 + a_1\xi^2 + a_2\xi + a_3)} - \frac{b_2}{\xi^2(b_1\xi + b_2)} - \frac{\tau}{\xi}.$$

Thus

$$\operatorname{sign}\left\{\frac{d(Re\xi)}{d\tau}\right\}_{\xi=i\omega_0} = \operatorname{sign}\left\{Re\left(\frac{d\xi}{d\tau}\right)^{-1}\right\}_{\xi=i\omega_0} = \operatorname{sign}\left\{Re\left[-\frac{2\xi^3 + a_1\xi^2 - a_3}{\xi^2(\xi^3 + a_1\xi^2 + a_2\xi + a_3)}\right]_{\xi=i\omega_0} - Re\left[\frac{b_2}{\xi^2(b_1\xi + b_2)}\right]_{\xi=i\omega_0}\right\}$$
$$= \operatorname{sign}\left\{Re\left[\frac{-a_1\omega^2 - a_3 - 2\omega^3 i}{\omega^2(a_3 - a_1\omega^2 + (a_2\omega - \omega^3)i)} + \frac{b_2}{\omega^2(b_2 + b_1\omega i)}\right]\right\}$$
$$= \operatorname{sign}\left\{\frac{2b_1^2\omega^6 + \left[(a_1^2 - 2a_2)b_1^2 + 3b_2^2\right]\omega^4 + 2(a_1^2 - 2a_2)b_2^2\omega^2 + a_2^2b_2^2 - 2a_1a_3b_2^2 - a_3^2b_1^2}{(b_1^2\omega^2 + b_2^2)[(a_3 - a_1\omega^2)^2 + (a_2\omega - \omega^3)^2]}\right\}.$$

The numerator is given by

$$f(\omega) = 2b_1^2\omega^6 + \left[(a_1^2 - 2a_2)b_1^2 + 3b_2^2\right]\omega^4 + 2(a_1^2 - 2a_2)b_2^2\omega^2 + a_2^2b_2^2 - 2a_1a_3b_2^2 - a_3^2b_1^2.$$

Let $V = \omega^2$, we get

$$f(V) = 2b_1^2V^3 + [(a_1^2 - 2a_2)b_1^2 + 3b_2^2]V^2 + 2(a_1^2 - 2a_2)b_2^2V + a_2^2b_2^2 - 2a_1a_3b_2^2 - a_3^2b_1^2$$

and

$$f'(V) = 6b_1^2V^2 + 2[(a_1^2 - 2a_2)b_1^2 + 3b_2^2]V + 2(a_1^2 - 2a_2)b_2^2 > 0 \quad \text{for } V > 0.$$

Therefore, $f(\omega)$ is monotonically increasing on $[0,+\infty)$. We know $f(0) = a_2^2b_2^2 - 2a_1a_3b_2^2 - a_3^2b_1^2 > 0$, so we have $f(\omega) > 0$ for $\omega > 0$. Then we obtain

$$\left.\frac{d(Re\xi)}{d\tau}\right|_{\tau=\tau_n,\omega=\omega_0} > 0.$$

Therefore, the transversality condition holds and a Hopf bifurcation occurs at $\tau = \tau_n$. This completes the proof of Theorem 2.3. □

In comparison with Theorem 2.2, where the time delay does not influence the stability of the uninfected steady state, we note that Theorem 2.3 indicates that the delay can lead to a Hopf bifurcation of periodic solutions near the infected steady state when τ reaches a certain value.

3. Numerical simulations

3.1. Numerical simulations of system (1)

We now numerically illustrate the change of the stability and the occurrence of a Hopf bifurcation by varying the time delay.

Considering Data1 values in Table 1, we find that $\eta_{crit} = 0.9677$ and $\eta_c = 0.5800$, $\eta_c = 0.7750$ and $\eta_c = 0.9200$, for each pair of (η_{crit}, η_{cs}) listed. Thus, $\eta_c < \eta_{crit}$. At the same time, the infected steady state for each pair (η_{crit}, η_c) is $\bar{E} = (114.2857, 39.6389, 7514.9000)$, $\bar{E} = (213.3333, 44.8604, 5467.4000)$ and $\bar{E} = (600.0000, 53.2051, 2881.9000)$, respectively. It follows that case (i) of Theorem 2.3 occurs, and the infected steady state $\bar{E}$ is locally asymptotically stable. Fig. 1 demonstrates that as η_c increases the total number of healthy and infected CD4$^+$ T-cells increase dramatically, while the number of the infectious virions decreases substantially.

Under the condition $\frac{\lambda}{\bar{T}} + d - r\left(1 - \frac{3\bar{T}}{T_{max}}\right) > 0$, the infected steady state is locally asymptotically stable independent of the size of the delay, though the time delay does cause transient oscillations in all components. Computer simulations confirm our analysis.

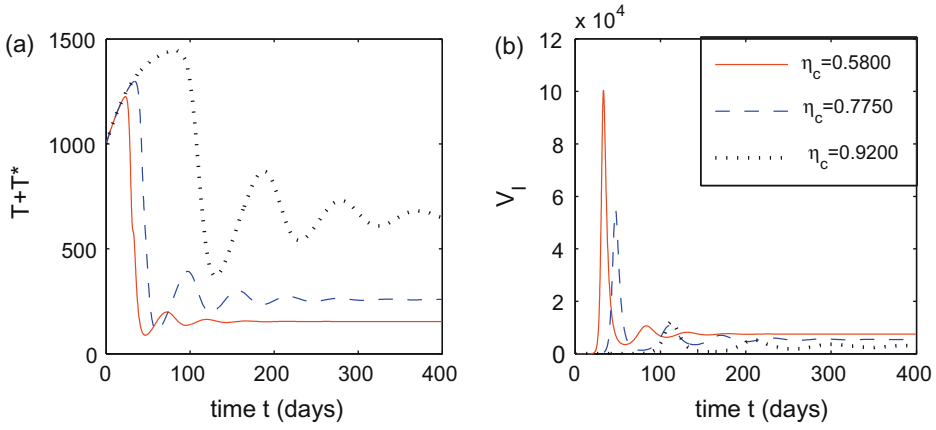

Fig. 1. Local asymptotic stability of the infected steady state $\bar{E}$. η_c changes from 0.5800 to 0.9200, all other parameters are given in Data1 values of Table 1. As η_c increases, the total number of the healthy and infected CD4$^+$ T-cells (a) increases, while the number of the infectious virions (b) decreases.

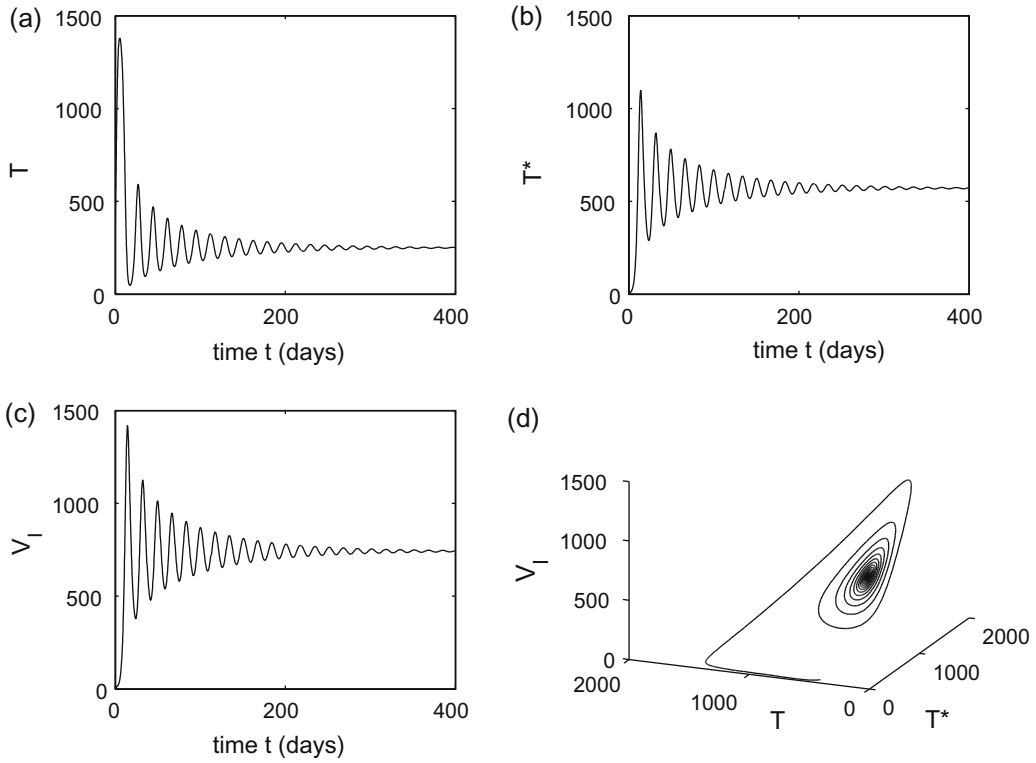

Fig. 2. Local asymptotic stability of the infected steady state $\overline{E}$. $\tau = 1 < \tau_0$, and all other parameters are given in Data2 values of Table 1.

Biologically, this implies that the intracellular delay can cause the cell and virus populations to fluctuate in the early stage of infection, in a longer term they will converge to the infected steady state values.

For the case (ii) of Theorem 2.3, we consider parameter listed in Data 2 of Table 1. Here, $\eta_{\text{crit}} = 0.9795$. For $n_{rt} = 0.6$ and $n_p = 0.7$, $\eta_c = 0.8800$ and $\eta_c < \eta_{\text{crit}}$. It follows that conditions (ii) of Theorem 2.3 are satisfied. Therefore, at $\tau_0 \approx 1.3395$ a Hopf bifurcation oc-

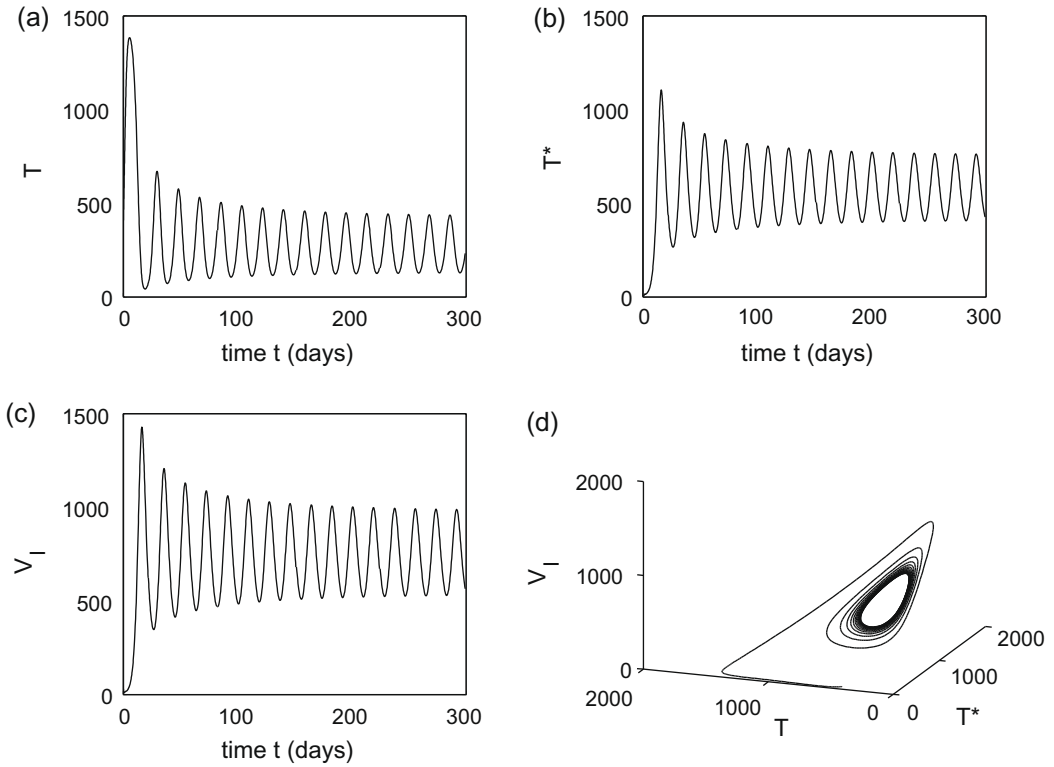

Fig. 3. Periodic solutions bifurcated from the infected steady state $\overline{E}$. $\tau = 1.5 > \tau_0$, and all other parameters are given in Data2 values of Table 1.

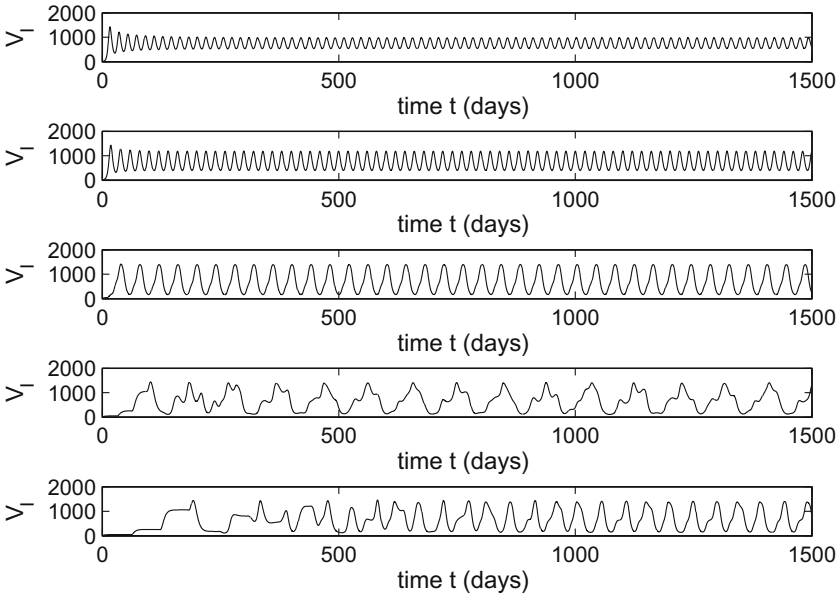

Fig. 4. Numerical simulations for infectious virus when the time delay gets larger (τ is larger than the critical value τ_0). From the top graph to bottom, the time delay is $\tau = 1.5$, $\tau = 2$, $\tau = 9$, $\tau = 30$ and $\tau = 60$, respectively; the periodicity of the periodic solutions approximates to 18.18 days, 20 days, 40 days, 178.57 days and 200 days, correspondingly. As time delay increases, the period of solutions also increases but the amplitude is only slightly changed.

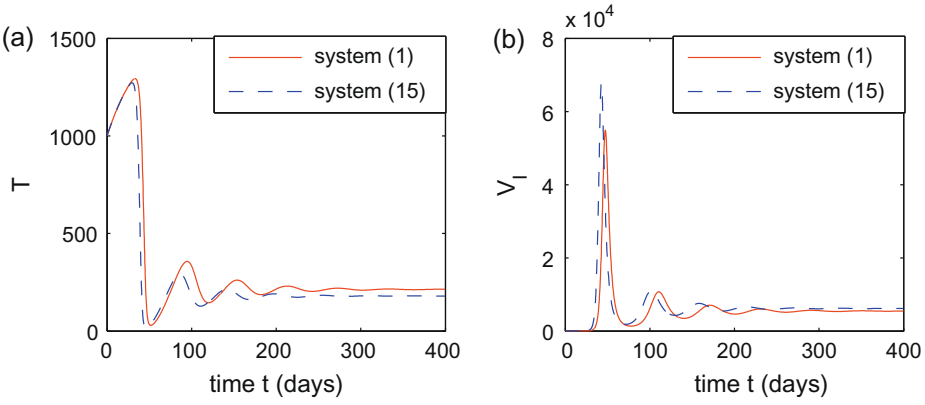

Fig. 5. Local asymptotic stability of the infected steady state $\overline{E}$. Under the same parameter values, the number of healthy CD4$^+$ T-cells (a) and infectious virions (b) of system (16) do not differentiate much from those of system (1).

curs. Figs. 2 and 3 plot the cell and virus populations and a phase plane diagram over time for a case when $\tau < \tau_0$ and $\tau > \tau_0$. When $\tau < \tau_0$ the infected steady state $\overline{E}$ is locally asymptotically stable (Fig. 2), however, if $\tau > \tau_0$ (Fig. 3) stable periodic solutions exists (Hopf bifurcation).

Reported ranges of τ are between 0 and 2 days [2,8]. We have shown that sustained oscillations via the mechanism of a Hopf bifurcation are possible in the realistic parameter space. It is, at least, theoretically interesting to see how these periodic solutions vary when τ varies, even beyond this range. For this purpose, we choose $\tau = 1.5$, $\tau = 2$, $\tau = 9$, $\tau = 30$ and $\tau = 60$, respectively. Fig. 4 plots V_I over time for these new values of τ. We note that as the time delay τ gets larger the infected steady state remains unstable and periodic solutions occur. Also, the period of periodic solutions increases. However, the amplitudes do not change dramatically.

3.2. Numerical simulations of a modified model

As an extension to (1) we consider a model including full logistic proliferation, an intracellular delay and a varying bud rate. The modified model is as follow:

$$
\begin{aligned}
\frac{d}{dt}T(t) &= \lambda - dT(t) + rT(t)\left(1 - \frac{T(t)+T^*(t)}{T_{\max}}\right) - k_I(1-n_{rt})V_I(t)T(t),\\
\frac{d}{dt}T^*(t) &= k_I e^{-m\tau}(1-n_{rt})V_I(t-\tau)T(t-\tau) - \delta T^*(t),\\
\frac{d}{dt}V_I(t) &= (1-n_p)N\delta T^*(t) - cV_I(t),\\
\frac{d}{dt}V_{NI}(t) &= n_p N\delta T^*(t) - cV_{NI}(t).
\end{aligned}
\tag{16}
$$

Here, $k_I e^{-m\tau}$ represents the infection rate where $1/m$ is the average time it takes for an infected cell to become productive. This is considered to be more biologically realistic since there is a probability that an infected cell survives the interval τ.

Theoretical study of (16) is more challenging. In the following, we present some numerical simulations for system (16). Consider $m = d = 0.007$, $n_{rt} = 0.5$ and $n_p = 0.55$, and parameter values listed in Data1 of Table 1. Numerical simulations show that trajectories of system (16) approach the infected steady state (see Fig. 5). However, if we consider $m = d = 0.03$ and $\tau = 1.5$ and Data2 values of Table 1 a Hopf bifurcation occurs (see Fig. 6).

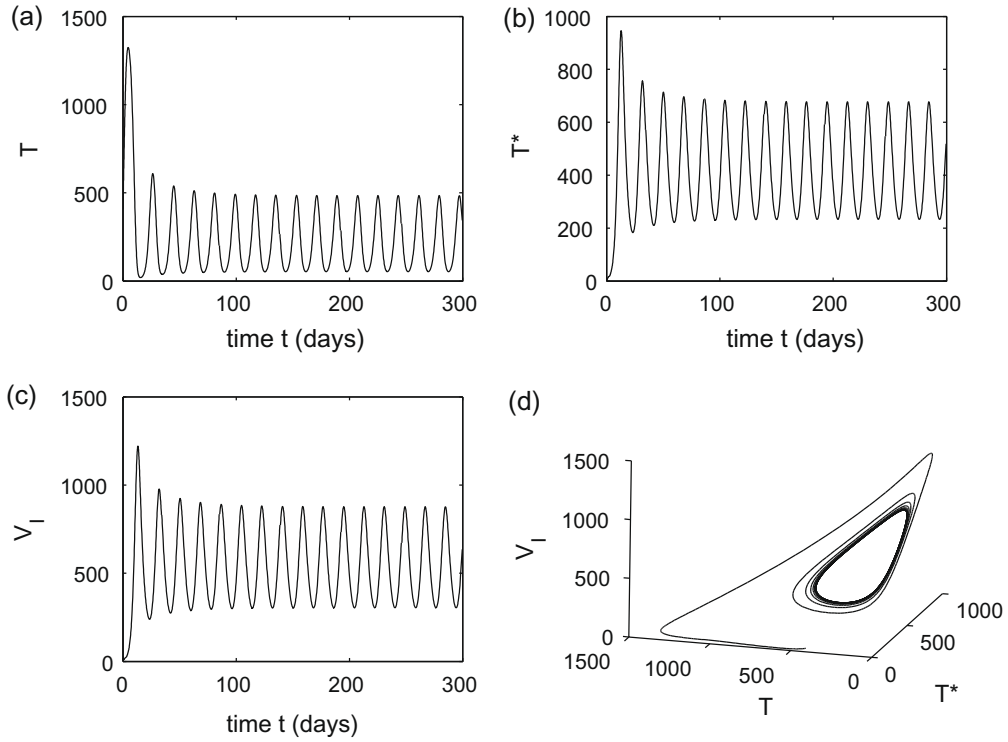

Fig. 6. Periodic solutions bifurcated from the infected steady state $\bar{E}$ of system (16). $m = d = 0.03$ and $\tau = 1.5$, and all other parameters are given in Data2 values of Table 1.

4. Conclusions and discussions

We have studied a HIV model including logistic growth, an intracellular delay and combination antiretroviral therapy. Sufficient conditions are established for the local asymptotic stability of the uninfected steady state and the infected steady state. Furthermore, we obtained the global asymptotic stability of uninfected steady state when $\eta_c > \eta_{\text{crit}}$. The influence of the time delay on the stability of equilibrium states is discussed. We showed that the local stability of the uninfected steady state is independent of the size of the delay; on the other hand, we proved that increasing the delay can destabilize the infected steady state leading to a Hopf bifurcation and periodic solutions. This clearly shows the importance of time delay on HIV dynamics under the influence of antiretroviral drug treatment. By numerical simulations, we observed that increasing the combination drug efficacy can increase the number of healthy $CD4^+$ T-cells and decrease the number of the infectious virions. We note that the models studied in [7,23] are the special case of system (1) with $\tau = 0$. In comparison to [5], where a Hopf bifurcation was not found in a realistic parameter space, we employ a simpler version of logistic growth. However, if we use an identical logistic growth term as that in [5] we find that our conclusion of the existence of a Hopf bifurcation with biologically realistic parameters remains true.

In the majority of existing mathematical models, as in our model, the treatment effect is assumed to be constant. However, in reality, the effect of antiviral treatment varies with time. Some mathematical models have been developed to study the effects of pharmacokinetic of drug therapies [8,13,17,30]. In future work, we propose to extend systems (1) and (16) to include pharmacokinetic of drug therapies as the following system:

$$\frac{d}{dt}T(t) = \lambda - dT(t) - k_I(1 - n_{rt}(t))V_I(t)T(t),$$
$$\frac{d}{dt}T^*(t) = k_I e^{-m\tau_1}(1 - n_{rt}(t-\tau_1))V_I(t-\tau_1)T(t-\tau_1) - \delta T^*(t),$$
$$\frac{d}{dt}V_I(t) = (1 - n_p(t-\tau_2))N\delta T^*(t) - cV_I(t),$$
$$\frac{d}{dt}V_{NI}(t) = n_p(t-\tau_2)N\delta T^*(t) - cV_{NI}(t).$$

The time-varying parameters are the drug efficacies of RTIs and PIs, respectively, and τ_1 and τ_2 are the pharmacological delays of RTIs and PIs, respectively. We expect that the interaction of our observed Hopf bifurcation with the periodicity of drug efficacies may lead to chaotic dynamics.

Much of the mathematical discussions can be extended to a more general system

$$\dot{x} = f(x) - xz,$$
$$\dot{y} = x(t-\tau))z(t-\tau) - y,$$
$$\dot{z} = y - z,$$

which, for example, can be used describe the interaction of caterpillars x, parasitic wasps z and parasitized caterpillars y. Therefore, our results can be applied in other settings beyond the actual application to HIV dynamics. It is possible to separate the biological and the mathematical arguments and prove the mathematical results for the above system with a much more general non-linearity f.

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