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Global properties and bifurcation analysis of an HIV-1 infection model with two target cells

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Abstract In this paper, the authors consider a four-compartmental HIV epidemiological model, which describes the interaction between HIV virus and two target cells, CD4 T cells and macrophages in vivo. It is proved that the bilinear incidence can cause the backward bifurcation, where a locally asymptotically stable disease-free equilibrium co-exists with a locally asymptotically stable endemic equilibrium when the basic reproduction number (R_0) is less than unity. It is shown that a sequence of Hopf bifurcations occur at the endemic equilibrium by choosing one parameter of the model as the bifurcation parameter. Meanwhile, the global asymptotic stabilities of the equilibria are established by constructing suitable Lyapunov functions under some conditions. Furthermore, the authors develop an extended model by incorporating with the intracellular delays and derive global asymptotic stability of the delayed model by constructing Lyapunov functions. Some numerical simulations for justifying the theoretical analysis results are also given.

Keywords HIV model · Global stability analysis · Backward bifurcation · Hopf bifurcation · Time delays

Mathematics Subject Classification 34D23 · 34D20

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1 Introduction

Human immunodeficiency virus (HIV), which mainly infects CD4 T cells and other target cells, threatens global human health and society development seriously (Perelson and Nelson 1999; Wodarz and Lloyd 1999). HIV, the cause of acquired immunodeficiency syndrome (AIDS), develops rapidly during the course of infection and the virus can evolve toward faster replication rates during late stages (Perelson and Nelson 1999; Regoes et al. 1998). There are approximately 6000 $mm^{-}3$ white blood cells in a healthy body. It is estimated that between 1 and 6% of these are macrophages and approximately 10% are CD4 T cells Kirschner (1999). Clinical studies show that most viruses come from the infected macrophages during the late stages of the disease. Macrophages play an important role as a viral source and are considered as the second target cell of HIV (Perelson and Essunger 1997; Kirschner 1999). Moreover, macrophages are also the crucial immune responses and can clear certain HIV virus (Adams and Banks 2005; Kirschner 1999).

Mathematical models have made great contributions to getting insights into HIV infection dynamics in vivo. Great efforts were made to describe the interaction between HIV and CD4 T cells (Leenheer and Smith 2003; Hossein et al. 2014; Wang and Wang 2012; Hu and Liu 2010). Some other HIV models consider the interaction process of HIV not only with CD4 T cells but also with macrophages (Elaiw 2010; Adams and Banks 2005; Wodarz and Lloyd 1999; Shu et al. 2013). Generally speaking, the models with two target cells are more suitable than the models with only CD4 T cells (Elaiw 2010; Perelson and Nelson 1999; Kirschner 1999). Particularly, Elaiw proposed one model with two target cells and obtained the global asymptotical stabilities of the equilibria of the model by means of Lyapunov functions in Elaiw (2010). However, we should consider some other features including the proliferation of CD4 T cells stimulated by HIV virus and the loss term of the virus killed by macrophages (Ouattara 2005; Xia 2007). Based on above works, we introduce a four-dimensional model which is formulated by the following system of non-linear differential equations:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \lambda_1 - \delta_1 T - \beta_1 T v + \beta_{12} T v, \tag{1}$$

$$\frac{\mathrm{d}T_m}{\mathrm{d}t} = \lambda_2 - \delta_2 T_m - \beta_2 T_m v + \beta_{22} T_m v, \tag{2}$$

$$\frac{\mathrm{d}T^*}{\mathrm{d}t} = \beta_1 T v + \beta_2 T_m v - a T^*, \tag{3}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = b T^* - c v - \beta_3 T_m v. \tag{4}$$

We briefly summarize the interpretation of different parameters in the model. T, T_m, T^*, and v represent the uninfected CD4 T cells population, the uninfected macrophages population, the infected cells population, and the virus particles population in the blood, respectively. The terms λ_1 and λ_2 are the constant sources of new CD4 T cells and macrophages, respectively. δ_1, δ_2, a, and c denote the death rates of uninfected CD4 T cells, macrophages, infected cells, and virus particles, respectively. $\beta_1 T v$ represents the infection rate of uninfected CD4 T cells by virus. Because the number of CD4 T cells is large, it is reasonable to use the bilinear incidence rate (Elaiw 2010; Wang et al. 2014). $\beta_{12} T v$ is a proliferation term due to CD4 T cells immune response. $\beta_2 T_m v$ and $\beta_{22} T_m v$ could be explained in the same manner. bT^* is the source of HIV virus population and the constant b is the production rate of HIV virus by the infected CD4 T cells and infected macrophages. $\beta_3 T_m v$ is the loss term of HIV virus since macrophages can kill virus particles. c is the loss rate of HIV virus because of nature death or other immune response. Suppose all the parameters are nonnegative. Simultaneously, we

give some brief definitions and reference values of the model parameters in Table 1. Denote $\beta_1' = \beta_1 - \beta_{12} > 0$ and $\beta_2' = \beta_2 - \beta_{22} > 0$. System (1–4) becomes the following system:

$$\frac{dT}{dt} = \lambda_1 - \delta_1 T - \beta_1' T v, \tag{5}$$

$$\frac{dT_m}{dt} = \lambda_2 - \delta_2 T_m - \beta_2' T_m v, \tag{6}$$

$$\frac{dT^*}{dt} = \beta_1 T v + \beta_2 T_m v - a T^*, \tag{7}$$

$$\frac{dv}{dt} = b T^* - c v - \beta_3 T_m v. \tag{8}$$

In this paper, we first discuss the positively invariant set, the equilibria and the backward bifurcation. By analyzing the characteristic equations, the local asymptotic stability of an endemic equilibrium of the model is established. Letting β_3 be the bifurcation parameter, we show that system (5–8) can undergo Hopf bifurcation, that is, a family of periodic solutions bifurcates from the infected equilibrium when β_3 passes through a critical value. To prove the global asymptotical stabilities of the equilibria, we construct Lyapunov functions, which are similar to those in Korobeinikov (2004), Elaiw (2010), Li et al. (2011), Tsuyoshi et al. (2015), Hossein et al. (2014), Roy and Roy (2016).

The intracellular delays, from entry into CD4 T cells or macrophages to the production of new viruses, have been incorporated into biological models in many papers (Wang et al. 2014; Regoes et al. 1998; Culshaw and Ruan 2000; Wang and Zhou 2009; Yuan et al. 2012). In this paper, we establish a delayed model based on system (5–8) to study the influence of the intracellular delays on the infection transmission. We construct Lyapunov functions to prove the global asymptotical stabilities for the delayed model (McCluskey 2010; Huang et al. 2010). It is theoretically shown that time delay has no effect on the asymptotic stability of the equilibria under some conditions.

The paper is ordered as follows: Equilibria and backward bifurcation are studied in Sect. 2. Hopf bifurcation of the model is discussed in Sect. 3. The global asymptotic stabilities of the two equilibria are considered in Sect. 4. Section 5 deals with the extended model with the intracellular delays. Finally, Sect. 6 presents the conclusions of the work.

2 Equilibria and backward bifurcation

In the absence of virus, it is easy to show that the number of CD4 T cells approaches $T_0 = \frac{\lambda_1}{\delta_1}$ and the number of macrophages approaches $T_{m0} = \frac{\lambda_2}{\delta_2}$. It is straightforward to prove the positive invariance of the nonnegative orthant R_+^4 because of biological sense by system (5–8). Furthermore, from (5) and (6), we obtain:

$$\frac{dT}{dt} \le \lambda_1 - \delta_1 T, \quad \frac{dT_m}{dt} \le \lambda_2 - \delta_2 T_m.$$

Therefore, we apply comparison lemma in Sharomi and Podder (2007) and obtain:

$$0 \le T \le \frac{\lambda_1}{\delta_1} + \left(T(0) - \frac{\lambda_1}{\delta_1}\right) e^{-\delta_1 t}, \quad 0 \le T_m \le \frac{\lambda_2}{\delta_2} + \left(T_m(0) - \frac{\lambda_2}{\delta_2}\right) e^{-\delta_2 t},$$

Table 1 Variables and parameters for the model

Variables and parameters	Range of the parameters	References
T = Uninfected CD4 T cell population		
T_m = Uninfected macrophages population		
T^* = Infected CD4 T cells and macrophages population		
v = HIV population		
λ_1 = CD4 T cells source term	0–10 cells mm^{-3} day^{-1}	Kirschner (1999), Duffin and Tullis (2002) , Xia (2007), Wang and Zhou (2009)
λ_2 = Macrophages source term	0–10 cells mm^{-3} day^{-1}	Adams and Banks (2005), Kirschner (1999)
δ_1 = The natural death rate of uninfected CD4 T cells	0.007–0.1 day^{-1}	Duffin and Tullis (2002), Culshaw and Ruan (2000), Wang and Zhou (2009)
δ_2 = The natural death rate of macrophages	0.003–0.01 day^{-1}	Adams and Banks (2005), Kirschner (1999)
β_1 = The infection rate of CD4 T cells by free virus	0.00025–0.5 mm^3 day^{-1}	Kirschner (1999), Culshaw and Ruan (2000), Wang and Zhou (2009)
β_2 = The infection rate of macrophages becomes by free virus	2×10^{-6} –0.1 $mm^3 day^{-1}$	Adams and Banks (2005), Kirschner (1999)
β_{12} = The proliferation rate of CD4 T cells	2×10^{-5} mm^3 day^{-1}	Kirschner (1999), Wang and Zhou (2009)
β_{22} = The proliferation rate of macrophages	2.5×10^{-7} mm^3 day^{-1}	Kirschner (1999)
a = The natural death rate of infected CD4 T cells and macrophages	0.2–0.5 day^{-1}	Culshaw and Ruan (2000), Wang and Zhou (2009)
b = The replication rate of infected CD4 T and macrophages	10–1000 day^{-1}	Kirschner (1999), Wang and Zhou (2009)
c = The clearance rate of HIV particles	2.4–3 day^{-1}	Duffin and Tullis (2002), Culshaw and Ruan (2000), Wang and Zhou (2009)
β_3 = The killed rate of HIV particles by macrophages	7.4×10^{-4}-0.05 mm^3 day^{-1}	Kirschner (1999)

where $T(0)$, $T_m(0)$ are the initial conditions. It can be seen that the uninfected CD4 T cells and macrophages are always bounded. For simplicity, we may take

$$x = \frac{\beta_1}{\beta_1'}T + \frac{\beta_2}{\beta_2'}T_m + T^*,\ \delta = \min\left\{\frac{\beta_1\delta_1}{\beta_1'}, \frac{\beta_2\delta_2}{\beta_2'}, a\right\},\ \text{and}\ \varpi = \frac{\beta_1\beta_2'\lambda_1 + \beta_1'\beta_2\lambda_2}{\beta_1'\beta_2'}.$$

From system (5-8), we have,

$$\frac{\mathrm{d}x}{\mathrm{d}t} \le \varpi - \delta x.$$

Therefore, T^* is bounded. From (8), we know that v is upper bounded too, say by $M = \frac{b\varpi}{c\delta}$. Define the region,

$$P = \{(T, T_m, T^*, v) \in R_+^4 : 0 \le T \le T_0, 0 \le T_m \le T_{m0}, x \le \frac{\varpi}{\delta}, v \le M\}.$$

Then P is positively invariant with respect to system (5–8). Any solution of system (5–8) with initial point in P will stay in P. Furthermore, if $T > T_0$ and $T_m > T_{m0}$, either the solution of system (5-8) enters P in finite time, or T approaches T_0 and T_m approaches T_{m0} asymptotically. Thus, P attracts all solutions in nonnegative orthant R_+^4. This leads to the following result:

Proposition 1 *The region P is positively invariant and attracting in nonnegative orthant R_+^4 for system (5–8).*

Next, we focus the dynamics behavior of system (5–8) in P. There always exists a disease-free equilibrium $E_0(T_0, T_{m0}, 0, 0)$, which represents the state with the absence of virus. The Jacobian matrix of system (5–8) at E_0 is given as

$$J(E_0) = \begin{pmatrix} -\delta_1 & 0 & 0 & -\beta_1'\frac{\lambda_1}{\delta_1} \\ 0 & -\delta_2 & 0 & -\beta_2'\frac{\lambda_2}{\delta_2} \\ 0 & 0 & -a & \beta_1\frac{\lambda_1}{\delta_1} + \beta_2\frac{\lambda_2}{\delta_2} \\ 0 & 0 & b & -c - \beta_3\frac{\lambda_2}{\delta_2} \end{pmatrix}$$

with the characteristic equation

$$(\lambda+\delta_1)(\lambda+\delta_2)\left[\lambda^2 + \left(a + c + \beta_3\frac{\lambda_2}{\delta_2}\right)\lambda + \frac{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3}{\delta_1\delta_2}\left(1 - \frac{\lambda_1 b\beta_1\delta_2 + \lambda_2\delta_1 b\beta_2}{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3}\right)\right] = 0.$$

According to the fact $|J(E_0)| = 0$, it follows that $\lambda_1 b\beta_1\delta_2 + \lambda_2\delta_1 b\beta_2 = ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3$. So, we define the basic reproduction number as

$$R_0 = \frac{\lambda_1 b\beta_1\delta_2 + \lambda_2\delta_1 b\beta_2}{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3},$$

which represents the average number of secondary cases that one infected case can generate. It can be easily verified that, E_0 is locally asymptotically stable when $R_0 < 1$ and is unstable when $R_0 > 1$ from the characteristic equation.

When $a\beta_3 = b\beta_2$, system (5–8) has no endemic equilibrium if $R_0 \le 1$ and has only one endemic equilibrium $\bar{E}_1(\bar{T}_1, \bar{T}_{m1}, \bar{T^*}_1, \bar{v}_1)$ if $R_0 > 1$, where

$$\bar{T}_1 = \frac{ac}{b\beta_1},\quad \bar{T}_{m1} = \frac{\lambda_2}{\delta_2 + \beta_2'\bar{v}_1},\quad \bar{T^*}_1 = \frac{ac\bar{v}_1}{b} + \beta_3\bar{T}_{m1}\bar{v}_1,\quad \text{and}\ \bar{v}_1 = \frac{\lambda_1 b\beta_1 - ac\delta_1}{\beta_1' ac}.$$

When $a\beta_3 \neq b\beta_2$, it can be computed that $v \neq 0$ satisfies

$$\frac{b\beta_1\lambda_1}{\delta_1+\beta_1' v}+\frac{\lambda_2(b\beta_2-a\beta_3)}{\delta_2+\beta_2' v}=ac,$$

which is equivalent to the quadratic equation

$$pv^2+qv+r=0, \tag{9}$$

where

$$p=ac\beta_1'\beta_2',\ q=(ac\delta_1\beta_2'+ac\delta_2\beta_1'+\lambda_2 a\beta_1'\beta_3-\lambda_2 b\beta_1'\beta_2-\lambda_1 b\beta_1\beta_2'),$$
$$r=(ac\delta_1\delta_2+\lambda_2\delta_1 a\beta_3)(1-R_0).$$

Therefore, we obtain the following result:

Proposition 2 *When $a\beta_3 \neq b\beta_2$, system (5–8) has:*

(1) *a unique endemic equilibrium if $R_0 > 1$;*
(2) *a unique endemic equilibrium if $q < 0$, and $R_0 = 1$ or $q^2 - 4pr = 0$;*
(3) *two endemic equilibria if $R_0 < 1$, $q < 0$ and $q^2 - 4pr > 0$;*
(4) *no endemic equilibrium otherwise.*

Item (3) in Proposition 2 indicates the possibility of backward bifurcation when $R_0 < 1$ (Sharomi and Podder 2007; Zhang and Liu 2008; Feng and Castillo-Chavez 2000). To verify the existence of backward bifurcation, we let the discriminant $q^2 - 4pr$ be 0 and solve the equation in term of R_0. We obtain

$$R_0^c = 1-\frac{q^2}{4ac\beta_1'\beta_2'(ac\delta_1\delta_2+\lambda_2\delta_1 a\beta_3)}.$$

It can be shown that backward bifurcation occurs for the values of R_0 if $R_0^c < R_0 < 1$. We explore this phenomenon via numerical simulations and use the following parameter values: $\lambda_1 = 8$; $\lambda_2 = 3$; $\delta_1 = 0.008$; $\delta_2 = 0.002$; $\beta_1' = 0.000012$; $\beta_2' = 0.0000211$; $\beta_1 = 0.0002$; $\beta_2 = 0.00025$; $a = 0.48$; $b = 50$; $c = 4.3$; $\beta_3 = 0.05$ (Kirschner 1999; Lu and Huang 2014; Xia 2007). Then, we obtain $R_0^c = 0.2321$, $R_0 = 0.7553$ and $R_0^c < R_0 < 1$. It is clear that system (5–8) has a disease-free equilibrium $E_0(1000, 1500, 0, 0)$ and two endemic equilibria, $\hat{E}_1(278.5310, 78.0510, 283.2904, 1.7268 \times 10^3)$ and $\check{E}_1(801.4765, 547.0186, 104.5313, 165.1315)$. The simulations depicted in Fig. 1 show that E_0 and $\hat{E}_1$ are locally asymptotically stable and $\check{E}_1$ is unstable. As a result, a stable endemic equilibrium co-exists with a stable disease-free equilibrium for system (5–8) if $R_0 < 1$. A bifurcation diagram is shown in Fig. 2. The above discussion is summarized below.

Theorem 1 *System (5–8) exhibits backward bifurcation when $q < 0$, $q^2 - 4pr > 0$, and $R_0^c < R_0 < 1$.*

It should be noted that the term $\beta_3 T_m v$ plays an important role on the backward bifurcation. The phenomenon of backward bifurcation has been established in many papers (Sharomi and Podder 2007; Qesmi and Wu 2010; Feng and Castillo-Chavez 2000). It is worth stating that bilinear incidence in our model also can exhibit backward bifurcation (Hadeler and Driessche 1997; Wang and Wang 2012). This phenomenon has an important influence to control the disease. The existence of multiple endemic equilibria indicates that the asymptotical behavior of system (5–8) should depend on initial conditions. It is not enough for the eradication of the disease if $R_0 < 1$. Therefore, it is equally important to identify possible backward bifurcation.

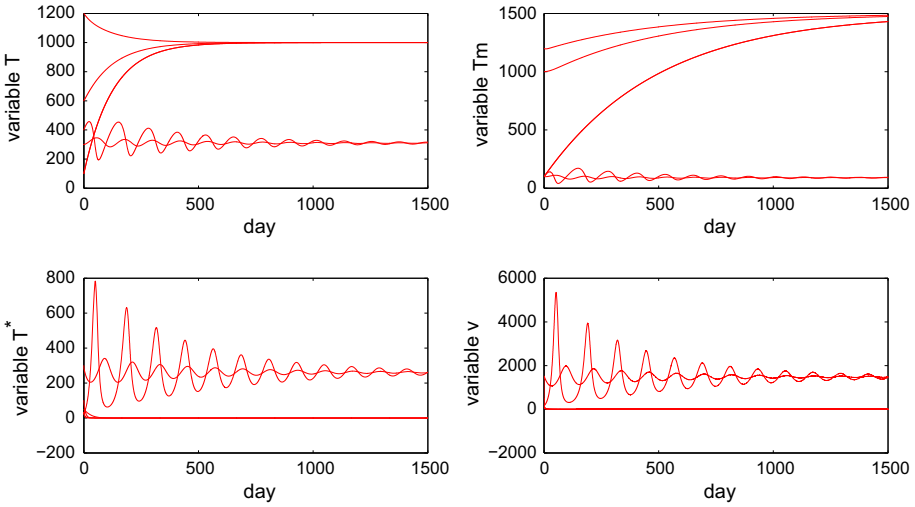

Fig. 1 Simulations of system (5–8). We choose several different initial conditions

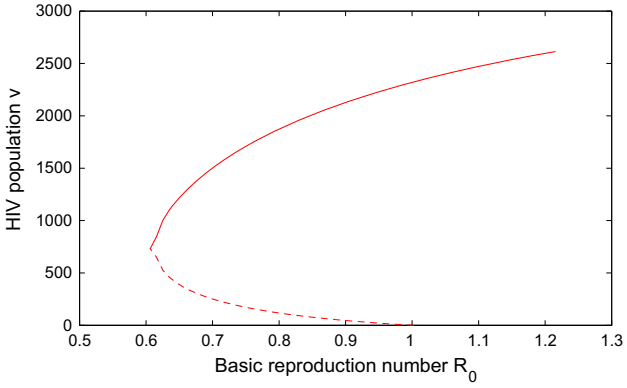

Fig. 2 Backward bifurcation of the endemic equilibria. The solid line and dashed line stand for stable equilibrium and unstable equilibrium, respectively

3 Existence of Hopf bifurcation at the endemic equilibrium

When $R_0 > 1$ and $a\beta_3 \neq b\beta_2$, it is easy to derive that system (5–8) has a unique endemic equilibrium $\tilde{E}_1(\tilde{T}_1, \tilde{T}_{m1}, \tilde{T}_1^*, \tilde{v}_1)$, where

$$\tilde{T}_1 = \frac{\lambda_1}{\delta_1 + \beta_1'\tilde{v}_1}, \tilde{T}_{m1} = \frac{\lambda_2}{\delta_2 + \beta_2'\tilde{v}_1}, \tilde{T}_1^* = \frac{\beta_1\tilde{T}_1\tilde{v}_1 + \beta_2\tilde{T}_{m1}\tilde{v}_1}{a}, \tilde{v}_1 = \frac{-q + \sqrt{q^2 - 4pr}}{2p}.$$

Therefore when $R_0 > 1$, we always have one endemic equilibrium $E_1(T_1, T_{m1}, T_1^*, v_1)$, where $E_1 = \bar{E}_1$ if the condition $a\beta_3 = b\beta_2$ is satisfied and $E_1 = \tilde{E}_1$ if the condition $a\beta_3 \neq b\beta_2$ is satisfied. The characteristic equation corresponding to E_1 is given by

$$\lambda^4 + a_1\lambda^3 + a_2\lambda^2 + a_3\lambda + a_4 = 0, \tag{10}$$

where

$$
\begin{aligned}
a_1 = a_1(\beta_3) &= \delta_1 + \beta_1' v_1 + \delta_2 + \beta_2' v_1 + a + c + \beta_3 T_{m1},\\
a_2 = a_2(\beta_3) &= (\delta_1 + \beta_1' v_1)(\delta_2 + \beta_2' v_1) + (\delta_1 + \beta_1' v_1\\
&\quad + \delta_2 + \beta_2' v_1)(a + c + \beta_3 T_{m1}) - \beta_2' \beta_3 T_{m1} v_1,\\
a_3 = a_3(\beta_3) &= (\delta_1 + \beta_1' v_1)(\delta_2 + \beta_2' v_1)(a + c + \beta_3 T_{m1}) + b\beta_2' \beta_2 T_{m1} v_1 + b\beta_1' T_1 \beta_1 v_1\\
&\quad - \beta_2' \beta_3 T_{m1} v_1 (a + \delta_1 + \beta_1' v_1),\\
a_4 = a_4(\beta_3) &= b\beta_2' \beta_2 T_{m1} v_1 (\delta_1 + \beta_1' v_1) + b\beta_1' \beta_1 T_1 v_1 (\delta_2 + \beta_2' v_1)\\
&\quad - \beta_2' \beta_3 T_{m1} v_1 a (\delta_1 + \beta_1' v_1).
\end{aligned}
$$

By the Routh–Hurwitz criterion, it follows that all eigenvalues of Eq. (10) have negative real parts if and only if

$$a_1 > 0,\ a_4 > 0,\ a_1 a_2 > a_3,\ \text{and}\ a_3(a_1 a_2 - a_3) > a_1^2 a_4.$$

By simply calculating, we derive that $a_1 > 0, a_2 > 0$, and $a_1 a_2 > a_3$. Moreover, when $a\beta_3 = b\beta_2$, we can obtain $a_4 > 0$. So we derive the following proposition:

Proposition 3 *When $R_0 > 1$, the infected equilibrium E_1 of system (5–8) is locally asymptotically stable if*

$$a_4 > 0,\quad a_3(a_1 a_2 - a_3) > a_1^2 a_4. \tag{11}$$

In the following, we discuss the conditions for which E_1 enters into Hopf bifurcation.

Theorem 2 *Suppose $a_3 > 0, a_4 > 0$ and $R_0 > 1$. If there exists a critical value $\beta_{30} > 0$ such that $\phi(\beta_{30}) = 0$ and $\phi'(\beta_{30}) \neq 0$, Hopf bifurcation occurs at E_1 of system (5–8) when β_3 passes through β_{30}. That is, periodic solutions bifurcate from E_1.*

Proof Suppose $a_3 > 0$ and $a_4 > 0$. Define the continuously differentiable function of β_3:

$$\phi(\beta_3) = a_3(\beta_3)(a_1(\beta_3)a_2(\beta_3) - a_3(\beta_3)) - a_1^2(\beta_3)a_4(\beta_3).$$

If there exists $\phi(\beta_{30}) = 0$, Eq. (10) becomes

$$(\lambda^2 + \frac{a_3(\beta_{30})}{a_1(\beta_{30})})(\lambda^2 + a_1(\beta_{30})\lambda + \frac{a_1(\beta_{30})a_4(\beta_{30})}{a_3(\beta_{30})}) = 0. \tag{12}$$

It is easy to show that (12) has a pair of purely imaginary roots and either another pair of complex roots with negative real parts or two negative real roots. Since $\phi(\beta_3)$ is one continuous function of all its roots in β_3, we can derive that Eq. (10) has a pair of complex conjugate roots in a neighborhood of β_{30}, denoted by λ_1 and λ_2. They are conjugated purely imaginary roots at $\beta_3 = \beta_{30}$. The transversality condition (Roy et al. 2017; Greenhalgh 1997; Liu 1994)

$$\frac{\mathrm{d}(Re\lambda_1(\beta_3))}{\mathrm{d}\beta_3}|_{\beta_{30}} \neq 0$$

is equivalent to

$$\phi'(\beta_{30}) = \frac{\mathrm{d}(\phi(\beta_3))}{\mathrm{d}\beta_3}|_{\beta_{30}} \neq 0.$$

This completes the proof.

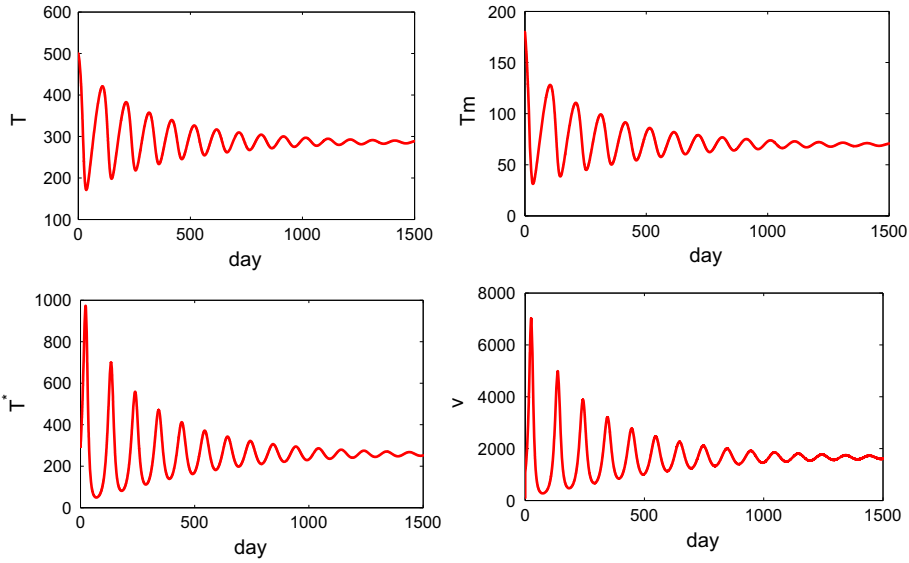

Fig. 3 Simulations of system (5–8). We choose $\beta_3 = 0.05 < \beta_{30}$. E_1 is locally asymptotically stable

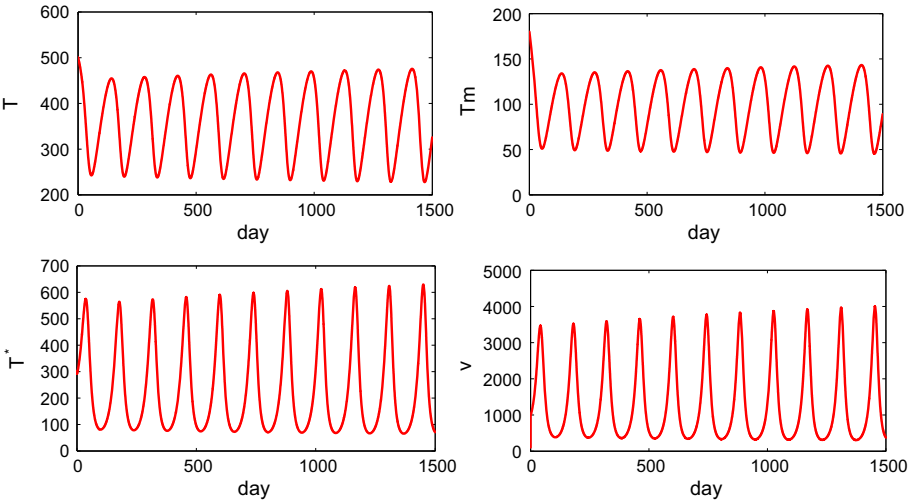

Fig. 4 Simulations of system (5–8). We choose $\beta_3 = 0.058 > \beta_{30}$. The bifurcating periodic solutions from E_1 occur

We present some numerical results of system (5–8) for different values of β_3 and use the parameter values as the same as in Sect. 2 except for $\delta_2 = 0.008$ and β_3. Let initial values be (500, 200, 300, 100). We obtain $\beta_{30} \approx 0.057$ from $\phi(\beta_3) = 0$. Numerical simulations show that E_1 is locally asymptotically stable if $\beta_3 = 0.05 < \beta_{30}$ (see Fig. 3). When $\beta_3 = \beta_{30}$, E_1 loses its stability and Hopf bifurcation occurs. When $\beta_3 = 0.058 > \beta_{30}$, E_1 becomes unstable and there are periodic solutions surrounding E_1 (see Fig. 4).

4 Global stability of two equilibria

Theorem 3 *If $R_0 \le 1$ and $b\beta_2 \ge a\beta_3$, the disease-free equilibrium E_0 of system (5–8) is globally asymptotically stable in P.*

Proof Define a Lyapunov function

$$L_1 = \frac{\beta_1}{\beta_1'}\left(T - T_0 - T_0 \ln \frac{T}{T_0}\right) + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\left(T_m - T_{m0} - T_{m0} \ln \frac{T_m}{T_{m0}}\right) + T^* + \frac{a}{b}v.$$

Calculating the time derivative of L_1 along the solution of system (5–8), we obtain

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t} &= \frac{\beta_1}{\beta_1'}\left(\lambda_1 - \delta_1 T - \beta_1' T v\right)\left(1 - \frac{T_0}{T}\right)\\ &\quad + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\left(\lambda_2 - \delta_2 T_m - \beta_2' T_m v\right)\left(1 - \frac{T_{m0}}{T_m}\right)\\ &\quad + \beta_1 T v + \beta_2 T_m v - aT^* + aT^* - \frac{ac}{b}v - \frac{a\beta_3}{b}T_m v. \end{aligned} \tag{13}$$

Note that $\lambda_1 = \delta_1 T_0$ and $\lambda_2 = \delta_2 T_{m0}$. It follows from (13) that

$$\begin{aligned}\frac{\mathrm{d}L_1}{\mathrm{d}t} &= \frac{\beta_1\lambda_1}{\beta_1'}\left(2 - \frac{T}{T_0} - \frac{T_0}{T}\right)\\ &\quad + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\lambda_2\left(2 - \frac{T_m}{T_{m0}} - \frac{T_{m0}}{T_m}\right) + \frac{R_0 - 1}{\delta_1\delta_2 b(ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3)}v.\end{aligned}$$

Apparently, we can obtain $2 - \frac{T}{T_0} - \frac{T_0}{T} \le 0$ and $2 - \frac{T_m}{T_{m0}} - \frac{T_{m0}}{T_m} \le 0$. So we obtain $\frac{\mathrm{d}L_1}{\mathrm{d}t} \le 0$ if $R_0 \le 1$. The largest compact invariant set in $\{(T, T_m, T^*, v) \in P : \frac{\mathrm{d}L_1}{\mathrm{d}t} = 0\}$ is the singleton $\{E_0\}$. Using the Lasalle invariant principle, we derive that all solutions with initial conditions in P converge to E_0. We complete the proof.

From Theorem 3, we obtain that the virus can be cleared under some conditions. In addition, we easily derive that system (5–8) does not exhibit backward bifurcation if $b\beta_2 \ge a\beta_3$.

Theorem 4 *If $R_0 > 1$, $b\beta_2 > a\beta_3$ and $b\lambda_1\beta_1\beta_2'\beta_3 \le \beta_1'(b\beta_2 - a\beta_3)(c\delta_2 - \lambda_2\beta_3)$, the endemic equilibrium E_1 of system (5–8) is globally asymptotically stable in P.*

Proof We consider a Lyapunov function

$$\begin{aligned}L_2 &= \frac{\beta_1}{\beta_1'}\left(T - T_1 - T_1 \ln \frac{T}{T_1}\right) + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\left(T_m - T_{m1} - T_{m1} \ln \frac{T_m}{T_{m1}}\right)\\ &\quad + \left(T^* - T_1^* - T_1^* \ln \frac{T^*}{T_1^*}\right) + \frac{a}{b}\left(v - v_1 - v_1 \ln \frac{v}{v_1}\right).\end{aligned}$$

Calculating the time derivative of L_1 along the solution of system (5–8), we obtain

$$\begin{aligned}\frac{\mathrm{d}L_2}{\mathrm{d}t} &= \frac{\beta_1}{\beta_1'}\left(\lambda_1 - \delta_1 T - \beta_1' T v\right)\left(1 - \frac{T_1}{T}\right) + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\left(\lambda_2 - \delta_2 T_m - \beta_2' T_m v\right)\left(1 - \frac{T_{m1}}{T_m}\right)\\ &\quad + \left(\beta_1 T v + \beta_2 T_m v - aT^*\right)\left(1 - \frac{T_1^*}{T^*}\right) + \frac{a}{b}\left(bT^* - cv - \beta_3 T_m v\right)\left(1 - \frac{v_1}{v}\right).\end{aligned}$$

From system (5–8), we obtain that

$$\lambda_1 = \delta_1 T_1 + \beta_1' T_1 v_1, \lambda_2 = \delta_2 T_{m1} + \beta_2' T_{m1} v_1,$$
$$aT_1^* = \beta_1 T_1 v_1 + \beta_2 T_{m1} v_1, b(\beta_1 T_1 + \beta_2 T_{m1}) = ac + a\beta_3 T_{m1}.$$

Then we get

$$\frac{\mathrm{d}L_2}{\mathrm{d}t} = \frac{\beta_1\delta_1 T_1}{\beta_1'}\left(2 - \frac{T}{T_1} - \frac{T_1}{T}\right) + \left(\frac{(b\beta_2 - a\beta_3)\,\delta_2 T_{m1}}{b\beta_2'} - \frac{a\beta_3 T_{m1} v_1}{b}\right)\left(2 - \frac{T_m}{T_{m1}} - \frac{T_{m1}}{T_m}\right)$$
$$+ \beta_1 T_1 v_1\left(3 - \frac{T_1}{T} - \frac{T_1^* T v}{T^* T_1 v_1} - \frac{T^* v_1}{T_1^* v}\right) + \beta_2 T_{m1} v_1\left(3 - \frac{T_{m1}}{T} - \frac{T_1^* T v}{T^* T_{m1} v_1} - \frac{T^* v_1}{T_1^* v}\right).$$

If $b\beta_2 > a\beta_3$ and $b\lambda_1\beta_1\beta_2'\beta_3 \le \beta_1'(b\beta_2 - a\beta_3)(c\delta_2 - \lambda_2\beta_3)$, we can obtain

$$v_1 < \frac{b\lambda_1\beta_1\beta_2' + \lambda_2\beta_1'\,(b\beta_2 - a\beta_3)}{ac\beta_1'\beta_2'} < \frac{(b\beta_2 - a\beta_3)\,\delta_2}{a\beta_3\beta_2'}.$$

Then, we have:

$$\frac{(b\beta_2 - a\beta_3)\,\delta_2}{b\beta_2'} - \frac{a\beta_3 v_1}{b} > 0.$$

Therefore, the endemic equilibrium E_1 is globally asymptotically stable by the similar analysis in Theorem 3. Especially, we know E_1 is globally asymptotically stable when $\beta_3 = 0$. The proof is completed.

5 Analysis of the delayed model

In this section, we consider one differential equation model with a time delay, which denotes the time for the viruses from entry into CD4 T cells or macrophages to the production of new viruses. The model is given as follows:

$$\frac{\mathrm{d}T}{\mathrm{d}t} = \lambda_1 - \delta_1 T - \beta_1' T v, \tag{14}$$
$$\frac{\mathrm{d}T_m}{\mathrm{d}t} = \lambda_2 - \delta_2 T_m - \beta_2' T_m v, \tag{15}$$
$$\frac{\mathrm{d}T^*}{\mathrm{d}t} = \beta_1 T(t-\tau)v(t-\tau) + \beta_2 T_m(t-\tau)v(t-\tau) - aT^*, \tag{16}$$
$$\frac{\mathrm{d}v}{\mathrm{d}t} = bT^* - cv - \beta_3 T_m v. \tag{17}$$

The positive constant τ represents the length of the delay. All the other parameters are the same as in system (5–8). The initial conditions are:

$$T(t) = \psi_1(t) \ge 0, T_m(t) = \psi_2(t) \ge 0, T^*(0) = \psi_3 \ge 0, v(t) = \psi_4(t) \ge 0, t \in [-\tau, 0],$$

where ψ_3 is a given constant, and $\psi_1, \psi_2, \psi_4 \in C([-\tau, 0], R_+)$ with $R_+ = [0, \infty)$.

Being similar to the analysis of system (5–8), we find system (14–17) always has one disease-free equilibrium $E_0(T_0, T_{m0}, 0, 0)$ and a unique positive equilibrium $E_1(T_1, T_{m1}, T_1^*, v_1)$ if $R_0 > 1$, where $T_0, T_{m0}, T_1, T_{m1}, T_1^*$, and v_1 are the same as in Sect. 2.

Let $\bar{E}(\bar{T}, \bar{T_m}, \bar{T^*}, \bar{v})$ be any equilibrium of system (14–17). Denote $X = (T, T_m, T^*, v)^T$. The linearized system in vector form is given as:

$$\frac{\mathrm{d}X}{\mathrm{d}t} = A_1 X + A_2 X(t-\tau),$$

where A_1 and A_2 are 4×4 matrices given by:

$$A_1 = \begin{pmatrix} -\delta_1 - \beta_1' \bar{v} & 0 & 0 & -\beta_1' \bar{T} \\ 0 & -\delta_2 - \beta_2' \bar{v} & 0 & -\beta_2' \bar{T_m} \\ 0 & 0 & -a & 0 \\ 0 & -\beta_3 \bar{v} & b & -c - \beta_3 \bar{T_m} \end{pmatrix}$$

and

$$A_2 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ \beta_1 \bar{v} & \beta_2 \bar{v} & 0 & \beta_1 \bar{T} + \beta_2 \bar{T_m} \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

The characteristic equation for system (14–17) is given by:

$$\det(\lambda I - A_1 - A_2 e^{-\lambda\tau}) = 0.$$

Theorem 5 *The disease-free equilibrium E_0 of system (14–17) is locally asymptotically stable for all $\tau \geq 0$ when $R_0 < 1$, and is unstable when $R_0 > 1$.*

Proof For the disease-free equilibrium E_0, the characteristic equation reduces to,

$$(\lambda + \delta_1)(\lambda + \delta_2)\left(\lambda^2 + \left(a + c + \beta_3 \frac{\lambda_2}{\delta_2}\right)\lambda + \frac{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3}{\delta_1\delta_2}\left(1 - R_0 e^{-\lambda\tau}\right)\right) = 0. \tag{18}$$

When $\tau = 0$, we know that E_0 is locally asymptotically stable if $R_0 < 1$ and is unstable if $R_0 > 1$ from former analysis. In the following, we discuss the case of $\tau \neq 0$. Equation (18) has two negative solutions $\lambda_1 = -\delta_1$ and $\lambda_2 = -\delta_2$. The other eigenvalues of Eq. (18) satisfy the following transcendental equation:

$$\lambda^2 + \left(a + c + \beta_3 \frac{\lambda_2}{\delta_2}\right)\lambda + \frac{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3}{\delta_1\delta_2}\left(1 - R_0 e^{-\lambda\tau}\right) = 0. \tag{19}$$

Denote,

$$F(\lambda) = \lambda^2 + \left(a + c + \beta_3 \frac{\lambda_2}{\delta_2}\right)\lambda + \frac{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3}{\delta_1\delta_2}\left(1 - R_0 e^{-\lambda\tau}\right).$$

For the case of $R_0 > 1$, we obtain $F(0) < 0$ and $F(\lambda) \to +\infty$ ($\lambda \to +\infty$). Thus, Eq. (19) has at least one positive real root. So E_0 is unstable. For the case of $R_0 < 1$, we assume that $\lambda = i\omega$, $\omega > 0$. Substituting $\lambda = i\omega$ into (19), we have:

$$-\omega^2 + \left(a + c + \beta_3 \frac{\lambda_2}{\delta_2}\right) i\omega + \frac{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3}{\delta_1\delta_2} - \frac{\lambda_1 b\beta_1\delta_2 + \lambda_2\delta_1 b\beta_2}{\delta_1\delta_2} cos(\omega\tau) + i\frac{\lambda_1 b\beta_1\delta_2 + \lambda_2\delta_1 b\beta_2}{\delta_1\delta_2} sin(\omega\tau) = 0.$$

We separate the real and imaginary parts and obtain,

$$-\omega^2 + \frac{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3}{\delta_1\delta_2} = \frac{\lambda_1 b\beta_1\delta_2 + \lambda_2\delta_1 b\beta_2}{\delta_1\delta_2} cos(\omega\tau), \tag{20}$$

$$\left(a + c + \beta_3\frac{\lambda_2}{\delta_2}\right)\omega = -\frac{\lambda_1 b\beta_1\delta_2 + \lambda_2\delta_1 b\beta_2}{\delta_1\delta_2} sin(\omega\tau). \tag{21}$$

Adding the squared Eqs. (20) and (21), it follows that,

$$\omega^4 + \left(a^2 + \left(c + \beta_3\frac{\lambda_2}{\delta_2}\right)^2\right)\omega^2 + \left(\frac{ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3}{\delta_1\delta_2}\right)^2 - \left(\frac{\lambda_1 b\beta_1\delta_2 + \lambda_2\delta_1 b\beta_2}{\delta_1\delta_2}\right)^2 = 0. \tag{22}$$

If $R_0 < 1$, Eq. (22) has no positive real roots and there is no $i\omega(\omega \neq 0)$ satisfying Eq. (18). Equation (18) has roots with positive real parts if and only if it has purely imaginary roots by Rouché's theorem (Culshaw and Ruan 2000). For all values of the delay $\tau \geq 0$, all eigenvalues of Eq. (18) have negative real parts. This completes the proof.

Theorem 6 *If $R_0 \leq 1$ and $b\beta_2 \geq a\beta_3$, the disease-free equilibrium E_0 of system (14–17) is globally asymptotically stable for any time delay $\tau \geq 0$.*

Proof Define a Lyapunov function L_3 as follows:

$$L_3 = \frac{\beta_1}{\beta_1'}\left(T - T_0 - T_0 \ln\frac{T}{T_0}\right) + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\left(T_m - T_{m0} - T_{m0}\ln\frac{T_m}{T_{m0}}\right) + T^* + \frac{a}{b}v + U_1(t),$$

where

$$U_1(t) = \int_{t-\tau}^{t} [\beta_1 T(s)v(s) + \beta_2 T_m(s)v(s)]\,\mathrm{d}s.$$

We calculate the time derivative of $U_1(t)$,

$$\frac{\mathrm{d}U_1(t)}{\mathrm{d}t} = \beta_1 T(t)v(t) + \beta_2 T_m(t)v(t) - [\beta_1 T(t-\tau)v(t-\tau) + \beta_2 T_m(t-\tau)v(t-\tau)].$$

Calculating the time derivative of L_1 along the solution of system (14-17), we obtain

$$\begin{aligned}\frac{\mathrm{d}L_3}{\mathrm{d}t} = {} & \frac{\beta_1}{\beta_1'}\left(\lambda_1 - \delta_1 T - \beta_1' T v\right)\left(1 - \frac{T_0}{T}\right) + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\left(\lambda_2 - \delta_2 T_m - \beta_2' T_m v\right)\left(1 - \frac{T_{m0}}{T_m}\right) \\ & + \beta_1 T(t-\tau)v(t-\tau) + \beta_2 T_m(t-\tau)v(t-\tau) - aT^* + aT^* - \frac{ac}{b}v - \frac{a\beta_3}{b}T_m v \\ & + \beta_1 T(t)v(t) + \beta_2 T_m(t)v(t) - [\beta_1 T(t-\tau)v(t-\tau) + \beta_2 T_m(t-\tau)v(t-\tau)].\end{aligned}$$

Note that $\lambda_1 = \delta_1 T_0$ and $\lambda_2 = \delta_2 T_{m0}$. Thus, we obtain

$$\begin{aligned}\frac{\mathrm{d}L_3}{\mathrm{d}t} = {} & \frac{\beta_1\lambda_1}{\beta_1'}\left(2 - \frac{T}{T_0} - \frac{T_0}{T}\right) \\ & + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\lambda_2\left(2 - \frac{T_m}{T_{m0}} - \frac{T_{m0}}{T_m}\right) + \frac{R_0 - 1}{\delta_1\delta_2 b\,(ac\delta_1\delta_2 + \lambda_2\delta_1 a\beta_3)}v.\end{aligned}$$

So, it follows that $\frac{\mathrm{d}L_3}{\mathrm{d}t} \leq 0$ if $R_0 \leq 1$ and $b\beta_2 \geq a\beta_3$. It is clear that E_0 is stable. Furthermore, the largest compact invariant set is the singleton $\{E_0\}$. Accordingly, it follows

from LaSalle invariance principle that E_0 is globally asymptotically stable. We complete the proof.

The characteristic equation for the linearized system around the infected equilibrium E_1 is given by

$$\lambda^4 + m_1\lambda^3 + m_2\lambda^2 + m_3\lambda + m_4 + (m_5\lambda^2 + m_6\lambda + m_7)e^{-\lambda\tau} = 0, \tag{23}$$

where

$$\begin{aligned}
m_1 &= \delta_1 + \beta_1' v_1 + \delta_2 + \beta_2' v_1 + a + c + \beta_3 T_{m1},\\
m_2 &= \left(\delta_1 + \beta_1' v_1\right)\left(\delta_2 + \beta_2' v_1\right) + \left(\delta_1 + \beta_1' v_1 + \delta_2 + \beta_2' v_1\right)(a + c + \beta_3 T_{m1})\\
&\quad + a\,(c + \beta_3 T_{m1}) - \beta_2'\beta_3 T_{m1} v_1,\\
m_3 &= \left(\delta_1 + \beta_1' v_1\right)\left(\delta_2 + \beta_2' v_1\right)(a + c + \beta_3 T_{m1}) + \left(\delta_1 + \beta_1' v_1 + \delta_2 + \beta_2' v_1\right) a\,(c + \beta_3 T_{m1})\\
&\quad - \beta_2'\beta_3 T_{m1} v_1\left(a + \delta_1 + \beta_1' v_1\right),\\
m_4 &= \left(\delta_1 + \beta_1' v_1\right)\left(\delta_2 + \beta_2' v_1\right) a\,(c + \beta_3 T_{m1}) - \beta_2'\beta_3 T_{m1} v_1 a\left(\delta_1 + \beta_1' v_1\right),\\
m_5 &= -b\,(\beta_1 T_1 + \beta_2 T_{m1}) = -a\,(c + \beta_3 T_{m1}),\\
m_6 &= b\beta_2' T_{m1}\beta_2 v_1 + b\beta_1' T_1\beta_1 v_1 - a\,(c + \beta_3 T_{m1})\left(\delta_1 + \beta_1' v_1 + \delta_2 + \beta_2' v_1\right),\\
m_7 &= b\beta_2' T_{m1}\beta_2 v_1\left(\delta_1 + \beta_1' v_1\right) + b\beta_1'\beta_1 T_1 v_1\left(\delta_2 + \beta_2' v_1\right)\\
&\quad - a\,(c + \beta_3 T_{m1})\left(\delta_1 + \beta_1' v_1\right)\left(\delta_2 + \beta_2' v_1\right).
\end{aligned}$$

Substituting $\lambda = i\omega$ with $\omega > 0$ into (23) and separating the real and imaginary parts, we yield

$$\begin{aligned}
\omega^4 - m_2\omega^2 + m_4 &= (m_5\omega^2 - m_7)\cos\omega\tau - m_6\omega\sin\omega\tau,\\
-m_1\omega^3 + m_3\omega &= (m_7 - m_5\omega^2)\sin\omega\tau - m_6\omega\cos\omega\tau.
\end{aligned}$$

Adding up the squares of above both equations, we obtain

$$\omega^8 + p_1\omega^6 + p_2\omega^4 + p_3\omega^2 + p_4 = 0, \tag{24}$$

where

$$\begin{aligned}
p_1 &= m_1^2 - 2m_2,\ \ p_2 = m_2^2 + 2m_4 - 2m_1m_3 - m_5^2,\\
p_3 &= m_3^2 + 2m_5m_7 - 2m_2m_4 - m_6^2,\ p_4 = m_4^2 - m_7^2.
\end{aligned}$$

We put $\omega^2 = \upsilon$ into Eq. (24) and obtain a fourth degree polynomial

$$\upsilon^4 + p_1\upsilon^3 + p_2\upsilon^2 + p_3\upsilon + p_4 = 0. \tag{25}$$

By directly calculating, it is easy to show that $p_1 > 0$ and $p_4 = (m_4 - m_7)(m_4 + m_7) > 0$ if $a_4 > 0$. Furthermore, we also obtain

$$\begin{aligned}
p_2 &> \left(\delta_1 + \beta_1' v_1\right)^2\left(\delta_2 + \beta_2' v_1\right)^2 + a^2\left(\left(\delta_1 + \beta_1' v_1\right)^2 + \left(\delta_2 + \beta_2' v_1\right)^2\right) > 0,\\
p_3 &= \left(\delta_1 + \beta_1' v_1\right)^2\left[\beta_2'\beta_3 T_{m1} v_1 - \left(\delta_2 + \beta_2' v_1\right)(c + \beta_3 T_{m1})\right]^2 + a^2\left(\beta_2'\beta_3 T_{m1} v_1\right)^2\\
&\quad + 2a^2\beta_2'\beta_3 T_{m1} v_1\left(\delta_1 + \beta_1' v_1\right)^2 + a^2\left(\delta_1 + \beta_1' v_1\right)^2\left(\delta_2 + \beta_2' v_1\right)^2\\
&\quad + 2a\,(c + \beta_3 T_{m1})\left(b\beta_2 T_{m1}\beta_2' v_1\left(\delta_2 + \beta_2' v_1\right) + b\beta_1 T_1\beta_1' v_1\left(\delta_1 + \beta_1' v_1\right)\right)\\
&\quad - 2a^2\left(\beta_2'\beta_3 T_{m1} v_1\right)\left(\delta_2 + \beta_2' v_1\right)(c + \beta_3 T_{m1}) - \left(b\beta_2 T_{m1}\beta_2' v_1 + b\beta_1 T_1\beta_1' v_1\right)^2.
\end{aligned}$$

If $p_3 \geq 0$, we know that Eq. (25) has no positive root. The real parts of all eigenvalues of Eq. (23) remain negative for all values of the delay $\tau > 0$. Considering the special case of $\beta_3 = 0$, we can obtain

$$p_3 \geq (\delta_1 + \beta_1' v_1)^2(\delta_2 + \beta_2' v_1)^2(a^2 + c^2) + (b\beta_2' T_{m1}\beta_2 v_1 - b\beta_1' T_2 \beta_1 v_1)^2 > 0.$$

Summarizing the above analysis, we have the following theorem.

Theorem 7 *Suppose that the conditions in* (11), $R_0 > 1$ *and* $p_3 \geq 0$ *hold, the infected equilibrium* E_1 *of system* (14–17) *is locally asymptotically stable for all* $\tau \geq 0$.

Although we introduce the delay, E_1 is also locally asymptotically stable under some conditions. Under the circumstances, system (14–17) does not undergo Hopf bifurcations.

Theorem 8 *If* $R_0 > 1$, $b\beta_2 > a\beta_3$ *and* $b\lambda_1\beta_1\beta_2'\beta_3 \leq \beta_1'(b\beta_2 - a\beta_3)(c\delta_2 - \lambda_2\beta_3)$, *the endemic equilibrium* E_1 *of system* (14–17) *is globally asymptotically stable for all* $\tau \geq 0$.

Proof We consider a Lyapunov function

$$\begin{aligned} L_4 = {} & \frac{\beta_1}{\beta_1'}\left(T - T_1 - T_1 \ln \frac{T}{T_1}\right) + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\left(T_m - T_{m1} - T_{m1} \ln \frac{T_m}{T_{m1}}\right) \\ & + \left(T^* - T_1^* - T_1^* \ln \frac{T^*}{T_1^*}\right) \\ & + \frac{a}{b}\left(v - v_1 - v_1 \ln \frac{v}{v_1}\right) + \beta_1 T_1 v_1 U_2 + \beta_2 T_{m1} v_1 U_3, \end{aligned}$$

where

$$\begin{aligned} U_2 &= \int_{t-\tau}^{t} \left[\frac{T(s)v(s)}{T_1 v_1} - 1 - \ln \frac{T(s)v(s)}{T_1 v_1}\right] \mathrm{d}s, \\ U_3 &= \int_{t-\tau}^{t} \left[\frac{T_m(s)v(s)}{T_{m1} v_1} - 1 - \ln \frac{T_m(s)v(s)}{T_{m1} v_1}\right] \mathrm{d}s. \end{aligned}$$

Calculating the time derivative of L_4 along the solution of system (14–17), we obtain

$$\begin{aligned} \frac{\mathrm{d}L_4}{\mathrm{d}t} = {} & \frac{\beta_1}{\beta_1'}\left(\lambda_1 - \delta_1 T - \beta_1' T v\right)\left(1 - \frac{T_1}{T}\right) + \frac{b\beta_2 - a\beta_3}{b\beta_2'}\left(\lambda_2 - \delta_2 T_m - \beta_2' T_m v\right)\left(1 - \frac{T_{m1}}{T_m}\right) \\ & + \left(\beta_1 T\left(t-\tau\right) v\left(t-\tau\right) + \beta_2 T_m\left(t-\tau\right) v\left(t-\tau\right) - aT^*\right)\left(1 - \frac{T_1^*}{T^*}\right) \\ & + \frac{a}{b}\left(bT^* - cv - \beta_3 T_m v\right)\left(1 - \frac{v_1}{v}\right) + \beta_1 T_1 v_1 \frac{\mathrm{d}U_2\left(t\right)}{\mathrm{d}t} + \beta_2 T_{m1} v_1 \frac{\mathrm{d}U_3\left(t\right)}{\mathrm{d}t}. \end{aligned}$$

We calculate the time derivative of $U_2(t)$ and $U_3(t)$,

$$\begin{aligned} \frac{\mathrm{d}U_2(t)}{\mathrm{d}t} &= \frac{T(t)v(t)}{T_1 v_1} - \frac{T(t-\tau)v(t-\tau)}{T_1 v_1} + \ln \frac{T(t-\tau)v(t-\tau)}{T(t)v(t)}, \\ \frac{\mathrm{d}U_3(t)}{\mathrm{d}t} &= \frac{T_m(t)v(t)}{T_m v_1} - \frac{T_m(t-\tau)v(t-\tau)}{T_{m1} v_1} + \ln \frac{T_{m1}(t-\tau)v(t-\tau)}{T_{m1}(t)v(t)}. \end{aligned}$$

From system (14–17), we obtain that

$$\begin{aligned} \lambda_1 &= \delta_1 T_1 + \beta_1' T_1 v_1, \lambda_2 = \delta_2 T_{m1} + \beta_2' T_{m1} v_1, \\ aT_1^* &= \beta_1 T_1 v_1 + \beta_2 T_{m1} v_1, b(\beta_1 T_1 + \beta_2 T_{m1}) = ac + a\beta_3 T_{m1}. \end{aligned}$$

Note that

$$\ln\frac{T(t-\tau)v(t-\tau)}{T(t)v(t)}=\ln\frac{T_1}{T(t)}+\ln\frac{T_1^*T(t-\tau)v(t-\tau)}{T^*(t)T_1v_1}+\ln\frac{T^*(t)v_1}{T_1^*v(t)},$$
$$\ln\frac{T_m(t-\tau)v(t-\tau)}{T_m(t)v(t)}=\ln\frac{T_{m1}}{T_m(t)}+\ln\frac{T_1^*T_m(t-\tau)v(t-\tau)}{T^*(t)T_{m1}v_1}+\ln\frac{T^*(t)v_1}{T_1^*v(t)}.$$

Then we yield

$$\begin{aligned}\frac{\mathrm{d}L_4}{\mathrm{d}t}=&\frac{\beta_1\delta_1T_1}{\beta_1'}\left(2-\frac{T}{T_1}-\frac{T_1}{T}\right)\\&+\left(\frac{(b\beta_2-a\beta_3)\,\delta_2T_{m1}}{b\beta_2'}-\frac{a\beta_3T_{m1}v_1}{b}\right)\left(2-\frac{T_m}{T_{m1}}-\frac{T_{m1}}{T_m}\right)\\&+\beta_1T_1v_1\left(1-\frac{T_1}{T}+\ln\frac{T_1}{T}\right)+\beta_1T_1v_1\left(1-\frac{T_1^*T\,(t-\tau)\,v\,(t-\tau)}{T^*\,(t)\,T_1v_1}\right.\\&\left.+\ln\frac{T_1^*T\,(t-\tau)\,v\,(t-\tau)}{T^*\,(t)\,T_1v_1}\right)\\&+\beta_1T_1v_1\left(1-\frac{T^*\,(t)\,v_1}{T_1^*v\,(t)}+\ln\frac{T^*\,(t)\,v_1}{T_1^*v\,(t)}\right)+\beta_2T_{m1}v_1\left(1-\frac{T_{m1}}{T_m\,(t)}+\ln\frac{T_{m1}}{T_m\,(t)}\right)\\&+\beta_2T_{m1}v_1\left(1-\frac{T_1^*T_m\,(t-\tau)\,v\,(t-\tau)}{T^*\,(t)\,T_{m1}v_1}+\ln\frac{T_1^*T_m\,(t-\tau)\,v\,(t-\tau)}{T^*\,(t)\,T_{m1}v_1}\right)\\&+\beta_2T_{m1}v_1\left(1-\frac{T^*\,(t)\,v_1}{T_1^*v\,(t)}+\ln\frac{T^*\,(t)\,v_1}{T_1^*v\,(t)}\right).\end{aligned}$$

It is known that the function $f(x)=1-x+\ln x$ is always non-positive for $x>0$, and $f(x)=0$ if and only if $x=1$. Therefore, E_1 is globally asymptotically stable by similar analysis as in Theorem 3. Especially, we know E_1 is global asymptotically stable when $\beta_3=0$. The proof is completed.

We use the parameter values in Sect. 2 except for $\beta_3=0.01$. The condition (11), $p_2>0$, and $p_3>0$ are all satisfied. We also get $R_0=3.1034>1$. It is shown that $E_1(164.3169, 40.7940, 319.2487, 1.3586\times10^3)$ is locally asymptotically stable for $\tau=1$ and $\tau=10$ via simulating results (see Fig. 5). Time delay τ does not change the stabilities of the equilibrium E_1.

6 Discussions and conclusions

In the present paper, we propose a mathematical model, which describe the interactions of HIV virus and two target cells. The model can undergo the phenomenon of backward bifurcation if $R_0<1$. Meanwhile, we find that Hopf bifurcation occurs under some conditions. By using Lyapunov functions, we obtain sufficient conditions for the global asymptotical stabilities of the equilibria. Especially, the two equilibria are globally asymptotically stable in case of $\beta_3=0$. We cannot ignore the fact that macrophages really influence dynamics behavior of HIV virus from our analysis. What is more, we establish an extended model, and derive that the local asymptotical stabilities of the uninfected and infected equilibria are independent of the size of the delay if $\beta_3=0$ by analyzing the transcendental characteristic equations. We also derive that the two equilibria are globally asymptotically stable for the delayed model under some conditions.

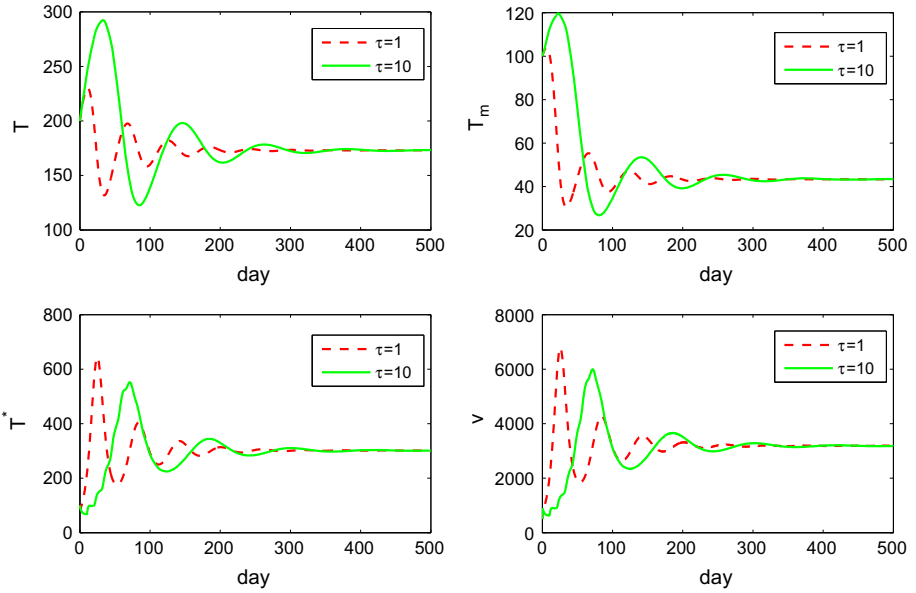

Fig. 5 Simulation of system (14–17). We choose the initial condition (200, 100, 100, 500), $\tau = 1$ and $\tau = 10$. E_1 is locally asymptotically stable

Finally, some interesting questions deserve further investigation about our model. One may consider the non-bilinear incidence rate for system (5–8). Moreover, we can study the influence of distributed delays not just discrete delays on system (14–17).

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