Communications in Mathematical Research
35(4)(2019), 301–317

Global and Bifurcation Analysis of an HIV Pathogenesis Model with Saturated Reverse Function

Liu Yong-qi[1] and Meng Xiao-ying[2]

(*1. College of Applied Mathematics, Beijing Normal University, Zhuhai, Guangdong, 519087*)

(*2. School of Statistics and Mathematics, Zhongnan University of Economics and Law, Wuhan, 430073*)

Communicated by Shi Shao-yun

Abstract: In this paper, an HIV dynamics model with the proliferation of CD4 T cells is proposed. The authors consider nonnegativity, boundedness, global asymptotic stability of the solutions and bifurcation properties of the steady states. It is proved that the virus is cleared from the host under some conditions if the basic reproduction number R_0 is less than unity. Meanwhile, the model exhibits the phenomenon of backward bifurcation. We also obtain one equilibrium is semi-stable by using center manifold theory. It is proved that the endemic equilibrium is globally asymptotically stable under some conditions if R_0 is greater than unity. It also is proved that the model undergoes Hopf bifurcation from the endemic equilibrium under some conditions. It is novelty that the model exhibits two famous bifurcations, backward bifurcation and Hopf bifurcation. The model is extended to incorporate the specific Cytotoxic T Lymphocytes (CTLs) immune response. Stabilities of equilibria and Hopf bifurcation are considered accordingly. In addition, some numerical simulations for justifying the theoretical analysis results are also given in paper.

Key words: HIV model; global asymptotical stability; center manifold theory; Hopf bifurcation; backward bifurcation

2010 MR subject classification: 34D23; 34D20

Document code: A

Article ID: 1674-5647(2019)04-0301-17

DOI: 10.13447/j.1674-5647.2019.04.02

Received date: March 18, 2017.

Foundation item: The Teacher Research Capacity Promotion Program of Beijing Normal University Zhuhai and the NSF (11871108) of China.

E-mail address: liuyongqi1980@163.com (Liu Y Q).

1 Introduction

Human Immunodeficiency Virus (HIV), which destroys CD4 T cells and decreases the resistance of the immune system. The count of CD4 T cells is a primary indicator used to measure progression of HIV infection. In a normal healthy individual's blood, the level of CD4 T cells is between 800 and 1200 mm^{-3} (see [1]–[3]). When CD4 T cells count of one patient reaches 200 mm^{-3} or below, the person is called AIDS patient. The amount of virus rises dramatically after primary infection and falls to a lower level after a few weeks to months. At first, it is estimated that as many as 10^{10} virions are produced and destroyed in an infected individual each day. The amount of virus rises again after ten years or so (see [1]). By utilizing mathematical models, we can better understand HIV dynamics, disease progress and interaction of HIV and the immune system. Many ordinary differential equations for HIV infection pathogenesis have been proposed and investigated by bio-mathematicians (see [1] and [3]–[5]). The basic mathematical model which describes HIV infection dynamics has been studied in [1] and [4]. Global stabilities have been established by using Lyapunov functions. Many papers consider the proliferation of the CD4 cells (see [3] and [6]). Motivated by the above works, we propose one HIV model which is described by the following system of differential equations

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = s - \delta T(t) - \beta T(t)v(t) + rT(t)\frac{v(t)}{k + v(t)}, \tag{1.1}$$

$$\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} = \beta T(t)v(t) - aT^*(t), \tag{1.2}$$

$$\frac{\mathrm{d}v(t)}{\mathrm{d}t} = bT^*(t) - cv(t). \tag{1.3}$$

State variables $T(t)$, $T^*(t)$ and $v(t)$ represent the concentration of uninfected CD4 T cells, infected CD4 T cells, and the HIV particles in the blood, respectively. The human body produces CD4 T cells at a constant rate s. The parameters δ, a and c denote the death rate of uninfected CD4 T cells, infected CD4 T cells and the virus particles, respectively. Here we use bilinear incident rate $\beta T(t)v(t)$ to describe the infection incident rate. The term $\dfrac{rT(t)v(t)}{k + v(t)}$ denotes saturated reverse function response, the proliferation of CD4 T cells, where r is the maximal proliferation rate, k is half-saturation constant of the proliferation process and can be considered as michaelis-menten constant. Free HIV are produced from actively infected cells at rate $bT^*(t)$ and are removed at rate $cv(t)$.

The main purpose of this paper is to analyse global properties for the system (1.1)–(1.3) and explore the impact of saturated reverse function response on the dynamical behavior of the system. We begin model analysis with proving the positivity and boundedness of the solutions of the system. We prove that system (1.1)–(1.3) exhibits the backward bifurcation and Hopf bifurcation under some conditions. We prove that the endemic equilibrium is globally asymptotically stable under some conditions by using the geometric approach, developed by Li and Muldowney (see [2], [7]–[8]). We also research the effect of CTLs on HIV infection and give the conditions of Hopf bifurcation.

This paper is ordered as follows: equilibria, properties analysis are studied when $R_0 < 1$ in Section 2. In Section 3, the global asymptotical stability of the endemic equilibrium and Hopf bifurcation are investigated when $R_0 > 1$. In Section 4, we consider the extended system and explore its stability and bifurcation. Section 5 gives numerical results for the system. Section 6 is conclusions. Section 7 is Appendix.

2 Equilibria and Stability when $R_0 < 1$

Before HIV infection invades the host, we have $T^* = v = 0$. It can be shown that CD4 T cells converge to the value $T = \frac{s}{\delta}$. We note that the basic reproduction number R_0 for the system is given by

$$R_0 = \frac{\beta bs}{\delta ac}.$$

If $R_0 < 1$, this means that an infected cell will on average produce less than one infected cell. The HIV infection cells are cleared from the CD4 T cells population. If $R_0 > 1$, this means that an infected cell will on average produce more than one newly infected cell in the host. The HIV infection will persist in the host. In classic epidemic theory, the basic reproduction number largely determines whether infection will be sustaining in a certain degree. We easily get the following results by letting the right sides of system (1.1)–(1.3) be zero.

Proposition 2.1 *For the system* (1.1)–(1.3),

(1) *the system always exists one nonnegative equilibrium* $P_0\left(\frac{s}{\delta}, 0, 0\right)$, *which represents the state that the virus are absent*;

(2) *the system has one positive equilibrium* $P_1(T_1, T_1^*, v_1)$ *if* $R_0 < 1$ *and* $r = \beta k + \delta(1 - R_0) + \sqrt{4\beta\delta k(1 - R_0)}$;

(3) *the system has two positive equilibria* $P_2(T_2, T_2^*, v_2)$, $P_3(T_3, T_3^*, v_3)$ *if* $R_0 \leq 1$ *and* $r > \beta k + \delta(1 - R_0) + \sqrt{4\beta\delta k(1 - R_0)}$;

(4) *the system has only one positive equilibrium* $P_4(T_4, T_4^*, v_4)$ *if* $R_0 > 1$;

(5) *otherwise, the system has no positive equilibrium, where*

$$T_1 = T_2 = T_3 = T_4 = \frac{ac}{\beta b},$$

$$T_1^* = \frac{cv_1}{b}, \quad T_2^* = \frac{cv_2}{b}, \quad T_3^* = \frac{cv_3}{b}, \quad T_4^* = \frac{cv_4}{b},$$

$$v_1 = \frac{-[(\beta k - r) + \delta(1 - R_0)]}{2\beta} = \frac{\sqrt{\beta\delta k(1 - R_0)}}{\beta},$$

$$v_2 = \frac{-[(\beta k - r) + \delta(1 - R_0)] - \sqrt{[(\beta k - r) + \delta(1 - R_0)]^2 + 4\beta\delta k(R_0 - 1)}}{2\beta},$$

$$v_3 = v_4 = \frac{-[(\beta k - r) + \delta(1 - R_0)] + \sqrt{[(\beta k - r) + \delta(1 - R_0)]^2 + 4\beta\delta k(R_0 - 1)}}{2\beta}.$$

Proposition 2.2 *All the solutions of the system* (1.1)–(1.3) *with positive initial conditions* $T(0) > 0$, $T^*(0) > 0$, $v(0) > 0$ *remain positive for all* $t \geq 0$.

Proof. Assume that there exists $t > 0$ at which $T(t)$, $T^*(t)$ or $v(t)$ is equal to 0. Denote

$$t^* = \min\{t > 0 : T(t)T^*(t)v(t) = 0\}.$$

If $T(t^*) = 0$, it follows that

$$\left.\frac{\mathrm{d}T(t)}{\mathrm{d}t}\right|_{t=t^*} = s - \delta T(t^*) - \beta T(t^*)v(t) + rT(t^*)\frac{v(t)}{k + v(t)} = s > 0.$$

However, from $T(0) > 0$ and $T(t^*) = 0$, we can obtain

$$\left.\frac{\mathrm{d}T(t)}{\mathrm{d}t}\right|_{t=t^*} \le 0.$$

That is a contradiction. Thus $T(t) > 0$ for all $t \ge 0$. If $T^*(t^*) = 0$, it follows that $T(t^*) > 0$, $v(t^*) \ge 0$ when $t \in [0,\ t^*]$. Then

$$\left.\frac{\mathrm{d}T^*(t)}{\mathrm{d}t}\right|_{t=t^*} = \beta T(t^*)v(t^*) - aT^*(t^*) \ge 0.$$

But we know that the set

$$Q = \left\{(T(t), T^*(t), v(t)) \in R^3;\ T(t) \ge 0,\ T^*(t) = v(t) = 0\right\}$$

is an invariant set with respect to system (1.1)–(1.3). So we get $v(t^*) > 0$. Therefore,

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

However, from $T^*(0) > 0$ and $T^*(t^*) = 0$, we can obtain

$$\left.\frac{\mathrm{d}T^*(t)}{\mathrm{d}t}\right|_{t=t^*} \le 0.$$

That is a contradiction. Thus $T^*(t) > 0$ for all $t \ge 0$. In a similar way, we can obtain $v(t) > 0$ for all $t \ge 0$. Solutions remain positive for positive initial conditions. This completes the proof.

Proposition 2.3 *When $\beta k + \delta \ge r$, for any positive solution of system* (1.1)–(1.3) *and sufficiently large t, there exists $M > 0$ such that $T(t) < M$, $T^*(t) < M$ and $v(t) < M$.*

Proof. We obtain

$$\beta T(t)v(t) - rT\frac{v(t)}{k + v(t)} > 0$$

from (1.1) when

$$v(t) > v_0 = \frac{r - \beta k}{\beta},$$

if $r - \beta k \le 0$, it is easy to get that $T(t)$, $T^*(t)$, $v(t)$ are bounded. So we get

$$\frac{\mathrm{d}T}{\mathrm{d}t} \le s - \delta T.$$

So there exists M_1 such that $T \le M_1$. Furthermore, we get

$$\begin{aligned}\frac{\mathrm{d}T(t)}{\mathrm{d}t} + \frac{\mathrm{d}T^*(t)}{\mathrm{d}t} &\le s + rT(t) - \delta T(t) - aT^*(t)\\ &\le s + rM_1 - \min\{\delta,\ a\}(T(t) + T^*(t)).\end{aligned}$$

Then there exists $M_2 > 0$ such that $T^* \le M_2$. Similarly, there exists $M_3 > 0$ such that $v \le M_3$. Therefore, we can obtain boundedness of $T(t)$, $T^*(t)$, and $v(t)$ when $v > v_0$.

If $v \le v_0$, we obtain

$$\begin{aligned}\frac{\mathrm{d}T(t)}{\mathrm{d}t} &= s - \frac{(\beta k + \delta - r)T(t)v(t) + \delta k T(t) + \beta T(t)v^2}{k + v(t)} \\ &\le s - \frac{\delta k}{k + v_0}T(t). \end{aligned} \tag{2.1}$$

It follows from (2.1) that $T(t)$ is bounded. Similarly, $T^*(t)$ and $v(t)$ are also bounded as well. So we show that all solutions of system (1.1)–(1.3) are uniformly bounded, say by M. This completes the proof.

Define the region

$$P = \left\{(T(t), T^*(t), v(t)) \in R^3_+;\ T(t), T^*(t), v(t) \le M\right\},$$

where R^3_+ denotes the non-negative cone. Obviously, solutions of system (1.1)–(1.3) remain non-negative for non-negative initial conditions. So P is a positively invariant set with respect to system (1.1)–(1.3). In the following, we investigate dynamic behavior in P.

Theorem 2.1 *For system* (1.1)–(1.3), *when* $\beta k + \delta \ge r$,

(1) *the disease-free equilibrium* P_0 *is local asymptotically stable in* P *if* $R_0 < 1$ *and is unstable if* $R_0 > 1$;

(2) *if* P_2 *and* P_3 *both exist*, P_3 *is locally asymptotically stable and* P_2 *is unstable*;

(3) *if* P_1 *exists*, *it is semi-stable.*

Proof. The Jacobian matrix of system (1.1)–(1.3) at P_0 is computed to be as

$$\boldsymbol{J}(P_0) = \begin{pmatrix} -\delta & 0 & -\beta\dfrac{s}{\delta} + \dfrac{rs}{k\delta} \\ 0 & -a & \dfrac{\beta s}{\delta} \\ 0 & b & -c \end{pmatrix}.$$

It is easy to see that all roots of the characteristic equation at P_0 have negative real parts if $R_0 < 1$, thus P_0 is locally asymptotically stable. The characteristic equation about P_0 has at least one positive root if $R_0 > 1$, therefore, P_0 is unstable.

The Jacobian matrix corresponding to P_i $(i = 1, 2, 3)$ is given by

$$\boldsymbol{J}(P_i) = \begin{pmatrix} -\delta - \beta v_i + \dfrac{r v_i}{k + v_i} & 0 & \dfrac{r T_i k}{(k + v_i)^2} - \beta T_i \\ \beta v_i & -a & \beta T_i \\ 0 & b & -c \end{pmatrix}.$$

The characteristic equation corresponding to P_i $(i = 1, 2, 3)$ is given by

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + m_i = 0,$$

where

$$a_1 = \delta R_0 + a + c, \quad a_2 = \delta R_0(a + c), \quad m_i = ac\left(\frac{-rkv_i}{(k + v_i)^2} + \beta v_i\right) \quad (i = 1, 2, 3).$$

Denote

$$\Delta = [(\beta k - r) + \delta(1 - R_0)]^2 + 4\beta\delta k(R_0 - 1).$$

We calculate m_2 and acquire

$$m_2 = acv_2\left(\frac{-rk}{(k + v_2)^2} + \beta\right) = ac\frac{\Delta + (\beta k - r + \delta(1 - R_0))\sqrt{\Delta}}{2\beta(k + v_2)} < 0.$$

We also compute m_3 and acquire

$$m_3 = acv_3\left(\frac{-rk}{(k+v_3)^2}+\beta\right) = ac\frac{\Delta-(\beta k-r+\delta(1-R_0))\sqrt{\Delta}}{2\beta(k+v_3)} > 0.$$

We also have

$$\begin{aligned}
a_1a_2-m_3 &= (\delta R_0+a+c)(a+c)\delta R_0 - ac\left(\frac{-rkv_3}{(k+v_3)^2}+\beta v_3\right)\\
&= (\delta R_0+a+c)(a+c)\delta R_0 - ac\left(\frac{-rkv_3}{(k+v_3)^2}+\frac{rv_3}{k+v_3}+\delta(R_0-1)\right)\\
&= (\delta R_0+a+c)(a+c)\delta R_0 - ac\left(\frac{rv_3^2}{(k+v_3)^2}+\delta(R_0-1)\right)\\
&\geq (\delta R_0+a+c)(a+c)\delta R_0 - ac(\beta v_3+\delta R_0).
\end{aligned}$$

Since $\beta k+\delta \geq r$, we obtain

$$-[(\beta k-r)+\delta(1-R_0)] \leq \delta R_0, \qquad \beta v_3 \leq \delta R_0.$$

Therefore, $a_1a_2-m_3>0$ and P_3 is locally asymptotically stable.

In the following, we discuss the local asymptotical stability of P_1. Since the characteristic equation around P_1 has two negative real parts roots and one zero root, we use the method of center manifold theory (see [9]–[10]).

Denote

$$T(t) = T_1(1+x), \quad T^*(t) = T_1^*(1+y), \quad v(t) = v_1(1+z). \tag{2.2}$$

Therefore, system (1.1)–(1.3) changes into

$$\frac{\mathrm{d}x}{\mathrm{d}t} = -\frac{s}{T_1}x - \frac{rkv_1^2}{(k+v_1)^3}z^2 + O(|xz^2|,\, |z^3|), \tag{2.3}$$

$$\frac{\mathrm{d}y}{\mathrm{d}t} = a(x+z-y+xz), \tag{2.4}$$

$$\frac{\mathrm{d}z}{\mathrm{d}t} = c(y-z). \tag{2.5}$$

Under non-singularity transformation

$$\begin{pmatrix}\bar{x}\\ \bar{y}\\ \bar{z}\end{pmatrix} = \begin{pmatrix}1 & 0 & 0\\ 0 & 1 & -1\\ \dfrac{cT_1}{s} & \dfrac{c}{a} & 1\end{pmatrix}\begin{pmatrix}x\\ y\\ z\end{pmatrix},$$

the system (2.3)–(2.5) becomes into the following form

$$\frac{\mathrm{d}\bar{x}}{\mathrm{d}t} = -\frac{s}{T_1}\bar{x} - \frac{rkv_1^2}{(k+v_1)^3}\left(\frac{aT_1}{s}\bar{x}+\bar{y}-\frac{a}{a+c}\bar{z}\right)^2 + O(|(\bar{x},\,\bar{y},\,\bar{z})^3|), \tag{2.6}$$

$$\begin{aligned}\frac{\mathrm{d}\bar{y}}{\mathrm{d}t} = &-a\bar{y} - \frac{aT_1rkv_1^2}{s(k+v_1)^3}\left(\frac{aT_1}{s}\bar{x}+\bar{y}-\frac{a}{a+c}\bar{z}\right)^2 -\\ &a\bar{x}\left(\frac{aT_1}{s}\bar{x}+\bar{y}-\frac{a}{a+c}\bar{z}\right) + O(|(\bar{x},\,\bar{y},\,\bar{z})^3|),\end{aligned} \tag{2.7}$$

$$\begin{aligned}\frac{\mathrm{d}\bar{z}}{\mathrm{d}t} = &-\frac{cT_1rkv_1^2}{s(k+v_1)^3}\left(\frac{aT_1}{s}\bar{x}+\bar{y}-\frac{a}{a+c}\bar{z}\right)^2 - c\bar{x}\left(\frac{aT_1}{s}\bar{x}+\bar{y}-\frac{a}{a+c}\bar{z}\right) +\\ &O(|(\bar{x},\,\bar{y},\,\bar{z})^3|).\end{aligned} \tag{2.8}$$

For system (2.6)–(2.8), we can get a local center manifold that has the form as follows: $W^c(0) = \{(\bar{x}, \bar{y}, \bar{z}) \in \mathbf{R}^3 \mid \bar{x} = h_1(\bar{z}), \bar{y} = h_2(\bar{z}), \|\bar{z}\| \le \varepsilon, h_i(0) = 0, Dh_i(0) = 0, i = 1, 2\}$. Then we let

$$\bar{x} = h_1(\bar{z}) = h_{11}\bar{z}^2 + h_{12}\bar{z}^3 + \cdots, \qquad \bar{y} = h_2(\bar{z}) = h_{21}\bar{z}^2 + h_{22}\bar{z}^3 + \cdots.$$

By simply computing, we obtain the solutions on the center manifold satisfy

$$\frac{\mathrm{d}\bar{z}}{\mathrm{d}t} = -\frac{ca^2T_1rkv_1^2}{s(a+c)^2(k+v_1)^3}\bar{z}^2 + o(|\,\bar{z}\,|^2).$$

When initial values $\bar{z}_0 > 0$, P_1 is locally asymptotically stable since

$$\frac{ca^2T_1rkv_1^2}{s(a+c)^2(k+v_1)^3} > 0.$$

If $\bar{z}_0 < 0$, we derive that P_1 is unstable. This completes the proof.

We can see that the disease will not die out under some conditions even $R_0 < 1$. Whether we can eradicate the disease or not is relate to the initiate states. We can see a stable endemic equilibrium coexists with a stable disease-free equilibrium when the associated reproduction number is less than unity. That is to say, the system can exhibit the phenomenon of backward bifurcation.

Theorem 2.2 *If $R_0 \le 1$ and $\beta k \ge r$ hold, the disease-free equilibrium P_0 is globally asymptotically stable in P.*

Proof. When $\beta k \ge r$, there is no other steady state except for P_0 if $R_0 \le 1$ from Proposition 2.1. We define a Lyapunov function

$$L = T^*(t) + \frac{a}{b}v(t).$$

Then the derivative of L along the solution of system (1.1)–(1.3) is

$$L' = \frac{\beta bT(t) - ac}{b}v(t) = \frac{ac}{b}\left(\frac{\beta b}{ac}T(t) - 1\right)v(t).$$

Since $\beta k \ge r$, then $T(t) \le \dfrac{s}{\delta}$ if t is sufficiently big. It is clear that $L' \le 0$ from $R_0 \le 1$. Furthermore, $L' = 0$ if and only if $v = 0$ or $R_0 = 1$ and $T = \dfrac{s}{\delta}$. The maximum invariant set is $\{P_0\}$. Then we yield that all solutions of the system (1.1)–(1.3) in P will converge to P_0 according to Lyapunov-LaSalle Theorem (see [5]). It means that all solutions, no matter what any initial value, approach the disease-free state steady P_0. This completes the proof.

3 Global Stability and Hopf Bifurcation when $R_0 > 1$

Theorem 3.1 *Suppose that $R_0 > 1$ and $\beta k + \delta \ge r$, the endemic equilibrium P_4 is locally asymptotically stable.*

Proof. The characteristic equation corresponding to P_4 is given by

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + m_4 = 0, \tag{3.1}$$

where

$$a_1 = \delta R_0 + a + c, \quad a_2 = \delta R_0(a+c), \quad m_4 = ac\left(\frac{-rkv_4}{(k+v_4)^2} + \beta v_4\right).$$

It can be seen easily that

$$\begin{aligned} m_4 &= ac\left(\frac{-rkv_4}{(k+v_4)^2}+\beta v_4\right) > \frac{-rv_4}{(k+v_4)}+\beta v_4=\delta(R_0-1)>0,\\ a_1a_2-m_4 &= (\delta R_0+a+c)(a+c)\delta R_0-ac\left(\frac{-rkv_4}{(k+v_4)^2}+\beta v_4 r\right)\\ &\geq (\delta R_0+a+c)(a+c)\delta R_0-ac\left(\frac{\beta k v_4^2}{(k+v_4)^2}+\delta R_0\right)\\ &> 0. \end{aligned}$$

The last step holds from $\beta k v_4^2 \leq \delta(R_0-1)k^2+k\delta R_0 v_4$. This completes the proof.

Next we discuss the global asymptotical stability of the endemic equilibrium P_4 by using the geometric approach based on the second additive compound matrix (see [2], [7]–[8]).

Definition 3.1 [7],[11] *System* (1.1)–(1.3) *is said to be uniformly persistent if there exists a constant $m>0$ such that each positive solution $(T(t), T^*(t), v(t))$ with initial conditions in the interior of P satisfies*

$$\min\left\{\liminf_{t\to\infty} T(t),\ \liminf_{t\to\infty} T^*(t),\ \liminf_{t\to\infty} v(t)\right\}\geq m.$$

Proposition 3.1 (1.1)–(1.3) *is uniformly persistent in the interior of P if $R_0>1$.*

Proof. When $R_0>1$, we see that P_0 is unstable. Solution which close to P_0 will leave its neighborhood except for solutions on the positively invariant T-axis. The interested reader can see [2], [7], [12]–[13].

Theorem 3.2 *The endemic equilibrium P_4 of* (1.1)–(1.3) *is globally asymptotically stable in P if $\delta>r$ and $R_0>1$.*

Proof. We use Lemma 7.1 in Appendix to prove the global asymptotical stability of endemic equilibrium. From above discussion, we know that interior of P is simply connected and P_4 is unique equilibrium in the interior of P. Both (H_1) and (H_2) in Appendix are satisfied. The uniform persistence of system when $R_0>1$, together with the boundedness of solutions, implies the existence a compact absorbing set $E\subset P$ (see [2], [7]). This verifies the assumption (H_3) in Appendix. P_4 is locally asymptotically stable when $\delta>r$ from Theorem 3.1. The Jacobian matrix $\boldsymbol{J}$ of system (1.1)–(1.3) is given as

$$\boldsymbol{J}=\begin{pmatrix} -\delta-\beta v+\dfrac{rv}{k+v} & 0 & \dfrac{rTk}{(k+v)^2}-\beta T\\ \beta v & -a & \beta T\\ 0 & b & -c \end{pmatrix},$$

and its second compound matrix $\boldsymbol{J}^{[2]}$

$$\boldsymbol{J}^{[2]}=\begin{pmatrix} -\delta-\beta v+\dfrac{rv}{k+v}-a & \beta T & -\dfrac{rTk}{(k+v)^2}+\beta T\\ b & -\delta-\beta v+\dfrac{rv}{k+v}-c & 0\\ 0 & \beta v & -(a+c) \end{pmatrix}.$$

Denote the function $Q = Q(T, T^*, v) = \operatorname{diag}\left\{1, \frac{T^*}{v}, \frac{T^*}{v}\right\}$, then

$$Q_f Q^{-1} = \operatorname{diag}\left\{0, \frac{T^{*\prime}}{T^*} - \frac{v'}{v}, \frac{T^{*\prime}}{T^*} - \frac{v'}{v}\right\},$$

$$\boldsymbol{B} = \begin{pmatrix} -\delta - \beta v + \frac{rv}{k+v} - a & \frac{\beta T v}{T^*} & \left(\beta T - \frac{rTk}{(k+v)^2}\right)\frac{v}{T^*} \\ \frac{bT^*}{v} & \frac{T^{*\prime}}{T^*} - \frac{v'}{v} - \delta - \beta v + \frac{rv}{k+v} - c & 0 \\ 0 & \beta v & \frac{T^{*\prime}}{T^*} - \frac{v'}{v} - a - c \end{pmatrix}$$
$$= \begin{pmatrix} \boldsymbol{B}_{11} & \boldsymbol{B}_{12} \\ \boldsymbol{B}_{21} & \boldsymbol{B}_{22} \end{pmatrix},$$

where

$$\boldsymbol{B}_{11} = -\delta - \beta v + \frac{rv}{k+v} - a,$$
$$\boldsymbol{B}_{12} = \left[\frac{\beta T v}{T^*}, \left(\beta T - \frac{rTk}{(k+v)^2}\right)\frac{v}{T^*}\right],$$
$$\boldsymbol{B}_{21} = \left[b\frac{T^*}{v}, 0\right]^{\mathrm{T}},$$
$$\boldsymbol{B}_{22} = \begin{pmatrix} \frac{T^{*\prime}}{T^*} - \frac{v'}{v} - \delta - \beta v + \frac{rv}{k+v} - c & 0 \\ \beta v & \frac{T^{*\prime}}{T^*} - \frac{v'}{v} - (a+c) \end{pmatrix}.$$

Let (u, v, w) denote the vectors in $\mathbf{R}^3$, choose a norm in $\mathbf{R}^3$ as

$$\|(u, v, w)\| = \max\{|u|, |v| + |w|\}$$

and let μ be the corresponding Lozinskiĭ measure (see [2], [12]). Then we have

$$\mu(\boldsymbol{B}) \le \max\{g_1, g_2\},$$

where $g_1 = \mu(\boldsymbol{B}_{11}) + \|\boldsymbol{B}_{12}\|$, $g_2 = \mu(\boldsymbol{B}_{22}) + \|\boldsymbol{B}_{21}\|$, and where $\|\boldsymbol{B}_{12}\|$, $\|\boldsymbol{B}_{21}\|$ are matrix norm with respect to l_1 vector norm. Then we obtain

$$\mu(\boldsymbol{B}_{11}) = -\delta - \beta v + r\frac{v}{k+v} - a, \quad \|\boldsymbol{B}_{12}\| = \beta T\frac{v}{T^*}, \quad \|\boldsymbol{B}_{21}\| = b\frac{T^*}{v},$$
$$\mu(\boldsymbol{B}_{22}) = \max\left\{\frac{T^{*\prime}}{T^*} - \frac{v'}{v} - \delta - \beta v + r\frac{v}{k+v} - c + \beta v, \frac{T^{*\prime}}{T^*} - \frac{v'}{v} - (a+c)\right\}$$
$$= \frac{T^{*\prime}}{T^*} - \frac{v'}{v} - c - \min\left\{a, \delta - r\frac{v}{k+v}\right\}.$$

Because of $\delta > r$, we obtain that

$$\delta - r\frac{v}{k+v} \ge \delta - r > 0.$$

From system (1.1)–(1.3), we have

$$\frac{T^{*\prime}}{T^*} = \frac{\beta}{T}vT^* - a, \qquad \frac{v'}{v} = \frac{bT^*}{v} - c.$$

Hence,

$$g_1 = -\delta - \beta v + r\frac{v}{k+v} - a + \beta T\frac{v}{T^*} \le \frac{T^{*\prime}}{T^*} - \delta,$$
$$g_2 = b\frac{T^*}{v} + \frac{T^{*\prime}}{T^*} - \frac{v'}{v} - c - \min\left\{a,\ \delta - r\frac{v}{k+v}\right\} \le \frac{T^{*\prime}}{T^*} - \min\{a,\ \delta - r\}.$$

Therefore we get

$$\mu(B) \le \frac{T^{*\prime}}{T^*} - \eta$$

for sufficiently large t with $\eta = \min\{a,\ \delta - r\}$.

Now, let $(T(t),\ T^*(t),\ v(t))$ be any solution starting in the compact absorbing set $E \subset P$ and $\bar{t}$ be sufficiently large such that $(T(t),\ T^*(t),\ v(t)) \in E$ for all $t > \bar{t}$. For $t > \bar{t}$, we have

$$\frac{1}{t}\int_0^t \mu(B)\mathrm{d}s \le \frac{1}{t}\int_0^{\bar{t}} \mu(B)\mathrm{d}s + \frac{1}{t}\ln\left(\frac{T^{*(t)}}{T^{*(\bar{t})}}\right) - \frac{t-\bar{t}}{t}\eta.$$

From the definition of $\bar{q}_2$, we finally get

$$\bar{q}_2 < -\frac{\eta}{2} < 0.$$

This completes the proof.

Meanwhile, we obtain that

$$a_1a_2 - m_4 = (\delta R_0 + a + c)(a+c)\delta R_0 - ac\left(\frac{-rkv_1}{(k+v_4)^2} + \beta v_4\right)$$

maybe less than 0 by numerical simulations if $\beta k + \delta < r$. Thus the Routh-Hurwitz criteria may not always be satisfied. So it is possible to occur Hopf bifurcation around positive interior equilibrium P_4. That is, a branch of periodic solutions splits off from an equilibrium when some parameters change. Here we have taken r as a bifurcation parameter.

Theorem 3.3 *If $R_0 > 1$, then system (1.1)–(1.3) around P_4 undergoes a simple Hopf bifurcation when r passes through one certain value r_0, which satisfies $a_1(r)a_2(r) = m_4(r)$.*

Proof. Denote

$$\psi(r) = a_1(r)a_2(r) - m_4(r).$$

Now we can obtain $r = r_0$ from $\psi(r) = 0$ and we have $a_1(r) > 0$, $a_2(r) > 0$, and $m_4(r) > 0$. (3.1) is given by

$$(\lambda^2 + a_2(r_0))(\lambda + a_1(r_0)) = 0. \tag{3.2}$$

It is easy to see that (3.2) have a pair of purely imaginary eigenvalues and a strictly negative real eigenvalue. For r in a neighbourhood of r_0, the characteristic equation (3.1) have a pair of complex eigenvalues $\lambda(r) = p_1(r) + \mathrm{i}p_2(r)$, $\bar{\lambda}(r) = p_1(r) - \mathrm{i}p_2(r)$, which are purely imaginary eigenvalues at $r = r_0$. Substituting $\lambda(r) = p_1(r) + \mathrm{i}p_2(r)$ into (3.1) and calculating the derivative, we obtain that the transversality condition is completely equivalent to $\psi'(r_0) \ne 0$ (see [9]). That is,

$$\frac{\mathrm{d}(\mathrm{Re}\lambda(r))}{\mathrm{d}r} = -\frac{\psi'(r)}{2(a_1^2(r) + a_2(r))} \qquad \text{at} \quad r = r_0.$$

By calculating we get

$$\psi'(r_0) = -\frac{acv_4^2}{(k+v_4)^2} - acr_0v_4'(r_0)\frac{2kv_4}{(k+v_4)^3} < 0,$$

where

$$v_4'(r_0) = \frac{1}{2\beta}\left(1 + \frac{(-\beta k + r_0) - \delta(1 - R_0)}{\sqrt{[(\beta k - r_0) + \delta(1 - R_0)]^2}}\right) > 0.$$

Therefore, we derive that the transversality condition (H_5) in Appendix holds. The conditions for Hopf bifurcation theorem are verified. This completes the proof.

4 The Extended Model

CTLs response is one major branch of the immune system to fight virus infections and it has been proved to have the potential to suppress HIV load. CTLs kill infected cells and enhance the immune response against HIV to get achieve long-term immunological control of the virus in the absence of continuous therapy (see [14]–[15]). An effective, sustained CTLs response can be established if virus load is contained at low levels. R denote the concentration of CTLs. m_1T^*R is the clearance rate of infected cells by CTLs, and m_2T^*R is the production rate of CTLs. Meanwhile, we use m_2T^* to be production rate. d is the natural death term of R. The expanded model is

$$\frac{\mathrm{d}T}{\mathrm{d}t} = -\delta T - \beta T v + rT\frac{v}{k+v}, \tag{4.1}$$

$$\frac{\mathrm{d}T^*}{\mathrm{d}t} = \beta T v - aT^* - m_1T^*R, \tag{4.2}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = bT^* - cv, \tag{4.3}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = m_2T^*R - dR. \tag{4.4}$$

We derive

$$R_1 = \frac{R_0(\delta k(cm_2)^2 + \delta cm_2bd)}{(\beta k + \delta - r)cm_2bd + \delta k(cm_2)^2 + \beta(bd)^2},$$

which represents the basic reproduction number of system (4.1)–(4.4). We have the following results:

Proposition 4.1 *For system* (4.1)–(4.4),

(1) *the system always exists one nonnegative equilibrium* $\bar{P}_0\left(\frac{s}{\delta}, 0, 0, 0\right)$, *which represents the state that the virus is absent*;

(2) *the system has another non-negative equilibrium* $\bar{P}_1(T_1, T_1^*, v_1, 0)$ *if* $R_0 < 1$, $R_1 < 1$, *and* $r = \beta k + \delta(1 - R_0) + \sqrt{4\beta\delta k(1 - R_0)}$;

(3) *the system has two non-negative equilibrium* $\bar{P}_2(T_2, T_2^*, v_2, 0)$, $\bar{P}_3(T_3, T_3^*, v_3, 0)$ *if* $R_0 \leq 1$, $R_1 < 1$, *and* $r > \beta k + \delta(1 - R_0) + \sqrt{4\beta\delta k(1 - R_0)}$;

(4) *the system has only one non-negative equilibrium* $\bar{P}_4(T_4, T_4^*, v_4, 0)$ *if* $R_0 > 1$ *and* $R_1 < 1$;

(5) *the system has only one positive equilibrium* $\bar{P}_5(T_5, T_5^*, v_5, R_5)$ *if* $R_1 > 1$;

(6) *otherwise, the system has no positive equilibrium, where* T_i, T_i^*, v_i $(i = 1, 2, 3, 4)$ *are the same as those in Section* 2,

$$T_5 = \frac{s(k(cm_2)^2 + cm_2bd)}{(\beta k + \delta - r)cm_2bd + \delta k(cm_2)^2 + \beta(bd)^2} = \frac{sR_1}{\delta R_0},$$

$$T_5^* = \frac{d}{m_2}, \quad v_5 = \frac{bd}{cm_2}, \quad R_5 = \frac{\beta b T_5 - ac}{cm_1}.$$

From the Jacobian matrix at $\bar{P}_i$, we get P_i and $\bar{P}_i$ have the same local asymptotical stability if $T_i^* < \dfrac{d}{m_2}$ $(i = 1, 2, 3, 4)$. If $T_i^* > \dfrac{d}{m_2}$, $\bar{P}_i$ $(i = 1, 2, 3, 4)$ is always unstable. We obtain $\bar{P}_0$ is locally asymptotically stable whenever $R_0 < 1$. The equilibrium P_5 contains CTLs immune response. When $R_0 < 1$ and $(\beta k - r)cm_2 + \beta bd \geq 0$, P_5 does not appear. When $R_0 > 1$ and $(\beta k - r)cm_2 + \beta bd < 0$, P_5 exists. The Jacobian matrix at P_5 is

$$\boldsymbol{J}(P_5) = \begin{pmatrix} -\delta - \beta v_5 + \dfrac{rv_5}{k + v_5} & 0 & \dfrac{rkT_5}{(k+v_5)^2} - \beta T_5 & 0 \\ \beta v_5 & -a - m_1 R_5 & \beta T_5 & -m_1 T_5^* \\ 0 & b & -c & 0 \\ 0 & m_2 R_5 & 0 & m_2 T_5^* - d \end{pmatrix}$$

with the characteristic equation

$$\lambda^4 + q_1\lambda^3 + q_2\lambda^2 + q_3\lambda + q_4 = 0, \tag{4.5}$$

where

$$\begin{aligned} q_1 &= \left(c + \frac{s}{T_5} + \frac{\beta b T_5}{c}\right), \\ q_2 &= \frac{s(a + c + m_1 R_5)}{T_5} + m_1 d R_5, \\ q_3 &= \beta b v_5 T_5 \left(\beta - \frac{rk}{(k+v_5)^2}\right) + m_1 d R_5 \left(c + \frac{s}{T_5}\right), \\ q_4 &= \frac{m_1 c d R_5 s}{T_5}. \end{aligned}$$

By the Routh-Hurwitz conditions, all eigenvalues of (4.5) have negative real parts if and only if

$$q_i > 0, \quad q_1q_2 - q_3 > 0, \quad (q_1q_2 - q_3)q_3 > q_1^2 q_4, \qquad i = 1, 2, 3, 4.$$

Theorem 4.1 *If $R_1 > 1$ and $\beta \geq \dfrac{rk}{(k+v_5)^2}$, then system (4.1)–(4.4) around $\bar{P}_5$ undergoes an Hopf bifurcation when a passes through a_0.*

Proof. Let $\varphi(a) = q_1(a)q_2(a)q_3(a) - q_3^2(a) - q_1^2(a)q_4(a)$ be differentiable function with respect to a. Suppose $\beta \geq \dfrac{rk}{(k+v_5)^2}$, the conditions of $q_i > 0$ $(i = 1, 2, 3, 4)$ are established. By solving the equation $\psi(a) = 0$, we can obtain that there exists $a = a_0$ such that $\psi(a_0) = 0$. At $a = a_0$, the characteristic equation (4.5) becomes

$$\left(\lambda^2 + \frac{p_3}{p_1}\right)\left(\lambda^2 + p_1\lambda + \frac{p_1p_4}{p_3}\right) = 0. \tag{4.6}$$

It is clear that the condition (H_4) in Appendix holds. We also obtain

$$\begin{aligned} \varphi'(a_0) &= (q_2'q_1q_3 + q_3'q_1q_2 - 2q_3q_3' - q_1^2q_4')|_{a=a_0} \\ &= \beta b v_5 T_5 \left(\beta - \frac{rk}{(k+v_5)^2}\right)(-q_1q_2(a_0) + q_3(a_0)) - \frac{\beta b d T_5}{c} q_3(a_0) \\ &< 0. \end{aligned}$$

Thus the condition (H_5) in Appendix are verified. This completes the proof.

5 Numerical Simulations

In this section, we carry out numerical simulations using Matlab to illustrate theoretical results. Our parameters mainly come from [3] and [6] and our adjustment. Fig. 5.1 shows the simulation of the system (1.1)–(1.3) with the parameter values $s = 0.46$, $\delta = 0.003$, $\beta = 1 \times 10^{-8}$, $r = 0.002$, $a = 0.06$, $b = 2600$, $c = 0.09$, $k = 9.5$, where the initial conditions $x_0 = [1000; 50; 500]$. We get $R_0 = 0.7383 < 1$. The solution trajectories tend to the stable equilibrium P_0. And Fig. 5.2 shows the simulation of the system (1.1)–(1.3) with the parameter values $s = 0.46$, $\delta = 0.003$, $\beta = 1 \times 10^{-8}$, $r = 0.002$, $a = 0.06$, $b = 2600$, $c = 0.09$, $k = 9.5$, where the initial conditions $x_0 = [500; 100; 500]$. we get $R_0 = 0.7383 < 1$. The solution trajectories tend to the stable equilibrium P_3. We can see that system (1.1)–(1.3) has two locally stable equilibria (P_0 and P_3) under the same parameters when $R_0 < 1$. The different initial conditions can lead to disappearance of the HIV infection or persistence. This phenomenon denotes the disease can not be eradicated only if $R_0 < 1$.

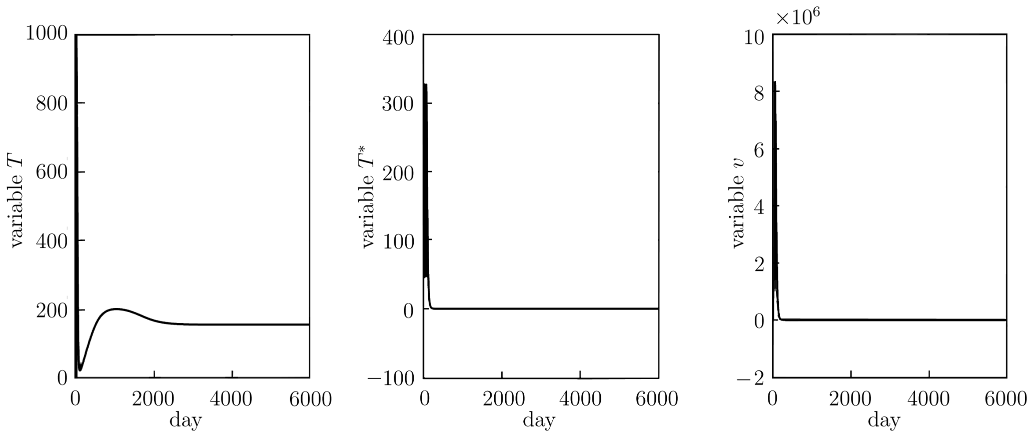

Fig. 5.1

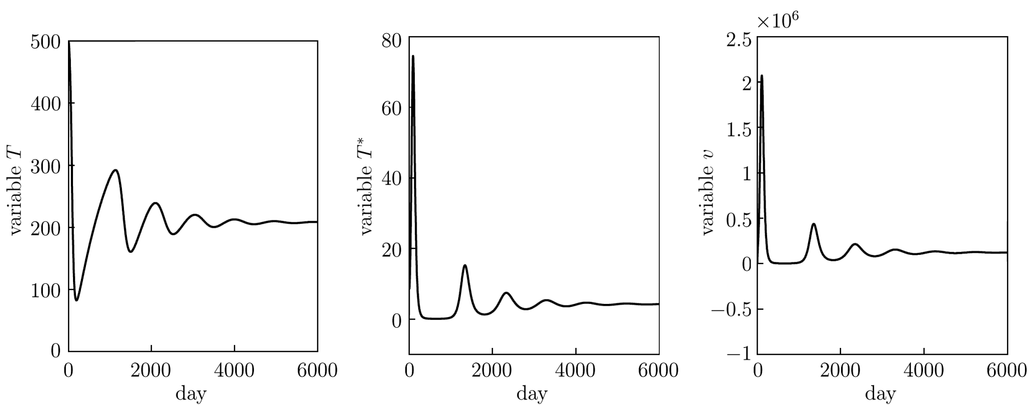

Fig. 5.2

Fig. 5.3 shows the simulation of the system (1.1)–(1.3) with $s = 0.46$, $\delta = 0.003$, $\beta = 1 \times 10^{-8}$, $r = 0.02$, $a = 0.06$, $b = 2600$, $c = 0.09$, $k = 9.5$, where the initial conditions

$x_0 = [500; 100; 500]$. We get $R_0 = 0.7383 < 1$. The stable periodic solutions occur. When the maximal proliferation rate r change the value, we find the system (1.1)–(1.3) exhibits periodic solutions though we do not give proof even if $R_0 < 1$. The maximal proliferation rate r plays a vital role in describing the behavior of system (1.1)–(1.3).

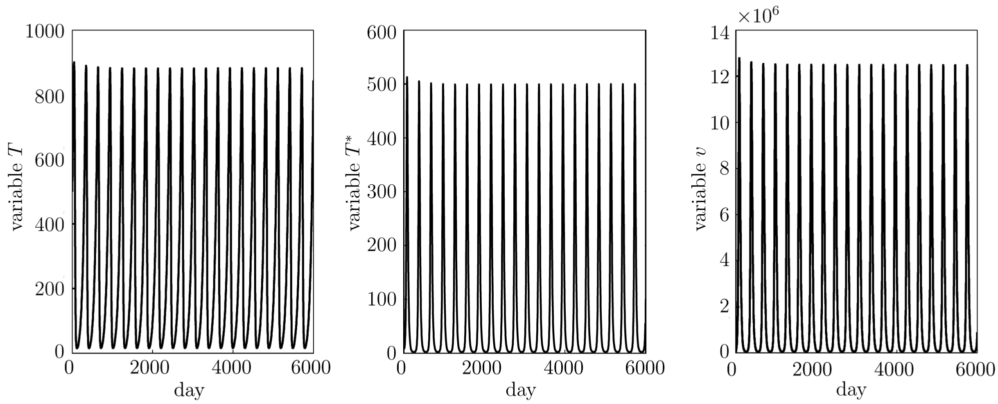

Fig. 5.3

For the following parameter values: $s = 0.46$, $\delta = 0.0002$, $\beta = 1 \times 10^{-8}$, $r = 0.0001$, $a = 0.06$, $b = 2600$, $c = 0.09$, $k = 9.5$, where the initial conditions $x_0 = [500; 100; 500]$. We get $R_0 = 11.07 > 1$. the conditions of Theorem 3.2 are satisfied. Then the positive equilibrium P_4 is globally asymptotically stable (see Fig. 5.4).

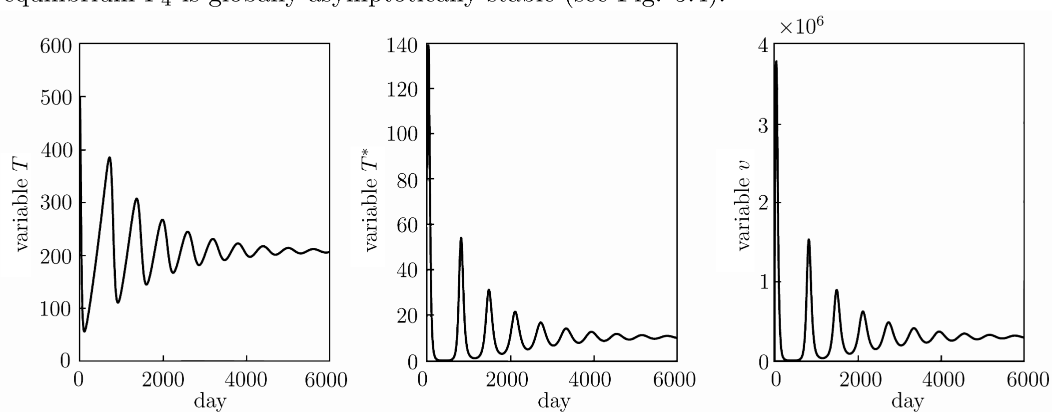

Fig. 5.4

Increasing the maximal proliferation rate $r = 0.02$, we observe that the system enter into an oscillatory steady state from a stable situation. Fig. 5.5 shows that the simulation of system (1.1)–(1.3) with $s = 0.46$, $\delta = 0.0002$, $\beta = 1 \times 10^{-8}$, $r = 0.02$, $a = 0.06$, $b = 2600$; $c = 0.09$, $k = 9.5$, where the initial conditions $x_0 = [500; 100; 500]$. We get $R_0 = 11.07 > 1$. The figure exists a stable periodic solution around P_4. We derive that the bifurcation parameter $r_0 \approx 0.009$ from the equation $a_1(r)a_2(r) - m_4(r) = 0$. Theorem 3.3 is verified.

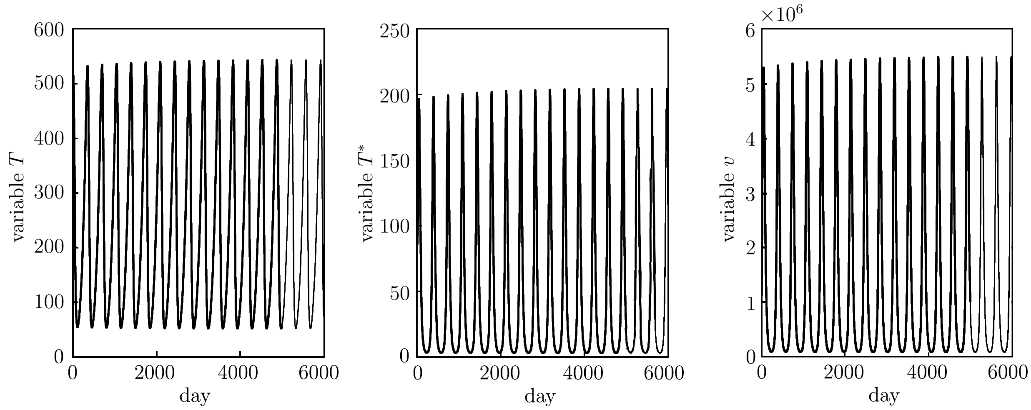

Fig. 5.5

6 Conclusions

In this paper, a deterministic HIV model for the transmission dynamics of nonlinear proliferation is designed and considered. Theoretical results and numerical simulations of the model have been shown. We investigated the qualitative behavior of the model such as positive invariance, boundedness, global stability and bifurcation. The basic reproduction number R_0 is obtained. It is not sufficient for disease elimination owing to the phenomenon of backward bifurcation. The disease can persist even $R_0 < 1$ and also persist when $R_0 > 1$. We have shown that there exists a critical value of the proliferation rate r, for which Hopf bifurcation takes place. That is, the asymptotically stable endemic equilibrium loses its stability and periodic oscillation appears. It is shown that system (1.1)–(1.3) also exhibits sustained oscillations from Fig. 5.3. Our system reveals many biology phenomena. The basic model in [4] can not exhibit bifurcation and sustained oscillations. It also is worth mentioning that, sustained oscillations, which can occur for biologically realistic parameter values (see [16]), are significant phenomena for many classes of epidemic models. Equilibria and Hopf bifurcation of the extended model with the CTLs response have been discussed and the conditions have been derived for the stability and Hopf bifurcation.

7 Appendix

We briefly describe below the geometric approach based on the second additive compound matrix, developed by Li and Muldowney (see [2], [7]–[8]). Let an open set $D \subseteq \mathbf{R}^n$ and the map $f : x \longmapsto f(x) \in \mathbf{R}^n$ for $x \in D$. Consider the differential equation

$$x' = f(x). \tag{7.1}$$

Let $x(t, x_0)$ is the solution of (7.1) such that $x(0, x_0) = x_0$. We assume that

(H_1) D is simply connected,

(H_2) $\overline{x}$ is only equilibrium point of (7.1) in D,

(H_3) there is a compact absorbing set $E \subset D$.

One set E is called absorbing in D for system (7.1) if $x(t, E_1) \subset E$ for each compact set $E_1 \subset E$ for sufficiently large t. For any square matrix $\boldsymbol{B}$, the Lozinskiĭ measure (see [2]) with respect to induced matrix norm $\|\cdot\|$ is defined as

$$\mu(\boldsymbol{B}) = \lim_{h\to 0} \frac{\|I + h\boldsymbol{B}\| - 1}{h}.$$

Let $\boldsymbol{Q} : x \longmapsto Q(x)$ be an $C_n^2 \times C_n^2$ matrix valued function that is C^1, and $Q^{-1}(x)$ exists for $x \in D$.

We define

$$\boldsymbol{B} = \boldsymbol{Q}_f \boldsymbol{Q}^{-1} + \boldsymbol{Q}\boldsymbol{J}^{[2]}\boldsymbol{Q}^{-1}.$$

The matrix $\boldsymbol{Q}_f$ is obtained by replacing each entry q_{ij} of $\boldsymbol{Q}$ by its derivative in the direction of f, and $\boldsymbol{J}^{[2]}$ is the second additive compound matrix of the Jacobian matrix $\boldsymbol{J}$ of system (7.1) (see [2]). If $\boldsymbol{M} = (m_{ij})$ is a 3×3 matrix, then

$$\boldsymbol{M}^{[2]} = \begin{pmatrix} m_{11} + m_{22} & m_{23} & -m_{13} \\ m_{32} & m_{11} + m_{33} & m_{12} \\ -m_{31} & m_{21} & m_{22} + m_{33} \end{pmatrix}.$$

Define a quantity $\bar{q}_2$ as

$$\bar{q}_2 = \limsup_{t\to\infty} \sup_{x_0 \in E} \frac{1}{t} \int_0^t \mu(B(x(s, x_0)))\mathrm{d}s.$$

In summary, the following result is established:

Lemma 7.1 *For system (7.1), if assumptions (H_1), (H_2) and (H_3) hold, then the unique equilibrium $\bar{x}$ is globally asymptotically stable in D if there exists a function $Q(x)$ and a Lozinskiĭ measure μ such that $\bar{q}_2 < 0$.*

Hopf bifurcation theorem is stated as follows (see [9], [17] and [18]).

Lemma 7.2 *Consider system of differential equations with a single parameter*

$$\dot{x} = f_\mu(x), \qquad x \in \mathbf{R}^n, \ \mu \in \mathbf{R} \tag{7.2}$$

with an equilibrium (x_0, μ_0), and $f \in C^\infty$. Assume that

(H_4) the Jacobian matrix $D_x f_{\mu_0}(x_0)$ has a simple pair of pure imaginary eigenvalues and other eigenvalues have negative real parts. Then there exists a smooth curve of equilibria $(x(\mu), \mu)$ of (7.2) with $x(\mu_0) = x_0$. The eigenvalues $(\lambda(\mu), \bar{\lambda}(\mu))$ of $D_x f_\mu(x)$ which are pure imaginary at $\mu = \mu_0$ vary smoothly with respect to μ. Moreover, if

(H_5) the transversality condition $\dfrac{\mathrm{d}(\mathrm{Re}\lambda(\mu_0))}{\mathrm{d}\mu} \neq 0,$

Then a simple Hopf bifurcation occurs at $\mu = \mu_0$.

References

[1] Perelson A S, Nelson P W. Mathematical analysis of HIV-1 dynamics in vivo. *SIAM Rev.*, 1999, **41**: 3–44.

[2] Wang L, Li M Y. Mathematical analysis of the global dynamics of a model for HIV infection of $CD4^+$ T cells. *Math. Biosci.*, 2006, **200**: 44–57.

[3] Xia X. Modelling of HIV infection: Vaccine readiness, drug effectiveness and therapeutical failures. *J. Process Contr.*, 2007, **17**: 253–260.

[4] Korobeinikov A. Global Properties of Basic Virus Dynamics Models. *Bull. Math. Biol.*, 2004, **66**: 879–883.

[5] Elaiw A M. Global properties of a class of HIV models. *Nonlinear Anal. Real World Appl.*, 2010, **11**: 2253–2263.

[6] Ouattara D A. Mathematical analysis of the HIV-1 infection: Parameter estimation, therapies effectiveness, and therapeutical failures, in 27th Annual International Conference of the IEEE Engineering in Medecine and Biology Society, Shanghai, China, September 2005.

[7] Li M Y. Graef J R, Wang L, Karsai J. Global dynamics of a SEIR model with varying total population size. *Math. Biosci.*, 1999, **160**: 191–213.

[8] Li M Y, Muldowney J S. A geometric approach to the global-stability problems. *SIAM J. Math. Anal.*, 1996, **27**: 1070–1083.

[9] Greenhalgh D. Hopf Bifurcation in epidemic models with a latent period and nonpermanent immunity. *Math. Comput. Modelling.*, 1997, **25**: 85–107.

[10] Zhou X, Shi X, Zhang Z, Song X. Dynamical behavior of a virus dynamics model with CTL immune response. *Appl. Math. Comput.*, 2009, **213**: 329–347.

[11] Butler G, Freedman H I, Waltman P. Uniform persistence system. *Proc. Amer. Math. Soc.*, 1986, **96**: 425–430.

[12] Sharma S, Samanta G P. Dynamical Behaviour of an HIV/AIDS Epidemic Model. *Differ. Equ. Dyn. Syst.*, 2014, **22**: 369–395.

[13] Wang X, Song X. Global stability and periodic solution of a model for HIV infection of $CD4^+$ T cells. *Appl. Math. Comput.*, 2007, **189**: 1331–1340.

[14] Wodarz D, Nowak M A. Specific therapy regimes could lead to long-term immunological control of HIV. *Proc. Natl. Acad. Sci. USA*, 1999, **96**: 14464–14469.

[15] Nowak M A, Bangham C R. Population dynamics of immune responses to persistent viruses. *Science*, 1996, **272**: 74–79.

[16] Wang Y, Zhou Y, Wu J, Heffernan J. Oscillatory viral dynamics in a delayed HIV pathogenesis model. *Math. Biosci.*, 2009, **219**: 104–112.

[17] Liu W. Criterion of Hopf bifurcations without using eigenvalues. *J. Math. Anal. Appl.*, 1994, **182**: 250–256.

[18] Egami C. Bifurcation analysis of the Nowak-Bangham model in CTL dynamics. *Math. Biosci.*, 2009, **221**: 33–42.