Stability and Bifurcation Analysis for an Improved HIV Model with Time Delay and Cure Rate

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Abstract: In this paper, a modified delayed mathematical model for the dynamics of HIV with cure rate is considered. By regarding the time delay as bifurcation parameter, stability and existence of local Hopf bifurcation are studied by analyzing the transcendental characteristic equation. Then the global existence of bifurcating periodic solutions is established with the assistance of global Hopf bifurcation theory. Finally, some numerical examples are given.

Key–Words: HIV, Hopf bifurcation, stability, delay

1 Introduction

Mathematical modeling in epidemiology provides understanding of the mechanisms that influence the spread of a disease and it suggests control strategies [1]. Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS). To understand HIV dynamics and disease progression, varieties of dynamic models based on differential equations have been proposed in [2, 3, 4, 5, 6].

We will consider some models for HIV–1 population dynamics below from [7, 8]. Here there are two components: x, the number of uninfected CD4$^+$ T–cells and y, the number of infected such cells. Then the evolution of the system is described as follows:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = s - \mu x - \beta xy, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \beta xy - vy, \end{cases}$$

where all the parameters and variables are non–negative. s denotes the rate of production of CD4$^+$ T–cells, μ is the per capita death rate, βxy denotes the rate of infection of CD4$^+$ T–cells by virus, and vy is the rate of disappearance of infected cells. The viral variable has been omitted for simplicity. A more complete model of HIV dynamics takes account of three components: the uninfected and infected CD4$^+$ T–cells, and the virus in plasma. Then the revised system is:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = s - \mu x - \beta xz, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = \beta xz - vy, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = cy - uz. \end{cases}$$

Here c is the rate of production of virions by infected cells, u is the death rate of virus particles. z is the number of virus particles.

In [9], Wang et al modified the term βxz into $\frac{\beta xz}{x+z}$ and studied the stability of equilibrium and basin of global attraction. Following the ideas in [10], Srivastava and Chandra assumed that a fraction of infected CD4$^+$ T cells returned to the uninfected class, and presented the following model by taking account of the evolution of drug resistance in [11]:

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = s - kxz - dx + by, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = kxz - (b+\delta)y, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = N\delta y - cz. \end{cases} \tag{1}$$

Here, all the coefficients are positive constants. The parameter s is the inflow rate of T cells and d is the natural death rate, k represents the rate of infection of T cells, δ represents the death rate of infected T cells and includes the possibility of death by bursting of infected T cells, hence $\delta \geq d$, b is the rate at which infected cells return to uninfected class, c is the death rate of virus and N is the average number of viral particles produced by infected cells. The local and global stabilitis of non–negative equilibria have been discussed by means of compound matrix.

Recently, it has been realized that time delay should be taken into consideration. Motivated by the method in [12], we introduce a time delay to represent the incubation time that the vectors need to become infectious. The new model is

$$\begin{cases} \frac{\mathrm{d}x}{\mathrm{d}t} = s - kx(t-\tau)z(t-\tau) - dx + by, \\ \frac{\mathrm{d}y}{\mathrm{d}t} = kx(t-\tau)z(t-\tau) - (b+\delta)y, \\ \frac{\mathrm{d}z}{\mathrm{d}t} = N\delta y - cz, \end{cases} \tag{2}$$

here τ is the time lag from infection of cells to the cells becoming actively infected.

If the first equation of (2) has no time delay, the stability of equilibria was studied in [11]. It was found that the delay has no effect on the stability result under certain conditions. However, for system (2), whether the time delay will lead to periodic oscillations from Hopf bifurcation is interesting. The theoretical analysis for exploring this phenomenon is more challenging and remains unknown.

It should be mentioned that some papers have focused on the stability and local Hopf bifurcation in delayed HIV model, such as [4, 13, 14, 15]. Nevertheless, there are few results about the global Hopf bifurcation for HIV model. Therefore, the main purpose of this paper is to discuss the stability of equilibria and establish the existence of local and global Hopf bifurcating periodic solutions.

The paper is organized as follows: in Section 2 and Section 3, the stability criterion and existence of local Hopf bifurcation are discussed. In Section 4, the global continuation of local bifurcation is done. In Section 5, some numerical examples are given to illustrate the theoretical analyses. Finally, conclusions are given.

2 Stability of Virus–free Equilibrium

In this section, we mainly focus on the local stability of uninfected equilibrium. Obviously, if $R_0 = \frac{N\delta ks}{cd(b+\delta)} > 1$, then there are two nonnegative equilibria:

$$E_1 = \left(\frac{s}{d}, 0, 0\right) \quad , \quad E_2 = (x^*, y^*, z^*).$$

Here,

$$x^* = \frac{(b+\delta)c}{N\delta k},$$

$$y^* = \frac{1}{\delta}\left(s - \frac{cd(\delta+b)}{N\delta k}\right),$$

$$z^* = \frac{N\delta y^*}{c}.$$

The Jacobian matrix of system (2) at virus–free equilibrium E_1 is

$$J_1 = \begin{bmatrix} -d & b & -\frac{ks}{d}e^{-\lambda\tau} \\ 0 & -(b+\delta) & \frac{ks}{d}e^{-\lambda\tau} \\ 0 & N\delta & -c \end{bmatrix},$$

and the characteristic equation is

$$\begin{aligned}&(\lambda+d)[\lambda^2 + (b+c+\delta)\lambda + (b+\delta)c \\ &-\tfrac{Nks\delta}{d}e^{-\lambda\tau}] = 0.\end{aligned} \tag{3}$$

It is well known that the stability of the equilibrium of delay differential equation depends on the distribution of the zeros of characteristic equation. In the following, we shall use the main results in Ruan and Wei [16], which is a generalization of the lemma in Cook and Grossman [17], to analyze the distribution of characteristic roots for (3). We first state the useful lemma as follows.

Lemma 1 *Consider the following exponential polynomial:*

$$\begin{aligned} & P(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2}, \ldots, e^{-\lambda\tau_m}) \\ = \; & \lambda^n + p_1^{(0)}\lambda^{n-1} + p_2^{(0)}\lambda^{n-2} + \ldots + p_n^{(0)} \\ & +[p_1^{(1)}\lambda^{n-1} + p_2^{(1)}\lambda^{n-2} + \ldots + p_n^{(1)}]e^{-\lambda\tau_1} \\ & + \ldots \\ & +[p_1^{(m)}\lambda^{n-1} + p_2^{(m)}\lambda^{n-2} + \ldots + p_n^{(m)}]e^{-\lambda\tau_m}, \end{aligned}$$

where $\tau_i \geq 0 (i = 1, 2, \ldots, m)$ and $p_j^{(i)} (i = 0, 1, \ldots, m; j = 1, 2, \ldots, n)$ are constants. As $(\tau_1, \tau_2, \ldots, \tau_m)$ vary, the sum of the orders of the zeros of $P(\lambda, e^{-\lambda\tau_1}, e^{-\lambda\tau_2}, \ldots, e^{-\lambda\tau_m})$ in the open right half plane can change only if a zero appears on or crosses the imaginary axis.

This means that the number of characteristic roots with positive real parts can change only if there exist purely imaginary roots.

If $\tau = 0$, from Routh–Hurwitz criterion, all roots of equation (3) have negative real part when $R_0 < 1$; only one root of (3) has positive real part when $R_0 > 1$.

For $\tau \neq 0$, we assume that $\lambda = i\omega(\omega > 0)$ is a root of equation (3). This is the case if and only if ω satisfies the following equation:

$$-\omega^2+i\omega(b+c+\delta)+(b+\delta)c = \frac{N\delta sk}{d}(\cos\omega\tau - i\sin\omega\tau).$$

Separating the real and imaginary parts, we have the following equations for ω:

$$\begin{cases} -\omega^2 + c(b+\delta) = \frac{N\delta sk}{d}\cos\omega\tau, \\ -\omega(b+c+\delta) = \frac{N\delta sk}{d}\sin\omega\tau. \end{cases}$$

It follows that

$$\omega^4 + A_1\omega^2 + A_2 = 0, \tag{4}$$

where

$$A_1 = b^2 + c^2 + \delta^2 - 2b\delta > 0,$$
$$A_2 = \left((b+\delta)c + \frac{N\delta sk}{d}\right)\left((b+\delta)c - \frac{N\delta sk}{d}\right).$$

Hence, if $R_0 > 1$, equation (4) has the unique positive root ω_{01} when $\tau = \tau_{l1} = \frac{1}{\omega_0}\arcsin\left(\frac{-d\omega_0(b+c\delta)}{N\delta sk} + 2l\pi\right)$ $(l = 0,1,2,\ldots)$; if $R_0 < 1$, equation (4) has no positive root. Moreover, equation (3) has a pair of purely imaginary roots when $R_0 > 1$, and has no purely imaginary root when $R_0 < 1$.

Then, let's consider the transversality condition. Differentiating equation (3) with respect to τ, we have

$$(2\lambda + b + c + \delta)\frac{d\lambda}{d\tau} + \frac{N\delta sk\tau}{de^{\lambda\tau}}\frac{d\lambda}{d\tau} = -\frac{\lambda N\delta sk}{de^{\lambda\tau}}.$$

Thus,

$$\begin{aligned}
& \operatorname{sign}\left\{\frac{d\mathrm{Re}(\lambda)}{d\tau}\bigg|_{\omega=\omega_{01},\tau=\tau_{l1}}\right\} \\
= & \operatorname{sign}\left\{\mathrm{Re}\left(\frac{d\lambda}{d\tau}\right)^{-1}\right\} \\
= & \operatorname{sign}\left\{\mathrm{Re}\left(-\frac{(2\lambda+b+c+\delta)d}{\lambda N\delta ske^{-\lambda\tau}} - \frac{\tau}{\lambda}\right)\right\} \\
= & \operatorname{sign}\left\{\mathrm{Re}\left(\frac{-(2\lambda+b+c+\delta)}{\lambda(\lambda^2+(b+c+\delta)\lambda+(b+\delta)c)}\right)\right\} \\
= & \operatorname{sign}\left\{\frac{i(2\omega i+b+c+\delta)}{\omega(-\omega^2+(b+c+\delta)\omega i+(b+\delta)c)}\right\} \\
= & \operatorname{sign}\left\{2\omega^2 - 2c(b+\delta) + (b+c+\delta)^2\right\} \\
= & \operatorname{sign}\left\{2\omega^2 + (b+\delta)^2 + c^2\right\} \\
> & \ 0.
\end{aligned}$$

According to Lemma 1, we can conclude the stability of virus–free equilibrium as follows:

Theorem 2 *For $R_0 < 1$, all roots of equation (3) have negative real parts for any $\tau > 0$, then the equilibrium E_1 is absolutely stable. For $R_0 > 1$, equation (3) has $(2l+3)$ roots with positive real parts for $\tau \in (\tau_{l1}, \tau_{(l+1)1})$ $(l = 0,1,2,\ldots)$, then E_1 is unstable.*

From Theorem 2, it is found that time delay has no effect on the dynamic behaviors of equilibrium E_1.

3 Existence of Hopf bifurcation

Next, we shall discuss the stability of infected equilibrium E_2. The linear part of system (2) at E_2 is

$$\frac{dX(t)}{dt} = AX(t) + BX(t-\tau), \tag{5}$$

where $X(t) = (x(t), y(t), z(t))^{\mathrm{T}}$,

$$A = \begin{bmatrix} -d & b & 0 \\ 0 & -(b+\delta) & 0 \\ 0 & N\delta & -c \end{bmatrix},$$

and

$$B = \begin{bmatrix} -kz^* & 0 & -kx^* \\ kz^* & 0 & kx^* \\ 0 & 0 & 0 \end{bmatrix}.$$

The characteristic equation of (5) is

$$\lambda^3 + a_0\lambda^2 + a_1\lambda + a_2 + (b_0\lambda^2 + b_1\lambda + B_2)e^{-\lambda\tau} = 0, \tag{6}$$

where

$$\begin{aligned}
a_0 &= b+c+d+\delta, \\
a_1 &= d(b+c+\delta) + c(b+\delta), \\
a_2 &= cd(b+\delta), \\
b_0 &= kz^*, \\
b_1 &= k(\delta+c)z^* - c(b+\delta), \\
b_2 &= \delta ckz^* - cd(b+\delta).
\end{aligned}$$

If $\tau = 0$, then all roots of equation (6) have negative real parts when $R_0 > 1$. If $\tau \neq 0$, this equation has infinitely many roots. Next, we shall discuss the sum of zeros of equation (6) in the open right half plane.

Let $\lambda = i\omega(\omega > 0)$ be a root of (6), then

$$\begin{aligned}
&-i\omega^3 - a_0\omega^2 + ia_1\omega + a_2 \\
&+(b_2 - b_0 + ib_1\omega)(\cos\omega\tau - i\sin\omega\tau) = 0.
\end{aligned}$$

Separating the real and imaginary parts, we have

$$\begin{cases} a_1\omega - \omega^3 = (b_2 - b_0\omega^2)\sin\omega\tau - b_1\omega\cos\omega\tau, \\ a_0\omega^2 - a_2 = (b_2 - b_0\omega^2)\cos\omega\tau + b_1\omega\sin\omega\tau. \end{cases} \tag{7}$$

Squaring and adding both equations of (7), we can obtain the following sixth–degree equation for ω:

$$\begin{aligned}&\omega^6 + (a_0^2 - b_0^2 - 2a_1)\omega^4 + (a_1^2 - 2a_1a_2\\&-b_1^2 + 2b_0b_2)\omega^2 + (a_2^2 - b_2^2) = 0.\end{aligned} \tag{8}$$

Putting $\omega^2 = u$ into (8), we can get the following cubic equation:

$$\begin{aligned}F(u) &= u^3 + (a_0^2 - b_0^2 - 2a_1)u^2 + (a_1^2 - 2a_1a_2\\&\quad -b_1^2 + 2b_0b_2)u + (a_2^2 - b_2^2)\\&= 0.\end{aligned}$$

Note that

$$\begin{aligned}F'(u) &= 3u^2 + 2(a_0^2 - b_0^2 - 2a_1)u\\&\quad +(a_1^2 - 2a_1a_2 - b_1^2 + 2b_0b_2).\end{aligned}$$

Let

$$\Delta = (a_0^2 - b_0^2 - 2a_1)^2 - 3(a_1^2 - 2a_1a_2 - b_1^2 + 2b_0b_2).$$

It is obvious that $a_2^2 - b_2^2 < 0$ if and only if $a_2 - b_2 < 0$. Since $\lim_{u\to+\infty} F(u) = +\infty$, if $F(0) = a_2^2 - b_2^2 < 0$, we know that $F(u) = 0$ has at least one positive root, and the characteristic equation has a pair of purely imaginary roots.

If $\Delta \le 0$, then $F'(u) \ge 0$, and thus $F(u)$ is monotonically increasing for $u \ge 0$. Hence $F(u) = 0$ has no positive root when $F(0) = a_2^2 - b_2^2 > 0$ and $\Delta \le 0$. Therefore, the characteristic equation has no purely imaginary root.

Besides, if $\Delta > 0$, then $F'(u) = 0$ has two real roots:

$$u_1 = \frac{-(a_0^2 - b_0^2 - 2a_1) + \sqrt{\Delta}}{3}$$

and

$$u_2 = \frac{-(a_0^2 - b_0^2 - 2a_1) - \sqrt{\Delta}}{3}.$$

If $u_1 > 0$ and $F(u_1) < 0$, then $F(u) = 0$ has positive roots.

Let $u_l (1 \le l \le 3)$ be the positive roots of $F(u) = 0$ and $\omega_l = \sqrt{u_l}$. By (7), we have

$$\cos\omega_l\tau = \frac{(b_1 - a_0b_0)\omega_l^4 + (a_2b_0 + a_0b_2 - a_1b_1)\omega_l^2 - a_2b_2}{(b_0\omega_l^2 - b_2)^2 + b_1^2\omega_l^2}.$$

Thus, if we denote

$$\tau_l^{(j)} = \frac{1}{\omega_l}\left\{\arccos A + 2j\pi\right\},$$

where $A = \frac{(b_1-a_0b_0)\omega_l^4+(a_2b_0+a_0b_2-a_1b_1)\omega_l^2-a_2b_2}{(b_0\omega_l^2-b_2)^2+b_1^2\omega_l^2}$, $l = 1, 2, 3$, $j = 0, 1, 2, \ldots$. Then $\pm i\omega_l$ is a pair of purely imaginary roots of (6) with $\tau = \tau_l^{(j)}$.

Define

$$\tau_0 = \tau_{l0}^{(0)} = \min_{l\in\{1,2,3\}}\{\tau_l^{(j)}\}, \quad \omega_0 = \omega_{l0},$$

and

$$\tau_j = \tau_0 + \frac{2j\pi}{\omega_0}, \quad j = 0, 1, 2, \ldots.$$

From Lemma 1, it can be concluded that all the characteristic roots have negative real parts for any $\tau \in [0, \tau_0)$. And then, we shall verify the transversality condition.

Lemma 3 *If $F'(\omega_0^2) \neq 0$ is satisfied, then*

$$\frac{d(Re\lambda(\tau_0))}{d\tau} > 0.$$

Proof: Differentiating both sides of equation (6) with respect to τ, we get

$$\left[\frac{\mathrm{d}\lambda(\tau)}{\mathrm{d}\tau}\right]^{-1} = \frac{e^{\lambda\tau}(3\lambda^2 + 2a_0\lambda + a_1) + 2b_0\lambda + b_1}{\lambda(b_0\lambda^2 + b_1\lambda + b_2)} - \frac{\tau}{\lambda}.$$

This gives

$$\begin{aligned}&\left[\frac{\mathrm{dRe}\lambda(\tau)}{\mathrm{d}\tau}\right]^{-1}_{\tau=\tau_0}\\
=\ & \mathrm{Re}\left[\frac{e^{\lambda\tau}(3\lambda^2 + 2a_0\lambda + a_1) + 2b_0\lambda + b_1}{\lambda(b_0\lambda^2 + b_1\lambda + b_2)}\right]_{\tau=\tau_0}\\
=\ & \frac{1}{b_1^2\omega_0^4 + (b_2 - b_0\omega_0^2)^2\omega_0^2}\{2b_0\omega_0^2(b_2 - b_0\omega_0^2)\\
& (a_1 - 3\omega_0^2)\omega_0[(b_2 - b_0\omega_0^2)\sin\omega_0\tau_0] - b_1^2\omega_0^2\\
& +2a_0\omega_0^2[(b_2 - b_0\omega_0^2)\cos\omega_0\tau_0 + b_1\omega_0\sin\omega_0\tau_0]\}\\
=\ & \frac{1}{b_1^2\omega_0^2 + (b_2 - b_0\omega_0^2)^2}\{3\omega_0^4 + 2(a_0^2 - b_0^2 - 2a_1)\omega_0^2\\
& +a_1^2 - 2a_1a_2 - b_1^2 + 2b_0b_2\}\\
=\ & \frac{F'(\omega_0^2)}{b_1^2\omega_0^2 + (b_2 - b_0\omega_0^2)^2}.\end{aligned}$$

Hence,

$$\mathrm{sign}\left\{\frac{\mathrm{dRe}\lambda(\tau)}{\mathrm{d}\tau}\right\}_{\tau=\tau_0} = \mathrm{sign}\{F'(\omega_0^2)\}.$$

Suppose for a moment that $\frac{\mathrm{d(Re}\lambda(\tau_0))}{\mathrm{d}\tau} < 0$, then equation (6) has roots with positive real parts for $\tau < \tau_0$ and close to τ_0. This contradicts the fact that characteristic equation has no root with positive real part for $\tau < \tau_0$. Thus, this completes the proof. □

From above analysis, we can establish the distribution of characteristic roots of (6) and can derive the stability of infected equilibrium and small amplitude periodic solutions due to Hopf bifurcation [18].

Theorem 4 *Suppose $R_0 > 1$. The following results can be obtained.*
(i) *If $\Delta \leq 0$, then all roots of (6) have negative real parts for any $\tau \geq 0$, and the virus–free equilibrium E_1 is absolutely stable.*
(ii) *If $a_2 - b_2 < 0$ or $\Delta > 0$, $u_1 > 0$, $F(u_1) < 0$, then all roots of (6) have negative real parts only when $\tau \in [0, \tau_0)$. Moreover, the infected equilibrium E_2 is stable when $\tau \in [0, \tau_0)$ and unstable when $\tau > \tau_0$. τ_0 is the Hopf bifurcation value, which means that periodic solutions will bifurcate from this positive equilibrium as τ passes through the critical value τ_0.*

This theorem can establish the existence of bifurcating periodic solutions. Further, by following the algorithm in [18], we can also determine the direction of Hopf bifurcation and stability of periodic solutions. However, that procedure is so tedious that we omit it.

4 Global Continuation of Local Hopf Bifurcation

It is known that the periodic solutions established by Theorem 4 only exit in a small neighborhood of the critical value. It is significant to explore the global existence of those bifurcating periodic solutions. Next, by using the global bifurcation theorem due to Wu [19], we shall study the global continuation of local Hopf bifurcation at infected equilibrium E_2.

For simplification of notation, setting $u_t = (x_t, y_t, z_t)^T$, system (2) can be rewritten as the following functional differential equation:

$$\dot{u}(t) = F(u_t, \tau, T), \tag{9}$$

where $u_t(\theta) = u(t + \theta) \in C([-\tau, 0], R^3)$.

Following the work of Wu [19], we need to define $X = C([-\tau, R^3])$,

$$\Sigma = Cl \left\{ \begin{array}{l} (u, \tau, T) \in X \times R \times R^+ : \\ u \text{ is a } T\text{-periodic solution of (9)} \end{array} \right\}$$

and

$$N = \{(\hat{u}, \tau, T) : F(\hat{u}, \tau, T) = 0\}$$

where $\hat{u}$ and u are the equilibrium and a nonconstant periodic solution of equation (9), respectively. Let $C(\hat{u}, \tau_j, 2\pi/\omega_0)$ denote the connected component through isolated center $(\hat{u}, \tau_j, 2\pi/\omega_0)$ in Σ.

Lemma 5 *All nonconstant periodic solutions of (2) with positive initial values are ultimately uniformly bounded when τ is bounded.*

Proof: It follows from (2) that

$$\begin{cases} x(t) = x(0) \exp\left\{ \int_0^t \left(\frac{s}{x(v)} - \frac{kx(v-\tau)z(v-\tau)}{x(v)} - d \right\} \right. \\ \qquad \left. + \frac{by(v)}{x(v)} \right) \mathrm{d}v \Big\}, \\ y(t) = y(0) \exp\left\{ \int_0^t \left(\frac{kx(v-\tau)z(v-\tau)}{y(v)} - (b+\delta) \right) \mathrm{d}v \right\}, \\ z(t) = z(0) \exp\left\{ \int_0^t \left(\frac{N\delta y(v)}{z(v)} - c \right) \mathrm{d}v \right\}, \end{cases}$$

which implies that the solutions of (2) cannot cross the coordinate axes. Therefore, we have $x(t) > 0$, $y(t) > 0$ and $z(t) > 0$ for $t \geq 0$ under the positive initial values.

From the first two equations of (2), we get

$$\begin{aligned} (x(t) + y(t))' &= s - dx(t) - \delta y(t) \\ &\leq s - \tilde{d}(x(t) + y(t)), \end{aligned}$$

where $\tilde{d} = \min\{d, \delta\}$, and thus

$$\limsup_{t \to +\infty} (x(t) + y(t)) \leq \frac{s}{\tilde{d}}.$$

Then,

$$\begin{aligned} (z(t))' &= N\delta y(t) - cz(t) \\ &\leq N\delta \frac{s}{\tilde{d}} - cz(t), \end{aligned}$$

and

$$\limsup_{t \to +\infty} z(t) \leq \frac{N\delta s}{c\tilde{d}}.$$

Therefore, $x(t)$, $y(t)$ and $z(t)$ are ultimately uniformly bounded. □

Lemma 6 *System (2) has no nonconstant periodic solutions with period τ when $R_0 > 1$.*

Proof: Note that if $u(t) = (x(t), y(t), z(t))^{\mathrm{T}}$ is a $\tau-$periodic solution of (2), then $u(t)$ is a nonconstant $\tau-$periodic solution of the corresponding ordinary differential system(1). It has been proved in [11] that the positive equilibrium E_2 is globally stable when $R_0 > 1$. Thus, system (1) has no nonconstant $\tau-$periodic solution. The proof is complete. □

Lemma 7 *The periods of periodic solutions of (2) are uniformly bounded.*

Proof: By the definition of τ_j in Section 3, when $j \geq 1$, we have $2\pi/\omega_0 \leq \tau_j$.For $\tau > \tau_j$, there exists an integer m, such that $\frac{\tau}{m} < 2\pi/\omega_0 < \tau$. As system (1.0) has no nontrivial $\tau-$periodic solution, for any integer n, (2) has no $\frac{\tau}{n}-$periodic solution. This implies that the period T of a periodic solution on the connected component $C(\hat{u}, \tau_j, 2\pi/\omega_0$ satisfies $\tau/m < p < \tau$. So we can know that the periods of the periodic solutions of (2) on $C(\hat{u}, \tau_j, \frac{2\pi}{\omega_0})$ are uniformly bounded. □

Theorem 8 *Suppose that $R_0 > 1$ and hypothesis (ii) in Theorem 4 are satisfied. Then system (2) still has periodic solutions even when $\tau > \tau_j (j = 1, 2, \ldots)$.*

Proof: By the definition of isolated center in [19], we can easily verify that (E_2, τ_j, T) is the unique isolated center. The characteristic equation of (2) at positive equilibrium E_2 is

$$\begin{aligned} & \Delta(E_2, \tau, p)(\lambda) \\ = \; & \lambda^3 + a_0\lambda^2 + a_1\lambda + a_2 + (b_0\lambda^2 + b_1\lambda + b_2)e^{-\lambda\tau}. \end{aligned}$$

There exist $\varepsilon > 0$, $\gamma > 0$ and a smooth curve $\lambda(\tau) : (\tau_j - \gamma, \tau_j + \gamma) \to C$, such that for any $\tau \in [\tau_j - \gamma, \tau_j + \gamma]$,

$$\Delta(\lambda(\tau)) = 0, |\lambda(\tau) - \omega_0 i| < \varepsilon,$$

and

$$\lambda(\tau_j) = i\omega_0,$$

$$\left.\frac{\mathrm{dRe}\lambda(\tau)}{\mathrm{d}\tau}\right|_{\tau=\tau_j} \neq 0.$$

Let $\Omega_{\varepsilon, \frac{2\pi}{\omega_0}} = \{(\eta, T) : 0 < \eta < \varepsilon, |T - \frac{2\pi}{\omega_0}| < \varepsilon\}$. If $|\tau - \tau_j| \leq \delta$ and $(\eta, T) \in \partial\Omega_{\varepsilon, 2\pi/\omega_0}$ are satisfied, then $\Delta(E_2, \tau, T)(\eta + \frac{2\pi}{T} i) = 0$ if and only if $\eta = 0$, $\tau = \tau_j, T = \frac{2\pi}{\omega_0}$.

If we put

$$H^{\pm}(E_2, \tau_j, \frac{2\pi}{\omega_0})(\eta, T) = \Delta(E_2, \tau_j \pm \gamma, T)(\eta + i\frac{2\pi}{T}),$$

then we have

$$\begin{aligned} \gamma(E_2, \tau_j, \frac{2\pi}{\omega_0}) &= \deg_B(H^-(E_2, \tau_j, \frac{2\pi}{\omega_0}), \Omega_{\varepsilon, \frac{2\pi}{\omega_0}}) \\ &\quad -\deg_B(H^+(E_2, \tau_j, \frac{2\pi}{\omega_0}), \Omega_{\varepsilon, \frac{2\pi}{\omega_0}}) \\ &= -1. \end{aligned}$$

According to Theorem 3.3 in [19], connected component $C(E_2, \tau_j, \frac{2\pi}{\omega_0})$ are unbounded. From Lemma 5 and Lemma 7, the projection of $C(E_2, \tau_j, \frac{2\pi}{\omega_0})$ onto $\tau-$space are unbounded.

As $\tau = 0$, system (2) has no nontrivial periodic solution, this implies that projection of $C(E_2, \tau_j, \frac{2\pi}{\omega_0})$ onto $\tau-$space must be positive and has a lower bound. Thus, periodic solutions still exist even if $\tau > \tau_j$. This completes the proof. □

5 Numerical Simulation

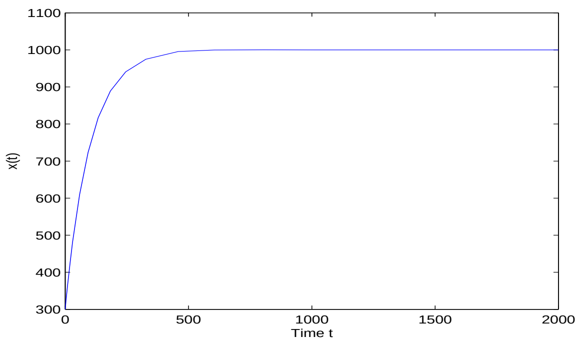
In this section, we try to present some numerical examples for system (2) to validate the previous main theorems. By extracting the values from [11], we choose a set of parameters as follows:

$$s = 10, \; b = 0.2, \; k = 0.000024, \; d = 0.01,$$
$$\delta = 0.16, \; c = 3.4, \; N = 1000.$$

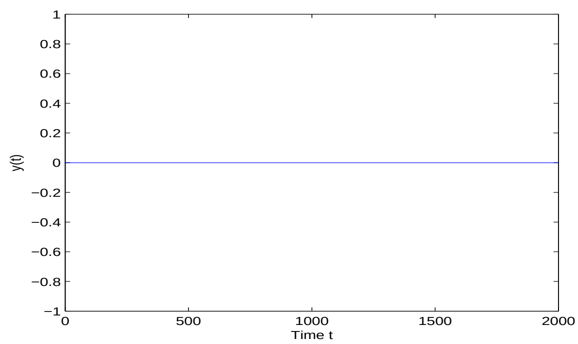
Then $R_0 = 3.13725$, $E_1 = (1000, 0, 0)$ and $E_2 = (318.75, 42.5781, 2003.68)$. By direct computation with Mathematica, we can also obtain that equation (8) has the unique positive root $\omega_0 = 0.00983002$, and $\tau_0 = 195.585$, $a_2 - b_2 = -0.00168$, $F'(\omega_0^2) = 0.455948 > 0$.

First, we set $\tau = 10$. From Fig.1 and Fig.2, it is clear that the solutions will converge to different equilibria with initial values $I_{10} = (300, 0, 0)$ and $I_{20} = (300, 0.001, 0)$, respectively. This means that even tiny infected CD4$^+$ T–cells may lead to the disease transmission.

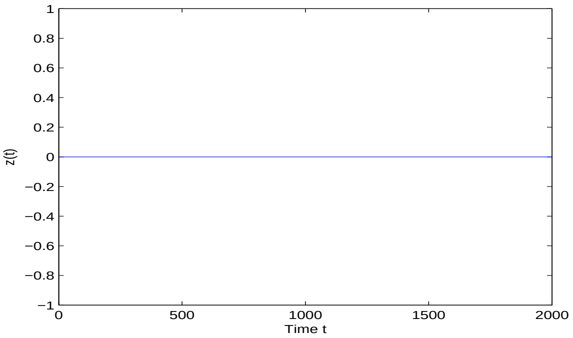
Next, we fix the initial value $I_{30} = (300, 40, 2000)$, the infected equilibrium E_2 is asymptotically stable as depicted in Fig.3 and Fig.4 when $\tau = 10$ or $\tau = 120$, which are smaller than τ_0. Fig.5 and Fig.6 show that periodic oscillations occur when τ is larger that τ_0, such as $\tau = 198$ and $\tau = 250$. Thus, we can claim that the time delay τ is vital to the solutions of system (2). The main results show that if we shorten the incubation period, we will control the disease.



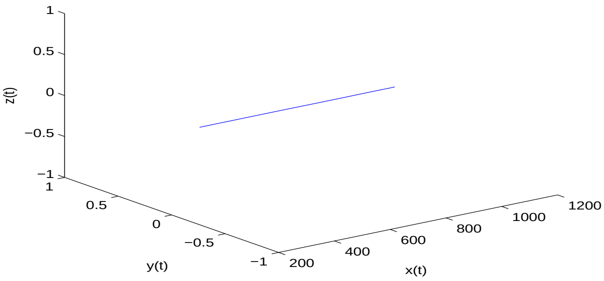
(a) $x - t$



(b) $y - t$

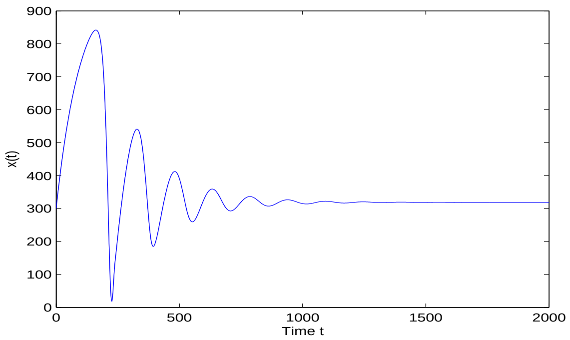


(c) $z - t$

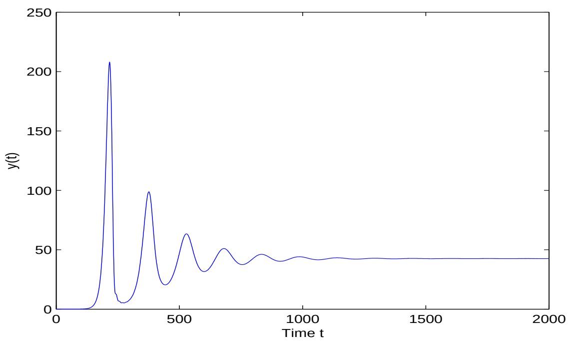


(d) $x - y - z$

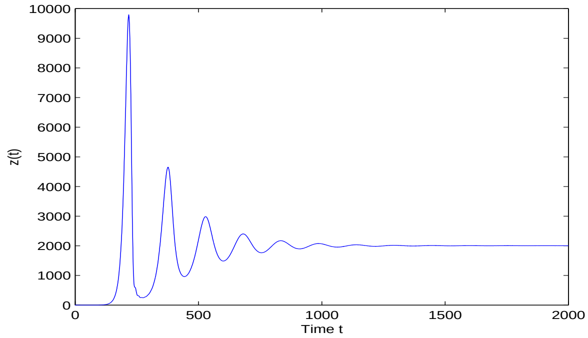
Fig. 1. Asymptotical stability of virus–free equilibrium E_1 for initial value $(300, 0, 0)$ with $\tau = 10$.



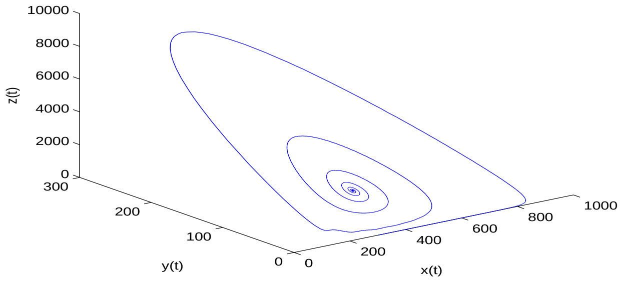
(a) $x - t$



(b) $y - t$

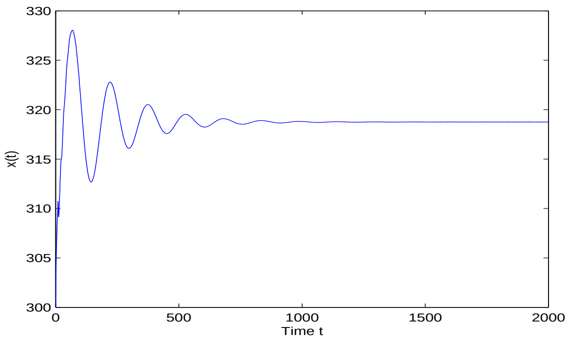


(c) $z - t$

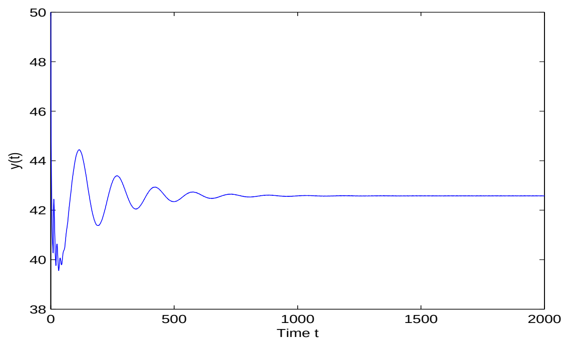


(d) $x - y - z$

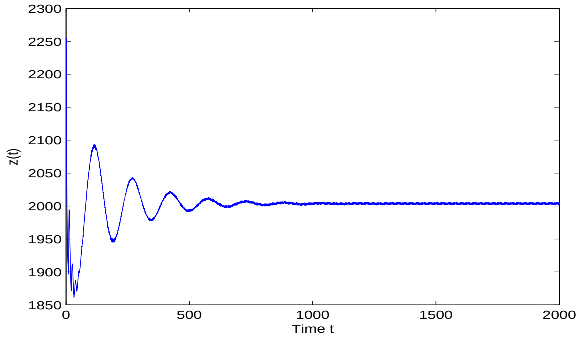
Fig. 2. Asymptotical stability of infected equilibrium E_2 for initial value $(300, 0.001, 0)$ with $\tau = 10$.



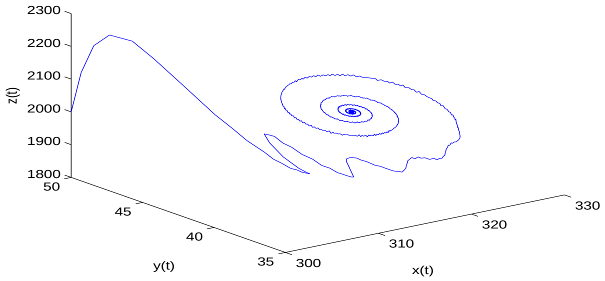
(a) $x - t$



(b) $y - t$

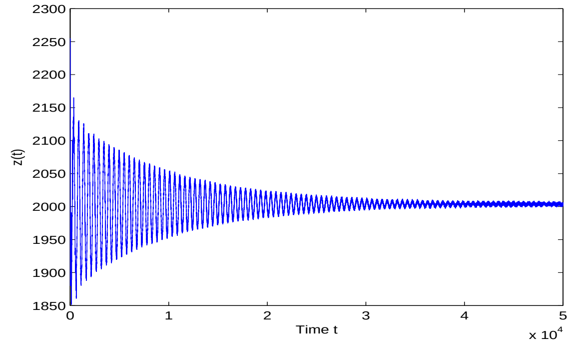


(c) $z - t$

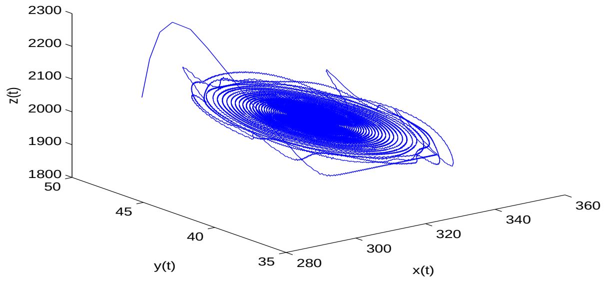


(d) $x - y - z$

Fig. 3. Asymptotical stability of infected equilibrium E_2 for initial value $(300, 40, 2000)$ with $\tau = 10 < \tau_0$.

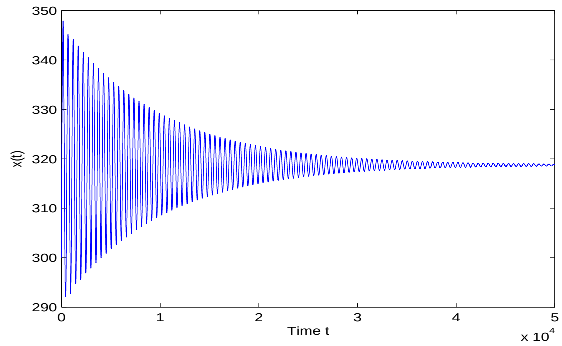


(c) $z - t$

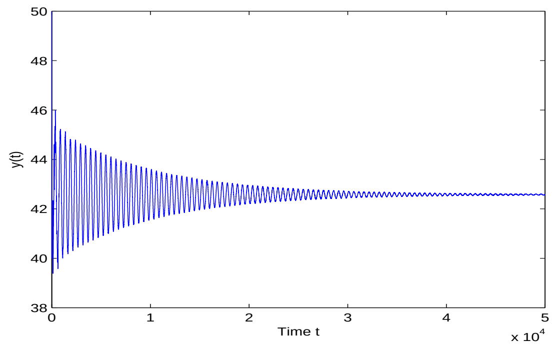


(d) $x - y - z$

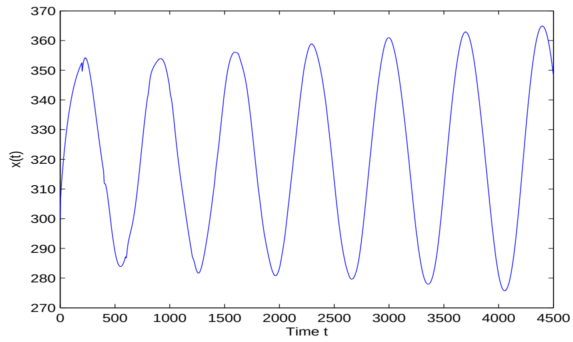
Fig. 4. Asymptotical stability of infected equilibrium E_2 for initial value $(300, 40, 2000)$ with $\tau = 120 < \tau_0$.



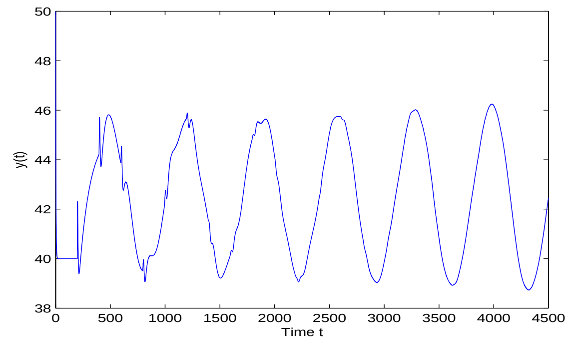
(a) $x - t$



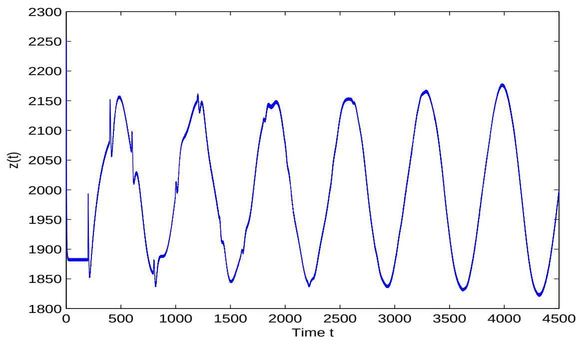
(b) $y - t$



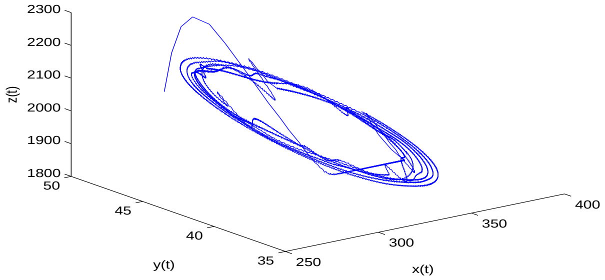
(a) $x - t$



(b) $y - t$

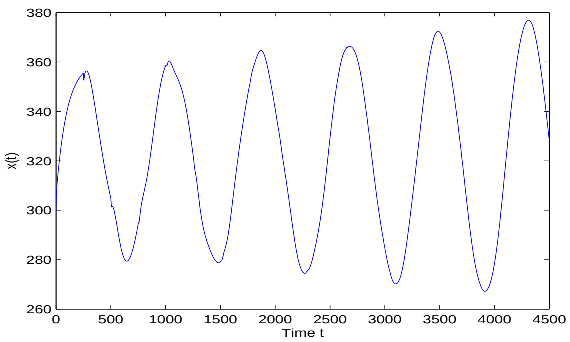


(c) $z - t$

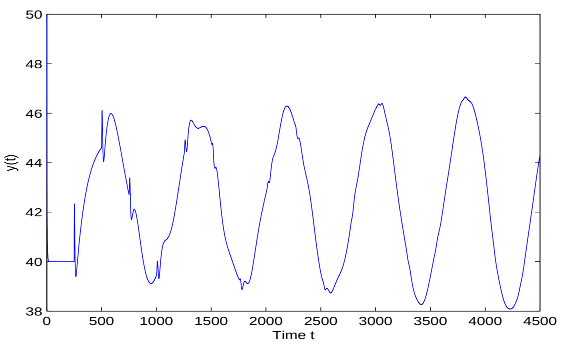


(d) $x - y - z$

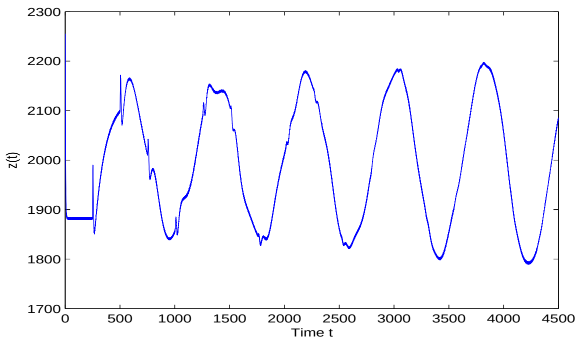
Fig. 5. Periodic solution of system (2) for initial value $(300, 40, 2000)$ with $\tau = 198 > \tau_0$.



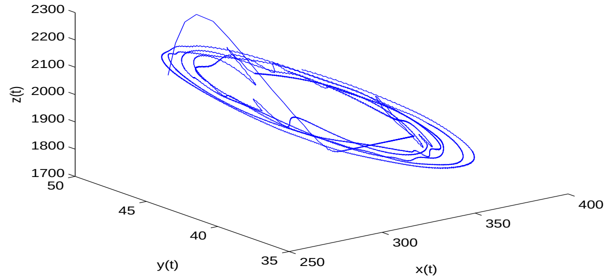
(a) $x - t$



(b) $y - t$



(c) $z - t$



(d) $x - y - z$

Fig. 6. Periodic solution of system (2) for initial value $(300, 40, 2000)$ with $\tau = 250 > \tau_0$.

6 Conclusion

In this paper, we have introduced time delay to a mathematical model for the dynamics of HIV and CD4$^+$ T cells with cure rate. Stabilities of the two nonnegative equilibria are investigated by analyzing the corresponding characteristic equations. By choosing the time delay as a bifurcation parameter, a sufficient condition has been established for local existence of Hopf bifurcation at the positive infected equilibrium. Then, with the help of global bifurcation theory due to Wu, global continuation of local bifurcation has been derived. Finally, through numerical simulations, it can be concluded that the latent period plays an important role in the disease spread and the disease may be controlled by shortening that latent period.

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