Available online at www.sciencedirect.com

ScienceDirect

J. Math. Anal. Appl. 342 (2008) 1342–1355

Journal of MATHEMATICAL ANALYSIS AND APPLICATIONS

www.elsevier.com/locate/jmaa

A differential equation model of HIV infection of CD4$^+$ T-cells with cure rate ☆

Xueyong Zhou [a], Xinyu Song [a,b,*], Xiangyun Shi [a]

[a] *Department of Mathematics, Xinyang Normal University, Xinyang 464000, Henan, PR China*

[b] *College of Mathematics and Information Science, Henan University, Kaifeng 475001, Henan, PR China*

Received 5 July 2006

Available online 13 January 2008

Submitted by G.F. Webb

Abstract

A differential equation model of HIV infection of CD4$^+$ T-cells with cure rate is studied. We prove that if the basic reproduction number $R_0 < 1$, the HIV infection is cleared from the T-cell population and the disease dies out; if $R_0 > 1$, the HIV infection persists in the host. We find that the chronic disease steady state is globally asymptotically stable if $R_0 > 1$. Furthermore, we also obtain the conditions for which the system exists an orbitally asymptotically stable periodic solution. Numerical simulations are presented to illustrate the results.

Keywords: HIV; Globally asymptotical stability; Periodic solution

1. Introduction

Although the correlates of immune protection in HIV infection remain largely unknown, our knowledge of viral replication dynamics and virus-specific immune responses has grown. Concurrent with these advances, there has been an abundance of mathematical models that attempt to describe these phenomena [1–11]. The models proposed have principally been linear and nonlinear ordinary differential equation models, both with and without delay terms. These models focus on the interactions of susceptible cells, infected cells, viruses, and immune cells. Simple HIV models have played a significant role in the development of a better understanding of the disease and the various drug therapy strategies used against it.

The simplest HIV dynamic model is

$$\frac{dV}{dt} = P - cV,$$

☆ This work is supported by the National Natural Science Foundation of China (No. 10771179), the Henan Innovation Project for University Prominent Research Talents (No. 2005KYCX017) and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry.

* Corresponding author at: Department of Mathematics, Xinyang Normal University, Xinyang 464000, Henan, PR China.
E-mail address: xysong88@163.com (X. Song).

0022-247X/$ – see front matter
doi:10.1016/j.jmaa.2008.01.008

where P is an unknown function representing the rate of virus production, c is a constant called the clearance rate constant, and V is the virus concentration.

The population dynamics of $CD4^+$ T cells in humans is not well understood. Nevertheless, a reasonable model for this population of cells is

$$\dot{T} = s - dT + aT\left(1 - \frac{T}{T_{\max}}\right),$$

where s represents the rate at which new T cells are created from sources within the body, such as the thymus, d is the death rate per T cell. T cells can also be created by proliferation of existing T cells. Here we represent the proliferation by a logistic function in which a is the maximum proliferation rate and $T_{\max}$ is the T cell population density at which proliferation shuts off. The human immune system can mount a highly specific response against virtually any foreign substance, even those never seen before in the course of evolution.

Like most viruses, HIV is a very simple creature. Viruses do not have the ability to reproduce independently. Therefore, they must rely on a host to aid reproduction. Most viruses carry copies of their DNA and insert this into the host cell's DNA. Then, when the host cell is stimulated to reproduce, it reproduces copies of the virus. When HIV infects the body, its target is $CD4^+$ T cells. Since $CD4^+$ T cells play the key role in the immune response, this is cause for alarm and a key reason for HIV's devastating impact. A protein on the surface of the virus has a high affinity for the $CD4^+$ protein on the surface of the T cell. Binding takes place, and the contents of the HIV is injected into the host T cell. HIV differs from most viruses in that it is a retrovirus: it carries a copy of its RNA which must first be transcribed into DNA. One of the mysteries to the medical community is why this class of virus has evolved to include this extra step. After the DNA of the virus has been duplicated by the host cell, it is reassembled and new virus particles bud from the surface of the host cell. This budding can take place slowly, sparing the host cell; or rapidly, bursting and killing the host cell. The course of infection with HIV is not clearcut. Clinicians are still arguing about what causes the eventual collapse of the immune system, resulting in death. What is widely agreed upon, however, is that there are four main stages of disease progression. First is the initial innoculum when virus is introduced into the body. Second is the initial transient—a relatively short period of time when both the T cell population and virus population are in great flux. This is followed by the third stage, clinical latency—a period of time when there are extremely large numbers of virus and T cells undergoing incredible dynamics, the overall result of which is an appearance of latency (disease steady state). Finally, there is AIDS—this is characterized by the T cells dropping to very low numbers (or zero) and the virus growing without bound, resulting in death. The transitions between these four stages are not well understood, and presently there is controversy concerning whether the virus directly kills all of the T cells in this final stage or if there is some other mechanism(s) at work.

Current combination antiretroviral therapies are widely used to treat HIV. The development of the drugs that are effective against HIV is a shining example of how understanding the basics of the genesis of HIV infection has led to the rapid development of drugs to combat the disease. And the principles for the treatment of HIV infection were developed simultaneously as a result of large, randomized, clinically controlled trials and because of the increasing understanding of the dynamics of HIV replication. Chemotherapy affects the virus once it enters the cell. Through chemotherapy, a part of infected cells can transform to target cells.

As with a single drug, the virus concentration in plasma fell dramatically for one to two weeks. However, under continued therapy, after this initial "first phase" of decline, the virus continued to fall but at a significantly slower rate. This variation may have been present in previous studies. In the work of Alan S. Perelson et al. [12], the results from Fig. 7.1 in [12] show a fast phase followed by what could be a flat second phase. The reason for this variation among individuals may lie in the important immunologic component of HIV infection. HIV is thought to be primarily a noncytopathic virus, and infected cells are lost either through death, mainly immune-mediated killing, or via "cure," i.e., loss of cccDNA. The second-phase decay has been associated with the rate of loss of productively infected cells. Antiviral therapy partially blocks the production of new virions and there is a rapid decline of plasma HIV RNA, but a vigorous immune response may be needed to drive second-phase decline, which involves the loss of cells still producing virus. Thus, some process may be slowing HIV clearance. We show that the pattern of HIV RNA decay can be more complex than the typical biphasic pattern, with some patients exhibiting additional phases, raising questions about the need to improve the basic viral dynamic model. We suggest that including both cytolytic and noncytolytic mechanisms of infected cell loss will make models more realistic as well as more accurate.

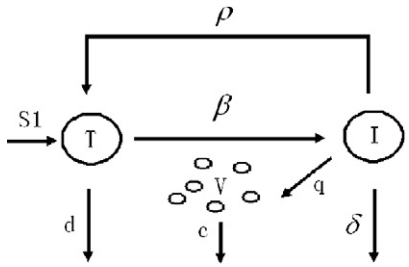

Fig. 1. Diagrammatic representation of the mathematical model for HIV treatment, where $S1 = s + aT(1 - \frac{T}{T_{\max}})$.

In this paper, we shall investigate a differential equation model of HIV infection of CD4$^+$ T-cells with cure rate. The transfer diagram is depicted in Fig. 1. The model considers a set of cells susceptible to infection, that is, target cells, T, which, through interactions with virus, V, become infected. In addition, infected cells may also revert to the uninfected state by loss of all cccDNA from their nucleus at a certain rate per infected cell, which is always omitted in many virus models, such as Alan S. Perelson et al. [12].

From Fig. 1, we can get a differential equation model of HIV infection of CD4$^+$ T-cells with cure rate:

$$\begin{cases} \dot{T} = s - dT + aT\left(1 - \dfrac{T}{T_{\max}}\right) - \beta TV + \rho I, \\ \dot{I} = \beta TV - \delta I - \rho I, \\ \dot{V} = qI - cV, \end{cases} \tag{1.1}$$

where T is the number of target cells, I is the number of infected cells, V is the viral load of the virions. The simplest and most common method of modeling infection is to augment (1.1) with a "mass-action" term in which the rate of infection is given by βTV, with β being the infection rate constant. This type of term is sensible, since virus must meet T cells in order to infect them and the probability of virus encountering a T cell at low concentrations (when V and T motions can be regarded as independent) can be assumed to be proportional to the product of their concentration, which is called linear infection rate. Thus, in what follows, the classical models assume that infected T cells at rate $-\beta TV$ and the generation of infected T cells at rate βTV. In model (1.1), s represents the rate at which new T cells are created from sources, a is the maximum proliferation rate of target cells, $T_{\max}$ is the T population density at which proliferation shuts off, d is death rate of the T cells, β is the infection rate constant, δ is the death rate of the infective cells, q is the reproductively rate of the infected cells, c is the clearance rate constant of virions, ρ is the rate of "cure," i.e. noncytolytic loss of infected cells. Thus the total rate of disappearance of infected cells is $\delta + \rho$. The average lifespan of a productively infected cell is $\frac{1}{\delta}$, and so if an infected cell produces a total of $\frac{q}{\delta}$ virions during its lifetime, the average rate of virus production per cell, q. Standard and simple arguments show that the solutions of system (1.1) exist and stay positive.

System (1.1) needs to be analyzed with the following initial conditions:

$$T(0) > 0, \qquad I(0) > 0, \qquad V(0) > 0. \tag{1.2}$$

We denote

$$R^3_+ = \{(T, I, V) \in R^3,\ T \geqslant 0,\ I \geqslant 0,\ V \geqslant 0\}.$$

2. Equilibria and their local stability

The nonnegative equilibria of system (1.1) are $\hat{E} = (\hat{T}, 0, 0)$, $\bar{E} = (\bar{T}, \bar{I}, \bar{V})$, where $\hat{T} = \frac{T_{\max}}{2a}(a - d + \sqrt{(a-d)^2 + \frac{4as}{T_{\max}}})$, $\bar{T} = \frac{c(\delta+\rho)}{\beta q}$, $\bar{I} = \frac{1}{\delta}[s - d\bar{T} + a\bar{T}(1 - \frac{\bar{T}}{T_{\max}})]$, $\bar{V} = \frac{q}{c}\bar{I}$.

Let $R_0 = \frac{\hat{T}}{\bar{T}}$. It is well known the importance of the value, R_0, which is called as the basic reproductive ratio of system (1.1). It represents the average number of secondary infection caused by a single infected T cells in an entirely susceptible T cells population throughout its infectious period. And it determines the dynamical properties of system (1.1) over a long period of time.

Now, we will begin to analyze the geometric properties of the equilibria of system (1.1).

Since $\hat{T}$ and $\bar{T}$ satisfy

$$s - d\hat{T} + a\hat{T}\left(1 - \frac{\hat{T}}{T_{\max}}\right) = 0,$$

$$s - d\bar{T} + a\bar{T}\left(1 - \frac{\bar{T}}{T_{\max}}\right) = \frac{1}{q\alpha}\left[q\beta\bar{T} - c(\delta+\rho)\right],$$

we can get

$$\bar{T} > \frac{c(\delta+\rho)}{\beta q} \quad \Rightarrow \quad s - d\hat{T} + a\hat{T}\left(1 - \frac{\hat{T}}{T_{\max}}\right) > 0 \quad \Rightarrow \quad \hat{T} > \bar{T}$$

and

$$\bar{T} < \frac{c(\delta+\rho)}{\beta q} \quad \Rightarrow \quad s - d\hat{T} + a\hat{T}\left(1 - \frac{\hat{T}}{T_{\max}}\right) < 0 \quad \Rightarrow \quad \hat{T} < \bar{T}.$$

Thus, if $R_0 > 1$, then the positive equilibrium $\bar{E} = (\bar{T}, \bar{I}, \bar{V})$ exists.

The *Jacobian matrix* of system (1.1) is

$$J = \begin{pmatrix} a - d - \frac{2aT}{T_{\max}} - \beta V & \rho & -\beta T \\ \beta V & -(\delta+\rho) & \beta T \\ 0 & q & -c \end{pmatrix}.$$

Let $E^*(T^*, I^*, V^*)$ be any arbitrary equilibrium. Then the characteristic equation about E^* is given by

$$\begin{vmatrix} \lambda - (a - d - \frac{2aT^*}{T_{\max}} - \beta V^*) & -\rho & \beta T^* \\ -\beta V^* & \lambda + \delta + \rho & -\beta T^* \\ 0 & -q & \lambda + c \end{vmatrix} = 0. \tag{2.1}$$

For equilibrium $\hat{E} = (\hat{T}, 0, 0)$, (2.1) reduces to

$$\left(\lambda - a + d + \frac{2a\hat{T}}{T_{\max}}\right)\left[\lambda^2 + (c+\delta+\rho)\lambda + c(\delta+\rho) - q\beta\hat{T}\right] = 0. \tag{2.2}$$

Hence, $\hat{E} = (\hat{T}, 0, 0)$ is locally asymptotically stable for $R_0 < 1$. And it is a saddle with $\dim W^s(\hat{E}) = 2$, $\dim W^u(\hat{E}) = 1$ for $R_0 > 1$. Then we have the following theorem.

Theorem 2.1. *If $R_0 < 1$, $\hat{E} = (\hat{T}, 0, 0)$ is locally asymptotically stable; if $R_0 > 1$, $\hat{E} = (\hat{T}, 0, 0)$ is unstable.*

Theorem 2.2. *There is $M > 0$ such that, for any positive solution $(T(t), I(t), V(t))$ of system (1.1), $T(t) \leqslant M$, $I(t) \leqslant M$ and $V(t) \leqslant M$, for all large t.*

Proof. Let $L_1(t) = T(t) + I(t)$. Calculating the derivative of $L_1(t)$ along the solution of system (1.1), we find

$$\begin{aligned} \dot{L}_1(t)|_{(1.1)} &= \dot{T}(t) + \dot{I}(t) \\ &= s - dT + aT\left(1 - \frac{T}{T_{\max}}\right) - \delta I \\ &= -dT - \delta I + aT - \frac{a}{T_{\max}}T^2 + s \\ &\leqslant -hL_1(t) + M_0, \end{aligned}$$

where $M_0 = \frac{T_{\max}a^2 + 4as}{4a}$, $h = \min(d, \delta)$. Then there exists $M_1 > 0$, depending only on the parameters of system (1.1), such that $L_1(t) < M_1$, for all t large enough. Then $T(t)$ and $I(t)$ have ultimately above bound. It follows from the third equation of system (1.1) that $V(t)$ has an ultimately above bound, say, their maximum is M. The proof is complete. □

Define $D = \{(T, I, V) \in R^3\colon\ 0 < T \leqslant M,\ 0 < I \leqslant M,\ 0 < V \leqslant M\}$. Obviously, D is convex.

Theorem 2.3. *Suppose that*

(i) $R_0 > 1$;
(ii) $(c+\delta+\rho+d-a+\frac{2a\bar{T}}{T_{\max}}+\beta\bar{V})[(-d+a-\frac{2a\bar{T}}{T_{\max}})(c+\delta+\rho)+\beta\bar{V}(c+\delta)] > 0$.

Then the positive equilibrium $\bar{E}(\bar{T},\bar{I},\bar{V})$ is locally asymptotically stable.

Proof. For equilibrium $\bar{E}(\bar{T},\bar{I},\bar{V})$, (2.1) reduces to

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{2.3}$$

where

$$a_1 = c+\delta+\rho+d-a+\frac{2a\bar{T}}{T_{\max}}+\beta\bar{V} > 0,$$
$$a_2 = \left(d-a+\frac{2a\bar{T}}{T_{\max}}+\beta\bar{V}\right)(c+\delta+\rho)-\rho\beta\bar{V} > 0,$$
$$a_3 = c\delta\beta\bar{V} > 0.$$

We also have

$$a_1a_2 - a_3 = \left(c+\delta+\rho+d-a+\frac{2a\bar{T}}{T_{\max}}+\beta\bar{V}\right)\left[\left(-d+a-\frac{2a\bar{T}}{T_{\max}}\right)(c+\delta+\rho)+\beta\bar{V}(c+\delta)\right] > 0.$$

By *Routh–Hurwitz criterion* [13], we have that $\bar{E}(\bar{T},\bar{I},\bar{V})$ is locally asymptotically stable. □

3. The permanence of system (1.1)

In this section, we shall present the permanence of the system (1.1).

Definition 3.1. System (1.1) is said to be persistent if there are positive constants m, M such that each positive solution $(T(t), I(t), V(t))$ of system (1.1) with initial conditions (1.2) satisfies

$$m \leqslant \lim_{t\to+\infty}\inf T(t) \leqslant \lim_{t\to+\infty}\sup T(t) \leqslant M,$$
$$m \leqslant \lim_{t\to+\infty}\inf I(t) \leqslant \lim_{t\to+\infty}\sup I(t) \leqslant M,$$
$$m \leqslant \lim_{t\to+\infty}\inf V(t) \leqslant \lim_{t\to+\infty}\sup V(t) \leqslant M.$$

Definition 3.2 *(Metzler matrix).* (See [14].) Matrix A is a *Metzler matrix* iff all its off-diagonal elements are nonnegative.

Lemma 3.1 *(Perron–Frobenius theorem). (See [14].) Let A be an irreducible* Metzler matrix. *Then, λ_M, the eigenvalue of A of largest real part is real, and the elements of its associated eigenvector v_M are positive. Moreover, any eigenvector of A with nonnegative elements belongs to span v_M.*

In order to prove permanence of system (1.1), we present the permanence theory for infinite dimensional system from Theorem 4.1 in [14]. Let X be a complete metric space. Suppose that $X^0 \in X$, $X_0 \in X$, $X^0 \cap X_0 = \emptyset$. Assume that $T(t)$ is a C_0 semigroup on X satisfying

$$T(t): X^0 \to X^0,$$
$$T(t): X_0 \to X_0. \tag{3.1}$$

Let $T_b(t) = T(t)|_{X_0}$ and let A_b be the global attractor for $T_b(t)$.

Lemma 3.2. *(See [15].) Suppose that $T(t)$ satisfies* (3.1) *and we have the following*:

(i) *there is $t_0 \geqslant 0$ such that $T(t)$ is compact for $t > t_0$*;
(ii) *$T(t)$ is point dissipative in X*;
(iii) *$\bar{A}_b = \bigcup_{x\in A_b} \omega(x)$ is isolated and has an acyclic covering M, where*

$$\bar{M} = \{M_1, M_2, \ldots, M_n\};$$

(iv) *$W^s(M_i) \cap X^0 = \emptyset$, for $i = 1, 2, \ldots, n$.*

Then X_0 is a uniform repeller with respect to X^0, i.e., there is $\epsilon > 0$ such that, for any $x \in X^0$,

$$\lim_{t\to+\infty} \inf d\big(T(t)x, X_0\big) \geqslant \epsilon,$$

where d is the distance of $T(t)x$ from X_0.

Theorem 3.1. *If $R_0 > 1$, then system* (1.1) *is permanent.*

Proof. The result follows from an application of Lemma 3.2. Let us define X_1 be the interior of R^3_+ and X_2 be the boundary of R^3_+, i.e., $X_1 = \text{int}(R^3_+)$ and $X_2 = \text{bd}(R^3_+)$. This choice is in accordance with the conditions stated in this theorem. We begin by showing that sets X_1 and X_2 repel the positive solution of system (1.1) uniformly. Furthermore, note that by virtue of Theorem 2.2, there exists a compact set B in which all solutions of system (1.1) initiated in R^3_+ ultimately enter and remain forever after. The compactness condition is easily verified for this set B. Denoting the ω-limit set of the solution $x(t, x_0)$ of system (1.1) starting in $x_0 \in R^3_+$ by $\omega(x_0)$, we need to determine the following set:

$$\Omega = \bigcup_{y\in Y_2} \omega(y), \quad \text{where } Y_2 = \big\{x_0 \in X_2 \,\big|\, x(t, x_0) \in X_2,\ \forall t > 0\big\}.$$

From the system (1.1), it follows that all solutions starting in $\text{bd}(R^3_+)$ but not on the T-axis leave $\text{bd}(R^3_+)$ and that the T-axis is an invariant set, implying that $Y_2 = \{(T, I, V)^T \in \text{bd}(R^3_+) \mid I = V = 0\}$. Furthermore, it is easy to see that $\Omega = \{\hat{E}\}$ as all solutions initiated on the T-axis converge to $\hat{E}$. In fact, in the set Y_2, system (1.1) becomes

$$\dot{T} = s - dT + aT\left(1 - \frac{T}{T_{\max}}\right).$$

It is easy to see that $\hat{E}$ is globally asymptotically stable. Hence, any solution $(T(t), I(t), V(t))$ of system (1.1) initiating from Y_2 is such that $(T(t), I(t), V(t)) \to \hat{E}(\hat{T}, 0, 0)$. Obviously, $\hat{E}$ are isolated invariant, $\{\hat{E}\}$ is isolated and is an acyclic covering. Next, we show that $W^s(\hat{E}) \cap X_1 = \emptyset$, i.e., $\hat{E}$ is a weak repeller for X_1.

By definition, $\hat{E}$ is a weak repeller for X_1 if for every solution starting in $x_0 \in X_1$,

$$\lim_{t\to+\infty} d\big(x(t, x_0), \hat{E}\big) > 0. \tag{3.2}$$

We claim that (3.2) is satisfied if the following holds:

$$W^s(\hat{E}) \cap \text{int}\big(R^3_+\big) = \emptyset. \tag{3.3}$$

To see this, suppose (3.2) does not hold for some solution $x(t, x_0)$ starting in $x_0 \in X_1$. In view of the fact that the closed positive orthant is positively invariant for system (1.1), it follows that $\lim_{t\to+\infty} d(x(t, x_0), \hat{E}) = 0$ and thus that $\lim_{t\to+\infty} x(t, x_0) = \hat{E}$, which is clearly impossible if (3.3) holds. What remains to be shown is that (3.3) holds. The *Jacobian matrix* of system (1.1) at $\hat{E}$ is given in the following:

$$J_0 = \begin{pmatrix} -d + a - \frac{2a\hat{T}}{T_{\max}} & \rho & \beta\hat{T} \\ 0 & -\delta - \rho & -\beta\hat{T} \\ 0 & q & -c \end{pmatrix}.$$

It is easy to see that J_0 is unstable if $R_0 > 1$. In particular, J_0 possesses one eigenvalue with positive real part, which we denote as λ_+, and two eigenvalues with negative real part, $-\sqrt{(a-d)^2 + \frac{4as}{T_{\max}}}$, and an eigenvalue which we

denote as λ_-. We proceed by determining the location of $E^s(\hat{E})$, the stable eigenspace of $\hat{E}$. Clearly, $(1,0,0)^T$ is an eigenvector of J_0 associated to $-\sqrt{(a-d)^2+\frac{4as}{T_{\max}}}$. If $\lambda_- \neq -\sqrt{(a-d)^2+\frac{4as}{T_{\max}}}$, then the eigenvector associated to λ_- has the following structure: $(0, p_2, p_3)^T$, where p_2, p_3 satisfy the eigenvector equitation

$$\begin{pmatrix} -(\delta+\rho) & \beta\hat{T} \\ q & -c \end{pmatrix}\begin{pmatrix} p_2 \\ p_3 \end{pmatrix} = \lambda_- \begin{pmatrix} p_2 \\ p_3 \end{pmatrix}. \tag{3.4}$$

If $\lambda_- = -\sqrt{(a-d)^2+\frac{4as}{T_{\max}}}$, then λ_- is a repeated eigenvalue, and associated generalized eigenvector will possess the following structure: $(*, p_2, p_3)^T$, where the value of $*$ is irrelevant for what follows and p_2 and p_3 also satisfy (3.4).

We claim that in both cases, the vector $(p_2, p_3)^T \notin R^2_+$. Obviously, the matrix in (3.4) is an irreducible *Metzler matrix*. From Definition 3.1, we know that it is a matrix with nonnegative off-diagonal entries. By using Lemma 3.1 (*Perron–Frobenius theorem*), we get that the matrix in (3.4) possesses a simple real eigenvalue which is larger then the real part of any other eigenvalue, also called the dominant eigenvalue. Clearly, the dominant eigenvalue here is λ_+. But the *Perron–Frobenius theorem* also implies that every eigenvector that is not associated with the dominant eigenvalue does not belong to the closed positive orthant. Applied here, this means that $(p_2, p_3)^T \notin R^2_+$. Consequently, $E^s(\hat{E}) \cap \operatorname{int}(R^3_+) = \emptyset$, and therefore also $W^s(\hat{E}) \cap \operatorname{int}(R^3_+) = \emptyset$, which concludes the proof. □

4. Global asymptotic stability of the disease steady state

In this section we provide sufficient conditions leading to a globally asymptotically stable disease steady state.

Definition 4.1. System (1.1) is said to satisfy the *Poincare–Bendixson property* if any nonempty compact ω-limit set of (1.1) that contains no equilibria is a closed orbit.

Definition 4.2. The autonomous system (1.1) is said to be competitive in D if, for some diagonal matrix $H = \operatorname{diag}(\epsilon_1, \epsilon_2, \ldots, \epsilon_n)$ where each ϵ_i $(i = 1, 2, \ldots, n)$ is either 1 or -1, $H\frac{\partial f}{\partial x}H$ has nonpositive off diagonal elements for all $x \in D$.

Theorem 4.1. *System* (1.1) *is a competitive system.*

Proof. By looking at the *Jacobian matrix* of system (1.1) and choosing the matrix H as

$$H = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix},$$

we see that system (1.1) is competitive in D, with respect to the partial order defined by the orthant $K = \{(T, I, V) \in R^3 \colon T \leqslant 0,\ I \geqslant 0,\ V \geqslant 0\}$. In fact, by simple calculating, we obtain

$$H\frac{\partial f}{\partial x}H = \begin{pmatrix} a-d-\frac{2aT}{T_{\max}}-\beta V & -\rho & -\beta T \\ -\beta V & -\delta-\rho & -\beta T \\ 0 & -q & -c \end{pmatrix}. \qquad \square$$

Remark 4.1. Because D is convex and system (1.1) is competitive in D. Then system (1.1) satisfies the *Poincare–Bendixson property*.

Lemma 4.1. *(See [16].) Assume that* $n = 3$ *and* D *is convex. Suppose* (1.1) *is competitive in* D *and* L *is a nonempty compact omega limit set of* (1.1)*. If* L *contains no equilibria, then* L *is a closed orbit.*

From Remark 4.1 and Lemma 4.1 we know that system (1.1) has nontrivial periodic orbits.

Let A be a linear operator on R^n and also denote its matrix representation with respect to the standard basis of R^n. Let $\bigwedge^2 R^n$ denote the exterior product of R^n. A induces canonically a linear operator $A^{[2]}$ on $\bigwedge^2 R^n$ for $u_1, u_2 \in R^n$,

define

$$A^{[2]}(u_1 \wedge u_2) := A(u_1) \wedge u_2 + A(u_2) \wedge u_1$$

and extend the definition over $\bigwedge^2 R^n$ by linearity. The matrix representation of $A^{[2]}$ with respect to the canonical basis in $\bigwedge^2 R^n$ is called the second additive compound matrix of A. This is an $\binom{n}{2}\binom{n}{2}$ matrix and satisfies the property $(A+B)^{[2]} = A^{[2]} + B^{[2]}$. In the special case when $n = 2$, we have $A^{[2]}_{2\times 2} = \operatorname{tr} A$. In general, each entry of $A^{[2]}$ is a linear expression of those of A. For instance, when $n = 3$, the second additive compound matrix of $A = (a_{ij})$ is

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

Let $\sigma(A) = \{\lambda_1, \ldots, \lambda_n\}$ be the spectrum of A. Then, $\sigma(A^{[2]}) = \{\lambda_i + \lambda_j \colon 1 \leqslant i \leqslant j \leqslant n\}$ is the spectrum of $A^{[2]}$.

Let $x \mapsto f(x) \in R^2$ be a C^1 function for x in an open set $D \in R^n$. Consider the differential equation

$$x' = f(x).$$

Denote by $x(t, x_0)$ be the solution to system (1.1) such that $x(0, x_0) = x_0$. A set K is said to be absorbing in D for (1.1) if $x(t, K_1) \subset K$ for each compact $K_1 \subset D$ and t sufficiently large. We make the following two basic assumptions:

(H_1) There exists a compact absorbing set $K \subset D$.
(H_2) Eq. (1.1) has a unique equilibrium $\bar{x}$ in D.

The equilibrium $\bar{x}$ is said to be globally stable in D if it is locally stable and all trajectories in D converge to $\bar{x}$. The assumptions (H_1) and (H_2) are satisfied if $\bar{x}$ is globally stable in D. For virus models and many other biological models where the feasible region is a bounded cone, (H_1) is equivalent to the uniform persistence of (1.1).

Lemma 4.2. *(See [17].) A periodic orbit $\Omega = \{p(t)\colon 0 < t < \omega\}$ of* (1.1) *is orbitally asymptotically stable with asymptotic phase if the linear system*

$$z'(t) = \frac{\partial f^{[2]}}{\partial x}\big(p(t)\big)z(t) \tag{4.1}$$

is asymptotically stable, where $\frac{\partial f^{[2]}}{\partial x}$ is the second additive compound matrix of the Jacobian matrix $\frac{\partial f}{\partial x}$ of f.

Lemma 4.3. *(See [17].) Assume that*

(1) *assumptions* (H_1) *and* (H_2) *hold*;
(2) *system* (1.1) *satisfies the* Poincare–Bendixson property;
(3) *for each periodic solution $x = p(t)$ to* (1.1) *with $p(0) \in D$, system* (4.1) *is asymptotically stable*;
(4) $(-1)^n \det(\frac{\partial f}{\partial x}(\bar{x})) > 0$.

Then the unique equilibrium $\bar{x}$ is globally asymptotically stable in D.

Theorem 4.2. *Suppose that*

(i) $R_0 > 1$;
(ii) $d - a + \frac{2aT}{T_{\max}} > 0$ *for arbitrary* $T \geqslant 0$.

Then the positive equilibrium $\bar{E}$ of system (1.1) *is globally asymptotically stable.*

Proof. Let $P(t) = (T(t), I(t), V(t))$ be a periodic solution whose orbit Γ is contained in $\operatorname{int}(R^3_+)$. The second compound equation is following periodic linear system:

$$Z'(t) = \frac{\partial f^{[2]}}{\partial x}\big(P(t)\big)Z(t), \tag{4.2}$$

where $Z = (Z_1, Z_2, Z_3)^T$ and $\frac{\partial f}{\partial x}$ is derived from the *Jacobian matrix* of system (1.1) and defined as follows:

$$\frac{\partial f^{[2]}}{\partial x} = \begin{pmatrix} -d + a - \frac{2aT}{T_{\max}} - \beta V - \delta - \rho & \beta T & \beta T \\ q & -d + a - \frac{2aT}{T_{\max}} - \beta V - c & \rho \\ 0 & \beta V & -(\delta + \rho + c) \end{pmatrix}.$$

For the solution $P(t)$, Eq. (4.2) becomes

$$\begin{cases} \dot{Z}_1(t) = \left(-d + a - \dfrac{2aT}{T_{\max}} - \beta V - \delta - \rho\right)Z_1 + \beta T Z_2 + \beta T Z_3, \\ \dot{Z}_2(t) = q Z_1 + \left(-d + a - \dfrac{2aT}{T_{\max}} - \beta V - c\right)Z_2 + \rho Z_3, \\ \dot{Z}_3(t) = \beta V Z_2 - (\delta + \rho + c)Z_3. \end{cases} \tag{4.3}$$

To prove that (4.3) is globally asymptotically stable, we shall use following *Lyapunov* function:

$$L\big(Z_1, Z_2, Z_3; T(t), I(t), V(t)\big) = \sup\left\{|Z_1|, \frac{I}{V}\big(|Z_2| + |Z_3|\big)\right\}. \tag{4.4}$$

Function (4.4) is positive, but not differentiable everywhere. Fortunately, this lack of differentiability can be remedied by using the right derivative of $L(t)$, denoted as $D_+L(t)$. Then we have the following equalities:

$$\begin{cases} \big|\dot{Z}_1(t)\big| \leqslant \left(-d + a - \dfrac{2aT}{T_{\max}} - \beta V - \delta - \rho\right)|Z_1| + \beta T|Z_2| + \beta T|Z_3|, \\ \big|\dot{Z}_2(t)\big| \leqslant q|Z_1| + \left(-d + a - \dfrac{2aT}{T_{\max}} - \beta V - c\right)|Z_2| + \rho|Z_3|, \\ \big|\dot{Z}_3(t)\big| \leqslant \beta V|Z_2| - (\delta + \rho + c)|Z_3|. \end{cases} \tag{4.5}$$

Therefore,

$$\begin{aligned} D_+\left(\frac{I}{V}\big(\big|Z_2(t)\big| + \big|Z_3(t)\big|\big)\right) &= \left(\frac{\dot{I}}{I} - \frac{\dot{V}}{V}\right)\frac{I}{V}\big(|Z_2| + |Z_3|\big) + \frac{I}{V}D_+\big(|Z_2| + |Z_3|\big) \\ &\leqslant \left(\frac{\dot{I}}{I} - \frac{\dot{V}}{V}\right)\frac{I}{V}\big(|\dot{Z}_2| + |\dot{Z}_3|\big) + \frac{qI}{V}|Z_1| \\ &\quad + \left(-d + a - \frac{2aT}{T_{\max}} - c\right)\frac{I}{V}|Z_2| - \frac{I}{V}(c + \delta)|Z_3|. \end{aligned}$$

Let $\alpha^* = \min_{T \geqslant 0}(d - a + \frac{2aT}{T_{\max}})$. Define

$$\begin{aligned} g_1(t) &= -d + a - \frac{2aT}{T_{\max}} - \beta V + \beta\frac{TV}{I} - \delta - \rho = \frac{\dot{I}}{I} - \left(d + a + \frac{2aT}{T_{\max}} + \beta V\right), \\ g_2(t) &= q\frac{I}{V} + \left(\frac{\dot{I}}{I} - \frac{\dot{V}}{V} - c - \min\big(\delta, \alpha^*\big)\right) = \frac{\dot{I}}{I} - \min\big(\delta, \alpha^*\big). \end{aligned} \tag{4.6}$$

Thus, we obtain

$$D_+L(t) \leqslant \sup\big\{g_1(t), g_2(t)\big\}. \tag{4.7}$$

Using the definition of α^*, it follows from (4.6) that $g_1(t) \leqslant \frac{\dot{I}}{I} - \alpha^*$ and thus that $g_1(t) \leqslant g_2(t)$. Then (4.7) can be rewritten as

$$D_+L(t) \leqslant g_2(t)L(t). \tag{4.8}$$

Using the fact that $Z(t)$ is a periodic solution of (1.1), we see that

$$\int_0^\omega g_2(t)\,dt \leqslant \int_0^\omega \left(\frac{\dot{I}}{I} - \min\bigl(\delta, \alpha^*\bigr)\right) = \ln I(\omega) - \ln I(0) - \omega\min\bigl(\delta, \alpha^*\bigr) = -\omega\min\bigl(\delta, \alpha^*\bigr). \tag{4.9}$$

From (4.8) and (4.9), we have $\lim_{t\to\infty} L(t) = 0$.

Therefore, $(Z_1(t), Z_2(t), Z_3(t)) \to (0,0,0)$ as $t \to \infty$.

Let $J(\bar{E})$ be the *Jacobian matrix* of (1.1) at $\bar{E}$. Then

$$\begin{aligned}
\det\bigl(J(\bar{E})\bigr) &= \begin{vmatrix} -d + a - \frac{2a\bar{T}}{T_{\max}} - \beta\bar{V} & -\rho & \beta\bar{T} \\ -\beta\bar{V} & \lambda+\delta+\rho & -\beta\bar{T} \\ 0 & -q & \lambda + c \end{vmatrix} \\
&= \left(-d + a - \frac{2a\bar{T}}{T_{\max}} - \beta\bar{V}\right)\bigl(c(\delta+\rho) - q\beta\bar{T}\bigr) - \beta\bar{V}(-\rho c + q\beta\bar{T}) \\
&= \left(-d + a - \frac{2a\bar{T}}{T_{\max}}\right)\bigl(c(\delta+\rho) - q\beta\bar{T}\bigr) - c\delta\beta\bar{V} \\
&= -c\delta\beta\bar{V} \\
&< 0.
\end{aligned} \tag{4.10}$$

This verifies the condition (4) of Lemma 4.3. Hence $\bar{E}$ is globally stable in D by Lemma 4.3. The proof of Theorem 4.2 is completed. □

From the proof of Theorem 4.2 and [18, Theorem 1.2], we can obtain the following theorem.

Theorem 4.3. *Suppose that*

(i) $R_0 > 1$;
(ii) $(c+\delta+\rho+d-a+\frac{2a\bar{T}}{T_{\max}}+\beta\bar{V})[(-d+a-\frac{2a\bar{T}}{T_{\max}})(c+\delta+\rho)+\beta\bar{V}(c+\delta)] < 0$.

Then system (1.1) *exists an orbitally asymptotically stable periodic orbit.*

5. Numerical simulations

In the previous sections, we introduced the analytical tools proposed and used them for a qualitative analysis of the system obtaining some results about the dynamics of the system. In this section, we perform a numerical analysis of the model based on the previous results.

Clinical data are becoming more available, making it possible to get actual values (or orders of values) directly for the individual parameters in the model. By this I mean that it is possible to calculate the actual rates for the different processes described above based on data collected from clinical experiments. For example, it has been shown that infected $CD4^+$ T cells live less than 1–2 days; therefore, we choose the rate of loss of infected T cells, δ, to be values between 0.5 and 1.0. When this type of information is not available, estimation of the parameters can be determined from simulations through behavior studies. Periodic solution and sensitivity analyzes can be carried out for each parameter to get a good understanding of the different behaviors seen for variations of these values. For example, the parameter a in the model (representing the maximum proliferation rate of target cells) is not verifiable clinically; however, since it is a bifurcation parameter, we know that for small values the infection would die out and that for large values the infection persists. This may be an indication to clinicians that finding a drug which lowers this viral production may aid in suppressing the disease. In general, this process can be helpful to clinicians, as a range for possible parameter values can be suggested. A complete list of parameters and their estimated values for this model is given in Table 1.

First we observe that there exists a unique interior equilibrium point $\bar{E}$ (31.56250000, 20.05054525, 3208.087240) with the set of parameter values from Table 1. Positive steady state is locally asymptotically stable, since the eigen-

Table 1
Variables and parameters for viral spread

Parameters and variables		Values
Dependent variables		
T	Uninfected CD4$^+$ T-cell population size	1000 mm^{-3}
I	Infected CD4$^+$ T-cell density	0
V	Initial density of HIV RNA	10^{-3} mm^{-3}
Parameters and constants		
s	Source term for uninfected CD4$^+$ T-cells	5 day^{-1} mm^{-3}
d	Natural death rate of CD4$^+$ T-cells	0.01 day^{-1}
a	Growth rate of CD4$^+$ T-cell population	0.5 day^{-1}
$T_{\max}$	Maximal population level of CD4$^+$ T-cells	1200 mm^3 day^{-1}
β	Rate CD4$^+$ T-cells become infected with virus	0.0002 mm^{-3}
ρ	Rate of cure	0.01 day^{-1}
δ	Blanket death rate of infected CD4$^+$ T-cells	1 day^{-1}
q	Reproductively rate of the infected CD4$^+$ T-cells	800 mm^3 day^{-1}
c	Death rate of free virus	5 day^{-1}

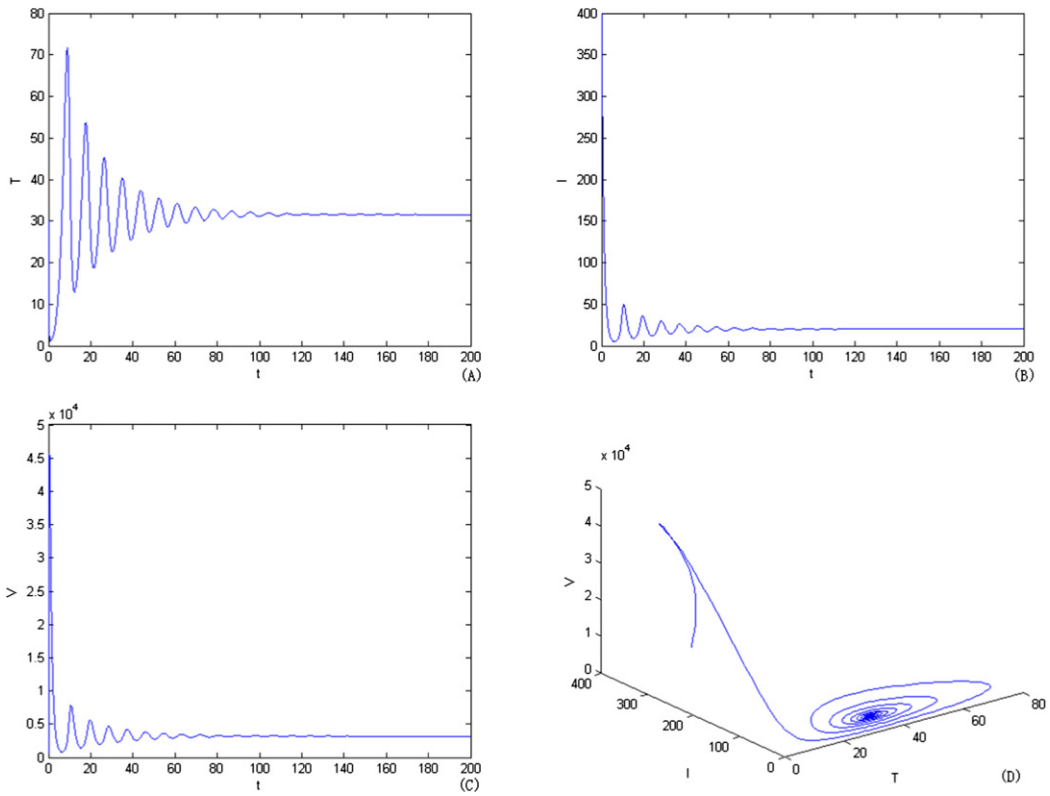

Fig. 2. (A)–(C) show that uninfected cells, infected cells and virus converge to their equilibrium with the parametric values as stated in the text. (D) shows that the equilibrium $\bar{E}$ (31.56250000, 20.05054525, 3208.087240) is asymptotically stable. The initial conditions are $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

values associated with the characteristic equation (2.3) at $\bar{E}$, given by

$$\lambda^3 + 6.187919531\lambda^2 + 1.062880209\lambda + 3.208087240 = 0,$$

have negative real parts ($\lambda_1 = -6.099892570$, $\lambda_2 = -0.04401348053 - 0.7238701657I$, $\lambda_3 = -0.04401348053 + 0.7238701657I$). Simulation of the model in this situation, produce stable dynamics as presented in Fig. 2. Plots (A)–(C) of Fig. 2 show that uninfected cells, infected cells and virus converge to their equilibrium with the parametric

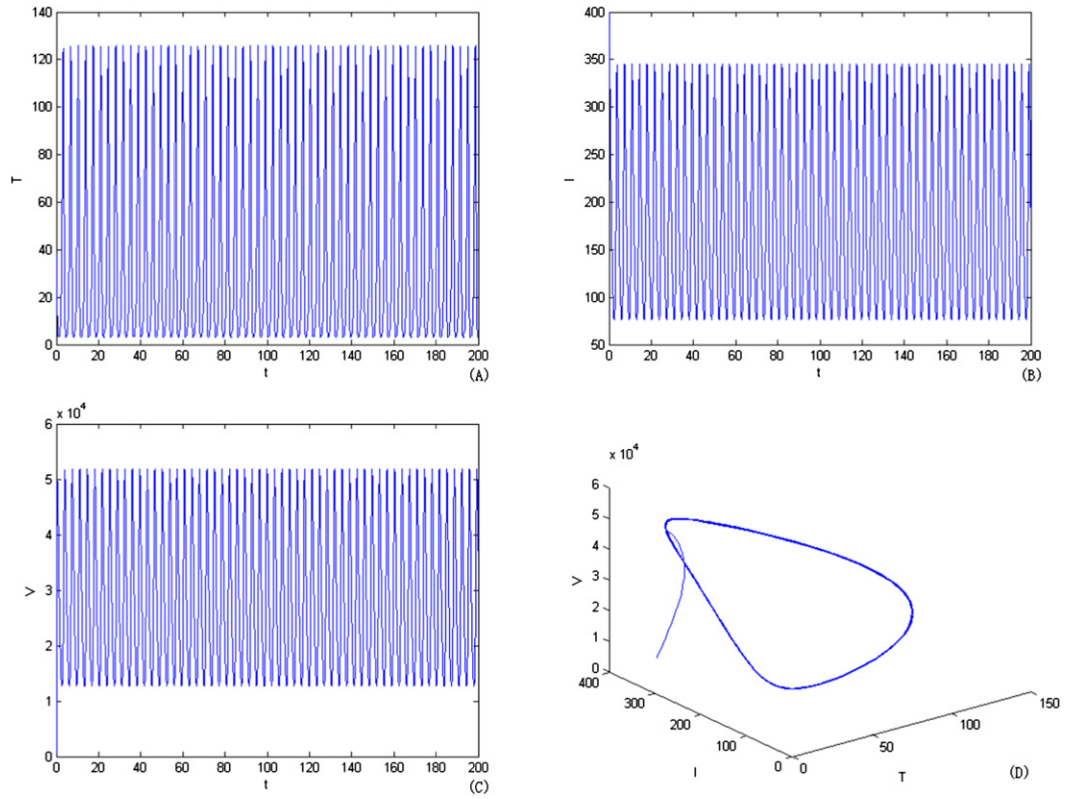

Fig. 3. (A)–(C) are the oscillations of uninfected cells, infected cells and virus. (D) shows that there is a periodic solution. The initial conditions are $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

values as stated in Table 1. Plot (D) of Fig. 2 shows that the equilibrium $\bar{E}$ (31.56250000, 20.05054525, 3208.087240) is asymptotically stable. The initial conditions are $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

Next, we use a same set of parameter values as those in Table 1, but we vary the value of a ($a = 5$). Thus the conditions of Theorem 4.3 are satisfied. Then the system (1.1) exists an orbitally asymptotically stable periodic orbit (see Fig. 3). Plots (A)–(C) of Fig. 3 are the oscillations of uninfected cells, infected cells and virus. Plot (D) of Fig. 3 shows that there is a periodic solution. The initial conditions are $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

We also find that the infection would always keep stability when the cure rate ρ is larger. This can be analyzed from the expression of R_0 and the conditions of Theorems 2.3 and 4.2. For example, we know that the oscillations of uninfected cells, infected cells and virus in Fig. 3. And if we select $\rho = 0.3$ and $a = 5$ (the value a is same as Fig. 3) and the other parameter values are same in Table 1 then the infection would be stale (see Fig. 4). Thus we can claim that the cure rate ρ is a very important parameter. The results show that if we improve the cure rate, we will control the disease.

6. Discussion

In this paper, we investigate a differential equation model of HIV infection of $CD4^+$ T-cells with cure rate. In this model, the basic reproduction number R_0 is identified and is established as a sharp threshold parameter. If $R_0 < 1$, the infected free equilibrium $\hat{E}$ is locally stable in the interior of the feasible region and the virus always dies out. If $R_0 > 1$, a unique endemic equilibrium $\bar{E}$ exists and is globally stable in the interior of the feasible region and once the virus appears, it eventually persists at the unique endemic equilibrium level. We also obtain the conditions for the system (1.1) exists an orbitally asymptotically stable periodic orbit. Biologically, it implies that the some parameter values can cause the cell and virus population to fluctuate.

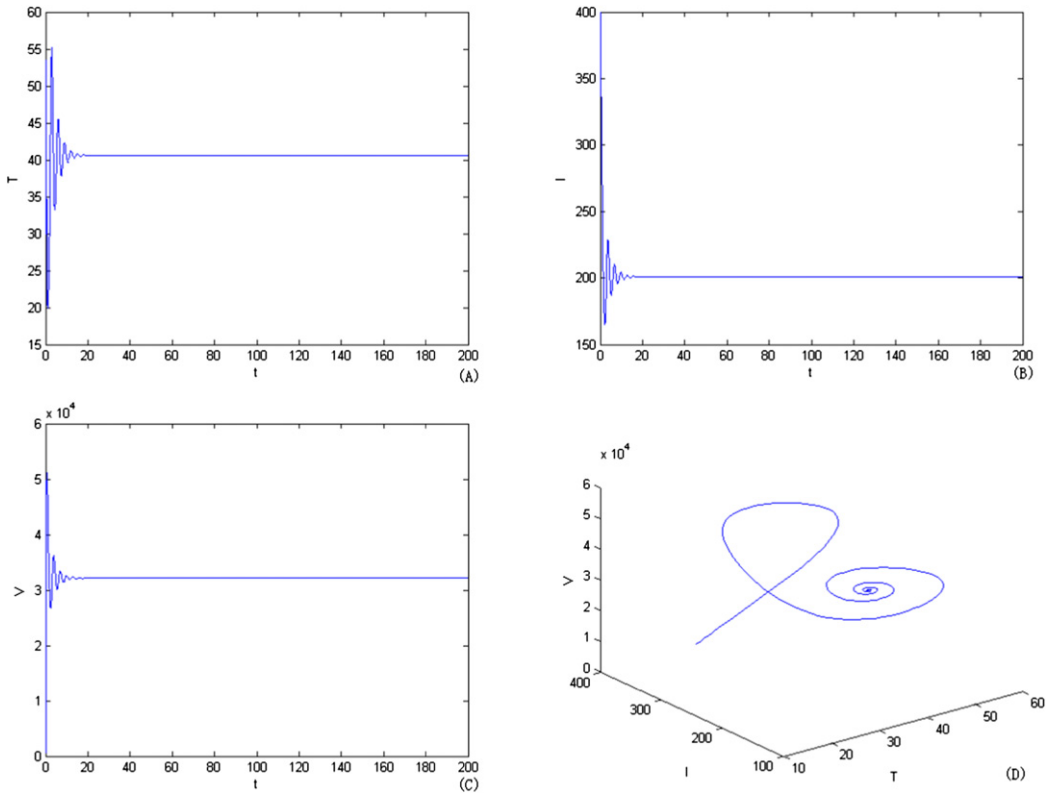

Fig. 4. (A)–(C) show that uninfected cells, infected cells and virus converge to their equilibrium with the parametric values as stated in the text. (D) shows that the equilibrium $\bar{E}$ is asymptotically stable. The initial conditions are $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

Mathematically, since $\bar{E}$ can be unstable and periodic solutions may exist for the model (1.1), it is important to investigate if the basin of attraction of $\bar{E}$ contains all points in the feasible region, namely, if $\bar{E}$ is globally stable. Clinical data an HIV positive patients do not show sustained oscillations. This suggests that simple model like (1.1), which ignore features such as chronically infected, latently infected cells, and drug sanctuaries that might damp the oscillations, are clinically relevant only in the parameter regions for which no oscillations exist, in particular, for which the chronic-infection equilibrium $\bar{E}$ is globally stable. Therefore, identifying parameter ranges in which $\bar{E}$ is globally stable is of both mathematical and biological significance.

If $\rho = 0$, we can find that the system (1.1) becomes

$$\begin{cases} \dot{T} = s - dT + aT\left(1 - \dfrac{T}{T_{\max}}\right) - \beta TV, \\ \dot{I} = \beta TV - \delta I, \\ \dot{V} = qI - cV. \end{cases} \tag{6.1}$$

Model (6.1) is founded and studied by Alan S. Pereson et al. [19]. And model (6.1) which incorporates delay is studied by Xinyu Song et al. [20]. From [19,20], we find that $R^0 = \frac{q\beta}{c\delta}\bar{T}$ is the basic reproduction number of system (6.1). $\bar{E}_1(\bar{T}_1, \bar{I}_1, \bar{V}_1)$ is the infected steady state of (6.1), where $\bar{T}_1 = \frac{c\delta}{\beta q}$, $\bar{I}_1 = \frac{1}{\delta}[s - d\bar{T} + a\bar{T}(1 - \frac{\bar{T}}{T_{\max}})]$, $\bar{V}_1 = \frac{q}{c}\bar{I}_1$. Obviously, $R_0 \leqslant R^0$. Thus, although the threshold behavior and dynamic behavior of system (1.1) in this paper are similar to those of system (6.1), the basic reproductive ratio R_0 of system (1.1) is less than R^0, the virus level of the endemic equilibrium state is less than those of (1.1). Which shows that the infection speed of the virus in our model is slower than the model without 'cure' rate. And the disease can easily be controlled if we improve the cure rate. Therefore, on the basis of these results, we reject the model (6.1) and favor the model (1.1).

Acknowledgments

We would like to thank the anonymous referees for their careful reading of the original manuscript and their many valuable comments and suggestions that greatly improve the presentation of this work.

References

[1] R.J. De Boer, A.S. Perelson, Target cell limited and immune control models of HIV infection: A comparison, J. Theoret. Biol. 190 (1998) 201–214.
[2] T.B. Kepler, A.S. Perelson, Cyclic re-entry of germinal center B cells and the efficiency of affinity maturation, Immunol. Today 14 (1993) 412–415.
[3] J.K. Percus, O.E. Percus, A.S. Perelson, Predicting the size of the T-cell receptor and antibody combining region from consideration of efficient self–nonself discrimination, Proc. Natl. Acad. Sci. USA 90 (1993) 1691–1695.
[4] T.W. McKeithan, Kinetic proofreading in T-cell receptor signal transduction, Proc. Natl. Acad. Sci. USA 92 (1995) 5042–5046.
[5] A.R. McLean, M.M. Rosado, F. Agenes, R. Vasconcellos, A.A. Freitas, Resource competition as a mechanism for B cell homeostasis, Proc. Natl. Acad. Sci. USA 94 (1997) 5792–5797.
[6] X.Y. Song, Avidan U. Neumann, Global stability and periodic solution of the viral dynamics, J. Math. Anal. Appl. 329 (1) (2007) 281–297.
[7] A.L. Lloyd, The dependence of viral parameter estimates on the assumed viral life cycle: Limitations of studies of viral load data, Proc. R. Soc. Lond. Ser. B 268 (2001) 847–854.
[8] Dan Li, Wanbiao Ma, Asymptotic properties of a HIV-1 infection model with time delay, J. Math. Anal. Appl. 335 (1) (2007) 683–691.
[9] A.R. McLean, T.B.L. Kirkwood, A model of human immunodeficiency virus infection in T helper cell clones, J. Theoret. Biol. 147 (1990) 177–203.
[10] A.R. McLean, M.A. Nowak, Models of interaction between HIV and other pathogens, J. Theoret. Biol. 155 (1992) 69–102.
[11] J.E. Mittler, B. Sulzer, A.U. Neumann, A.S. Perelson, Influence of delayed viral production on viral dynamics in HIV-1 infected patients, Math. Biosci. 152 (1998) 143–163.
[12] Alan S. Perelson, P. Essunger, Y. Cao, M. Vesanen, A. Hurley, K. Saksela, M. Markowitz, D.D. Ho, Decay characteristics of HIV-1-infected compartments during combination therapy, Nature 387 (1997) 188–191.
[13] Y. Kuang, Delay Differential Equations with Applications in Population Dynamics, Academic Press, London, 2004.
[14] F.R. Gantmacher, The Theory of Matrices, Chelsea Publ. Co., New York, 1959.
[15] J.K. Hale, P. Waltman, Persistence in infinite-dimensional systems, SIAM J. Math. Anal. 20 (1989) 388–396.
[16] H.L. Smith, Monotone Dynamical Systems, an Introduction to the Theory of Competitive and Cooperative Systems, Math. Surveys Monogr., vol. 41, Amer. Math. Soc., Providence, RI, 1995.
[17] Michael Y. Li, L. Wang, Global stability in some SEIR models, IMA Math. Appl. 126 (2002) 295–311.
[18] H.R. Zhu, H.L. Smith, M.W. Hirsch, Stable periodic orbits for a class of three dimensional competitive systems, J. Differential Equations 110 (1994) 143–156.
[19] Alan S. Perelson, P.W. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, SIAM Rev. 41 (1999) 3–44.
[20] X.Y. Song, S.H. Cheng, A delay-differential equation model of HIV infection of $CD4^+$ T-cells, J. Korean Math. Soc. 42 (5) (2005) 1071–1086.