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Analysis of a differential equation model of HIV infection of $CD4^+$ T -cells with saturated reverse function

Xiangyun Shi, Gang Li, Xueyong Zhou and Xinyu Song

Abstract

In this paper, an ordinary differential equation model of HIV infection of $CD4^+$ T -cells with saturated reverse function is studied. We prove that if the basic reproduction number $R_0 < 1$, the virus-free equilibrium is locally asymptotically stable. And there will exhibit backward bifurcation when $R_0 < 1$. If $R_0 > 1$, some feasibly sufficient conditions are obtained for the global asymptotic stability of a positive equilibrium of the model by using the theory of competitive systems, compound matrices and stability of periodic orbits. Furthermore, we also obtain the conditions for which the model exists an orbitally asymptotically stable periodic solution. Numerical simulations are presented to illustrate the results.

Key Words: HIV infection, globally asymptotical stability, periodic solution, permanence

1. Introduction

There has been much interest in mathematical modeling of epidemic and viral dynamics (see, for example, [2, 6, 9, 11, 16, 22, 29, 30] and the references cited therein). This is because epidemic models can be very useful in the control of epidemic diseases, and viral models can provide insights into the dynamics of viral load in vivo and may play a significant role in the development of a better understanding of diseases and various drug therapy strategies against them.

Like most viruses, HIV is a very tiny, simple organism. Viruses can not 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 [18]. 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. 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 [7]. 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 [7, 8]. 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 [7].

Currently, there are several drugs licensed for treatment of individuals infected with HIV. Drugs, such as reverse transcriptase (RT) inhibitors, protease inhibitors and fusion inhibitors, have been developed so as to attack on different phases of viral life cycle during infection [14, 15]. Reverse transcriptase (RT) inhibitors work by inhibiting the action of reverse transcriptase. There are two classes of reverse transcriptase (RT) inhibitors: nucleoside analogs (nucleoside RT inhibitors; NRTIs) and nonnucleoside RT inhibitors (NNRTIs). NRTIs are incorporated into viral DNA during reverse transcription and terminate the synthesis of the viral DNA chain, whereas NNRTIs bind directly to RT near the polymerase active site, blocking the chemical step of DNA synthesis and preventing RT from copying the viral RNA genome into DNA [28]. Protease inhibitors work by blocking a part of HIV called protease. When protease is blocked, HIV makes copies of itself that can't infect new cells. Studies have shown that protease inhibitors can reduce the amount of virus in the blood and increase $CD4^+$ T cell counts. In some cases these drugs have improved $CD4^+$ T cell counts even when they were very low or zero.

In this paper, we will construct and analyse an HIV infection model with reverse transcriptase (RT) inhibitors. 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, we assume that a virus enters a resting $CD4^+$ T cell, the viral RNA may not be completely reverse transcribed into DNA and the un-integrated virus may decay with time and partial DNA transcripts are labile and degrade quickly [26, 27]. Moreover, Srivastava et al. [23] subdivided the infected cells class in two subclasses: pre-RT and post-RT. It is argued that the RT inhibitors will prevent the infected cells in pre-RT class from proceeding to the post-RT class. If the efficacy of drug is not 100% then a fraction of infected cells in pre-RT class will revert back to uninfected class and remaining will proceed to post-RT class [23]. Therefore, a certain quantity of infected cells will revert back to uninfected class, which is always omitted in many virus models, such as Alan S. Perelson et al. [17].

Since only small fraction on infected cells will revert back due to incompleteness of reverse transcription [3], the reverse will reach to its maximum. Hence, we propose a function $h(I) = \frac{pI}{1+aI}$ with the form in the assumptions, where p is the reverse rate. Now we can see that this function is more realistic than the linear one. For small I , $h(I) \sim pI$, whereas for large I , $h(I) \sim \frac{p}{a}$. This just characterizes the saturated phenomenon of the reverse by a continuous and differentiable function. And when $a = 0$, the saturated treatment function returns to the linear one [24].

In this paper, we shall investigate an ordinary differential equation model of HIV infection of $CD4^+$

T-cells with saturated reverse function

$$\begin{cases} \frac{dT}{dt} = s - dT - \beta TV + \frac{pI}{1+aI}, \\ \frac{dI}{dt} = \beta TV - \delta I - \frac{pI}{1+aI}, \\ \frac{dV}{dt} = qI - cV, \end{cases} \tag{1.1}$$

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, β is the infection rate constant, d is death rate of the T cells, δ is the death rate of the infective cells (δ includes the possibility of death by bursting of infected T cells, hence $\delta \geq d$), q is the reproductive rate of the infected cells, c is the clearance rate constant of virions. $h(I) = pI/(1+aI)$ is the reverse from the infected compartment. Here, p gives the maximum reverse per unite of time, and a , the infected size at which is 50% saturation ($h(a) = \frac{pa}{1+a^2}$), measures how soon saturation occurs. 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 is 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:

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

We denote

$$R_+^3 = \{(T, I, V) \in R^3 \mid T \geq 0, I \geq 0, V \geq 0\}.$$

2. Equilibria and their local stability

System (1.1) always has a viral free equilibrium (i.e., boundary equilibrium) $E_1(T_1, 0, 0)$, where $T_1 = \frac{s}{d}$. The regions of parameter space for which the system (1.1) admits feasible interior equilibria must correspond to a positive root I^* of the quadratic equation

$$b_0 I^2 + b_1 I + b_2 = 0, \tag{2.1}$$

where b_0, b_1, b_2 are given by

$$b_0 = a\beta q\delta, \quad b_1 = \beta q\delta + adc\delta - a\beta qs, \quad b_2 = \delta dc + pdc - \beta qs.$$

Let $R_0 = \frac{q\beta s}{(\delta + p)cd}$. 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.

The quadratic (2.1) can be analyzed for the possibility of multiple endemic equilibria when $R_0 < 1$. It is worth noting that the coefficient b_0 is always positive and b_2 is positive (negative) if R_0 is less than (greater than) unity. Hence, the following result is established.

Theorem 2.1 *The system (1.1) has*

- (i) *a unique endemic equilibrium if $b_2 < 0 \Leftrightarrow R_0 > 1$;*
- (ii) *a unique endemic equilibrium if $b_1 < 0$ and $b_2 = 0$ or $b_1^2 - 4b_0b_2 = 0$;*
- (iii) *two endemic equilibria if $b_2 > 0$, $b_1 < 0$ and $b_1^2 - 4b_0b_2 > 0$;*
- (iv) *no endemic equilibrium otherwise.*

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

The Jacobian matrix of system (1.1) is

$$J = \begin{pmatrix} -d - \beta V & \frac{p}{(1 + aI)^2} & -\beta T \\ \beta V & -\delta - \frac{p}{(1 + aI)^2} & \beta T \\ 0 & q & -c \end{pmatrix}.$$

Let $\bar{E}(\bar{T}, \bar{I}, \bar{V})$ be any arbitrary equilibrium. Then the characteristic equation about \bar{E} is given by

$$\begin{vmatrix} -d - \beta\bar{V} - \lambda & \frac{p}{(1 + a\bar{I})^2} & -\beta\bar{T} \\ \beta\bar{V} & -\delta - \frac{p}{(1 + a\bar{I})^2} - \lambda & \beta\bar{T} \\ 0 & q & -c - \lambda \end{vmatrix} = 0. \tag{2.2}$$

For equilibrium $E_1(T_1, 0, 0)$, (2.2) reduces to

$$(\lambda + d)[\lambda^2 + (p + c + \delta)\lambda + (p + \delta)c - q\beta T_1] = 0.$$

Hence, $E_1(T_1, 0, 0)$ is locally asymptotically stable when $R_0 < 1$. And it is a saddle with $\dim W^s(\hat{E}) = 2$, $\dim W^u(\hat{E}) = 1$ for $R_0 > 1$.

Theorem 2.2 *If $R_0 < 1$, $E_1(T_1, 0, 0)$ is locally asymptotically stable. If $R_0 > 1$, $E_1(T_1, 0, 0)$ is a saddle point with a two-dimensional stable manifold and a one-dimensional unstable manifold.*

Remark 2.3 *It is clear from Theorem 2.1 (Case (i)) that the system (1.1) has a unique endemic equilibrium whenever $R_0 > 1$. Further, Case (iii) indicates the possibility of backward bifurcation (where a locally asymptotical stable viral free equilibrium coexists with a locally asymptotical stable endemic equilibrium when $R_0 < 1$ [1]) in the system (1.1) when $R_0 < 1$. In such a scenario, viral elimination would depend upon the initial sizes of the populations of the model.*

In the following, we will discuss the locally asymptotical stability of the endemic equilibrium when $R_0 > 1$.

When $R_0 > 1$, the only positive root of equation (2.1) is given by $I^* = \frac{1}{2b_0}[-b_1 + \sqrt{b_1^2 - 4b_0b_2}]$.

Additionally, $T^* = \frac{1}{a}(s - \delta I^*)$, $V^* = \frac{q}{c}I^*$. Hence, the endemic equilibrium is $E^*(T^*, I^*, V^*)$.

The Jacobian matrix $J^* = J(T^*, I^*, V^*)$ of system (1.1) at E^* takes the form

$$J(E^*) = \begin{pmatrix} -d - \beta V^* & \frac{p}{(1 + aI^*)^2} & -\beta T^* \\ \beta V^* & -\delta - \frac{p}{(1 + aI^*)^2} & \beta T^* \\ 0 & q & -c \end{pmatrix}. \tag{2.3}$$

The eigenvalue problem for the Jacobian matrix (2.3) provides the characteristic equation

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{2.4}$$

where the coefficients a_i , $i = 1, 2, 3$, are

$$\begin{aligned} a_1 &= c + \delta + \frac{p}{(1 + aI^*)^2} + d + \beta V^*, \\ a_2 &= c\left(\delta + \frac{p}{(1 + aI^*)^2}\right) - q\beta T^* + d(c + \delta) + \beta V^*(c + \delta) + \frac{pd}{(1 + aI^*)^2}, \\ a_3 &= dc\delta + \frac{dcp}{(1 + aI^*)^2} + \beta c\delta V^* - dq\beta T^*. \end{aligned}$$

Note that $a_1 > 0$. And if $dc\delta + \frac{dcp}{(1+aI^*)^2} + \beta c\delta V^* > dq\beta T^*$, then $a_3 > 0$.

Furthermore,

$$\begin{aligned} \Delta &= a_1a_2 - a_3 \\ &= [c + \delta + \frac{p}{(1+aI^*)^2} + d + \beta V^*][c\delta + \frac{cp}{(1+aI^*)^2} - q\beta T^* + (d + \beta V^*)(c + \delta) \\ &\quad + \frac{dp}{(1+aI^*)^2}] - dc\delta - \frac{dcp}{(1+aI^*)^2} - \beta c\delta V^* + dq\beta T^*. \end{aligned}$$

By the Routh-Hurwitz criterion, we know that the unique endemic equilibrium E^* is locally asymptotically stable if it exists and the following conditions hold

- (A₁): $R_0 > 1$;
- (A₂): $dc\delta + \frac{dcp}{(1+aI^*)^2} + \beta c\delta V^* > dq\beta T^*$,
- (A₃): $[c + \delta + \frac{p}{(1+aI^*)^2} + d + \beta V^*][c\delta + \frac{cp}{(1+aI^*)^2} - q\beta T^* + (d + \beta V^*)(c + \delta) + \frac{dp}{(1+aI^*)^2}] + dq\beta T^* > dc\delta + \frac{dcp}{(1+aI^*)^2} + \beta c\delta V^*$.

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*

$$m \leq \liminf_{t \rightarrow +\infty} T(t) \leq \limsup_{t \rightarrow +\infty} T(t) \leq M,$$

$$m \leq \liminf_{t \rightarrow +\infty} I(t) \leq \limsup_{t \rightarrow +\infty} I(t) \leq M,$$

$$m \leq \liminf_{t \rightarrow +\infty} V(t) \leq \limsup_{t \rightarrow +\infty} V(t) \leq M.$$

Definition 3.2 [4] (Metzler matrix) Matrix A is a Metzler matrix iff all its off-diagonal elements are non-negative.

Lemma 3.3 [4] (Perron-Frobenius Theorem) 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 non-negative elements belongs to the span v_M .

In order to prove the permanence of system (1.1), we firstly present the following useful lemma. Firstly, we require the following compactness condition.

Condition 3.4 There exist $\epsilon > 0$ and a subset B of X with the following properties:

(1) If $x \in X$ and $d(x, X_2) < \epsilon$, then $d(\Phi_t(X), B) \rightarrow 0$ as $t \rightarrow \infty$.

(2) The intersection $B \cup B_\epsilon(X_2)$ of B with the ϵ -neighborhood of X_2 , $B_\epsilon(X_2) = \{x \in X; d(x, X_2) < \epsilon\}$ has compact closure.

Lemma 3.5 [25] Let X_1 be open in X and forward invariant under Φ . Further, let the compactness assumption (Condition 3.4) hold. Assume the Ω_2 ,

$$\Omega_2 = \cup_{y \in Y_2} \omega(y), \quad Y_2 = \{x \in X_2; \Phi_t \in X_2, \forall t > 0\}$$

has an acyclic isolated covering $M = \cup_{k=1}^m M_k$ such that each part M_k of M is a weak repeller of X_1 . Then X_2 is a uniform strong repeller for X_1 .

Theorem 3.6 There is an $M > 0$ such that, for any positive solution $(T(t), I(t), V(t))$ of system (1.1), $T \leq M$, $I \leq M$ and $V \leq M$ 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

$$\begin{aligned} \frac{dL_1(t)}{dt} |_{(1.1)} &= \frac{dT(t)}{dt} + \frac{dI(t)}{dt} \\ &= s - dT - \delta I \\ &\leq s - dL_1(t). \end{aligned}$$

Thus $\frac{dL_1(t)}{dt} + dL_1(t) \leq s$. Applying a theorem in differential inequalities, we obtain

$$0 \leq L_1(T(t), I(t)) \leq \frac{s}{d}(1 - e^{-dt}) + L_1(T(0), I(0))e^{-dt}$$

and, for $t \rightarrow +\infty$, $0 \leq L_1 \leq \frac{s}{d}$. Then $T(t)$ and $I(t)$ ultimately have above bound $\frac{s}{d} + \epsilon$ for any $\epsilon > 0$. It follows from the third equation of system (1.1) that $V(t)$ ultimately has an above bound, say, their maximum is M . The proof is complete.

Define $\Omega = \{(T, I, V) | 0 \leq T \leq M, 0 \leq I \leq M, 0 \leq V \leq M\}$. □

Theorem 3.7 *If $R_0 > 1$, then system (1.1) is permanent.*

Proof. The result follows from an application of Lemma 3.5. Let us define X_1 to 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 3.6, 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:

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

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 $Y_2 = \{(T, I, V)^T \in \text{bd}(R_+^3) | I = V = 0\}$. Furthermore, it is easy to see that $\Omega = \{E_1\}$ as all solutions initiated on the T -axis converge to E_1 . In fact, in the set Y_2 , system (1.1) becomes

$$\dot{T} = s - dT.$$

It is easy to see that the equilibrium of the above equation is globally asymptotically stable. Hence, any solution $(T(t), I(t), V(t))$ of system (1.1) initiating from Y_2 is such that $(T(t), I(t), V(t)) \rightarrow E_1(T_1, 0, 0)$. E_1 is isolated invariant set because it is a saddle, as we will show soon. And $\{E_1\}$ is isolated and is an acyclic covering. Next, we show that $W^s(E_1) \cap X_1 = \emptyset$, i.e., E_1 is a weak repeller for X_1 .

By definition, E_1 is a weak repeller for X_1 if for every solution starting in $x_0 \in X_1$

$$\lim_{t \rightarrow +\infty} d(x(t, x_0), E_1) > 0. \tag{3.2}$$

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

$$W^s(E_1) \cap \text{int}(R_+^3) = \emptyset. \tag{3.3}$$

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 $\lim_{t \rightarrow +\infty} d(x(t, x_0), E_1) = 0$ and thus that $\lim_{t \rightarrow +\infty} x(t, x_0) = E_1$, 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 E_1 is

$$J(E_1) = \begin{pmatrix} -d & p & -\beta T_1 \\ 0 & -\delta - p & \beta T_1 \\ 0 & q & -c \end{pmatrix}.$$

It is easy to see that $J(E_1)$ is unstable if $R_0 > 1$. In particular, $J(E_1)$ possesses one eigenvalue with positive real part, which we denote as λ_+ , and two eigenvalues with negative real part, $-d$, and an eigenvalue which we denote as λ_- . We proceed by determining the location of $E^s(E_1)$, the stable eigenspace of E_1 . Clearly, $(1, 0, 0)^T$ is an eigenvector of J_0 associated to $-d$. If $\lambda_- \neq -d$, then the eigenvector associated to λ_- has the

following structure: $(0, p_2, p_3)^T$, where p_2, p_3 satisfy the eigenvector equation

$$\begin{pmatrix} -(\delta + p) & \beta T_1 \\ q & -c \end{pmatrix} \begin{pmatrix} p_2 \\ p_3 \end{pmatrix} = \lambda_- \begin{pmatrix} p_2 \\ p_3 \end{pmatrix}. \tag{3.4}$$

If $\lambda_- = -d$, 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 3.3 (Perron-Frobenius Theorem), we get that the matrix in (3.4) possesses a simple real eigenvalue which is larger than 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, $E^s(E_1) \cap \text{int}(R_+^3) = \emptyset$, and therefore also $W^s(E_1) \cap \text{int}(R_+^3) = \emptyset$, which concludes the proof. \square

4. Global asymptotical stability of equilibria

In this section we will prove the global asymptotical stability of the nonnegative equilibria.

Theorem 4.1 *Under the assumption $\beta sq \leq \delta cd + \frac{cpd^2}{d+as}$, the local stability of $E_1(T_1, 0, 0)$ implies its global stability.*

Proof. By Theorem 3.6, $\limsup_{t \rightarrow +\infty} (T(t) + I(t)) \leq \frac{s}{d}$. Hence, for any $\epsilon > 0$, for large enough time one has the inequality

$$\frac{dI}{dt} \leq \beta \frac{s + \epsilon}{d} V - \delta I - \frac{pI}{1 + a \frac{s + \epsilon}{d}}.$$

So, from the last two equations of system (1.1), for $t > t_1$, we have

$$\begin{cases} \frac{dI}{dt} \leq \beta \frac{s + \epsilon}{d} V - \delta I - \frac{pI}{1 + a \frac{s + \epsilon}{d}}, \\ \frac{dV}{dt} = qI - cV. \end{cases} \tag{4.1}$$

Consider the following equations

$$\begin{cases} \frac{du_1}{dt} = \beta \frac{s + \epsilon}{d} u_2 - \delta u_1 - \frac{pu_1}{1 + a \frac{s + \epsilon}{d}}, \\ \frac{du_2}{dt} = qu_1 - cu_2. \end{cases} \tag{4.2}$$

Since $R_0 < 1$, we can select any $\epsilon > 0$ such that $\beta sq < \delta cd + \frac{cpd^2}{d+as}$. Obviously, for any solution of (4.2) with nonnegative initial values we have $\lim_{t \rightarrow \infty} u_i(t) = 0$ ($i = 1, 2$). Hence, we have $\lim_{t \rightarrow \infty} I(t) = 0$ and $\lim_{t \rightarrow \infty} V(t) = 0$.

Thus, for any $\varepsilon > 0$, we have $-\varepsilon \leq I \leq \varepsilon$ and $-\varepsilon \leq V \leq \varepsilon$. From the first equation of (1.1), we obtain

$$s - dT - \varepsilon\beta T - \frac{p\varepsilon}{1 - a\varepsilon} \leq \frac{dT}{dt} \leq s - dT + \varepsilon\beta T + \frac{p\varepsilon}{1 - a\varepsilon}.$$

Hence, $\lim_{t \rightarrow \infty} T(t) = \frac{s}{d}$.

In the following, we provide sufficient conditions leading to a globally asymptotically stable endemic equilibrium when $R_0 > 1$.

Firstly, we will present the main results related to our research.

Let $D \in R^n$ be an open set, and $x \mapsto f(x) \in R^n$ be a C^1 function defined in D . We consider the autonomous system in R^n given by

$$\frac{dX}{dt} = F(X), \quad X \in D, \tag{4.3}$$

System (4.3) is competitive in D [5, 19, 20, 21] if, for some diagonal matrix $H = \text{diag}(\epsilon_1, \epsilon_2, \dots, \epsilon_n)$, where ϵ_i is either 1 or -1 , $H(DF(X))H$ has nonpositive off-diagonal elements for $X \in D$, where $DF(X)$ is the Jacobian of Eq. (4.3). It is shown in [21] that if D is convex the flow of such a system preserves for $t < 0$ the partial order in R^3 defined by the orthant

$$K_1 = \{(X_1, X_2, \dots, X_n) \in R^n \mid \epsilon_i X_i \geq 0\}.$$

By looking at its Jacobian matrix and choosing the matrix H as

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

we can see that system (1.1) is competitive in Ω , with respect to the partial order defined by the orthant $K_1 = \{(T, I, V) \in R^3 : T \geq 0, I \leq 0, V \geq 0\}$.

Hirsch [5] and Smith [19, 21] proved that three-dimensional competitive systems that live in convex sets have the Poincare-Bendixson property [13]; that is, any nonempty compact omega limit set that contains no equilibria must be a closed orbit. □

Lemma 4.2 *Assume $n = 3$, and D is convex and bounded. Suppose system (4.3) is competitive and permanent and has the property of stability of periodic orbits. If \bar{x}_0 is the only equilibrium point in $\text{int}D$ and if it is locally asymptotically stable, then it is globally asymptotically stable in $\text{int}D$.*

Our main results will follow from this observation and the above lemma.

Theorem 4.3 *Suppose that*

- (i) $R_0 > 1$;
- (ii) $dq\beta T^* < dc\delta + \frac{dcp}{(1+aT^*)^2} + \beta c\delta V^*$.

Then system (1.1) has the property of stability of periodic orbits.

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

$$Z'(t) = \frac{\partial f^{[2]}}{\partial x}(P(t))Z(t), \tag{4.4}$$

where $Z = (Z_1, Z_2, Z_3)^T$ and $\frac{\partial f^{[2]}}{\partial x}$ is derived from the Jacobian matrix of system (1.1) and defined as follows:

$$\frac{\partial f^{[2]}}{\partial x} = \begin{pmatrix} -d - \beta V - \delta - \frac{p}{(1+aI)^2} & \beta T & \beta T \\ q & -d - \beta V - c & \frac{p}{(1+aI)^2} \\ 0 & \beta V & -(\delta + c + \frac{p}{(1+aI)^2}) \end{pmatrix}.$$

For the solution $P(t)$, equation (4.4) becomes

$$\begin{cases} \dot{Z}_1(t) = (-d - \beta V - \delta - \frac{p}{(1+aI)^2})Z_1 + \beta T Z_2 + \beta T Z_3, \\ \dot{Z}_2(t) = qZ_1 + (-d - \beta V - c)Z_2 + \frac{p}{(1+aI)^2} Z_3, \\ \dot{Z}_3(t) = \beta V Z_2 - (\delta + c + \frac{p}{(1+aI)^2})Z_3. \end{cases} \tag{4.5}$$

To prove that (4.5) is globally asymptotically stable, we shall use following Lyapunov function

$$L(Z_1, Z_2, Z_3; T(t), I(t), V(t)) = \|Z_1(t), \frac{I}{V}Z_2(t), \frac{I}{V}Z_3(t)\|,$$

where $\|\cdot\|$ is the norm in R^3 defined by

$$\|(Z_1, Z_2, Z_3)\| = \sup\{|Z_1|, |Z_2| + |Z_3|\}.$$

From Theorem 3.7, we obtain that the orbit of $P(t)$ remains at a positive distance from the boundary of D . Therefore $T(t) > 0, I(t) > 0, V(t) > 0$. Hence the function L is well defined along $P(t)$ and there exists constant $\eta > 0$ such that

$$L(Z_1, Z_2, Z_3; T(t), I(t), V(t)) \geq \eta\|(T, I, V)\|.$$

Along a solution $(Z_1(t), Z_2(t), Z_3(t))$ of system (4.5), L becomes

$$L(t) = \sup\{|Z_1(t)|, \frac{I}{V}(|Z_2(t)| + |Z_3(t)|)\}. \tag{4.6}$$

Function (4.6) is positive, but not differentiable everywhere. Fortunately, this lack of differentiability can be remedied by using the right derivative of $L(t)$, denoted as $D_+L(t)$. The right-hand derivative of $L(t)$ exists and its calculation is described in [10, 12]. Then we have the following equalities:

$$\begin{cases} D_+|Z_1(t)| \leq (-d - \beta V - \delta - \frac{p}{(1+aI)^2})|Z_1| + \beta T|Z_2| + \beta T|Z_3|, \\ D_+|Z_2(t)| \leq q|Z_1| + (-d - \beta V - c)|Z_2| + \frac{p}{(1+aI)^2}|Z_3|, \\ D_+|Z_3(t)| \leq \beta V|Z_2| - (\delta + c + \frac{p}{(1+aI)^2})|Z_3|. \end{cases} \tag{4.7}$$

Therefore,

$$\begin{aligned} D_+(\frac{I}{V}(|Z_2(t)| + |Z_3(t)|)) &= (\frac{\dot{I}}{I} - \frac{\dot{V}}{V})\frac{I}{V}(|Z_2| + |Z_3|) + \frac{I}{V}D_+(|Z_2| + |Z_3|) \\ &\leq (\frac{\dot{I}}{I} - \frac{\dot{V}}{V})\frac{I}{V}(|Z_2| + |Z_3|) + \frac{qI}{V}|Z_1| \\ &\quad + (-d - c)\frac{I}{V}|Z_2| - (c + \delta)\frac{I}{V}|Z_3|. \end{aligned}$$

Define

$$\begin{aligned} g_1(t) &= -d - \beta V + \beta \frac{TV}{I} - \delta - \frac{p}{(1+at)^2} \\ &= \frac{\dot{I}}{I} - (d + \beta V) \end{aligned} \tag{4.8}$$

and

$$\begin{aligned} g_2(t) &= q \frac{I}{V} + \frac{\dot{I}}{I} - \frac{\dot{V}}{V} - 2c - d - \delta \\ &= \frac{\dot{I}}{I} - (d + \delta + c) \\ &\leq \frac{\dot{I}}{I} - d. \end{aligned}$$

Thus, we obtain

$$D_+L(t) \leq \sup\{g_1(t), g_2(t)\}L(t). \tag{4.9}$$

It follows from (4.8) that $g_1(t) \leq \frac{\dot{I}}{I} - d$ and thus that $g_1(t) \leq g_2(t)$. Then (4.9) can be rewritten as

$$D_+L(t) \leq g_2(t)L(t). \tag{4.10}$$

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

$$\int_0^\omega g_2(t)dt \leq \int_0^\omega \left(\frac{\dot{I}}{I} - d\right) = \ln I(\omega) - \ln I(0) - \omega d = -\omega d. \tag{4.11}$$

From (4.10) and (4.11), we have $\lim_{t \rightarrow \infty} L(t) = 0$.

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

This implies that the linear system (4.2) is asymptotically stable and therefore the periodic solution is asymptotically orbitally stable. This proves Theorem 4.3. □

Theorem 4.4 *Suppose that (A_1) , (A_2) and (A_3) hold true and $dq\beta T^* < dc\delta + \frac{dcp}{(1+aI^*)^2} + \beta c\delta V^*$. Then the unique positive equilibrium E^* of system (1.1) is globally asymptotically stable.*

Proof. Since system (1.1) is competitive, permanent if $R_0 > 1$, and E^* is locally asymptotically stable if conditions (A_1) , (A_2) and (A_3) hold true. Moreover, E^* is the only equilibrium point in $\text{int}D$. Theorem 4.3 shows that system (1.1) has the property of stability of periodic orbits. Hence, all the conditions of Lemma 4.2 are satisfied. Therefore, the unique positive equilibrium E^* of system (1.1) is globally asymptotically stable. □

5. Existence of a stable periodic orbit

Our main result below gives sufficient conditions that almost every solution is asymptotically periodic.

The noncontinuable solution of (4.3) satisfying $X(0) = X_0$ is denoted by $X(t, X_0)$, the positive (negative) semi-orbit through X_0 is denoted by $\phi^+(X_0)$ ($\phi^-(X_0)$), and the orbit through X_0 is denoted by $\phi(0) = \phi^-(X_0) \cup \phi^+(X_0)$. We use the notation $\omega(X_0)$ ($\alpha(X_0)$) for the positive (negative) limit set of $\phi^+(X_0)$ ($\phi^-(X_0)$), provided the latter semi-orbit has compact closure in D .

The following lemma is proved in [19].

Lemma 5.1 [19] *Let (4.3) be a competitive system in $D \subset \mathbb{R}^3$ and suppose that D contains a unique equilibrium point X^* which is hyperbolic and assume that $DF(X^*)$ is irreducible. Suppose further that $W^s(X^*)$, the stable manifold of X^* , is one dimensional. If $q \in D \setminus W^s(X^*)$ and $\phi^+(q)$ has compact closure in D , then $\omega(q)$ is a nontrivial periodic orbit.*

The existence of an orbitally stable periodic solution can also be proved. We introduce the following hypotheses:

(H1) System (4.3) is dissipative: For each $X \in D$, $\phi^+(X)$ has compact closure in D . Moreover, there exists a compact subset B of D with property that for each $\bar{X} \in D$ there exists $T(\bar{X}) > 0$ such that $X(t, \bar{X}) \in B$ for $t \geq T(\bar{X})$.

(H2) System (4.3) is competitive and irreducible in D .

(H3) D is an open, p -convex subset of \mathbb{R}^3 .

(H4) D contains a unique equilibrium point X^* and $\det(DF(X^*)) < 0$. The following result holds [13]:

Lemma 5.2 [19] *Let (H1)–(H4) hold. Then either*

(a) X^* is stable or

(b) there exists a nontrivial orbitally stable periodic orbit in D . In addition, let us assume that F is analytic in D . If X^* is unstable, then there is at least one but no more than finitely many periodic orbits for (4.3) and at least one of these is orbitally asymptotically stable.

Theorem 5.3 *Suppose $R_0 > 1$ and (A_2) hold. Then the positive equilibrium is locally asymptotically stable if (A_3) holds. There exists a one-dimensional stable manifold $W^s(E^*)$ if (A_3) is reversed. Furthermore, there exists an orbitally asymptotically stable periodic orbit, and the omega limit set of every solution $(T(t), I(t), V(t))$ with $T(0) > 0$, $I(0) > 0$, $V(0) > 0$ and $(T(0), I(0), V(0)) \notin W^s(E^*)$ is a nonconstant periodic orbit.*

Proof. It suffices to prove the second assumption of Theorem 5.3. We apply Lemmas 5.1 and 5.2 to the following transform system. A change of variables $w_1 = -T$, $w_2 = I$, $w_3 = -V$ transforms system (1.1) into

$$\begin{cases} \frac{dw_1}{dt} = -s - dw_1 + \beta w_1 w_3 - \frac{pw_2}{1 + aw_2}, \\ \frac{dw_2}{dt} = \beta w_1 w_3 - \delta w_2 - \frac{pw_2}{1 + aw_2}, \\ \frac{dw_3}{dt} = -qw_2 - cw_3. \end{cases} \tag{5.1}$$

If we write (5.1) as $\frac{dw}{dt} = f(w)$, the Jacobian matrix of f at w is

$$J(E^*) = \begin{pmatrix} -d - \beta w_3 & -\frac{p}{(1 + aw_2)^2} & \beta w_1 \\ \beta w_3 & -\delta - \frac{p}{(1 + aw_2)^2} & \beta w_1 \\ 0 & -q & -c \end{pmatrix}.$$

$J(w)$ has nonpositive off-diagonal elements at each point of $D = \{(w_1, w_2, w_3) : w_1 < 0, w_2 > 0, w_3 < 0\}$. Let $w_1^* = T^*$, $w_2^* = I^*$, $w_3^* = V^*$. It is obvious that (w_1^*, w_2^*, w_3^*) is the unique equilibrium of Eq. (5.1). Since the inequality $(A3)$ is reversed, the analysis in Section 2 shows that (w_1^*, w_2^*, w_3^*) is unstable and $\det J(w^*) < 0$. Furthermore, we see that the stable manifold of E^* is one dimensional. The existence of an

orbitally asymptotically stable periodic orbit follows from Lemma 5.2 and the analytical of the vector field. Moreover, since Eq. (1.1) is permanent, there exists a compact subset B of D such that, for each $w_0 \in D$, there exists a $T(w_0)$ such that $w(t, w_0) \in B$ for all $t \geq T(w_0)$. Note that (H1)–(H4) hold and using Lemmas 5.1 and 5.2 implies the final assertion. \square

6. 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 we 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 analysis 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 p in the model (representing the cure rate) is not verifiable clinically; however, since it is a important parameter (a bifurcation parameter), we know that for large values the infection would die out and that for small 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.

Table. Parameter values for viral spread.

Parameters	Meanings	Values
s	Source term for uninfected $CD4^+$ T-cells	$5 \text{ (day)}^{-1}(\text{mm}^{-3})$
d	atural death rate of $CD4^+$ T-cells	0.01 day^{-1}
β	Rate $CD4^+$ T-cells become infected with virus	0.00025 mm^{-3}
a	Infected size at which is 50% saturation	1 mm^{-3}
δ	Blanket death rate of infected $CD4^+$ T-cells	1 day^{-1}
q	Reproductively rate of the infected $CD4^+$ T-cells	$800 \text{ mm}^3 \text{ day}^{-1}$
c	Death rate of free virus	8 day^{-1}
p	Cure rate	0.55 day^{-1}

First we observe that there exists a unique interior equilibrium point E^* (43.95652516, 4.560434748, 456.0434748) with the set of parameter values from Table. The positive steady state is locally asymptotically stable, since the eigenvalues associated with the characteristic equation (2.3) at E^* , given by

$$\lambda^3 + 9.141799609\lambda^2 + 0.4672805933\lambda + 0.9055969983 = 0$$

have negative real parts ($\lambda_1 = -9.101390438$, $\lambda_2 = -0.02020458552 - 0.3147899698I$, $\lambda_3 = -0.02020458552 + 0.3147899698I$). Simulation of the model in this situation, produce stable dynamics as is presented in Figure 1. Plots (A)–(C) of Figure 1 show that uninfected cells, infected cells and virus converge to their equilibrium with

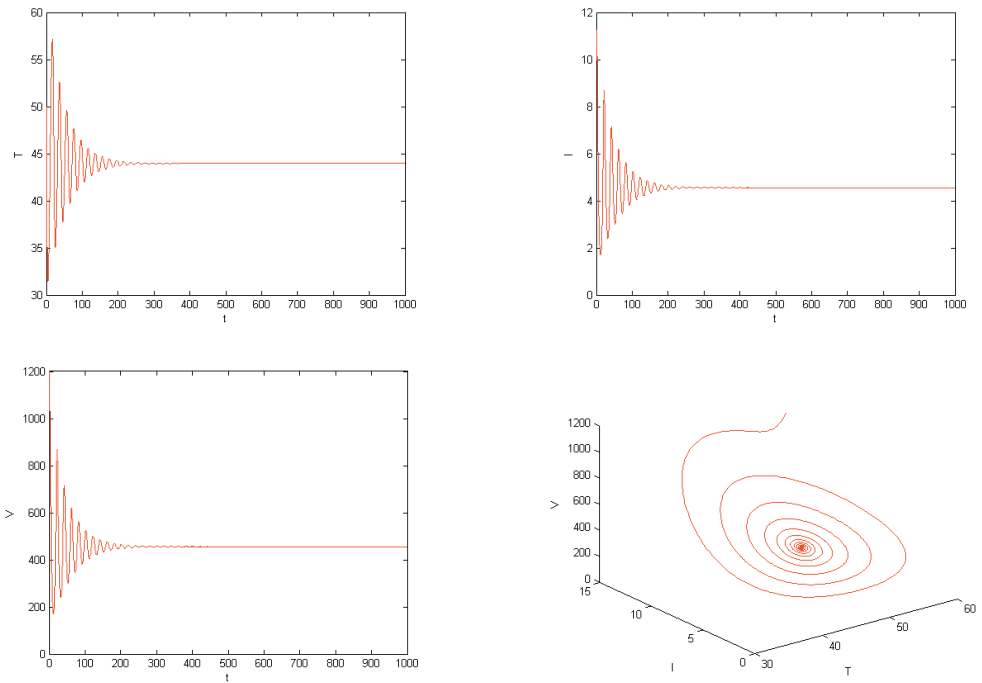


Figure 1. (A)–(C) show that uninfected cells, infected cells and virus converge to their equilibrium with the parametric values as stated in the text. (D) shows that the equilibrium E^* is asymptotically stable. The initial conditions are $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

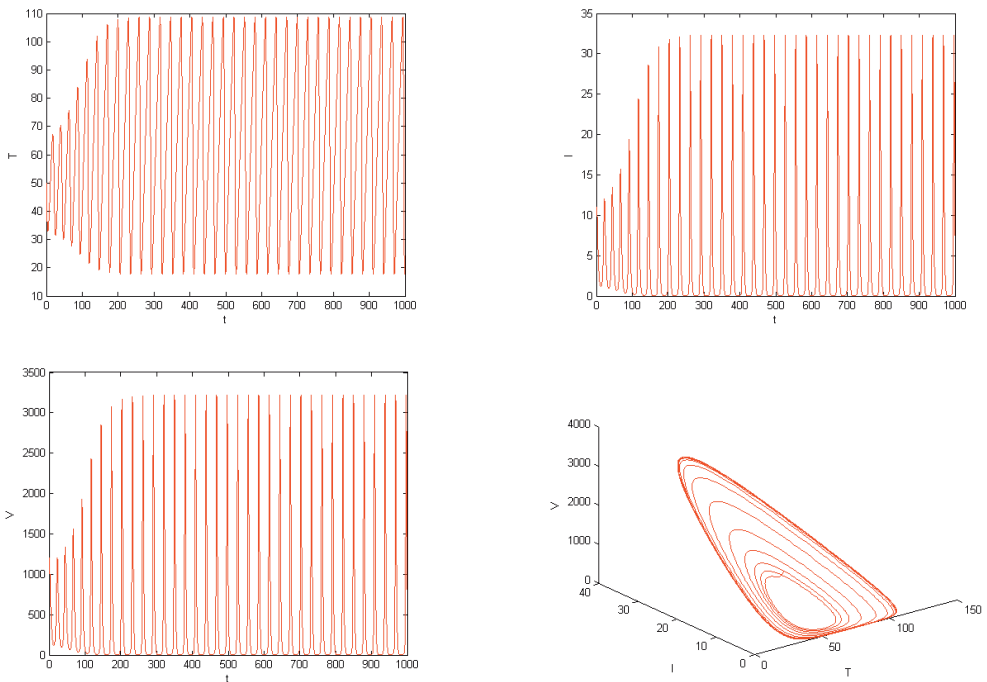


Figure 2. (A)–(C) are the oscillations of uninfected cells, infected cells and virus. (D) shows that there are a periodic solution. The initial conditions is $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

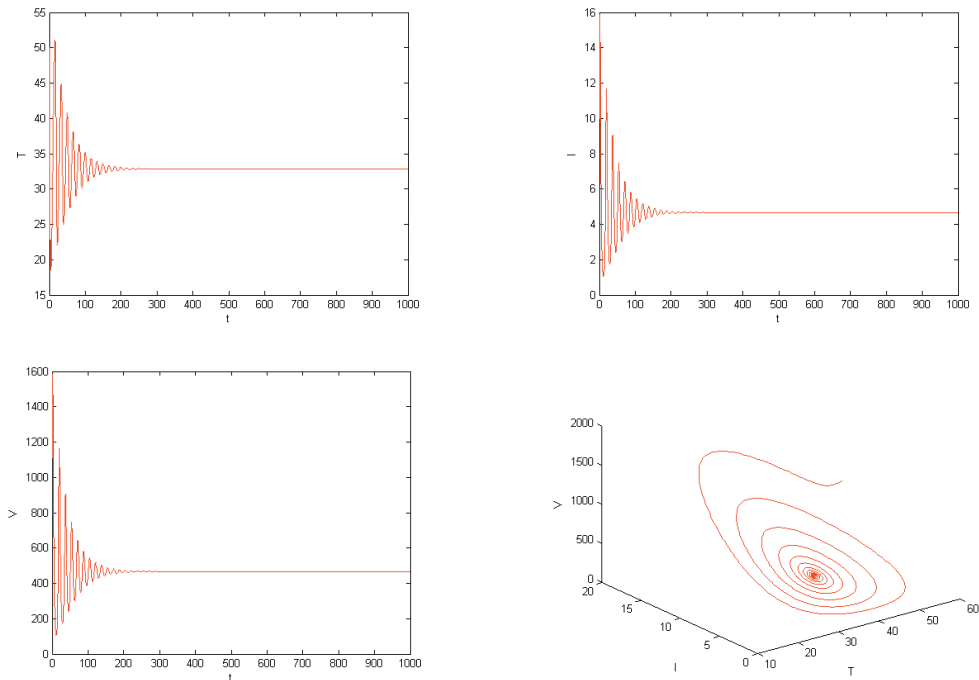


Figure 3. (A)–(C) show that uninfected cells, infected cells and virus converge to their equilibrium with the parametric values as stated in the text. (D) shows that the equilibrium E^* is asymptotically stable. The initial conditions are $T(0) = 30$, $I(0) = 400$, $V(0) = 600$.

the parametric values as stated in Table. Plot (D) of Figure 1 shows that the equilibrium E^* (43.95652516, 4.560434748, 456.0434748) is asymptotically stable. The initial conditions is $T(0) = 50$, $I(0) = 10$, $V(0) = 1200$.

Next, we use a same set of parameter values as those in Table, but we vary the value of p ($p = 0.85$). We can obtain that the characteristic roots of Eq. (2.3) at E^* are $\lambda_1 = -9.158539698$, $\lambda_2 = 0.002894150908 - 0.3128262370I$, $\lambda_3 = 0.002894150908 + 0.3128262370I$. It is easy to see that the conditions of Theorem 5.3 are satisfied. Then the system (1.1) exists an orbitally asymptotically stable periodic orbit (See Figure 2). Plots (A)–(C) of Figure 2 are the oscillations of uninfected cells, infected cells and virus. Plot (D) of Figure 2 shows that there is a periodic solution. The initial conditions are $T(0) = 50$, $I(0) = 10$, $V(0) = 1200$.

We also find that the infection would always keep stability when the rate of infection β is larger. This can be analyzed from the expression of R_0 and the conditions of Theorems 3.7 and 4.4. For example, we show the oscillations of uninfected cells, infected cells and virus in Figure 3. If we select $\beta = 0.00035$ and $p = 0.85$ (the value p is same as Figure 2) and the other parameter values are same in Table then the infection would be stale (See Figure 3). Thus, we can claim that the infective rate β is a very important parameter. The results show that if we improve the infective rate, we will control the disease.

7. Discussion

In this paper, we have investigated 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 E^* is locally stable in the interior of the feasible region. Furthermore, there will exhibit backward bifurcation when $R_0 < 1$. That is to say, viral elimination would depend upon the initial sizes of the populations of the model. If $R_0 > 1$, then system (1.1) is permanent. And if $R_0 > 1$, a unique endemic equilibrium E^* exists and is globally stable in the interior of the feasible region when the conditions of Theorem 4.4 are satisfied. We also obtain the conditions (i.e., conditions of Theorem 5.3) for the system (1.1) exists an orbitally asymptotically stable periodic orbit. Biologically, it implies that some parameter values can cause the cell and virus population to fluctuate.

In [24], Srivastava and Chandra have obtained that the infection is cleared out when $R_0|_{a=0} < 1$, i.e., the uninfected steady state is globally stable, whereas the infection persists and the steady state is globally stable when $R_0|_{a=0} > 1$. That is to say system (1.1) does not have periodic solutions when $a = 0$. Hence, $a > 0$ is necessary for the occurrence of undamped oscillations. This would help much in understanding the mechanisms that may lead to undamped oscillations in this model. Mathematically, since 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 E^* contains all points in the feasible region, namely, if 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 E^* is globally stable. Therefore, identifying parameter ranges in which E^* is globally stable is of both mathematical and biological significance.

Finally, we need the drug to be highly effective if we use single drug to treat. Hence, combination anti-HIV therapy is now the standard of care for people with HIV. Therefore, considering the effects of both RTIs and PIs, model (1.1) can be modified to

$$\begin{cases} \frac{dT}{dt} = s - dT - \beta TV_1 + \frac{pI}{1+aI}, \\ \frac{dI}{dt} = \beta TV_1 - \delta I - \frac{pI}{1+aI}, \\ \frac{dV_1}{dt} = (1-p)N\delta I - cV_1, \\ \frac{dV_2}{dt} = pN\delta I - cV_2, \end{cases} \tag{7.1}$$

where variables V_1 and V_2 denotes infectious and non-infectious virus, respectively. Parameter p ($0 \leq p < 1$) is the protease inhibitor efficacy. Study on the dynamic behavior of system (7.1) and the effect of the PIs will be obtained in the future.

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