



Mathematical analysis of the global dynamics of a model for HIV infection of $CD4^+$ T cells

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Abstract

A mathematical model that describes HIV infection of $CD4^+$ T cells is analyzed. Global dynamics of the model is rigorously established. We prove that, if the basic reproduction number $R_0 \leq 1$, the HIV infection is cleared from the T-cell population; if $R_0 > 1$, the HIV infection persists. For an open set of parameter values, the chronic-infection equilibrium P^* can be unstable and periodic solutions may exist. We establish parameter regions for which P^* is globally stable.

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1. Introduction

The Human Immunodeficiency Virus (HIV) mainly targets a host's $CD4^+$ T cells. Chronic HIV infection causes gradual depletion of the $CD4^+$ T cell pool, and thus progressively compromises the host's immune response to opportunistic infections, leading to Acquired Immunodeficiency Syndrome (AIDS). For this reason, the count of $CD4^+$ T cells is a primary indicator used to measure progression of HIV infection. In a normal person, the level of $CD4^+$ T cells in the peripheral

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blood is regulated at a level between 800 and 1200 mm^{-3} . The body is believed to produce CD4^+ T cells from precursors in the bone marrow and thymus at a constant rate s , and T cells have a natural turn-over rate α . When stimulated by antigen or mitogen, T cells multiply through mitosis with a rate r . Thus the CD4^+ T cell dynamics can be modelled by the following logistic equation:

$$\frac{dT}{dt} = s - \alpha T + rT \left(1 - \frac{T}{T_{\max}} \right), \quad (1)$$

where T is the concentration of CD4^+ T cells, and T_{\max} is the maximum level of CD4^+ T-cell concentration in the body [1,2]. HIV infection will interrupt the normal CD4^+ T-cell dynamics. The total concentration of CD4^+ T cells is now $T + T^*$, where T is the concentration of susceptible CD4^+ T cells and T^* the concentration of infected CD4^+ T cells by the HIV viruses. The T-cell dynamics will be determined by the interactions among susceptible CD4^+ T cells, infected CD4^+ T cells, and free HIV viruses. Several mathematical models have been proposed to describe the in vivo dynamics of T cell and HIV interaction, see [1–6] for review and references. Of particular interest to us is a model in [1], which is given by the following system of differential equations:

$$\begin{aligned} \frac{dT}{dt} &= s - \alpha T + rT \left(1 - \frac{T + T^*}{T_{\max}} \right) - kVT, \\ \frac{dT^*}{dt} &= kVT - \beta T^*, \\ \frac{dV}{dt} &= N\beta T^* - \gamma V. \end{aligned} \quad (2)$$

In this model, T , T^* and V denote the concentration of susceptible CD4^+ T cells, infected CD4^+ T cells, and free HIV virus particles in the blood, respectively. Parameters α , β , and γ are natural turn-over rates of uninfected T cells, infected T cells, and virus particles, respectively. Because of the viral burden on the HIV infected T cells, we assume that $\alpha \leq \beta$. The logistic growth of the healthy CD4^+ T cells is now described by $rT(1 - \frac{T+T^*}{T_{\max}})$, and proliferation of infected CD4^+ T cells is neglected. The term kVT describes the incidence of HIV infection of health CD4^+ T cells, where $k > 0$ is the infection rate. Each infected CD4^+ T cell is assumed to produce N virus particles during its life time, including any of its daughter cells.

A model for HIV infection similar to (2) but using a simplified logistic growth $rT(1 - T/T_{\max})$ for susceptible CD4^+ T cells has been proposed in Perelson and Nelson [2], its global dynamics are analyzed in De Leenheer and Smith [6]. The global dynamics of model (2), however, have not been rigorously established in the literature. The difference in the proliferation term does not change the basic reproduction number. It will not change the CD4 count at equilibrium level, as we will show, but it changes the equilibrium level of viral load during chronic infection. It is of interest to investigate if the difference in logistic terms will cause qualitative changes in the dynamics. The main difficulty of the mathematical analysis lies in the determination of the basin of attraction of the chronic-infection equilibrium P^* . This is done by identifying the range of parameters for which P^* is globally asymptotically stable in the entire feasible region. The global-stability analysis is significant since models of this type are known to possess periodic solutions for an open set of parameter values.

Models considered in [2,6] with a simplified logistic term are competitive systems. The global analysis in [6] relies in an essential way on properties of competitive systems. With a full logistic

term, model (2) is no longer competitive, and the global stability of P^* needs to be established using a different approach. In the present paper, we adopt the approach developed in Li and Muldowney [7], which has been successfully applied to many epidemic and in-host models that are not competitive or monotone (see [8,9]).

For system (2), we show that, if the basic reproduction number $R_0 \leq 1$, the infection-free equilibrium P_0 is globally asymptotically stable, the virus is cleared and no HIV infection persists. If $R_0 > 1$, P_0 becomes unstable and the HIV infection persists in the T-cell population. In this case, a unique chronic-infection equilibrium P^* exists. The local stability of P^* is described in term of the proliferation rate r of healthy T cells. We show that P^* can be unstable for a range of r . Numerical simulations show periodic solutions may exist. It is therefore important to investigate the basin of attraction of P^* when it is locally stable. For an open set of r values that are biologically reasonable, we show that the basin of attraction of P^* includes the whole feasible region.

2. Equilibria

The non-negative octant \mathbb{R}_+^3 is positively invariant with respect to (2). In the absence of infection, the dynamics of healthy T cells are governed by Eq. (1). It can be shown that the T-cell concentration stabilizes at a level T_0 given by

$$T_0 = \frac{T_{\max}}{2r} \left[(r - \alpha) + \sqrt{(r - \alpha)^2 + \frac{4sr}{T_{\max}}} \right]. \quad (3)$$

From the first equation of (2), we know $T(t) \leq T_0$ if $T(0) \leq T_0$. Adding the first two equations of (2) gives $T' + T^{*'} \leq s + rT_0 - \alpha T - \beta T^* \leq s + rT_0 - \alpha(T + T^*)$, since $\alpha \leq \beta$. Therefore $T + T^*$ is bounded, and thus T^* is bounded, say by M . Clearly, V is bounded from the third equation, say by K . So we proved that the set

$$\Gamma = \{(T, T^*, V) \in \mathbb{R}_+^3 : T \leq T_0, T^* \leq M, V \leq K\}$$

is positively invariant with respect to (2). Let

$$R_0 = \frac{kNT_0}{\gamma}$$

denote the basic reproduction number as given in [1]. It represents the average number of secondary infection caused by a single infected T cell in an entirely susceptible T cell population, throughout its infectious period. We have the following result.

Proposition 1. *If $R_0 \leq 1$ the infection-free equilibrium $P_0 = (T_0, 0, 0)$ is the only equilibrium in Γ ; if $R_0 > 1$ there are two equilibria in Γ : P_0 and a unique chronic-infection equilibrium $P^* = (\bar{T}, \bar{T}^*, \bar{V}) \in \Gamma$, the interior of Γ , where*

$$\bar{T} = \frac{\gamma}{Nk}, \quad \bar{T}^* = \frac{\gamma}{N\beta} \bar{V}, \quad \bar{V} = \frac{sp^2 + (r - \alpha)\gamma p - \frac{r}{T_{\max}}\gamma^2}{k\gamma \left(p + \frac{r\gamma}{\beta T_{\max}} \right)}$$

and $p = kN$.

For the models considered in [2,6] that use a simplified logistic growth for T , the coordinates of the chronic-infection equilibrium are given by

$$\bar{T} = \frac{\gamma}{Nk}, \quad \bar{T}^* = \frac{\gamma}{N\beta} \bar{V}, \quad \bar{V} = \frac{sp^2 + (r - \alpha)\gamma p - \frac{r}{T_{\max}} \gamma^2}{k\gamma p}.$$

In comparison, we see that the CD4 count (\bar{T}) is not affected by the difference in logistic terms, while viral load (\bar{V}) is. The full logistic term produces a lower viral load at the chronic-infection equilibrium.

3. Stability of the infection-free equilibrium P_0

The Jacobian matrix of (2) at P_0 is

$$J(P_0) = \begin{bmatrix} -\alpha + r\left(1 - \frac{T_0}{T_{\max}}\right) - \frac{rT_0}{T_{\max}} & -\frac{rT_0}{T_{\max}} & -kT_0 \\ 0 & -\beta & kT_0 \\ 0 & N\beta & -\gamma \end{bmatrix}.$$

An eigenvalue of $J(P_0)$ is

$$-\alpha + r\left(1 - \frac{T_0}{T_{\max}}\right) - \frac{rT_0}{T_{\max}} = -\frac{s}{T_0} - \frac{rT_0}{T_{\max}} < 0$$

from the first equation of (2). The other two eigenvalues have negative real parts if and only if $\beta\gamma - N\beta kT_0 > 0$, i.e., $R_0 < 1$. If $R_0 = 1$, one eigenvalue is 0 and it is simple. If $R_0 > 1$, $J(P_0)$ has a positive eigenvalue. P_0 is thus unstable with a two-dimensional stable manifold and a one-dimensional unstable manifold. We arrive at the following local stability result for P_0 .

Proposition 2. *If $R_0 < 1$, P_0 is locally asymptotically stable. If $R_0 = 1$, P_0 is locally stable. If $R_0 > 1$, P_0 is a saddle point with a two-dimensional stable manifold and a one-dimensional unstable manifold.*

We will show that instability of P_0 leads to chronic HIV infection, which is described in terms of uniform persistence of system (2). System (2) is said to be uniformly persistent in Γ if there exists constant $c > 0$, independent of initial data in Γ , such that, all solutions $(T(t), T^*(t), V(t))$ of (2) satisfy

$$\liminf_{t \rightarrow \infty} T(t) > c, \quad \liminf_{t \rightarrow \infty} T^*(t) > c, \quad \liminf_{t \rightarrow \infty} V(t) > c$$

provided $(T(0), T^*(0), V(0)) \in \overset{\circ}{\Gamma}$.

Theorem 3. *If $R_0 \leq 1$, the infection-free equilibrium P_0 is globally asymptotically stable in Γ . If $R_0 > 1$, P_0 is unstable, and solutions starting sufficiently close to P_0 move away from P_0 , except those starting on the invariant T -axis which approach P_0 along the T -axis. In particular, system (2) is uniformly persistent in Γ .*

Proof. Let $L = NT^* + V$. Then the derivative of L along a solution of (2) is

$$L' = \gamma V \left(\frac{KN}{\gamma} T - 1 \right) = \gamma V \left(R_0 \frac{T}{T_0} - 1 \right) \leq 0, \quad \text{if } R_0 \leq 1,$$

since $T \leq T_0$ in Γ . Furthermore, $L' = 0$ if and only if $V = 0$ or if $R_0 = 1$ and $T = T_0$. The maximum invariant set in $\{(T, T^*, V) \in \Gamma : L' = 0\}$ is $\{P_0\}$. LaSalle's Invariance Principle [10] implies that all solutions in Γ converge to P_0 . The global attractivity of P_0 and its local stability as established in Proposition 2 imply the global stability as claimed.

When $R_0 > 1$, we have $L' > 0$ for solutions starting in Γ and sufficiently close to P_0 , and thus these solutions leave a neighborhood of P_0 . Solutions on the positively invariant T -axis satisfies Eq. (1). Thus $T(t) \rightarrow T_0$ as $t \rightarrow \infty$. Therefore solutions converge to P_0 along the T -axis. It can be shown that the instability of P_0 and the local behaviours of solutions near P_0 imply the uniform persistence of system (2), using a uniform persistence result in [11] and a similar argument as in the proof of Proposition 3.2 in [12]. \square

Theorem 3 completely determines the global dynamics of (2) in Γ when $R_0 \leq 1$. All solutions with initial conditions in Γ converge to P_0 . Biologically, this implies that, when the basic reproduction number $R_0 \leq 1$, the infected T cells and virus particles are cleared from the T-cell population. If $R_0 > 1$, then any initial HIV infection will progress to chronic infection.

4. Local stability of the chronic-infection equilibrium P^*

To investigate the fashion in which the HIV infection persists when $R_0 > 1$, we examine the local stability of P^* . The Jacobian matrix of (2) at P^* is

$$J(P^*) = \begin{bmatrix} -\bar{a} & -\frac{r\bar{T}}{T_{\max}} & -k\bar{T} \\ k\bar{V} & -\beta & k\bar{T} \\ 0 & N\beta & -\gamma \end{bmatrix},$$

where $\bar{a} = \alpha - r \left(1 - \frac{\bar{T} + \bar{T}^*}{T_{\max}} \right) + \frac{r\bar{T}}{T_{\max}} + k\bar{V} = \frac{\alpha}{r} + \frac{r\bar{T}}{T_{\max}} > 0$. The characteristic polynomial of $J(P^*)$ is

$$P(\lambda) = \lambda^3 + (\bar{a} + \beta + \gamma)\lambda^2 + \left[\bar{a}(\beta + \gamma) + \frac{kr}{T_{\max}} \bar{V} \bar{T} \right] \lambda + \frac{kr\gamma}{T_{\max}} \bar{V} \bar{T} + k\beta\gamma\bar{V}.$$

Note that all coefficients of $P(\lambda)$ are positive. Thus by the Routh–Hurwitz criteria, all zeros of $P(\lambda)$ have negative real parts if and only if

$$\Delta = (\bar{a} + \beta + \gamma) \left[\bar{a}(\beta + \gamma) + \frac{kr}{T_{\max}} \bar{V} \bar{T} \right] - \frac{kr\gamma}{T_{\max}} \bar{V} \bar{T} - k\beta\gamma\bar{V} > 0. \quad (4)$$

Let $\rho = r/T_{\max}$. Then Δ can be rewritten as $\Delta = F/(\beta + \bar{T}\rho)$, where

$$F(\rho) = A\rho^3 + B\rho^2 + C\rho + D, \quad (5)$$

and

$$\begin{aligned}
 A &= \left[(\beta + \gamma) + \beta \left(\frac{T_{\max}}{\bar{T}} - 1 \right) \right] \bar{T}^3, \\
 B &= \left\{ \left(\frac{s}{\bar{T}} + \beta \right) \left[\beta + \gamma + \beta \left(\frac{T_{\max}}{\bar{T}} - 1 \right) \right] + \left(\frac{s}{\bar{T}} + \gamma \right) (2\beta + \gamma) + \beta(\beta - \alpha) \right\} \bar{T}^2, \\
 C &= \left\{ \left(\frac{s}{\bar{T}} + \beta \right) \left[(\beta + \gamma) \left(\frac{s}{\bar{T}} + \beta + \gamma \right) + \beta \left(\frac{s}{\bar{T}} - \alpha \right) \right] \right\} \bar{T} \\
 &\quad + \left[\beta \left(\frac{s\beta + s\gamma}{\bar{T}} + \beta\gamma \right) - \frac{\beta^2\gamma}{\bar{T}} T_{\max} \right] \bar{T}, \\
 D &= (\beta + \gamma) \left(\frac{s}{\bar{T}} + \beta \right) \frac{s\beta}{\bar{T}} + \frac{s\beta\gamma^2}{\bar{T}} + \alpha\beta^2\gamma.
 \end{aligned} \tag{6}$$

Clearly, $A > 0$, $B > 0$ and $D > 0$ since $\bar{T} < T_{\max}$ and $\alpha \leq \beta$. Observe that $F(0) = D > 0$, thus F has at least one negative zero. Function $F(\rho)$ is negative for some positive value ρ if and only if $F(\rho)$ has two positive zeros. The following result in [13] deals with the existence of positive zeros of cubic polynomials.

Lemma 4. *Let $g(\lambda) = \lambda^3 + l\lambda^2 + m\lambda + n$ with $n > 0$ and $\Sigma = l^2 - 3m$.*

- (i) *If $\Sigma < 0$, then $g(\lambda)$ has no positive zeros.*
- (ii) *$g(\lambda)$ has positive zeros if and only if $\bar{\lambda} = \sqrt{\Sigma} - l > 0$ and $g(\bar{\lambda}/3) \leq 0$.*

In fact, if $\bar{\lambda} > 0$, then $g(\lambda)$ has a local minimum at $\bar{\lambda}/3$. If $g(\bar{\lambda}/3) = 0$, g has only one positive zero $\bar{\lambda}/3$. If $g(\bar{\lambda}/3) < 0$, then $g(\lambda)$ has two positive zeros λ_1 and λ_2 with $\lambda_1 < \bar{\lambda}/3 < \lambda_2$. Applying Lemma 4 to polynomial $F(\rho)$, we set

$$\Sigma = \frac{B^2 - 3AC}{A^2}, \quad \bar{\rho} = \frac{\sqrt{B^2 - 3AC} - B}{A}. \tag{7}$$

Note that $\bar{\rho} > 0$ if and only if $C < 0$. We thus obtain the following result.

Theorem 5. *Let F , A , B , and C be defined in (5) and (6).*

- (a) *If $B^2 < 3AC$, then $F(\rho) > 0$ for all $\rho \geq 0$, and P^* is locally asymptotically stable for all $r \geq 0$.*
- (b) *If $B^2 \geq 3AC$, let $\bar{\rho}$ be as in (7), then $F(\rho)$ has two positive roots if and only if $C < 0$ and $F(\bar{\rho}/3) < 0$. Let $0 < \rho_1 < \rho_2$ be two positive roots of $F(\rho)$. Then P^* is locally asymptotically stable if $0 \leq r < \rho_1 T_{\max}$ or $r > \rho_2 T_{\max}$; P^* is unstable if $\rho_1 T_{\max} < r < \rho_2 T_{\max}$.*

It follows from Theorem 5 that, if $C < 0$ and $F(\bar{\rho}/3) < 0$, then P^* is unstable for r in the range

$$\rho_1 T_{\max} < r < \rho_2 T_{\max}.$$

To explore the dynamics for r in this range, we carried out numerical simulations which consistently show the existence of periodic solutions. Output of one of the numerical simulations is shown in Fig. 2. We would like to remark that clinical data on HIV infection do not show

sustained oscillations. This implies that if a simple model like (2) is to be used to interpret data, one needs to focus on the range of r values for which P^* is stable.

While Theorem 5 gives a complete description of the stability of P^* , it is useful to have a simpler sufficient condition for stability. If we rewrite Δ in (4) as

$$\begin{aligned}\Delta &= (\bar{a} + \beta) \left[\bar{a}(\beta + \gamma) + \frac{kr}{T_{\max}} \bar{V} \bar{T} \right] + \bar{a}(\beta + \gamma)\gamma - k\beta\gamma\bar{V} \\ &= (\bar{a} + \beta) \left[\bar{a}(\beta + \gamma) + \frac{kr}{T_{\max}} \bar{V} \bar{T} \right] + \bar{b}(\beta + \gamma)\gamma + k\gamma^2\bar{V},\end{aligned}$$

where $\bar{b} = \bar{a} - k\bar{V} = \alpha - r + r(2\bar{T} + \bar{T}^*)/T_{\max}$. Then $\Delta > 0$ if $\bar{b} \geq 0$. We thus obtain the following stability condition, which includes as a special case a stability condition derived in [6] for a model with a simplified logistic term.

Proposition 6. P^* is locally asymptotically stable if

$$\alpha - r + r \frac{2\bar{T} + \bar{T}^*}{T_{\max}} \geq 0. \quad (8)$$

5. Global stability of P^*

When r belongs to the range for which P^* is locally asymptotically stable, it is of interest to know the basin of attraction of P^* . In particular, we would like to know if the basin of attraction includes all points in the feasible region Γ , namely, if P^* is globally asymptotically stable. Establishing the range of r values for which P^* is globally stable is especially important given that model (2) is capable of having periodic solutions.

Global stability of P^* for model (2) when the logistic term does not contain T^* was established in [6]. The approach in [6] depends crucially on the fact that the system is competitive. Model (2) with the full logistic term is no longer competitive. To investigate the global stability of P^* , we apply the approach developed in Li and Muldowney [7], which we briefly summarize in the following.

Let $G \subset \mathbb{R}^n$ be an open set and function $f : x \mapsto f(x) \in \mathbb{R}^n$ be C^1 for $x \in G$. Consider the differential equation

$$x' = f(x). \quad (9)$$

Denote by $x(t, x_0)$ the solution to (9) such that $x(0, x_0) = x_0$. A set E is said to be *absorbing* in G for system (9) if $x(t, E_1) \subset E$ for each compact set $E_1 \subset G$ when t is sufficiently large. The following assumptions are made:

- (H₁) System (9) has a unique equilibrium point \bar{x} in G .
- (H₂) System (9) has a compact absorbing set $E \subset G$.

Let M be an $n \times n$ matrix. The *second additive compound matrix* of M , denoted by $M^{[2]}$, is an $\binom{n}{2} \times \binom{n}{2}$ matrix. For instance, if $M = (m_{ij})$ is a 3×3 matrix, then

$$M^{[2]} = \begin{bmatrix} m_{11} + m_{22} & m_{23} & -m_{13} \\ m_{32} & m_{11} + m_{33} & m_{12} \\ -m_{31} & m_{21} & m_{22} + m_{33} \end{bmatrix}. \tag{10}$$

For definition and discussions of compound matrices and their applications in differential equations, we refer the reader to [14,15]. Let $|\cdot|$ denote a vector norm in \mathbb{R}^n and the induced matrix norm in $\mathbb{R}^{n \times n}$, the space of all $n \times n$ matrices. For each matrix N in $\mathbb{R}^{n \times n}$, the *Lozinskiĭ* measure with respect to norm $|\cdot|$ is defined as (see [16, p. 41])

$$\mu(N) = \lim_{h \rightarrow 0^+} \frac{|I + hN| - 1}{h}.$$

Let $Q : x \mapsto Q(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 and $Q^{-1}(x)$ exists for $x \in G$, and let μ be a Lozinskiĭ measure on $\mathbb{R}^{d \times d}$, where $d = \binom{n}{2}$. Define a quantity \bar{q}_2 as

$$\bar{q}_2 = \limsup_{t \rightarrow \infty} \sup_{x_0 \in E} \frac{1}{t} \int_0^t \mu(M(x(s, x_0))) \, ds, \tag{11}$$

where

$$M = Q_f Q^{-1} + Q J^{[2]} Q^{-1} \tag{12}$$

the matrix Q_f is obtained by replacing each entry q_{ij} of Q by its derivative in the direction of f , $(q_{ij})_f$, and $J^{[2]}$ is the second additive compound matrix of the Jacobian matrix J of system (9). The following result is established in Li and Muldowney [7].

Theorem 7. *For system (9), assume that G is simply connected and that the assumptions (H_1) and (H_2) hold. Then the unique equilibrium \bar{x} is globally asymptotically stable in G if there exist a function $Q(x)$ and a Lozinskiĭ measure μ such that $\bar{q}_2 < 0$.*

From the discussion in Section 2, we know that $\overset{\circ}{\Gamma}$ is simply connected and P^* is the unique equilibrium in $\overset{\circ}{\Gamma}$. The uniform persistence of system (2) when $R_0 > 1$ as shown in Theorem 3, together with the boundedness of solutions, implies the existence a compact absorbing set $E \subset \overset{\circ}{\Gamma}$, see [17,18]. Therefore, both assumptions (H_1) and (H_2) are satisfied by system (2) when $R_0 > 1$. The next lemma is needed for establishing the global stability result. Observe that in the absence of the HIV infection, T-cell concentration T remains below the maximum capacity T_{\max} , we should naturally have $s < \alpha T_{\max}$. Since $\alpha \leq \beta$, we have

$$s < \beta T_{\max}.$$

Let $0 < p < 1$ be such that

$$s < p\beta T_{\max}. \tag{13}$$

Lemma 8. *Let $0 < p < 1$ be as in (13). There exists $\bar{t} > 0$ such that all solutions in the compact absorbing set E to (2) satisfy*

$$T(t) + T^*(t) \geq \frac{ps}{\beta}, \quad t \geq \bar{t}. \quad (14)$$

Proof. From (2), we have

$$(T + T^*)' = s - \alpha T - \beta T^* + rT \left(1 - \frac{T + T^*}{T_{\max}} \right) \geq s - \beta(T + T^*).$$

This implies that

$$T(t) + T^*(t) \geq \frac{s}{\beta} + \left[T(0) + T^*(0) - \frac{s}{\beta} \right] e^{-\beta t} \geq \frac{ps}{\beta},$$

for any $0 < p < 1$, as long as t is sufficiently large. This proves the lemma. \square

Theorem 9. Assume that $R_0 > 1$. Then P^* is globally asymptotically stable in $\overset{\circ}{\Gamma}$ if r satisfies

$$r \left(1 - \frac{ps}{\beta T_{\max}} \right) < \alpha \quad \text{and} \quad \frac{rT_0}{T_{\max}} < \beta, \quad (15)$$

where $0 < p < 1$ is defined in (13).

We would like to remark on the range of parameters defined by (15). In the absence of HIV infection, T-cell concentration is capable to stabilize at T_0 . It is natural to expect that $r \geq \alpha$ ($\geq \beta$). Combine this with the condition (15), we have the following range of r values for which P^* is globally stable

$$\alpha \leq r < \min \left\{ \frac{\beta T_{\max}}{\beta T_{\max} - ps} \alpha, \frac{T_{\max}}{T_0} \beta \right\}. \quad (16)$$

Note that $T_0 < T_{\max}$, the region defined by condition (16) is non-empty and biologically feasible.

Proof of Theorem 9. The Jacobian matrix J associated with a general solution $(T(t), T^*(t), V(t))$ to (2) is

$$J = \begin{bmatrix} -a & -\frac{rT}{T_{\max}} & -kT \\ kV & -\beta & kT \\ 0 & N\beta & -\gamma \end{bmatrix}$$

and its second additive compound matrix $J^{[2]}$ is, by (10),

$$J^{[2]} = \begin{bmatrix} -a - \beta & kT & kT \\ N\beta & -a - \gamma & -\frac{rT}{T_{\max}} \\ 0 & kV & -\beta - \gamma \end{bmatrix},$$

where $a = \alpha - r \left(1 - \frac{T+T^*}{T_{\max}} \right) + \frac{rT}{T_{\max}} + kV$. Set the function $Q = Q(T, T^*, V) = \text{diag} \{1, T^*/V, T^*/V\}$. Then $Q_f Q^{-1} = \text{diag} \{0, T^{*'} / T^* - V' / V, T^{*'} / T^* - V' / V\}$, and

$$M = Q_f Q^{-1} + QJ^{[2]}Q^{-1} = \begin{bmatrix} -a - \beta & \frac{kTV}{T^*} & \frac{kTV}{T^*} \\ \frac{N\beta T^*}{V} & \frac{T^{*'}}{T^*} - \frac{V'}{V} - a - \gamma & -\frac{rT}{T_{\max}} \\ 0 & kV & \frac{T^{*'}}{T^*} - \frac{V'}{V} - \beta - \gamma \end{bmatrix} = \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix},$$

where $M_{11} = [-a - \beta]$, $M_{12} = [kTV/T^*, kTV/T^*]$, $M_{21} = [N\beta T^*/V, 0]^T$, and

$$M_{22} = \begin{bmatrix} \frac{T^{*'}}{T^*} - \frac{V'}{V} - a - \gamma & -\frac{rT}{T_{\max}} \\ kV & \frac{T^{*'}}{T^*} - \frac{V'}{V} - \beta - \gamma \end{bmatrix}.$$

Let (u, v, w) denote the vectors in \mathbb{R}^3 , choose a norm in \mathbb{R}^3 as $|(u, v, w)| = \max \{|u|, |v| + |w|\}$ and let μ be the corresponding Lozinskiĭ measure. Then we have the following estimate, see [19]:

$$\mu(M) \leq \max\{g_1, g_2\}, \tag{17}$$

where

$$g_1 = \mu_1(M_{11}) + |M_{12}| \quad \text{and} \quad g_2 = |M_{21}| + \mu_1(M_{22}),$$

$|M_{12}|, |M_{21}|$ are matrix norms with respect to the l_1 vector norm, and μ_1 is the Lozinskiĭ measure with respect to l_1 norm. More specifically, $\mu_1(M_{11}) = -a - \beta$, $|M_{12}| = kTV/T^*$, $|M_{21}| = N\beta T^*/V$, and $\mu_1(M_{22})$ can be evaluated as follows, see [16]:

$$\begin{aligned} \mu_1(M_{22}) &= \max \left\{ \frac{T^{*'}}{T^*} - \frac{V'}{V} - a - \gamma + kV, \frac{T^{*'}}{T^*} - \frac{V'}{V} - \beta - \gamma + \frac{rT}{T_{\max}} \right\} \\ &= \frac{T^{*'}}{T^*} - \frac{V'}{V} - \gamma + \max \left\{ -b, -\beta + \frac{rT}{T_{\max}} \right\}, \end{aligned}$$

where

$$b = \alpha - r(1 - (T + T^*)/T_{\max}) + rT/T_{\max} \geq \alpha - r \left(1 - \frac{ps}{\beta T_{\max}} \right), \quad t \geq \bar{t}, \tag{18}$$

by (14). From (2) we have

$$\frac{T^{*'}}{T^*} = \frac{kVT}{T^*} - \beta, \quad \frac{V'}{V} = \frac{N\beta T^*}{V} - \gamma.$$

Substitute these relations into those of g_1 and g_2 , we obtain

$$\begin{aligned} g_1 &= -a - \beta + \frac{kTV}{T^*} = \frac{T^{*'}}{T^*} - a < \frac{T^{*'}}{T^*} - b, \\ g_2 &= \frac{N\beta T^*}{V} + \frac{T^{*'}}{T^*} - \frac{V'}{V} - \gamma + \max \left\{ -b, -\beta + \frac{rT}{T_{\max}} \right\} < \frac{T^{*'}}{T^*} - \min \left\{ b, \beta - \frac{rT_0}{T_{\max}} \right\}. \end{aligned} \tag{19}$$

Therefore $\mu(M) \leq T^*/T^* - \eta$ for t sufficiently large by (17) and (19), where

$$\eta = \min \left\{ \alpha - r \left(1 - \frac{ps}{\beta T_{\max}} \right), \beta - \frac{rT_0}{T_{\max}} \right\} > 0$$

by (15). Let $(T(t), T^*(t), V(t))$ be any solution starting in the compact absorbing set $E \subset \Gamma$ and let \bar{t} be sufficiently large such that $(T(t), T^*(t), V(t)) \in E$ for all $t \geq \bar{t}$ and that (14) holds. Then along each solution $(T(t), T^*(t), V(t))$ such that $(T(0), T^*(0), V(0)) \in E$ we have, for $t > \bar{t}$,

$$\frac{1}{t} \int_0^t \mu(M) \, ds \leq \frac{1}{t} \int_0^{\bar{t}} \mu(M) \, ds + \frac{1}{t} \ln \frac{T^*(t)}{T^*(\bar{t})} - \frac{t - \bar{t}}{t} \eta. \tag{20}$$

The boundedness of T^* and (11) imply $\bar{q}_2 < 0$, completing the proof. \square

6. Numerical simulations

We have shown in Theorem 5(b) that, when $R_0 > 1$, the chronic-infection equilibrium P^* may only be stable for r small or large. In these parameter regions, the stability of P^* can be lost as r increases and then regained as r further increases. We carried out numerical simulations using *Mathematica* to illustrate such a change in stability. Furthermore, our numerical simulations consistently show the existence of periodic solutions when P^* is unstable. For the simulations, we use a similar set of parameter values as those in [2,6], but vary the values of r . More specifically, $s = 0.1 \text{ day}^{-1} \text{ mm}^{-3}$, $\alpha = 0.02 \text{ day}^{-1}$, $\beta = 0.3 \text{ day}^{-1}$, $\gamma = 2.4 \text{ day}^{-1}$, $k = 0.0027 \text{ mm}^{-3} \text{ day}^{-1}$, $T_{\max} = 1500 \text{ mm}^{-3}$, $N = 10$. The polynomial F defined in (5) is

$$F(\rho) = 5.24 \times 10^6 \rho^3 + 7.5 \times 10^4 \rho^2 - 110\rho + 0.6 \times 10^{-2},$$

whose three roots are $\rho_1 = 0.000062302$, $\rho_2 = 0.0012745$, and $\rho_3 = -0.0157105$. Thus P^* is unstable if r is between 0.093453 and 1.9118 by Theorem 5(b). Outputs of three simulations are shown in Figs. 1–3, for values $r = 0.05$, $r = 0.8$, and $r = 3$, respectively. We see that P^* is globally stable for $r = 0.05$ and $r = 3$, whereas P^* is unstable and a stable periodic solution exist for $r = 0.8$. Simulations also reveal that solutions converge to P^* as damped oscillations when P^* is stable, and

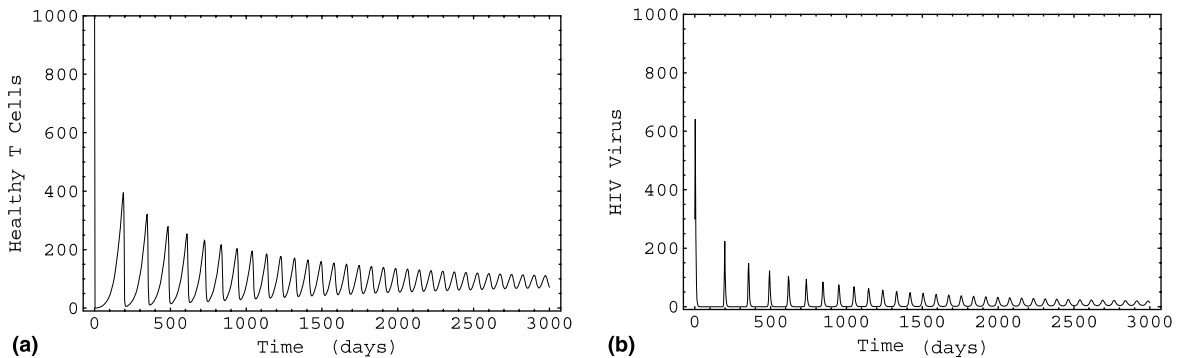


Fig. 1. With parameter values as chosen in Section 6, P^* is shown to be globally stable when $r = 0.05$, $R_0 = 10.16$.

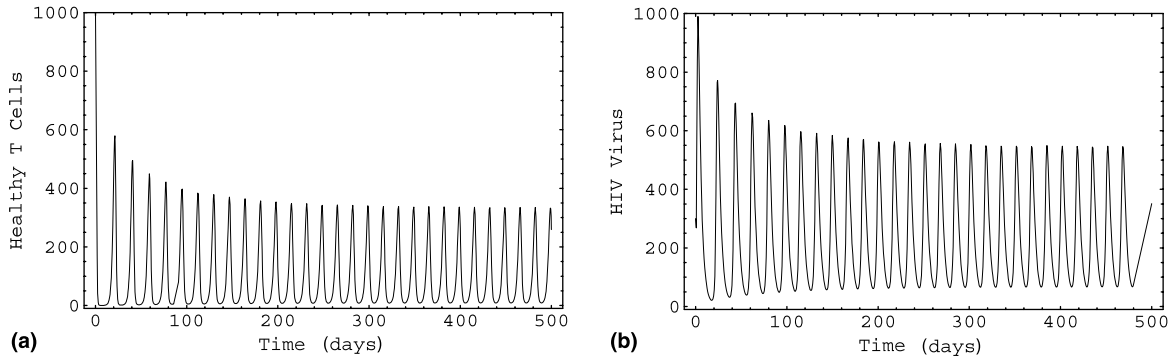


Fig. 2. A periodic solution is shown when $r = 0.8$, $R_0 = 16.45$.

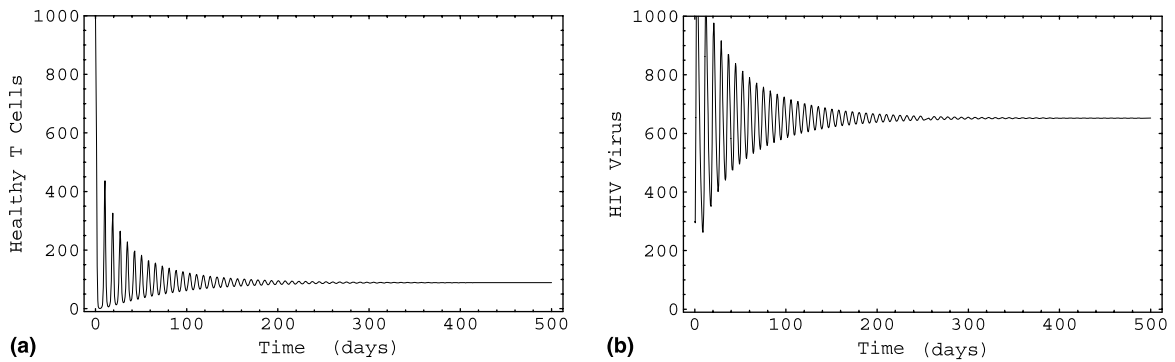


Fig. 3. When $r = 3$, $R_0 = 16.76$, P^* is shown to be globally stable.

that the damping factor is in proportion to r . When $r = 3$, initial oscillations effectively disappear after 200 days, whereas when $r = 0.05$, damped oscillations are clearly visible after 2000 days. We also observe that the HIV viral load at chronic stage is in reverse proportion to r ; the viral load when $r = 3$ persists at 600 mm^{-3} while it is below 100 mm^{-3} when $r = 0.05$. We also note that the values for R_0 in the three cases are 10.16, 16.45, and 16.76, respectively. While the values of R_0 in the last two cases are very close, the dynamics shown in Figs. 2 and 3 are drastically different because of the different r values.

7. Discussion

In-host models for the HIV infection of CD4^+ T cells are considered in [2,6], where the growth of susceptible T cells is assumed to be unaffected by the HIV infection, and follows a simplified logistic growth:

$$rT \left(1 - \frac{T}{T_{\max}} \right)$$

during the course of infection. In model (2) considered in the present paper, a full logistic growth term

$$rT \left(1 - \frac{T + T^*}{T_{\max}} \right)$$

is used for the growth of healthy T cells, where T^* is the concentration of infected $CD4^+$ T cells. This assumes that the growth of healthy T cells slows down during the course of HIV infection. Our analysis shows that such a difference in the growth term does not alter the qualitative behaviours of solutions. More specifically, models with these two different growth terms have the same basic reproduction number

$$R_0 = \frac{kNT_0}{\gamma},$$

where T_0 is the equilibrium of $CD4^+$ T cells in the absence of HIV infection. Furthermore, for both models, the infection-free equilibrium $P_0 = (T_0, 0, 0)$ is globally stable if $R_0 \leq 1$, and a unique chronic-infection equilibrium P^* exists if $R_0 > 1$. P^* can be unstable for a open set of parameter values, and periodic solutions may exist. Quantitatively, both growth forms produce the same level of CD4 count at the chronic-infection equilibrium P^* , while the full logistic term leads to a lower level of viral load at the equilibrium P^* .

Mathematically, since P^* can be unstable and periodic solutions may exist for these models, it is important to investigate if the basin of attraction of P^* contains all points in the feasible region, namely, if P^* is globally stable. Clinical data on HIV positive patients do not show sustained oscillations. This suggests that simple models like (2), 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 P^* is globally stable. Therefore, identifying parameter ranges in which P^* is globally stable is of both mathematical and biological significance.

The global stability of P^* is established in [6] for HIV models with simplified logistic growth. The analysis in [6] relies in an essential way on the fact that the model is competitive. Models (2), with a complete logistic term, is no longer competitive. To establish the global stability of P^* , we adopted a general approach of Li and Muldowney [7], which is developed for higher dimensional systems irrespective if they are competitive. The parameter range produced by our global-stability analysis are also biologically reasonable. While the approach of Li and Muldowney has been successfully applied to many classes of epidemic models, we demonstrated in the present paper, for the first time, that this approach is also applicable to in-host HIV models.

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