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GLOBAL MATHEMATICAL ANALYSIS OF AN HIV-1 INFECTION MODEL WITH HOLLING TYPE-II INCIDENCE

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ABSTRACT. In this paper, we study an HIV-1 infection mathematical model with Holling type-II incidence. Both local and global mathematical analysis is carried out. By identifying a basic reproduction number R_0, we show that if $R_0 \leq 1$, the uninfected steady state P_0 is the only equilibrium in the feasible region, and P_0 is globally asymptotically stable. Therefore, no HIV-1 infection persists and infected T cells and HIV-1 virus are cleared over time. However, if $R_0 > 1$, a unique infected steady state P^* emerges in the interior of the feasible region and P_0 becomes unstable. We show that the system is uniformly persistent and the unique infected steady state P^* is globally asymptotically stable in the interior of the feasible region. Therefore, HIV-1 infection persists and the concentrations of the healthy cells, infected cells, and HIV-1 virus will settle at the level of P^*.

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1. INTRODUCTION

To describe the interaction of HIV-1 virus and T cells, we partition the total T cells into healthy(uninfected) T cells and infected T cells and study the dynamics between healthy T cells, infected T cells, and HIV-1 free virus with their concentrations represented by $T(t), T^*(t)$ and $V(t)$ at time t, respectively. Then a basic mathematical model describing the HIV-1 infection can be written in the following form, see [1-8]:

$$\begin{aligned} \dot{T} &= s - \alpha T - kVT, \\ \dot{T}^* &= kVT - \beta T^*, \\ \dot{V} &= N\beta T^* - \epsilon V. \end{aligned} \tag{1}$$

The human body produces T cells and it is assumed that T cells are produced at a constant rate s and that newly produced T cells are susceptible and healthy. Parameters α, β, and ϵ are the per-capita death rates of the healthy T cells, infected T cells, and the virus particles, respectively. The infection is through a direct contact between

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virus and healthy T cells. The incidence is described by a simple mass-action term kVT, where $k > 0$ is the contact rate between virus and healthy T cells. Infected T cells produce virus and each infected T cell produces N virus during its lifetime. Other mathematical models have also been developed to describe the HIV-1 infection in which a logistic proliferation in T cells is assumed, see [8-13] and references therein.

In this paper, we will focus on system (1) with a more general Holling type-II incidence.

$$\begin{aligned} \dot{T} &= s - \alpha T - \frac{kVT}{1+aV}, \\ \dot{T^*} &= \frac{kVT}{1+aV} - \beta T^*, \\ \dot{V} &= N\beta T^* - \epsilon V, \end{aligned} \tag{2}$$

where $a \geq 0$, and if $a = 0$ system (2) becomes system (1). Li and Ma [5] studied system (2) with $a = 1$ and with a time delay; local stability of the uninfected and infected steady states and global stability of the uninfected steady state are established. In this paper, for system (2) we will carry out a complete mathematical analysis. Local and global stability for both the uninfected and infected steady states are carried out.

In the next section, we establish that all solutions of system (2) are bounded and that a certain bounded region Γ in the nonnegative orthant $\mathbf{R}^3_+$ is positively invariant with respect to (2). After identifying a basic reproduction number R_0, we show that system (2) has a unique uninfected steady state P_0 if $R_0 \leq 1$; whereas if $R_0 > 1$, system (2) has two steady states in $\Gamma : P_0$ and a unique infected steady state $P^* \in \overset{\circ}{\Gamma}$, the interior of Γ. Then in Section 3, It is shown that if P_0 is the only steady state in Γ, then it is globally asymptotically stable. However, if $R_0 > 1$, then P^* emerges, P_0 becomes unstable, and all solutions initiating sufficiently close to P_0 move away from P_0 except those starting on the invariant T axis. In this case, the system is uniformly persistent. In Section 4, stability of the infected steady state P^* is investigated. We show that once the uninfected steady state P^* emerges, it is globally asymptotically stable. The result is obtained using a global stability criterion developed by Li and Moldulwney [14].

2. BOUNDEDNESS, POSITIVE INVARIANCE, AND STEADY STATES

It is easy to see that system (2) is positively invariant with respect to the nonnegative orthant $\mathbf{R}^3_+ = \{(T, T^*, V) : T \geq 0, T^* \geq 0, V \geq 0\}$.

It follows from the first equation of system (2) that if $T(0) < s/\alpha$, then $T(t) < s/\alpha$ for all $t > 0$. Furthermore, adding the first two equations of system (2) gives

$$\dot{T} + \dot{T^*} = s - \alpha T - \beta T^* \leq s - \eta(T + T^*),$$

where $\eta = \min\{\alpha, \beta\}$. Therefore $T + T^*$ is bounded, and so is T^*. Obviously, V is bounded from the third equation if T^* is bounded. We thus proved that there exists a number $M > 0$ such that the set

$$\Gamma = \{(T, T^*, V) \in \mathbf{R}^3_+ : T \le s/\alpha, T^* \le M, V \le M\}$$

is positively invariant with respect to (2). In the following, we only study the system (2) in the positively invariant region Γ.

Clearly, $P_0 = (s/\alpha, 0, 0)$ is a steady state of (2) and it exists for all feasible parameter values. The steady state P_0 is referred to as *the uninfected steady state.* Define

$$R_0 = \frac{skN}{\alpha\epsilon} \tag{3}$$

as the basic reproduction number. Then the following result establishes the existence and the uniqueness of *the infected steady state* $P^* = (\bar{T}, \bar{T}^*, \bar{V})$.

Proposition 2.1. *If $R_0 \le 1$, then system (2) has only the uninfected steady state $P_0 = (s/\alpha, 0, 0)$; whereas if $R_0 > 1$, then system (2) has two steady states: P_0 and a unique infected steady state $P^* = (\bar{T}, \bar{T}^*, \bar{V})$, where $\bar{T} > 0, \bar{T}^* > 0$, and $\bar{V} > 0$ and*

$$\bar{T} = \frac{asN + \epsilon}{N(a\alpha + k)}, \quad \bar{T}^* = \frac{skN - \alpha\epsilon}{\beta N(a\alpha + k)}, \quad \bar{V} = \frac{skN - \alpha\epsilon}{\epsilon(a\alpha + k)}.$$

3. STABILITY OF THE UNINFECTED STEADY STATE P_0 AND UNIFORM PERSISTENCE

Proposition 2.1 shows that system (2) has at most two steady states in Γ. In this subsection, we study the stability of the uninfected steady state P_0. We show that if P_0 is the only steady state in Γ, then it is globally asymptotically stable. However, when the infected steady state P^* emerges in $\overset{\circ}{\Gamma}$, P_0 becomes unstable. The following theorem describes the local stability of P_0.

Theorem 3.1. *If $R_0 < 1$, then P_0 is locally asymptotically stable. If $R_0 = 1$, then P_0 is locally stable. If $R_0 > 1$, then P_0 is unstable and solutions starting sufficiently close to P_0 move away from P_0 except those starting in the invariant T axis.*

Proof. The Jacobian matrix of system (2) at P_0 is

$$J(P_0) = \begin{bmatrix} -\alpha & 0 & -ks/\alpha \\ 0 & -\beta & ks/\alpha \\ 0 & N\beta & -\epsilon \end{bmatrix}.$$

One eigenvalue of $J(P_0)$ is $\lambda_1 = -\alpha < 0$. The other two eigenvalues are determined by the quadratic equation

$$\lambda^2 + (\beta + \epsilon)\lambda + \beta\epsilon - N\beta ks/\alpha = 0,$$

and they have negative real parts if and only if $\beta\epsilon - N\beta ks/\alpha > 0$, which is equivalent to $R_0 < 1$. If $R_0 = 1$, one eigenvalue is 0 and it is simple. So P_0 is stable. If $R_0 > 1$, one eigenvalue is positive. Therefore P_0 is unstable. The last assertion comes from the instability result for P_0 and the first equation of system (2). □

Using a uniform persistence result in [15] and a similar argument as in the proof of Proposition 3.2 in [16], we can show that, when P_0 is unstable, system (2) is uniformly persistent, that is, there exists a constant $c > 0$, independent of the initial data in $\overset{\circ}{\Gamma}$, such that any solution $(T(t), T^*(t), V(t))$ of (2) satisfies

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

provided $(T(0), T^*(0), V(0)) \in \overset{\circ}{\Gamma}$. The uniform persistence of (2), together with the boundedness of solutions proved above, implies the existence of a compact absorbing set $K \subset \overset{\circ}{\Gamma}$, see [17, 18]. We thus proved the following result.

Proposition 3.2. *If $R_0 > 1$, then system (2) is uniformly persistent, and there exists a compact absorbing set $K \subset \overset{\circ}{\Gamma}$.*

Local stability of P_0 is established in Theorem 3.1 when $R_0 \leq 1$. The following result shows that P_0 is globally asymptotically stable in Γ.

Theorem 3.3. *Assume that $R_0 \leq 1$; then P_0 is globally asymptotically stable in Γ.*

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

$$L' = \frac{NkVT}{1+aV} - \epsilon V = \epsilon V \left(\frac{NkT}{\epsilon(1+aV)} - 1 \right) \leq \epsilon V \left(R_0 - 1 \right) \leq 0$$

in Γ. $L' = 0$ if and only if $V = 0$ or $R_0 = 1$ and $T = s/\alpha$. The maximum invariant set in $\{(T, T^*, V) \in \Gamma : L' = 0\}$ is the singleton P_0. LaSalle's Invariance Principle [19, 20] implies that all solutions converge to P_0. This and the local stability of P_0 established in Theorem 3.1 imply the global asymptotic stability of P_0. □

Example 3.4. We choose parameter values $s = 20; a = 1; \alpha = 0.02; \beta = 0.3; \epsilon = 2.4; k = 0.00018$; and $N = 10$. Then $R_0 = 0.75$, and $P_0 = (1002.97, 0, 0)$. Numerical simulations with these parameter values indicate that all solutions converge to P_0, see Figure 1.

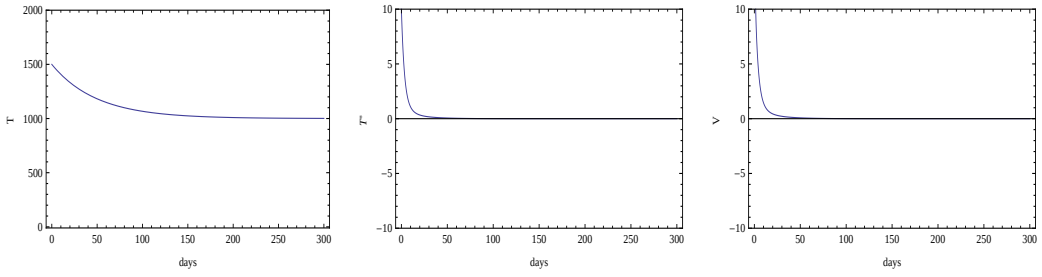

Figure 1. Global stability of P_0 when $R_0 \leq 1$.

Theorem 3.3 determines the global dynamics of (2) in Γ when $R_0 \leq 1$. Biologically, it implies that if $R_0 \leq 1$, then all infected T cells and virus particles are cleared over time and no HIV-1 infection persists. The disease dies out and the uninfected T cell population settles at s/α.

4. STABILITY OF THE INFECTED STEADY STATE P^*

Proposition 2.1 shows that the infected steady state $P^* \in \overset{\circ}{\Gamma}$ exists if $R_0 > 1$. Theorem 3.1 implies that if P^* emerges, then P_0 becomes unstable. In this section, we study the stability behavior of P^*. First, we investigate the local stability of P^*.

The Jacobian matrix of system (2) at $P^* = (\bar{T},\ \bar{T}^*,\ \bar{V})$ is

$$J(P^*) = \begin{bmatrix} -\alpha - \frac{k\bar{V}}{1+a\bar{V}} & 0 & -\frac{k\bar{T}}{(1+a\bar{V})^2} \\ \frac{k\bar{V}}{1+a\bar{V}} & -\beta & \frac{k\bar{T}}{(1+a\bar{V})^2} \\ 0 & N\beta & -\epsilon \end{bmatrix}.$$

Notice that $\frac{k\bar{T}}{1+a\bar{V}} = \frac{\epsilon}{N}$ and the characteristic polynomial associated with $J(P^*)$ can be simplified as

$$\begin{aligned} P(\lambda) = \lambda^3 &+ \left(\alpha + \beta + \epsilon + \frac{k\bar{V}}{1+a\bar{V}}\right)\lambda^2 \\ &+ \left[(\beta+\epsilon)\left(\alpha + \frac{k\bar{V}}{1+a\bar{V}}\right) + \frac{\beta\epsilon\bar{V}}{1+a\bar{V}}\right]\lambda + \frac{\beta\epsilon(k+\alpha)\bar{V}}{1+a\bar{V}}. \end{aligned}$$

All coefficients are positive. Thus, by the Routh-Hurwitz conditions, all zeros of $P(\lambda)$ have negative real parts if and only if

$$\begin{aligned} \Delta = &\left(\alpha + \beta + \epsilon + \frac{k\bar{V}}{1+a\bar{V}}\right)\left[(\beta+\epsilon)\left(\alpha + \frac{k\bar{V}}{1+a\bar{V}}\right) + \frac{\beta\epsilon\bar{V}}{1+a\bar{V}}\right] \\ &- \frac{\beta\epsilon(k+\alpha)\bar{V}}{1+a\bar{V}} > 0. \end{aligned} \tag{4}$$

Obviously, the last term can be canceled by some terms from the distribution of the first product. We thus have:

Proposition 4.1. *Let $R_0 > 1$; then the infected steady state P^* is locally asymptotically stable.*

To establish the global stability of P^*, we apply a criterion developed by Li and Muldowney [14] which we briefly summarize here.

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

$$x' = f(x). \tag{5}$$

Denote by $x(t, x_0)$ the solution to (5) such that $x(0, x_0) = x_0$. A set K is said to be absorbing in D for system (5) if $x(t, K_1) \subset K$ for each compact set $K_1 \subset D$ and sufficiently large t. We make the following assumptions:

(H_1) System (5) has a unique equilibrium point $\bar{x}$ in D.

(H_2) System (5) has a compact absorbing set $K \subset D$.

Let $|\cdot|$ denote a vector norm in R^n and also denote the induced matrix norm in $R^{n\times n}$, the space of all $n \times n$ matrices. For each matrix X in $R^{n\times n}$, define *the Lozinskiĭ measure* with respect to the norm $|\cdot|$ as (see [21], p. 41)

$$\mu(X) = \lim_{h\to 0^+} \frac{|I + hX| - 1}{h}.$$

Then $\mu(X)$ is well defined and $\mu(X)$ dominates the real part of eigenvalues of matrix X, see [21].

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

$$X^{[2]} = \begin{bmatrix} x_{11} + x_{22} & x_{23} & -x_{13} \\ x_{32} & x_{11} + x_{33} & x_{12} \\ -x_{31} & x_{21} & x_{22} + x_{33} \end{bmatrix}. \tag{6}$$

For a complete discussion of compound matrices and their applications in differential equations, we refer the readers to [22, 23].

Let $P : D \longmapsto P(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that belongs to C^1 on D and let μ be a Lozinskiĭ measure on $R^{N\times N}$, where $N = \binom{n}{2}$. Define a quantity $\bar{q}_2$ by

$$\bar{q}_2 = \limsup_{t\to\infty} \sup_{x_0\in K} \frac{1}{t} \int_0^t \mu(X(x(s, x_0)))ds, \tag{7}$$

where

$$X = P_f P^{-1} + P J^{[2]} P^{-1},$$

the matrix P_f is obtained by replacing each entry p_{ij} of P by its derivative in the direction of f, $(p_{ij})_f$, and $J^{[2]}$ is the second additive compound matrix of the Jacobian matrix J of system (5). The following result is proved by Li and Muldowney in [14].

Lemma 4.2. *For system* (5)*, assume that D is simply connected and that the assumptions (H_1) and (H_2) hold. Then the unique equilibrium $\bar{x}$ is globally asymptotically stable in D if there exists a function P and a Lozinskiĭ measure μ such that $\bar{q}_2 < 0$.*

Apparently, $\overset{\circ}{\Gamma}$ is simply connected and P^* is the unique equilibrium in $\overset{\circ}{\Gamma}$ when $R_0 > 1$. Proposition 3.1 implies the existence of a compact absorbing set $K \subset \overset{\circ}{\Gamma}$. Now we prove that P^* is globally asymptotically stable.

Theorem 4.3. *Assume that $R_0 > 1$. Then P^* is globally asymptotically stable in $\overset{\circ}{\Gamma}$.*

Proof. To use Lemma 4.1, we need to show that there exists a function P and a Lozinskiĭ measure μ such that $\bar{q}_2$ defined in (7) satisfies $\bar{q}_2 < 0$.

The Jacobian matrix J associated with the general solution $(T(t), T^*(t), V(t))$ to (2) is

$$J = \begin{bmatrix} -\alpha - \frac{kV}{1+aV} & 0 & -\frac{kT}{(1+aV)^2} \\ \frac{kV}{1+aV} & -\beta & \frac{kT}{(1+aV)^2} \\ 0 & N\beta & -\epsilon \end{bmatrix}$$

and its second additive compound matrix $J^{[2]}$ is, by (6),

$$J^{[2]} = \begin{bmatrix} -\alpha - \beta - \frac{kV}{1+aV} & \frac{kT}{(1+aV)^2} & \frac{kT}{(1+aV)^2} \\ N\beta & -\alpha - \epsilon - \frac{kV}{1+aV} & 0 \\ 0 & \frac{kV}{1+aV} & -\beta - \epsilon \end{bmatrix}.$$

Set the function $P(x) = P(T, T^*, V) = \text{diag}\{1, T^*/V, T^*/V\}$. Then we have

$$P_f P^{-1} = \text{diag}\{0,\ \dot{T}^*/T^* - \dot{V}/V, \dot{T}^*/T^* - \dot{V}/V\},$$

and

$$\begin{aligned} X &= P_f P^{-1} + P J^{[2]} P^{-1} \\ &= \begin{bmatrix} -\alpha - \beta - \frac{kV}{1+aV} & \frac{kTV}{(1+aV)^2 T^*} & \frac{kTV}{(1+aV)^2 T^*} \\ \frac{N\beta T^*}{V} & \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \alpha - \epsilon - \frac{kV}{1+aV} & 0 \\ 0 & \frac{kV}{1+aV} & \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \beta - \epsilon \end{bmatrix} \\ &= \begin{bmatrix} X_{11} & X_{12} \\ X_{21} & X_{22} \end{bmatrix} \end{aligned}$$

where $X_{11} = [-\alpha - \beta - -\frac{kV}{1+aV}]$, $X_{12} = [\frac{kTV}{(1+aV)^2 T^*}, \frac{kTV}{(1+aV)^2 T^*}]$, $X_{21} = [N\beta T^*/V, 0]^T$, and

$$X_{22} = \begin{bmatrix} \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \alpha - \epsilon - \frac{kV}{1+aV} & 0 \\ \frac{kV}{1+aV} & \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \beta - \epsilon \end{bmatrix}.$$

It is easy to see that $|(u, v, w)| = \max\{|u|, |v| + |w|\}$ defines a norm in $\mathbf{R}^3$. Let μ be the Lozinskiĭ measure with respect to this norm. Then we have the estimate, (see [24]),

$$\mu(X) \leq \max\{g_1, g_2\} \tag{8}$$

where

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

and $|X_{12}|, |X_{21}|$ are the matrix norm with respect to the l_1 vector norm, and μ_1 is the Lozinskiĭ measure with respect to l_1 norm. More specifically, $\mu_1(X_{11}) = -p -$

$\beta, |X_{12}| = kTV/T^*, |X_{21}| = N\beta T^*/V$, and $\mu_1(X_{22})$ can be evaluated by the following, (see [21]),

$$\begin{aligned}\mu_1(X_{22}) &= \max\left\{\frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \alpha - \epsilon, \quad \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \beta - \epsilon\right\} \\ &= \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \epsilon + \max\{-\alpha, -\beta\} \leq \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \epsilon - \min\{\alpha, \beta\}.\end{aligned}$$

Using the fact that $\dot{T}^*/T^* = \frac{kVT}{(1+V)T^*} - \beta$ and $\dot{V}/V = N\beta T^*/V - \epsilon$, it follows that

$$\begin{aligned}g_1 &= -\alpha - \beta - \frac{kV}{1+aV} + \frac{kTV}{(1+aV)^2 T^*} \\ &\leq -\alpha - \beta - \frac{kV}{1+aV} + \frac{kTV}{(1+aV)T^*} \leq \frac{\dot{T}^*}{T^*} - \alpha \\ g_2 &\leq \frac{N\beta T^*}{V} + \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - \epsilon - \min\{\alpha, \beta\} = \frac{\dot{T}^*}{T^*} - \min\{\alpha, \beta\}\end{aligned}$$

Therefore $\mu(X) \leq \frac{\dot{T}^*}{T^*} - \eta$ as t becomes large, where $\eta = \min\{\alpha, \beta\}$.

Let $(T(t), T^*(t), V(t))$ be any solution initiating in K and let $\bar{t}$ be the uniform time such that $(T(t), T^*(t), V(t)) \in K$ for all $t \geq \bar{t}$. Then along each such solution $(T(t), T^*(t), V(t))$ to (2) such that $(T(0), T^*(0), V(0)) \in K$ and $t > \bar{t}$, we have

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

The boundedness of T^* implies $\bar{q}_2 < 0$, completing the proof. □

Example 4.4. We choose parameter values $s = 20; a = 1; \alpha = 0.02; \beta = 0.3; \epsilon = 2.4; k = 0.0018$; and $N = 10$. Then $R_0 = 7.5$, and $P^* = (928.44, 4.7706, 5.9633)$. Numerical simulations with these parameter values indicate that all solutions converge to P^*, see Figure 2.

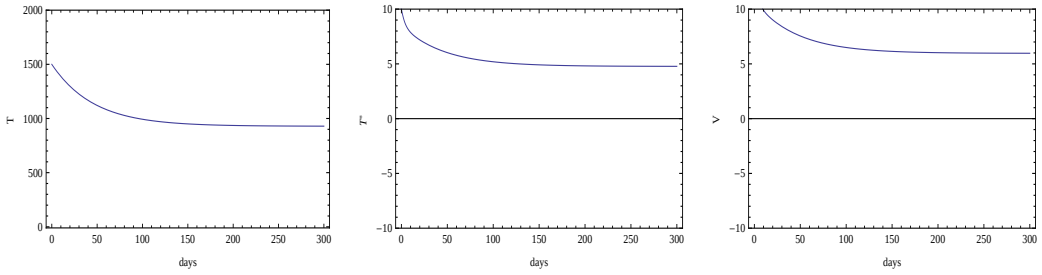

Figure 2. Global stability of P^* when $R_0 > 1$.

5. DISCUSSION

In this paper, we study a mathematical model that describes the interaction between HIV-1 virus and T cells. A general Holling type-II incidence form is applied. By identifying a basic reproduction number R_0, we show that if $R_0 \leq 1$ only the uninfected steady state P_0 exists and it is globally asymptotically stable in the feasible

region. Therefore, all infected T cells and HIV virus will be cleared over time and the HIV infection will die out. However, if $R_0 > 1$, there is a unique infected steady state emerges and it becomes globally asymptotically stable in the interior of the feasible region. Therefore, the HIV infection will persist and the concentrations of T healthy T cells, infected T cells and free HIV virus will settle at the level of P^*.

Oscillations have been observed from HIV models with a logistic growth governing term. However, in our model, numerical simulations show that no oscillations occur as solutions converge to either R_0 or R^*. This is consistent with the clinical data on positive HIV patients, in particular, when solutions converge to the global stable equilibrium P^*.

When showing the global stability of the uninfected steady state P_0, a Lyapunov function is found and used. The global stability of the infected steady state P^* is established by using a new global stability criterion developed by Li and Muldowney [14], which has been used successfully in other higher dimensional mathematical models [12, 13, 16].

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