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Stability and Hopf Bifurcation of a Mathematical Model of HIV-1 with Two Saturation Responses

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Abstract

In this manuscript, the dynamical behavior of an HIV-1 infection model with logistic target cell growth and two major transmissions will be studied. Functional response and saturation response are nonlinear in the model. The positivity and boundedness of the solutions will be proven. The reproduction number will be computed as the sum of reproduction numbers determined by any method of disease transmission. It will be shown that the infection-free equilibrium is globally asymptotically stable if the reproduction number is less than one and if it is more than one, then the infection-free equilibrium is unstable. We find that within certain conditions, positive equilibrium is locally asymptotically stable and the Hopf bifurcation can occur.

Keywords: HIV-1 infection, stability, hopf bifurcation, dynamical systems, ODE.
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1. Introduction

The Human Immunodeficiency Virus (HIV) seeks to destroy cells in the body, the most important of which is a type of white blood cells called alpha. The immune system of the body weakens after the virus enters at

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a rate determined by the stage of the disease. By weakening the immune system, it becomes vulnerable to a variety of infections, and this process eventually leads to Acquired Immune Deficiency Syndrome (AIDS), which is the last stage of the disease. The virus is located in the body fluids of infected people and can be transmitted through these fluids ([1]). AIDS is one of the major causes of death, with about one million people dying from this disease each year. ([5]).

In the acute HIV infection (AHI) stage, activated $CD4^+$ T cells become infected with HIV. HIV-specific $CD8^+$ T cells kill most of these infected cells or they are destroyed for cytopathic effects of the virus, or their immune contraction. After AHI, HIV-infected cells survive and convert to resting memory T cells. Their survival is guaranteed by homeostatic reproduction without active virus manufacture or antigen-driven enlargement. HIV-specific $CD8^+$ T cells cannot detect and kill resting $CD4^+$ T cells because they are silent and have no viral proteins expression ([15]). The rate of HIV infection progression is determined by the number of $CD4^+$ T cells and this number in healthy people is at level between 800 and 1200 mm^{-3} ([17]). It is well discovered that HIV has a lengthy incubation and infectious period ([2]).

Using nonlinear ordinary differential equations (ODEs), various mathematical models have been developed to explain how the disease has spread among human populations. These models help us to understand, analysis, control and improve our insights of the disease. The first attempt to explain mathematical model for HIV infection has been introduced in [10] and [7]. Recentally, he Authores in [4], [6] and [12] have considered some HIV models and investigated the stability of the models

Xu in [18] introduced a mathematical model for HIV-1 infection with saturation infection rate. Also, Considering saturated CTL response and separate transmission incidences, Carvalho and Pinto investigated an HIV-1 infection model ([3]).

Lai and Zou in [8] investigated the dynamical analysis of HIV by model

$$\begin{aligned}
\frac{dT(t)}{dt} &= rT(t)(1-\frac{T(t)+\alpha T^*(t)}{T_M}) - \beta_1 T(t)V(t) - \beta_2 T(t)T^*(t),\\
\frac{dT^*(t)}{dt} &= \beta_1 T(t)V(t) + \beta_2 T(t)T^*(t) - d_{T^*}T^*(t),\\
\frac{dV(t)}{dt} &= \gamma T^*(t) - d_V V(t),
\end{aligned} \tag{1.1}$$

where target cells are susceptible $CD4^+$ T cells and $T(t)$, $T^*(t)$ and $V(t)$ illustrate the target cells, productively infected T cells and virus particles at time t, respectively. $\beta_1 T(t)V(t)$ and $\beta_2 T(t)T^*(t)$ represent the rate at which target cells become infected by viral particles and productively infected cells, respectively. Infected cells produce viral particles at rate $\gamma T^*(t)$. The death rate of target cells, productively infected cells and viruses are $d_T T(t)$, $d_{T^\cap{}^\alpha} T^*(t)$ and $d_V V(t)$, respectively. The carrying capacity of target cells, T_M is a bound for target cells growth rate, r. The constant α represents the limitation of infected cells imposed on the cell growth of target cells, in general $\alpha \geq 1$ ([8]). Two response functions, representing two modes of spread of HIV, has been considered in this model.

Model (1.1) contains a logistic target cell growth and two simple linear response functions. However, in real world infection rate presumably is not linear. Therefore, it is reasonable for us to assume that the infection rate of system is given by saturated infection $\frac{\beta TV}{1+aT}$ where a is positive constant. In this manuscript the same notations as in [8] are used to consider the model:

$$\begin{aligned}
\frac{dT(t)}{dt} &= rT(t)(1-\frac{T(t)+\alpha T^*(t)}{T_M}) - \frac{\beta_1 T(t)V(t)}{1+aT(t)} - \frac{\beta_2 T(t)T^*(t)}{1+aT(t)},\\
\frac{dT^*(t)}{dt} &= \frac{\beta_1 T(t)V(t)}{1+aT(t)} + \frac{\beta_2 T(t)T^*(t)}{1+aT(t)} - d_{T^*}T^*(t),\\
\frac{dV(t)}{dt} &= \gamma T^*(t) - d_V V(t),
\end{aligned} \tag{1.2}$$

in which $\frac{\beta_1 T(t)V(t)}{1+aT(t)}$ and $\frac{\beta_2 T(t)T^*(t)}{1+aT(t)}$ are saturation responses of the infection rate that show the rate of infection

target cells, by free viral particles and infectious cells, respectively. Parameters and variables of system (1.2) are presented in Table 1. The paper is organized as follows: positivity and boundedness of solutions of system

Table 1: Parameters and Variables.

T	concentrations of susceptible $CD4^+$ T cells at time t
T^*	concentrations of susceptible productively infected T cells at time t
V	concentrations of susceptible free virus particles at time t
r	target cell growth rate
α	limitation of infected cells imposed on the cell growth of target cells,
T_M	carrying capacity of target cells
a	positive constant or zero
$\gamma T^*(t)$	rate of release of free viral particles by infected cells at time t
$d_{T^*}T^*(t)$	losing rate of productively infected cells
$d_V V(t)$	losing rate of free viruses
β_1,β_2	positive constants that describe the infection rate from each other population

(1.2) considered in section 2. Local stability of equilibria and the basic reproduction number is described in section 3. Section 4 deals with persistence of infection of system (1.2). Section 5 is devoted to studying the dynamical behavior of the positive equilibrium and Hopf bifurcation. The paper ends with a discussion in section 6.

2. Positivity and boundedness of solutions

In this section the positivity and boundedness of the solutions of system (1.2) with the initial conditions

$$T(0) = T_0 > 0, \quad T^*(0) = T_0^* > 0, \quad V(0) = V_0 > 0, \quad T_0 + T_0^* \leq T_M \tag{2.1}$$

will be considered.

It is easy to show that the functions in the right-hand side of (1.2) satisfy the Lipschitz condition. Next, the fundamental existence-uniqueness theorem in [11] can be used to prove the existence and uniqueness of solutions of system (1.2) with the initial conditions (2.1).

Theorem 2.1. *The solution of system* (1.2) *with initial conditions* (2.1) *is positive and bounded.*

Proof. Suppose that $(T(t), T^*(t), V(t))$ be the solution of system (1.2) satisfying the initial conditions (2.1). We show that

$$0 < T(t) \leq T_M, \quad 0 < T^*(t) \leq T_M, \quad 0 < V(t) \leq V(0) + \frac{\gamma T_M}{d_V}$$

for all $t \geq 0$. Moreover, $T(t) + T^*(t) \leq T_M$ for all $t \geq 0$.

We prove the theorem by contradiction. Let t_i, $i \in \{1, 2, 3\}$ as the first time that $T(t), T^*(t), V(t)$ vanish, respectively; and $t_0 = \min\{t_1, t_2, t_3\}$.

First, suppose that $T(t_1) = 0$, $T^*(t_1) > 0$, $V(t_1) > 0$, i.e. $t_0 = t_1$, $t_0 \neq t_2$ and $t_0 \neq t_3$. Hence, $T(t), T^*(t)$ and $V(t)$ are positive for all $t \in [0, t_1)$. From the two first equations in (2.1) it is easy to see that

$$\frac{d}{dt}[T(t) + T^*(t)] = rT(t)(1 - \frac{T(t) + \alpha T^*(t)}{T_M}) - d_{T^*}T^*(t), \qquad \forall t \in [0, t_1]. \tag{2.2}$$

Now, using the method of [8], rescale (2.2) by

$$u(t) = \frac{T(t)}{T_M}, \qquad w(t) = \frac{T^*(t)}{T_M}, \qquad \tilde{t} = d_{T^*}t, \qquad \frac{r}{d_{T^*}} = \delta. \tag{2.3}$$

From (2.2) and (2.3) for all $t \in [0, t_1]$ it can be concluded that

$$\begin{aligned}\frac{d}{dt}[u(t)+w(t)] &= \delta u(t)[1-u(t)-\alpha w(t)] - w(t) \\ &= \delta u(t)[1-(u(t)+w(t))] - \delta(\alpha-1)w(t)u(t) - w(t).\end{aligned} \tag{2.4}$$

Now for any $t^* \in [0, t_1]$ satisfying $u(t^*) + w(t^*) = 1$ we have

$$\frac{d}{dt}[u(t)+w(t)]_{t=t^*} = -\delta(\alpha-1)u(t^*)w(t^*) - w(t^*) \leq -w(t^*) < 0.$$

Therefore, $u(t) + w(t) \leq 1$ for all $t \in [0, t_1]$. This means that $T(t) + T^*(t) \leq T_M$ for all $t \in [0, t_1]$. Thus, $T(t) \leq T_M$ and $T^*(t) \leq T_M$ for $t \in [0, t_1]$.

It follows from the third equation in (1.2) that

$$\frac{dV}{dt} \leq \gamma T_M - d_V V.$$

Hence,

$$V(t) \leq V(0)e^{-d_V t} + \frac{\gamma T_M}{d_V} - e^{-d_V t}\frac{\gamma T_M}{d_V} \leq V(0)e^{-d_V t} + \frac{\gamma T_M}{d_V}, \qquad t \in [0, t_1]. \tag{2.5}$$

Again it follows from the first equation in (1.2) that for all $t \in [0, t_1]$,

$$\frac{dT(t)}{dt} \geq -[\frac{\beta_1 V(t)}{1+aT(t)} + (\frac{\beta_2}{1+aT(t)} + \frac{r\alpha}{T_M})T^*(t)]T(t) \geq -[\beta_1 V(t) + (\beta_2 + \frac{r\alpha}{T_M})T^*(t)]T(t).$$

Thus, for all $t \in [0, t_1]$,

$$T(t) \geq T(0)e^{-\int_0^t -[\beta_1 V(s) + (\beta_2 + \frac{r\alpha}{T_M})T^*(s)]ds}. \tag{2.6}$$

From (2.5) and (2.6) it can be written that,

$$T(t_1) \geq T(0)e^{-\int_0^{t_1} -[\beta_1[V(0)e^{-d_V t} + \frac{\gamma T_M}{d_V}] + (\beta_2 + \frac{r\alpha}{T_M})T^*(s)]ds} > 0,$$

this is an obvious contradiction with $T(t_1) = 0$.

Now let $T^*(t_2) = 0$, $T(t_2) \geq 0$, $V(t_2) \geq 0$, and for $t \in [0, t_2)$, $T(t), T^*(t), V(t) > 0$. It follows from (1.2) that

$$\frac{dT^*(t)}{dt} \geq -d_{T^*}T^*(t).$$

Thus,

$$T^*(t_2) \geq T^*(0)e^{-t_2} > 0,$$

this is impossible given $T^*(t_2) = 0$.

Now suppose that $t_0 = t_3$; and therefore, $V(t_3) = 0$, $T(t_3) \geq 0$, $T^*(t_3) \geq 0$, and for $t \in [0, t_3)$, $T(t), T^*(t), V(t) > 0$. It follows from the third equation in (1.2) that

$$\frac{dV(t)}{dt} \geq -d_V V, \qquad t \in [0, t_3].$$

Thus, $V(t_3) \geq V(0)e^{-d_V t_3} > 0$, this is another contradiction with regard to $V(t_3) = 0$.

These two last cases include the cases of $t_2 \neq t_1$ or $t_2 \neq t_3$ or $t_1 = t_2 \neq t_3$ or $t_2 = t_3 \neq t_1$ or $t_1 = t_2 = t_3$ or $t_3 \neq t_1$ or $t_3 \neq t_2$ or $t_3 = t_1 \neq t_2$.

With the obtained contradictions in all cases, it can be concluded that the solution of system (1.2) is positive for all $t \geq 0$.

From (2.2), (2.4), (2.5) and the positivity of the solutions of (1.2) it can be concluded that

$$T(t) + T^*(t) \leq T_M, \qquad V(t) \leq V(0) + \frac{\gamma T_M}{dV}, \qquad \forall t \geq 0,$$

and this completes the proof. □

In the next section the basic reproduction number R_0, and trivial, infection-free and positive equilibria of (1.2) will be identified. The stability of the equilibria will also be considered.

3. Stability of equilibria and the reproduction number

System (1.2) has the trivial equilibrium $E_0 = (0, 0, 0)$, the infection-free equilibrium $E_1 = (T_M, 0, 0)$ and positive equilibrium $\bar{E} = (\bar{T}, \bar{T^*}, \bar{V})$, where

$$\begin{aligned}
\bar{T} &= \frac{T_M}{R_0 + (R_0 - 1)aT_M}, \\
\bar{T^*} &= \frac{rT_M(1 + aT_M)(R_0 - 1)}{(\alpha r + ((R_0 - 1)aT_M + R_0)d_{T^*})((R_0 - 1)aT_M + R_0)}, \\
\bar{V} &= \frac{\gamma}{d_V}\bar{T^*}.
\end{aligned}$$

Let $p = R_0 + R_0 aT_M - aT_M$ and rewrite positive equilibrium as following:

$$\bar{T} = \frac{T_M}{p}, \quad \bar{T^*} = \frac{rT_M(p-1)}{(\alpha r + pd_{T^*})p}, \quad \bar{V} = \frac{\gamma}{d_V}\bar{T^*}.$$

The basic reproduction number R_0 for system (1.2) with saturation response function is given by,

$$R_0 = R_{01} + R_{02}$$

where

$$R_{01} = \frac{\beta_1 T_M \gamma}{d_V d_{T^*}(1 + aT_M)}, \qquad R_{02} = \frac{\beta_2 T_M}{d_{T^*}(1 + aT_M)}.$$

Epidemiologically, the reproduction number gives the number of secondary infections that an infected person produces in a population of susceptible individuals ([9]).

In the other word, it denotes the average number of infected T cells derived from one infected T cell. In the following, the stability of the equilibria will be considered.

Theorem 3.1. *The trivial equilibrium E_0 of (1.2) is always unstable.*

Proof. Using the linearized system and Jacobian matrix of (1.2), instability of E_0 will be proven. The Jacobian matrix of (1.2) at E_0 is given by

$$J_0 = \begin{bmatrix} r & 0 & 0 \\ 0 & -d_{T^*} & 0 \\ 0 & \gamma & -d_V \end{bmatrix},$$

which has a positive eigenvalue $\lambda = r$. Therefore, E_0 is always unstable. □

Theorem 3.2. *If $R_0 < 1$, then the infection-free equilibrium E_1 of system (1.2) is locally asymptotically stable. If $R_0 > 1$, then E_1 is unstable.*

Proof. Consider the Jacobian matrix of (1.2) at E_1,

$$J_1 = \begin{bmatrix} -r & -r\alpha - \frac{\beta_2 T_M}{1+aT_M} & -\frac{\beta_1 T_M}{1+aT_M} \\ 0 & \frac{\beta_2 T_M}{1+aT_M} - d_T^* & \frac{\beta_1 T_M}{1+aT_M} \\ 0 & \gamma & -d_V \end{bmatrix}.$$

It is clear that it has a negative eigenvalue, $\lambda_1 = -r < 0$. The other eigenvalues of J_1 are the roots of characteristic equation of matrix

$$J_{10} = \begin{bmatrix} \frac{\beta_2 T_M}{1+aT_M} - d_T^* & \frac{\beta_1 T_M}{1+aT_M} \\ \gamma & -d_V \end{bmatrix}$$

which is given by:

$$\lambda^2 + (d_V + d_{T^*} - \frac{\beta_2 T_M d_V}{(1+aT_M)})\lambda + (d_V d_{T^*} - \frac{\beta_2 T_M d_V}{1+aT_M} - \frac{\beta_1 T_M \gamma}{1+aT_M}) = 0.$$

Let

$$a_1 = d_V + d_{T^*} - \frac{\beta_2 T_M d_V}{(1+aT_M)} = d_V + d_{T^*}(1 - R_{02}),$$
$$a_2 = d_V d_{T^*} - \frac{\beta_2 T_M d_V}{1+aT_M} - \frac{\beta_1 T_M \gamma}{1+aT_M} = d_V d_{T^*} - \frac{\beta_2 T_M d_V + \beta_1 T_M \gamma}{1+aT_M} = d_V d_{T^*}(1 - R_0).$$

If $R_0 < 1$, then $a_1 > 0$ and $a_2 > 0$. Therefore, all eigenvalues have negative real parts. If $R_0 > 1$, then $a_2 < 0$ and J_{10} has at least one positive eigenvalue and this implies instability of E_1. □

Theorem 3.3. *The infection-free equilibrium E_1 of (1.2) is globally asymptotically stable if $R_0 < 1$.*

proof. Consider a linear cooperative system that is given by,

$$\begin{aligned} \frac{d\bar{T}^*(t)}{dt} &= \beta_1 \bar{V}(t) + \beta_2 \bar{T}^*(t) - d_{T^*}\bar{T}^*(t), \\ \frac{d\bar{V}(t)}{dt} &= \gamma \bar{T}^*(t) - d_V \bar{V}(t). \end{aligned} \tag{3.1}$$

Suppose that for $K > 0$, $(\bar{T}^*(t), \bar{V}(t)) = Ke^{\lambda_0 t}\epsilon_0$ be a solution of system (3.1), that λ_0 is principal eigenvalue associated with strictly positive eigenvector ε_0. It is easy to see that

$$(T^*(0), V(0)) \leq (\bar{T}^*(0), \bar{V}(0)).$$

In fact, $T(t) \leq T_M$ for all $t \geq 0$, and

$$\begin{aligned} \frac{dT^*(t)}{dt} &\leq \beta_1 V(t) + \beta_2 T^*(t) - d_{T^*}T^*(t), \\ \frac{dV(t)}{dt} &\leq \gamma T^*(t) - d_V V(t). \end{aligned}$$

Thus, by the comparison principal, for all $t \geq 0$, it can be concluded that

$$(T^*(t), V(t)) \leq Ke^{\lambda_0 t}\varepsilon_0. \tag{3.2}$$

On the other hand, we see that if $R_0 < 1$, then all eigenvalues have negative real parts. Thus, $\lambda_0 < 0$ and from (3.2) it can be concluded that

$$\lim_{t\to+\infty} T^*(t) = 0, \qquad \lim_{t\to+\infty} V(t) = 0.$$

Applying the above results, suggest the equation

$$\frac{d\bar{T}(t)}{dt} = r\bar{T}(t)(1 - \frac{\bar{T}(t)}{T_M}).$$

Therefore,

$$\bar{T}(t) = \frac{e^{r\bar{T}(t)}T_M}{e^{r\bar{T}(t)} + cT_M}.$$

Thus, $\lim_{t\to+\infty} \bar{T}(t) = T_M$. It follows from Corollary 4.3 in [16] that, $\lim_{t\to+\infty} T(t) = T_M$. Therefore, $\lim_{t\to+\infty}(T, T^*, V) = (T_M, 0, 0)$ and this completes the proof.

Now we introduce a set and in the next section, it will be shown that this is the invariant set for the solution semiflow of (1.2). From (2.5) it can be seen that

$$V(t) \leq e^{-d_V t}(V_0 - \frac{\gamma T_M}{d_V}) + \frac{\gamma T_M}{d_V}.$$

Therefore, if $V(0) \leq \frac{\gamma T_M}{dV}$, then $V(t) \leq \frac{\gamma T_M}{dV}$ for all $t \geq 0$. Hence, consider the following set.

$$Y := \{(T, T^*, V) \in R^3, T \geq 0, T^* \geq 0, V \geq 0, T + T^* \leq T_M, V \leq \frac{\gamma T_M}{dV}\}.$$

4. Persistence of infection

In this section the persistence of the infection will be considered. For this purpose, suppose that $T_0 \neq 0$. If $T_0 = 0$, then the system cannot be persistence, because the unique solution of (1.2)-(2.1) for $t > 0$ is given by,

$$T(t) = 0, \qquad T^*(t) = T_0^* e^{-d_{T^*}}, \qquad V(t) = e^{-d_V}[V_0 + T_0^* \int_0^t e^{(d_V - d_{T^*})s} ds].$$

It is clear that $T(t) \to 0$ and $V(t) \to 0$, as $t \to +\infty$.

Applying Theorem 1.3.2 in [20], the uniformly persistence of the infection can be proven. First, consider the following two lemmas.

Lemma 4.1. *Let ϕ_t is the solution semiflow defined by (1.2) and suppose that X, X_0, ∂X_0 and M_∂, is given by*

$$X := \{(T, T^*, V) \in R^3 | T > 0, \ T^* \geq 0, \ V \geq 0, \ T + T^* \leq T_M, \ V \leq \frac{\gamma T_M}{d_V}\},$$

$$X_0 := \{(T, T^*, V) \in X | \ T^* \geq 0 \quad and \quad V \geq 0\},$$

$$\partial X_0 := X \setminus X_0 = \{(T, T^*, V) \in X | T^* = 0 \ \ or \ \ V = 0\}$$

and

$$M_\partial := \{(T_0, T_0^*, V_0) | \phi_t(T_0, T_0^*, V_0) \in \partial X_0, t \geq 0\}.$$

Then,

(a) $\phi_t(X) \subset X$ and $\phi_t(X_0) \subset X_0$, for all $t \geq 0$,

(b) $M_\partial = \{(\hat{T}, 0, 0) | 0 < \hat{T} \leq T_M\}$.

Proof. Let $(T_0, T_0^*, V_0) \in X$. The different cases of T_0^* and V_0 will be considered.

(i) If $T_0^* = 0$ and $V_0 = 0$ then,

$$T(t) = \frac{e^{rt}T_M T_0}{T_0 e^{rt} + (T_M - T_0)} > 0, \qquad T^*(t) = 0, \qquad V(t) = 0. \quad \forall t \geq 0 \tag{4.1}$$

(ii) If $T_0^* = 0$ and $V_0 > 0$ then,

$$\frac{d}{dt}T^*(0) = \frac{\beta_1 T(0)V(0)}{1 + aT(0)} = \frac{\beta_1 T_0 V_0}{1 + aT_0} > 0.$$

It is clear that if there exists $\varepsilon > 0$ that $t \in (0, \varepsilon)$, then $T^*(t) > 0$. By the same way of the proof of Theorem 2.1, it can be concluded that $T(t) > 0$, $T^*(t) > 0$ and $V(t) > 0$.

(iii) If $T^*(0) > 0$ and $V_0 = 0$, then

$$\frac{d}{dt}V(0) = \gamma T^*(0) = \gamma T_0^* > 0.$$

Similarly it can be seen that $T(t) > 0$, $T^*(t) > 0$ and $V(t) > 0$.

(iv) If $T_0^* > 0$ and $V_0 > 0$, then it follows from Theorem 2.1 that $T(t) > 0$, $T^*(t) > 0$ and $V(t) > 0$. This completes the proof of (a).

Now let $(T_0, T_0^*, V_0) \in M_\partial$. From the definition of M_∂, it can be concluded that $\phi_t(T_0, T_0^*, V_0) \in \partial X_0$. Hence, only case (i) can happen. That is $T_0^* = 0$ and $V_0 = 0$, and this completes the proof of (b). □

In the following it can be considered persistence of infection of system (1.2) for some $\eta_0 > 0$.

Lemma 4.2. *The infection-free equilibrium E_1 is isolated invariant set for $R_0 > 1$.*

Proof. E_1 is an equilibrium of (1.2); and therefore, it is an invariant set. Now it is sufficient to show that the solution $(T(t), T^*(t), V(t))$ of (1.2) with initial value $(T_0, T_0^*, V_0) \in X$ satisfies

$$\limsup_{t\to\infty} ||(T(t), T^*(t), V(t)) - (T_M, 0, 0)|| \geq \eta_0.$$

Suppose that for the solution with initial value $(T_0, T_0^*, V_0) \in X$,

$$\limsup_{t\to\infty} ||(T(t), T^*(t), V(t)) - (T_M, 0, 0)|| < \eta_0.$$

Therefore, there exists $t_0 > 0$ such that for $t \geq t_0$,

$$T(t) > T_M - \eta_0, \qquad T^*(t) < \eta_0, \qquad V(t) < \eta_0.$$

Using this inequality and putting $\frac{\beta_1}{1+aT_M} = \zeta_1$ and $\frac{\beta_2}{1+aT_M} = \zeta_2$, rewrite the second equation in (1.2) as follows:

$$\begin{aligned}\frac{dT^*(t)}{dt} &= \frac{\beta_1 T(t)V(t)}{1 + aT(t)} + \frac{\beta_2 T(t)T^*(t)}{1 + aT(t)} - d_{T^*}T^*(t) > \zeta_1 T(t)V(t) + \zeta_2 T(t)T^*(t) - d_{T^*}T^* \\ &> \zeta_1(T_M - \eta_0)V(t) + \zeta_2(T_M - \eta_0)T^*(t) - d_{T^*}T^*.\end{aligned}$$

From this inequality and the third equation of (1.2), the system;

$$\begin{aligned}\frac{d\bar{T}^*(t)}{dt} &= \zeta_1(T_M - \eta_0)\bar{V}(t) + \zeta_2(T_M - \eta_0)\bar{T}^*(t) - d_{T^*}T^*, \\ \frac{d\bar{V}(t)}{dt} &= \gamma T^*(t) - d_V\bar{V}(t)\end{aligned} \tag{4.2}$$

can be introduced.

On the other hand, it can be seen that all elements of J_{10} are non-negative except for those on the main diagonal. Therefore, it is a quasi-positive matrix. Using the notation in [13], let $\lambda_0(T_M) = \max\{Re(\lambda)|\lambda \in \sigma(J_{10})\}$ as principal eigenvalue of J_{10} where $\sigma(J_{10})$ is the set of eigenvalues of matrix J_{10}.

Suppose that $\lambda_0(T_M - \eta_0)$ and $(\epsilon_1, \epsilon_2)^T$ are the principal eigenvalue and the associated strictly positive eigenvector of (1.2). The solution of (4.2) is given by

$$(\bar{T}^*, \bar{V})^T = e^{\lambda_0(T_M-\eta_0)t}(\epsilon_1, \epsilon_2)^T.$$

Since $T^*(t_0)$ and $V(t_0)$ are positive, there is a $\xi > 0$ such that $(T^*(t_0), V(t_0))^T \geq \xi(\bar{T}^*(t_0), \bar{V}(t_0))^T$. Therefore,

$$(T^*(t), V(t))^T \geq \zeta e^{\lambda_0(T_M-\eta_0)t}(\epsilon_1, \epsilon_2)^T, \qquad \forall t \geq t_0. \tag{4.3}$$

If $R_0 > 1$, then $\lambda_0(T_M - \eta_0) > 0$ for some $\eta_0 > 0$. Therefore, $T^*(t)$ and $V(t)$ are unbounded and this contradiction completes the proof. □

From [14] we know that the no-cycle condition is a fundamental assumption in the theory of persistence. Remember that if M chains to M, then this chain is called a cycle and if $M = (T_M, 0, 0)$, then there is no cycle in M_∂ from M to M. We know from [20] that a function $g : X \to X$ is uniformly persistent with respect to $(X_0, \partial X_0)$ if there exists $\epsilon > 0$ such that $\liminf_{n\to\infty} d(g^n(x), \partial X_0) \geq \epsilon$.

Theorem 4.3. *For system (1.2) the infection is uniformly persistent with respect to $(X_0, \partial X_0)$, when $R_0 > 1$.*

Proof. First, define a continuous function $p : X \to R_+$ by

$$p(x) = \min\{T_0^*, V_0\}, \qquad \forall x = (T_0, T_0^*, V_0) \in X.$$

It is easy to see that p is a generalized distance function for the semiflow $\phi_t : X \to X$ (see [8]). It follows from Lemma 4.1 that X_0 is positively invariant for the solution semiflow ϕ_t defined by (1.2). We know that ϕ_t is compact and point dissipative; that is, if there is a bounded set B in X, then B attracts each point (compact set) in X. Theorem 1.1.3. in [20] says that if $f : X \to X$ is compact and point dissipative, then there is a connected global attractor A that attracts each bounded set in X. Hence, there is a global attractor A for ϕ_t. On the other hand, Lemma 4.1 implies that M_∂ is an invariant set in ∂X_0 which is maximal and compact. Let $M = (T_M, 0, 0)$. Since the equilibria are invariant sets, M is a nonempty invariant set, and from Lemma 4.2, M is an isolated invariant set in X. Next, if $W^s(M) := \{x \in X : \lim_{t\to\infty} d(\phi_t(x), M) = 0\}$ be the stable set of M, then from the definition of X_0 and Lemma 4.2, it can be concluded that $W^s(M) \cap X_0 = \emptyset$.

On the other hand, the omega limit set is defined by $\omega(x) = \cap_{t\geq 0} \cup_{s\geq t} \phi_s(x)$ and it is clear that no subset of M forms a cycle in M_∂. Therefore, from (4.1) it can be concluded that $\cup_{x\in M_\partial} \omega(x) = \{M\}$.

Now by Theorem 1.3.2 in [20] it is easy to see that there exists an $\eta > 0$ such that

$$\min_{x\in\omega(y)} p(x) > \eta, \qquad \forall y \in X_0.$$

Therefore,

$$\liminf_{t\to\infty} T^*(t) \geq \eta, \qquad \liminf_{t\to\infty} V(t) \geq \eta.$$

This completes the proof. □

5. Positive equilibrium and Hopf bifurcation

In this section, dynamical behavior and stability of the positive equilibrium $\bar{E}$ will be considered. The Jacobian matrix of (1.2) at $\bar{E} = (\bar{T}, \bar{T}^*, \bar{V})$ is given by,

$$\bar{J} = \begin{bmatrix} \frac{rT_M - 2r\bar{T} - \alpha r\bar{T}^*}{T_M} - \frac{\beta_1\bar{V}+\beta_2\bar{T}^*}{(1+a\bar{T})^2} & -\frac{\alpha r\bar{T}}{T_M} - \frac{\beta_2\bar{T}}{1+a\bar{T}} & -\frac{\beta_1\bar{T}}{1+a\bar{T}} \\ \frac{\beta_1\bar{V}+\beta_2\bar{T}^*}{(1+a\bar{T})^2} & \frac{\beta_2\bar{T}}{1+a\bar{T}} - d_{T^*} & \frac{\beta_1\bar{T}}{1+a\bar{T}} \\ 0 & \gamma & -d_V \end{bmatrix}.$$

Now, rescale $\bar{J}$ by,

$$\begin{aligned}
x &= \frac{\beta_2\bar{T}}{1+a\bar{T}} = \frac{\beta_2 T_M}{p+aT_M},\\
y &= \frac{\beta_1\bar{V}+\beta_2\bar{T^*}}{(1+a\bar{T})^2} = \frac{r(R_0-1)pd_{T^*}}{R_0(\alpha r+pd_{T^*})} = \frac{rp(p-1)d_{T^*}}{(p+aTM)(\alpha r+pd_{T^*})},\\
z &= \frac{rT_M-2r\bar{T}-\alpha r\bar{T^*}}{T_M} = \frac{rp-2r}{p} - \frac{\alpha r^2(p-1)}{p(\alpha r+pd_{T^*})},\\
x^{'} &= \frac{\beta_1\bar{T}}{1+a\bar{T}} = \frac{\beta_1 T_M}{p+aT_M},\\
z^{'} &= \frac{\alpha r\bar{T}}{T_M} = \frac{\alpha r}{p}.
\end{aligned}$$

Therefore,

$$\bar{J} = \begin{bmatrix} z-y & -z^{'}-x & -x^{'} \\ y & x-d_{T^*} & x^{'} \\ 0 & \gamma & -d_V \end{bmatrix}.$$

The corresponding characteristic equation is

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{5.1}$$

where

$$\begin{aligned}
a_1 &= d_{T^*} + d_V + y - x - z,\\
a_2 &= d_V d_{T^*} - xd_V + yd_{T^*} + yd_V - zd_V - zd_{T^*} + xz - x^{'}\gamma + yz^{'},\\
a_3 &= yz^{'}d_V + yd_V d_{T^*} - zd_V d_{T^*} + x^{'}\gamma z + xzd_V,\\
a_1a_2 - a_3 &= d_V^2 d_{T^*} + d_V d_{T^*}^2 + 2yd_V d_{T^*} + y^2 d_V + y^2 d_{T^*} + yd_{T^*}^2 + yd_V^2\\
&\quad + z^2 d_{T^*} + z^2 d_V + 2xzd_V + 2xzd_{T^*} + xyz + x^{'}\gamma x + yz^{'}d_{T^*}\\
&\quad + y^2 z^{'} + x^2 d_V - 2xd_V d_{T^*} - xd_V^2 - 2xyd_V - xyd_{T^*} - 2zyd_V\\
&\quad - 2zyd_{T^*} - 2zd_V d_{T^*} - x^2 z - xz^2 - zd_{T^*}^2 - zd_V^2 - x^{'}\gamma d_V \quad - x^{'}\gamma d_{T^*} - x^{'}\gamma y - xyz^{'} - zyz^{'}.
\end{aligned}$$

By Routh-Hurwitz criterion, a necessary and sufficient condition that all roots of (5.1) have negative real parts is, $a_1 > 0$, $a_2 > 0$, $a_3 > 0$ and $a_1a_2 > a_3$.

If $y = x + z$, then

$$\frac{rpd_{T^*}(p-1)}{(p+aT_M)(\alpha r+pd_{T^*})} + \frac{\alpha r^2(p-1)}{p(\alpha r+pd_{T^*})} = \frac{\beta_2 pT_M + r(p-2)(p+aT_M)}{p(p+aT_M)}.$$

Therefore,

$$rp^2 d_{T^*}(p-1) + \alpha r^2(p-1)(p+aT_M) = (\alpha r+pd_{T^*})(\beta_2 pT_M + r(p-2)(p+aT_M)). \tag{5.2}$$

Since the left hand side of (5.2) is positive, $p > 2$ or $\beta_2 pT_M \geq r(p-2)(p+aT_M)$. The first one is a sufficient condition for the right-hand side to be positive. Therefore, it is necessary but not sufficient condition for $y = x + z$.

Theorem 5.1. *Suppose that*

(i) $R_0 > 1$,

(ii) $y = x + z$.

Then, $\bar{E} = (\bar{T}, \bar{T^*}, \bar{V})$ *is locally asymptotically stable.*

Proof. If $R_0 > 1$, then $p = R_0 + R_0 a T_M - a T_M > 0$; as a result, $x > 0, y > 0, x^{'} > 0$ and $z^{'} > 0$. On the other hand, it is easy to see that $d_{T^*} > x$ and $d_{T^*} d_V \geq x^{'}\gamma$. In fact, from $R_0 = R_{01} + R_{02}$, it will be observed that $R_0 = \frac{R_0 x^{'}\gamma}{d_{T^*} d_V} + \frac{R_0 x}{d_{T^*}}$. Hence, from the result above and $y = x + z$, it can be concluded that,

$$a_1 > 0, \quad a_2 > 0, \quad a_3 > 0, \quad \textit{and} \quad a_1 a_2 > a_3,$$

and this completes the proof.

We see that if $R_0 > 1$ and $y = x + z$, then $\bar{E}$ is locally asymptotically stable. Let

$$p^* = (\beta_1^*, \beta_2^*, d_{T^*}^*, d_V^*, \gamma^*, T_M^*, \alpha^*, a^*, r^*)$$

and rewrite $a_1(p^*)a_2(p^*) - a_3(p^*)$ as $F(p^*)G(p^*)$, where

$$F(p^*) = \frac{1}{p^2(p + aT_M)^2(\alpha r + p d_{T^*})^2}$$

and

$$\begin{aligned}
G(p^*) =& p^2(p + aT_M)^2(\alpha r + p d_{T^*})^2 d_V d_{T^*}(d_V + d_{T^*}) \\
&+ r p^3(p-1) d_V d_{T^*}^2 (rp(p-1) + 2(\alpha r + p d_{T^*})(p + aT_M)) \\
&+ p^2(\alpha r + p d_{T^*})^2(\beta_2 T_M)^2 d_V + r^2 p^3 (p-1)^2 d_{T^*}^2 (\alpha r + p) \\
&+ 2p(\alpha r + p d_{T^*})(p + aT_M)(\beta_2 T_M)((rp - 2r)(\alpha r + p d_{T^*}) - \alpha r^2(p-1))(d_V + d_{T^*}) \\
&+ (p + aT_M)^2((rp - 2r)^2(\alpha r + p d_{T^*})^2 - \alpha^2 r^4 (p-1)^2)(d_V + d_{T^*}) \\
&+ rp(p-1)p^2(p + aT_M)(\alpha r + p d_{T^*}) d_{T^*}(d_V^2 + d_{T^*}^2) \\
&+ p(\beta_2 T_M)(rp(p-1)d_{T^*})((rp - 2r)(\alpha r + p d_{T^*}) - \alpha r^2(p-1)) \\
&+ (\alpha r + p d_{T^*})^2 p^2(\beta_1 \beta_2 T_M^2 \gamma) + p(p + aT_M)(\alpha r + p d_{T^*}) r^2 p \alpha (p-1) d_{T^*}^2 \\
&- (p + aT_M)(\alpha r + p d_{T^*})^2 p^2 \beta_2 T_M d_V (2d_{T^*} + d_V) \\
&- (\alpha r + p d_{T^*}) p^2 \beta_2 T_M r p (p-1) d_{T^*}(2d_V + d_{T^*}) \\
&- 2(p + aT_M) r p^2 (p-1) d_{T^*}((rp - 2r)(\alpha r + p d_{T^*}) - \alpha r^2(p-1))(d_V + d_{T^*}) \\
&- (p + aT_M)^2(\alpha r + p d_{T^*}) p((rp - 2r)(\alpha r + p d_{T^*}) - \alpha r^2(p-1))(d_V + d_{T^*})^2 \\
&- (\alpha r + p d_{T^*}) p(\beta_2 T_M)^2((rp - 2r)(\alpha r + p d_{T^*}) - \alpha r^2(p-1)) \\
&- (p + aT_M)(\beta_2 T_M)((rp - 2r)^2(\alpha r + p d_{T^*})^2 - \alpha^2 r^4 (p-1)^2) \\
&- (p + aT_M)(\alpha r + p d_{T^*})^2 p^2 \beta_1 T_M \gamma (d_V + d_{T^*}) \\
&- (\alpha r + p d_{T^*}) p \beta_1 T_M \gamma r p (p-1) d_{T^*} - (\alpha r + p d_{T^*}) p^2 \beta_2 T_M \alpha r^2 (p-1) d_{T^*} \\
&- (p + aT_M) p((rp - 2r)(\alpha r + p d_{T^*}) - \alpha r^2(p-1)) \alpha r^2 (p-1) d_{T^*}.
\end{aligned}$$

Suppose that there is a $\bar{p^*} > 0$ such that $G(\bar{p^*}) = 0$. Hence, $a_1(p^*)a_2(p^*) - a_3(p^*) = 0$. It can be concluded from Theorem 2 in [19] that, there is Hopf bifurcation at $\bar{E}$ and roots of characteristic equation (5.1) are $\lambda_1^* = -a_1(\bar{p^*})$ and $\lambda_{2,3}^* = \pm i\sqrt{a_2(\bar{p^*})}$. We choose one parameter as bifurcation parameter and fixed other parameters from p^*. Then, consider the Hopf bifurcation at $\bar{E}$. For example let β_2^* is a bifurcation parameter and $G(\bar{p^*})$ is a function of $\bar{\beta_2^*}$. If $\beta_1 T_M \gamma = (1 + \sqrt{1 + \frac{\alpha r}{d_T^*}} + aT_M) d_{T^*} d_V$ and let $\bar{\beta_2^*} = 0$, then $G(\beta_2^*) = G(0) > 0$. On the other hand, $\lim_{\bar{\beta_2^*} \to +\infty} G(\bar{\beta_2^*}) = -\infty$. Hence, $G(\bar{\beta_2}^*) = 0$ has at least one positive root. Therefore, if there is a critical $\bar{\beta_2^*} > 0$ with above conditions, then a Hopf bifurcation occurs at $\bar{E}$ while β_2^* changes near $\bar{\beta_2^*}$. Again by choosing β_1^* as bifurcation parameter, different Hopf bifurcation will be observed. □

6. Conclusion and discussion

In this paper, based on a previously published paper by Lai and Zou ([8]), we have described and analyzed an HIV-1 dynamics model with two infection rates that are concerned with the cell-to-cell transfer, cell-free

virus spread and saturation response of the infection rate. The existence, positivity and boundedness of solutions of the system (1.2) with initial conditions (2.1) have been proven. The reproduction number has been computed as the sum of basic reproduction numbers determined by cell-to-cell and cell-free virus transmission. It has been shown that the trivial equilibrium of the system is always unstable and the infection-free equilibrium is locally and globally asymptotically stable if $R_0 < 1$ and it is unstable if $R_0 > 1$. For the case $R_0 > 1$, a solution space is defined to investigate the uniformly persistence of the system. Establishing some conditions, we could show that if $R_0 > 1$, then the positive equilibrium is stable and Hopf bifurcations occur.

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