Dynamics of an HIV pathogenesis model with CTL immune response and two saturated rates

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Abstract. In this paper, we propose an HIV infection model with CTL immune response which includes the cure of infected cells and the effect of immune impairment caused by HIV infection. Both the infection transmission process and the proliferation of CTL immune response are modeled by two saturated functions. Moreover, the qualitative analysis of the model is investigated and numerical simulations are given to illustrate our theoretical results.

Keywords: HIV infection, CTL immune response, saturated rate, stability

1 Introduction

Human immunodeficiency virus (HIV) is a virus that causes acquired immunodeficiency syndrome (AIDS). According to the World Health Organization (WHO) more than 35.3 million people living with HIV, 2.5 million new infections, and 1.6 million AIDS-related deaths in 2012[^1]. Therefore, mathematical models have been used in order to understand the dynamics of HIV infection[^2-11].

In this paper, we consider the basic model presented by Nowak and Bangham in [2], this model contains four variables, that are, uninfected cells \((T)\), infected cells \((I)\), free virus \((V)\), and Cytotoxic T Lymphocytes (CTL) cells \((Z)\). The model is given by the following nonlinear system of differential equations:

\[
\begin{align*}
\frac{dT}{dt} &= s - dT - \beta VT \\
\frac{dI}{dt} &= \beta VT - \delta I - pIZ \\
\frac{dV}{dt} &= N\delta I - \mu V \\
\frac{dZ}{dt} &= cIZ - bZ,
\end{align*}
\]

where \(T(0) = T_0, I(0) = I_0, V(0) = V_0\) and \(Z(0) = Z_0\) are given. Susceptible host cells \(CD4^+\) T-cells \((T)\) are produced at a rate \(s\), die at a rate \(dT\) and become infected by virus at a rate \(\beta VT\). Infected cells die at a rate \(\delta I\) and are killed by the CTL response at a rate \(pIZ\). Free virus is produced by infected cells at a rate \(N\delta I\) and decays at a rate \(\mu V\). CTLs expand in response to viral antigen derived from infected cells at a rate \(cIZ\) and decay in the absence of antigenic stimulation at a rate \(bZ\).

Note that the rate of infection in Eq. (1) is assumed to be bilinear in the virus \(V\) and the uninfected target cells \(T\), which is not reasonable to describe the HIV infection. Hence, we replace this bilinear form

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by a saturated mass action presented by Song and Neumann in [12]. Furthermore, the proliferation of CTL response in Eq. (1) is bilinear in I and Z. However, in the presence of immune impairment effects caused by HIV infection, CTL proliferation is reduced [13]. On the other hand, the cure of infected cells by non-cytolytic elimination of the cccDNA in their nucleus, was omitted in Eq. (1). Recently, this cure of infected cells is considered by several works [13-5, 10, 14-16]. For these three reasons, we extend the basic model (1) to following model given by

\[
\begin{align*}
\frac{dT}{dt} &= s - dT - \frac{\beta VT}{1+aV} + \rho I \\
\frac{dI}{dt} &= \frac{\beta VT}{1+aV} - (\delta + \rho)I - pIZ \\
\frac{dV}{dt} &= N\delta I - \mu V \\
\frac{dZ}{dt} &= \alpha IZ - bZ,
\end{align*}
\]  

(2)

where \(\rho\) is the cure rate of infected cells and \(\alpha\) represents the immune impairment rate. When \(a = \rho = \alpha = 0\), we obtain the basic model (1).

The aim of this work is to study the dynamical behavior of our Eq. (2) which includes the effect of immune impairment caused by HIV infection and the cure of infected cells.

The rest of the paper is organized as follows. Section 2 illustrates some properties of the model’s solutions. The model analysis and simulation are given in section 3. Discussion and conclusion of this research are presented in section 4.

2 Positivity and boundedness of solutions

In this section, we establish the positivity and boundedness of solutions of Eq. (2) because this model describes the evolution of a cell population. Hence the cell densities should remain non-negative and bounded. These properties imply global existence of the solutions. In addition, for biological reasons, we assume that the initial data for system (2) satisfy :

\[ T_0 \geq 0, \quad I_0 \geq 0, \quad V_0 \geq 0, \quad Z_0 \geq 0. \]

**Proposition 2.1** All solutions starting from non-negative initial conditions exist for all \(t > 0\) and remain bounded and nonnegative. Moreover we have

i) \( T_1(t) \leq T_1(0) + \frac{s}{\delta_1}t \),

ii) \( V(t) \leq V(0) + N\delta \| I \|_\infty \),

iii) \( Z(t) \leq Z(0) + \frac{b}{\delta} [\max(1; 2 - \frac{a}{b})T(0) + I(0) + \max(\frac{a}{b}, \frac{s}{\delta}) + \max(0; 1 - \frac{a}{b}) \| I \|_\infty] \)

where \( T_1(t) = T(t) + I(t) \) represents the T-cells and \( \delta_1 = \min(d, \delta) \).

**Proof.** For positivity, we show that any solution starting in non negative orthant \( \mathbb{R}^4_+ = \{(T, I, V, Z) \in \mathbb{R}^4 : T \geq 0, I \geq 0, V \geq 0, Z \geq 0\} \) remains there forever. In fact, \( (T(t), I(t), V(t), Z(t)) \in \mathbb{R}^4_+ \) we have \( \dot{T} |_{T=0} = s + \rho I \geq 0, \dot{I} |_{I=0} = \frac{\beta VT}{1+aV} \geq 0, \dot{V} |_{V=0} = N\delta I \geq 0, \dot{Z} |_{Z=0} = 0 \geq 0 \)

Hence, positivity of all solutions initiating in \( \mathbb{R}^4_+ \) is guaranteed.

Now, we prove that the solutions are bounded. As \( \dot{T}_1 = s - dT - \delta I - pZ \), we deduce that

\[ T_1(t) \leq T_1(0)e^{-\delta_1 t} + \frac{s}{\delta_1} \left( 1 - e^{-\delta_1 t} \right), \]  

(3)

since \( 0 \leq e^{-\delta_1 t} \leq 1 \) and \( 1 - e^{-\delta_1 t} \leq 1 \), thus i).

Now we show ii). The equation \( \dot{V} = N\delta I - \mu V \), implies that

\[ V(t) = V(0)e^{-\mu t} + N\delta \int_0^t I(\xi)e^{-(\xi-t)\mu}d\xi, \]  

(4)

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then,

\[ V(t) \leq V(0) + \frac{N \delta}{\mu} \| I \|_\infty (1 - e^{-\mu t}). \]

Since \( 1 - e^{-\mu t} \leq 1 \), we deduce \( ii \). Finally, we show \( iii \). The equation \( \dot{Z} = \frac{cI}{1+\alpha I} - bZ \) implies that

\[ \dot{Z} - bZ \leq cIZ. \]

Since

\[ cIZ = \frac{c}{p} \left[ s - (\dot{T} + dT) + (I + \delta I) \right], \]

we get

\[ Z(t) \leq \left[ \frac{c}{p} \left( T(0) + I(0) - \frac{s}{b} \right) + Z(0) \right] e^{-bt} \]

\[ + \frac{c}{p} \left( \frac{s}{b} + \int_0^t \left[ (b - d)T(\xi) + (b - \delta)I(\xi) \right] e^{b(\xi-t)} \xi - T(t) - I(t) \right]. \]

(5)

If \( b - d \leq 0 \) and \( b - \delta \leq 0 \), we have

\[ Z(t) \leq Z(0) + \frac{c}{p} \left[ \frac{s}{b} + T(0) + I(0) \right]. \]

(6)

If \( b - d \leq 0 \) and \( b - \delta \geq 0 \), we have

\[ Z(t) \leq Z(0) + \frac{c}{p} \left[ \frac{s}{b} + T(0) + I(0) + \left( 1 - \frac{\delta}{b} \right) \| I \|_\infty \right]. \]

(7)

If \( b - d \geq 0 \) and \( b - \delta \leq 0 \), we have

\[ Z(t) \leq Z(0) + \frac{c}{p} \left[ \frac{s}{b} + \left( 2 - \frac{d}{b} \right) T(0) + I(0) \right]. \]

(8)

If \( b - d \geq 0 \) and \( b - \delta \geq 0 \), we have

\[ Z(t) \leq Z(0) + \frac{c}{p} \left[ \frac{s}{b} + \left( 2 - \frac{d}{b} \right) T(0) + I(0) + \left( 1 - \frac{\delta}{b} \right) \| I \|_\infty \right]. \]

(9)

From Eq. (5)-(9), we deduce \( iii \).

3 Analysis of the model

In this section, we show that there exists a disease free equilibrium point and two infection equilibrium points, we study the stability of these equilibrium points.

3.1 Stability of free equilibria

By a simple calculation, system (2) has always one disease-free equilibrium \( E_f = (\frac{s}{d}, 0, 0, 0) \), corresponding to the maximal level of healthy CD4+ T-cells. Therefore, the basic reproduction number of (2) is given by

\[ R_0 = \frac{\beta N \delta s}{d \mu(\delta + \rho)}. \]

(10)

The Jacobian matrix of the system (2) at an arbitrary point is given by

\[ J = \begin{pmatrix} -d - \frac{\beta V}{1+\alpha V} & \rho & -\frac{\beta T}{(1+\alpha T)^2} & 0 \\ \frac{\beta V}{1+\alpha V} & -(\delta + \rho) - pZ & -\frac{\beta T}{(1+\alpha V)^2} & -pI \\ 0 & N\delta & -\mu & 0 \\ 0 & \frac{cI}{(1+\alpha I)^2} & 0 & \frac{cI}{1+\alpha I} - b \end{pmatrix}. \]

(11)
1. If $R_0 < 1$, then the disease free equilibrium, $E_f$, is locally asymptotically stable.
2. If $R_0 > 1$, then $E_f$ is unstable.

**Proof.** The Jacobian matrix evaluated at $E_f$ is

$$
J_{E_f} = \begin{pmatrix}
-d & \rho & -\frac{\beta_s}{\theta d} & 0 \\
0 & -(\delta + \rho) & \frac{\beta_s}{\theta d} & 0 \\
0 & N\delta & -\mu & 0 \\
0 & 0 & 0 & -b
\end{pmatrix}.
$$

(12)

The characteristic polynomial of $J_{E_f}$ is

$$
P_{E_f}(\xi) = (\xi + d)(\xi + b)[\xi^2 + (\delta + \rho + \mu)\xi + (\delta + \rho + \mu)(1 - R_0)],
$$

then the eigenvalues of the matrix $J_{E_f}$ are

$$
\begin{align*}
\xi_1 &= -d, \\
\xi_2 &= -b, \\
\xi_3 &= -\frac{(\delta + \rho + \mu) - \sqrt{(\delta + \rho + \mu)^2 - 4(\delta + \rho + \mu)(1 - R_0)}}{2}, \\
\xi_4 &= -\frac{(\delta + \rho + \mu) + \sqrt{(\delta + \rho + \mu)^2 - 4(\delta + \rho + \mu)(1 - R_0)}}{2},
\end{align*}
$$

it is clear that $\xi_1$, $\xi_2$ and $\xi_3$ are negative. Moreover, $\xi_4$ is negative when $R_0 < 1$, thus $E_f$ is locally asymptotically stable.

![Fig. 1. The infection dies out when $R_0 < 1$ as shown in the case of the equilibrium $E_f$. For this simulation, we choose $s = 5$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 500$, $\mu = 3$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$ and $b = 0.2$](image-url)
3.2 Infection steady states

In this section, we focus on the existence and stability of the no-disease-free disease steady states that we are going to name: infection steady states. In fact, it is easily verified that the system (2) has two of them: 

\[ E_1 = (T_1, I_1, V_1, 0), \]

where 

\[ T_1 = \frac{s}{d} aN_{s} + \mu R_0, \quad I_1 = \frac{\mu (R_0 - 1)}{aN_{s} + \mu R_0}, \quad V_1 = \frac{N_{s} (R_0 - 1)}{aN_{s} + \mu R_0}; \]

\[ E_2 = (T_2, I_2, V_2, Z_2), \]

where 

\[ T_2 = \frac{(aN\delta)^2 I_2^2 + (aN\delta + \mu)I_2 + \mu s}{N\delta(ad + \beta)I_2 + \mu d}, \]

\[ I_2 = \frac{b}{c - ab}, \]

\[ V_2 = \frac{N\delta I_2}{\mu}, \]

\[ Z_2 = \frac{-N\delta(ad\rho + \delta(ad + \beta))I_2 + (\beta N\delta - d\mu(\rho + \delta))}{p(N\delta(ad + \beta)I_2 + \mu d)}. \]

From the biological point of view, the point \( E_1 \) represents absent of CTL immune response and \( E_2 \) represents HIV chronic of disease with CTL response. In order to study the local stability of the points \( E_1 \) and \( E_2 \), we define the following numbers:

\[ D_0 = \frac{cs}{b\delta}; \]  
\[ \tilde{D}_0 = D_0 \frac{\mu \delta R_0}{\delta (aN_{s} + \mu R_0) + \alpha \mu s (R_0 - 1)}; \]

\[ H_0 = \frac{1}{R_0 + 1/\tilde{D}_0}. \]

The number \( D_0 \) represents the basic defence rate and \( H_0 \) is the half harmonic mean of \( R_0 \) and \( \tilde{D}_0 \). The importance of these parameters is related the following results.

**Theorem 3.2**

1. If \( R_0 < 1 \), then the point \( E_1 \) does not exists and \( E_1 = E_f \) when \( R_0 = 1 \).
2. If \( R_0 > 1 \) and \( H_0 < 1 \), then \( E_1 \) is locally asymptotically stable.
3. If \( R_0 > 1 \) and \( H_0 > 1 \), then \( E_1 \) is unstable.

**Proof.** It easy to verified that if \( R_0 < 1 \), then the point \( E_1 \) does not exists and \( E_1 = E_f \) when \( R_0 = 1 \). We assume that \( R_0 > 1 \), the Jacobian matrix at \( E_1 \) is

\[
J = \begin{pmatrix}
-d - \beta V_1 / (1 + aV_1) & \rho & -\beta V_1 / (1 + aV_1) & 0 \\
\beta V_1 / (1 + aV_1) & -(\delta + \rho) & -pI_1 & 0 \\
0 & N\delta & -\mu & 0 \\
0 & 0 & 0 & cI_1 / (1 + aI_1) - b
\end{pmatrix}.
\]

The characteristic equation associated with \( J_{E_1} \) is given by

\[
(\xi + b - cI_1 / (1 + aI_1)) (\xi^3 + a_1 \xi^2 + a_2 \xi + a_3) = 0,
\]

where

\[
a_1 = d + \delta + \mu + \rho + \beta V_1 / (1 + aV_1),
\]

\[
a_2 = (\delta + \mu + \rho) d + (\mu + \delta) \beta V_1 / (1 + aV_1) + \mu (\delta + \rho) aV_1 / (1 + aV_1),
\]

\[
a_3 = \mu d (\delta + \rho) aV_1 / (1 + aV_1) + \mu \delta \beta V_1 / (1 + aV_1).
\]
If $\frac{cI_1}{1+\alpha I_1} - b = \frac{b\bar{D}_0(H_0-1)}{H_0}$ is an eigenvalue of $J_{E_1}$. The sign of the eigenvalue $\frac{b\bar{D}_0(H_0-1)}{H_0}$ is negative if $H_0 < 1$. Then the stability of $E_1$ is determined by the distribution of the roots of the equation $\xi^3 + a_1\xi^2 + a_2\xi + a_3 = 0$.

Using the same technique as that defined in [4] by K. Hattaf and N. Yousfi, and from the Routh-Hurwitz Theorem given in [17], the equation $\xi^3 + a_1\xi^2 + a_2\xi + a_3 = 0$ has all its roots negative real parts if $R_0 > 1$. Then $E_1$ is locally asymptotically stable when $R_0 > 1$ and $H_0 < 1$. If $H_0 > 1$, the eigenvalue $\frac{b\bar{D}_0(H_0-1)}{H_0}$ is not negative, then $E_1$ is unstable.

As shown in Fig. 2, the situation where $R_0 > 1$ and $H_0 < 1$ is characterized by the fast decline of the CTLs cells, and the persistence of the infection when time goes by. By a simple calculation, we can show that if $R_0 > 1$ then the condition of local asymptotic stability of $E_1$ is equivalent to

$$D_0 < \left( \frac{R_0}{R_0-1} \right) \left( \frac{\delta(aNs+\mu R_0)+\alpha\mu s(R_0-1)}{\mu\delta R_0} \right),$$

which means that if the basic defense number by CTLs response is below the threshold $\left( \frac{R_0}{R_0-1} \right) \left( \frac{\delta(aNs+\mu R_0)+\alpha\mu s(R_0-1)}{\mu\delta R_0} \right)$, then immune response cannot keep up with the infection, and it eventually vanishes.

**Theorem 3.3**

1. If $\alpha > \frac{c}{b}$ or $H_0 < 1$, then the point $E_2$ does not exists and $E_2 = E_1$ when $H_0 = 1$.
2. If $\alpha < \frac{c}{b}$ and $H_0 > 1$, then $E_2$ is locally asymptotically stable.

**Proof.** We notice that the condition $\alpha < \frac{c}{b}$ and $H_0 > 1$ is equivalent to $I_2 < I_1$.

Then it easy to verified that the point $E_2$ does not exists if $H_0 < 1$ or $\alpha > \frac{c}{b}$ and $E_2 = E_1$ when $H_0 = 1$. We assume that $\alpha < \frac{c}{b}$ and $H_0 > 1$, the Jacobian matrix at $E_2$ is

$$J_{E_2} = \begin{pmatrix}
-d - C_1 & \rho - \delta - pZ_2 & -C_2 & 0 \\
C_1 & 0 & pI^* & -pI^* \\
0 & N\delta & -\mu - \xi & 0 \\
0 & \frac{cZ_2}{(1+\alpha I_2)^2} & 0 & 0
\end{pmatrix},$$

where $C_1 = \frac{\beta V_2}{1+\alpha I_2}$ and $C_2 = \frac{\beta V_2}{(1+\alpha I_2)^2}$. The characteristic equation associated with $J_{E_2}$ is given by

$$(\xi^4 + b_1\xi^3 + b_2\xi^2 + b_3\xi + b_4) = 0,$$

where

$$b_1 = d + C_1 + \mu + \rho + \delta + pZ_2,$$
$$b_2 = \mu(d + C_1 + \rho + (d + C_1)(\delta + pZ_2) + p\frac{b}{(1+\alpha I_2)}Z_2 + d\rho,$$
$$b_3 = \mu d\rho + \mu C_1(\delta + pZ_2) + p\frac{b}{(1+\alpha I_2)}Z_2(\mu + d + C_1),$$
$$b_4 = p\frac{b}{(1+\alpha I_2)}Z_2\mu(d + C_1).$$

From the Routh-Hurwitz Theorem given in [17], the eigenvalues of the above matrix have negative real parts when $H_0 > 1$. Consequently, $E_2$ is locally asymptotically stable when $H_0 > 1$.

As shown in Fig. 3, the situation where $\alpha < \frac{c}{b}$ and $H_0 > 1$ is characterized by an increase CD4$^+$ cells number and a light decrease of the virus load. By a simple calculation, we show that under the condition $\alpha < \frac{c}{b}$, $E_2$ is locally asymptotically stable is equivalent to
Fig. 2. The virus persists in the absence of the CTLS response as shown in the case of the equilibrium $E_1$. For this simulation, we choose $s = 5, \beta = 0.000024, d = 0.02, \delta = 0.5, p = 0.001, N = 1200, \mu = 3, \rho = 0.01, \alpha = 0.001, c = 0.03$ and $b = 0.2$, which correspond to $R_0 > 1$ and $H_0 < 1$.

$$D_0 > \left( \frac{R_0}{R_0 - 1} \right) \left( \frac{\delta(aNs + \mu R_0) + \alpha \mu s (R_0 - 1)}{\mu \delta R_0} \right),$$

which means that if the basic defense number by CTL response is above the threshold $(\frac{R_0}{R_0 - 1}) \left( \frac{\delta(aNs + \mu R_0) + \alpha \mu s (R_0 - 1)}{\mu \delta R_0} \right)$, then immune response CTL can reduce the concentration of virus.

4 Discussion and conclusion

In this work, we gave a rigorous local stability analysis of a new mathematical model describing the interactions between human immunodeficiency virus (HIV) infection of CD4+ T-cells and cytotoxic T lymphocytes (CTL) immune response. The disease free equilibrium is locally asymptotically stable if the basic infection reproduction number satisfies $R_0 < 1$. For $R_0 > 1$, the stability of the two endemic equilibrium points is dependent on the basic defence number by CTLs response $D_0$. Indeed, If

$$D_0 < \left( \frac{R_0}{R_0 - 1} \right) \left( \frac{\delta(aNs + \mu R_0) + \alpha \mu s (R_0 - 1)}{\mu \delta R_0} \right),$$

then $E_1$ is locally asymptotically stable while $E_2$ is is locally asymptotically stable, when

$$D_0 > \left( \frac{R_0}{R_0 - 1} \right) \left( \frac{\delta(aNs + \mu R_0) + \alpha \mu s (R_0 - 1)}{\mu \delta R_0} \right).$$

From the $R_0$ formula, we notice that $R_0$ is independent of the parameters of the activation of CTL that are $b, c, \alpha$ and $p$, which means that CTL do not permit to eliminate the virus. However, they can reduce the concentration of viral load and increase the concentration of CD4+ healthy cells, this can be seen when comparing the components of the viral load and those of the concentration of CD4+ before and after the
Fig. 3. an increase of the CD4$^+$ cells and light decrease of the virus load as shown in the case of the equilibrium $E_2$. For this simulation, we choose $s = 10$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c=0.03$ and $b = 0.2$, which correspond to $H_0 > 1$ and $\alpha < \frac{c}{\beta}$.

activation of CTL, that is to say under the condition $H_0 > 1$. In fact, By simple calculations show that: $T_1 < T_2$ and $V_2 < V_1$ where $T_1$, $T_2$, $V_1$ and $V_2$ are given above. So the cellular immune can control the load of virus.

References


