Mathematical Modeling for

HIV-1 and the CD4+ T Cells Stability

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Abstract

This paper analyzes the mathematical modeling for the interaction of HIV-1 (human immunodeficiency retrovirus) and CD4+ T helper cells considering four variables: uninfected CD4+ T cells, infected CD4+ T cells, infectious HIV virus, and the non-infectious free virus. The paper also discusses system boundedness, stability and instability of the equilibrium point. The basic productive number $R_0$, reflecting the stability of the disease-free equilibrium, is analyzed and shows that when $R_0 < 1$ then the equilibrium point is globally stable. When $R_0$ becomes greater than 1, it implies the ratio of the natural death of the T cells and the death rate of the infected cells to the virus clearance rate is greater than the supply of the T cells, so the equilibrium point becomes unstable and the human immunodeficiency retrovirus leads to acquired immune deficiency syndrome. Numerical simulations of the model are performed to validate this theoretical result, which is compatible with the theoretical analyses.

Keywords: HIV infection; CD4+ T cells; Dynamical systems; Stability analysis

1. Introduction

HIV-1 is a retrovirus discovered in 1984 [8, 10, and 24], initially proposed in the early 1980s [38]. HIV-1 targets the CD4+ T cells, destroying up to 60% of these cells in the first period of infection [22, 36] using these cells as a host to make millions of copies of themselves. There is no cure for HIV infection [25]. Retroviruses target CD4+ T cells affecting their function (human T cell leukemia virus, HTLV) or destroying them (immunodeficiency virus, HIV) [7, 9, 40]. There are four distinct CD4+ T cells Th1, Th2, Th17, and iTreg cells (for more details see [45]). These play a central role in the immune system, which protects the body
against any foreign invaders (antigens) through fighting infection. CD4+ T cells are produced in the bone marrow; in a healthy body, each cubic milliliter of blood contains around 1100 CD4+ T cells with half-lives of 87 days and production rates of 10 cells per milliliter per day [11]. These cells secrete chemical substances to innervate cytotoxic T cells and B cells. The first one functions by killing cells infected by the virus, and the second marks the antigens, and the B cells become memory cells to protect the body from the same invaders in the future.

The HIV-1 virus is related to SIVcpz GAB1 [13, 34] and can persist on inanimate surfaces for more than one week [3, 15, and 33]. When there are less than 200 cells per cubic milliliters of blood, the immune system of an HIV+ person fails to control viruses leading to AIDS (acquired immune deficiency syndrome) [16,20,41]. This loss of immunity takes between 2 to 20 years or more to appear with a median of 9 years [21]. It is still difficult to understand how the HIV virus leads to AIDS [1, 35]. The latest report in 2013 from the Joint United Nations Program on HIV/AIDS (UNAIDS) shows that, globally, 17.8 million children have lost one or both parents to AIDS, and every hour 50 young women are newly infected with HIV [see 39]. According to the World Health Organization (WHO, 2014) the total number of people living with HIV was estimated at approximately 35.0 million at the end of 2013[42].

Mathematical models describing the interaction of the immune system with HIV have been studied by Merrill, Nowak, May, McLean, Anderson, Nelson, Perelson, Harnevo, and Kirschner [see, e.g., 14, 18, 23, 26, 27, 28, 29, 30]. Their research focused on the stability of the immune system and its interaction with the HIV-1 viruses.

The basic reproduction number $R_v$ reflects the stability of the disease-free equilibrium. When $R_v < 1$, this equilibrium point is stable and predicts that the pathogen will be cleared. In general, the larger the value of $R_v$, the harder it is to control the infection [12, 29] and the HIV infection leads to AIDS. The purpose of this paper is to evaluate and analyze $R_v$ (basic reproduction number) of the 4-dimensional system (1), using the stability method with the equilibrium point.

$$\begin{align*}
\frac{dT}{dt} &= s - aT - kVT \\
\frac{dT_i}{dt} &= kVT - \delta T_i \\
\frac{dV}{dt} &= n\beta T_i - \gamma V \\
\frac{dV_i}{dt} &= n(1-\beta)T_i - \gamma V_i
\end{align*}$$

(1)

The variables and parameters in (1): $T$ represents the uninfected target CD4+ T cells’ density. $T_i$ represents the infected target CD4+ T cells’ density. $V$ is the
concentration of infectious HIV-1 RNA viruses, and \( V_i \) represents the non-infectious free viruses. The total amount of the virus is equal to the sum of \( V \) and \( V_i \). The target cells constantly enter the system at rate \( s \). This is the daily production of the target cells. They die at a natural death rate of \( \alpha \) and become infected by the virus at a constant rate of \( k \). The parameter \( \gamma \) is the clearance rate of the free virus (viruses are removed from the system at rate \( \gamma \)) per virion.

Infected cells \( T_i \) produce viruses at rate \( n\beta \) and die at the rate of \( \delta \) per cell. The average virion life span is \( 1/\delta (\delta \geq \alpha) \). All parameters are positive. If \( \beta = 1 \), then

\[
\frac{dV_i}{dt} = -\gamma V_i \quad \text{i.e.} \quad V_i \rightarrow 0 \quad \text{as} \quad t \rightarrow \infty , \quad \text{being a perfect drug \[32\].}
\]

The equilibrium point is called a health state where there is no virus \((V = 0)\) and is called a seropositivity state where the viruses coexist \((V \neq 0)\) \[6\]. Researchers first considered the basic interaction between the immune system and the virus using the following system of the differential equations to model the immune response during the viral infection \[2, 4, \text{and } 5\]

\[
\begin{align*}
\frac{dV}{dt} &= s - \alpha (V + T) - kVT \\
\frac{dT}{dt} &= s - \alpha T - kVT - \delta T_i \\
\frac{dV_i}{dt} &= kVT - \delta T_i \\
\frac{dT_i}{dt} &= n\beta T_i - \gamma V_i
\end{align*}
\]

(2)

The stability of the health equilibrium point, or seropositivity equilibrium point, for the system (1) when \( s = \alpha \), has been discussed by F. Dubois et al. see \[6\].

### 2. Model boundedness, boundary equilibrium points and stability

**Theorem 1.** All solutions of the system (1) which start in \( \mathbb{R}^4_+ \) are bounded.

Proof. By using Gronwall inequality theorem \[19, 37\] it can be shown easily that the solution \( T(t) \) of the system (1) is bounded.

From the first equation

\[
T(t) = e^{-\int_0^t (\alpha + kV(\tau)) d\tau} T(0) + \int_0^t e^{-\int_\tau^t (\alpha + kV(u)) du} s \, d\tau
\]

\[
T(t) \leq T(0) e^{-\int_0^t \alpha \, d\tau} + s e^{-\int_0^t \int_\tau^t kV(u) \, du} \int_0^t e^{-\int_\tau^t kV(u) \, du} \, d\tau
\]

\[
e^{-\int_0^t \alpha \, d\tau} \cdot e^s \text{ is bounded as } t \rightarrow \infty , \text{ then}
\]

\[
\lim_{t \rightarrow \infty} T(t) \text{ is bounded, so } T(t) \text{ is bounded for } t > 0.
\]

From the second equation
\( T_i(t) = e^{-\theta} [I(0) + \int_0^t e^{\sigma} k V(\tau) T(\tau) d\tau] \) is also bounded. From the third equation 

\( V(t) \) is bounded for large \( t \). Hence with \( T(0) \geq 0, \ T_i(0) \geq 0, \ V(0) \geq 0, \) and \( V_i(0) \geq 0 \) all solutions are bounded. 

**Theorem 2.** The system (1) has exactly two equilibrium points. The first one \((V = 0)\) is

\[
F_0^* = (T^*, T_i^*, V^*, V_i^*) = \left( \frac{s}{\alpha}, 0, 0, 0 \right) \text{ with } s > \alpha,
\]

The second one \((V > 0)\) is:

\[
F_1^* = (T^*, T_i^*, V^*, V_i^*) = \left( \frac{\alpha \gamma}{R_c}, \frac{\alpha s}{k R_c}, \frac{\alpha s}{k R_c}, -1 \right), \frac{\alpha}{K} (1 - 1) (\frac{s}{k R_c} - 1))
\]

where \( R_c = \frac{\alpha \gamma}{kn \beta s} \)

**Proof.** The first equilibrium point is \( s - \alpha T - k VT = 0 \) and \( V = 0, \) then \( T^* = \frac{s}{\alpha} \)

The second equilibrium point is \( T^* = \frac{\delta y}{kn \beta}, I^* = \frac{\gamma}{n \beta} V^* \)

and \( V^* = 1 \left( \frac{s}{k} - \alpha \right), V^* > 0, \) then

\( T^* < \frac{s}{\alpha}, \) and

\[ \frac{\delta y}{kn \beta} < \frac{s}{\alpha}, \]

\[ kn \beta s - \alpha \delta y > 0, \]

\[ k \alpha s - \alpha \delta y > 0 \]

Infected cells produce viruses at the rate \( \sigma = n \beta. \)

If they are defined so that the basic productive number is \( R_s, \) then \( R_s \) becomes:

\[
R_s = \frac{\alpha \delta y}{k \sigma s} < 1.
\]

so \( T^* = \frac{s}{\alpha} R_c, \)

\[
V^* = \frac{1}{k} \left( \frac{s}{k T^*} - \alpha \right)
\]

\[ = \frac{\alpha}{k} \left( \frac{1}{R_c} - 1 \right) \]
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\[ I^* = \frac{\gamma}{n\beta} V^* \]
\[ = \frac{\alpha\gamma}{kn\beta} \left( \frac{1}{R_0} - 1 \right) \]
\[ V_i^* = \left( \frac{1}{\beta} - 1 \right)V^* \]

and the second equilibrium point is

\[ (T^*, T_i^*, V^*, V_i^*) = \left( \frac{s}{\alpha} R, \frac{\gamma}{n\beta} V^*, V^*, \left( \frac{1}{\beta} - 1 \right)V^* \right) \text{ where } V^* = \frac{\alpha}{k} \left( \frac{1}{R_0} - 1 \right) \]

**Theorem 3.** The equilibrium point \( F_0^* \) is stable if and only if \( R_0 < 1 \).

Proof.

The Jacobian matrix \( A \) becomes

\[
A(T^*, T_i^*, V^*, V_i^*) = \begin{bmatrix}
-\alpha - kV^* & 0 & -kT^* & 0 \\
-\delta & kT^* & 0 & 0 \\
0 & n\beta & -\gamma & 0 \\
0 & n(1-\beta) & 0 & -\gamma
\end{bmatrix}
\]

In the case of a health state \( (V^* = 0) \), \( (T^*, T_i^*, V^*, V_i^*) = \left( \frac{s}{\alpha}, 0, 0, 0 \right) \), then

\[
A\left( \frac{s}{\alpha}, 0, 0, 0 \right) = \begin{bmatrix}
-\alpha & 0 & -\frac{ks}{\alpha} & 0 \\
0 & -\delta & -\frac{ks}{\alpha} & 0 \\
0 & n\beta & -\gamma & 0 \\
0 & n(1-\beta) & 0 & -\gamma
\end{bmatrix}
\]

At \( F_0^* \); the characteristic matrix is

\[
\lambda I - A = \begin{bmatrix}
\lambda + \alpha & 0 & \frac{ks}{\alpha} & 0 \\
0 & \lambda + \delta & -\frac{ks}{\alpha} & 0 \\
0 & -n\beta & \lambda + \gamma & 0 \\
0 & n(\beta-1) & 0 & \lambda + \gamma
\end{bmatrix}
\]

the characteristic equation is \( (\lambda + \alpha)(\lambda + \gamma)[\lambda^2 + (\delta + \gamma)\lambda + (\delta\gamma - \frac{ksn\beta}{\alpha})] = 0 \).

For \( [\lambda^2 + (\delta + \gamma)\lambda + (\delta\gamma - \frac{ksn\beta}{\alpha})] = 0 \),

\[ \delta + \gamma > 0, \text{ and if } R_0 < 1 \text{ then } ksn\beta < \alpha\delta\gamma \text{ and hence } \delta\gamma - \frac{ksn\beta}{\alpha} > 0 \]
All coefficients are positive, then all eigenvalues
\[ \lambda_i = -\gamma, \lambda_2 = -\alpha, \lambda_{3,4} = \frac{1}{2}((\delta + \gamma) \pm \sqrt{\alpha(\delta - \gamma)^2 + 4ksn\beta}) \] have negative real parts (stable) [43].

**Theorem 4.** If \( R_0 < 1 \), the equilibrium point \( F_1^* \) is locally asymptotically stable.

Proof. At \( F_1^* \) the Jacobian matrix \( J \) becomes:

\[
J(T^*, T^*_i, V^*, V^*_i) = \begin{bmatrix}
-\frac{skn\beta}{\delta}\gamma & 0 & -\frac{n\beta}{\delta}\gamma & 0 \\
-\frac{skn\beta}{\delta}\gamma & -\delta & \frac{\gamma n\beta}{\delta} & 0 \\
0 & n\beta & -\gamma & 0 \\
0 & n(1-\beta) & 0 & -\gamma
\end{bmatrix}
\]

\[
= \begin{bmatrix}
-\frac{\alpha}{R_0} & 0 & -\frac{k\alpha}{\gamma} & 0 \\
\alpha(\frac{1}{R_0}-1) & -\delta & \frac{\gamma k\alpha}{\gamma} & 0 \\
0 & n\beta & -\gamma & 0 \\
0 & n(1-\beta) & 0 & -\gamma
\end{bmatrix}.
\]

At \( F_1^* \); the characteristic matrix is

\[
\lambda I - J(F_1^*) = \begin{bmatrix}
\lambda + \frac{\alpha}{R_0} & 0 & \frac{k\alpha}{\gamma} & 0 \\
\alpha(\frac{1}{R_0}) & \lambda + \delta & -\frac{k\alpha}{\gamma} & 0 \\
0 & -\delta & \lambda + \gamma & 0 \\
0 & n(1-\beta) & 0 & \lambda + \gamma
\end{bmatrix}
\]

the eigenvalues satisfy

\[
(\lambda + \gamma) \begin{bmatrix}
\lambda + \frac{\alpha}{R_0} & 0 & \frac{k\alpha}{\gamma} \\
\alpha(\frac{1}{R_0}) & \lambda + \delta & -\frac{k\alpha}{\gamma} \\
0 & -\delta & \lambda + \gamma
\end{bmatrix} = 0.
\]

The determinant of the characteristic matrix, which gives the characteristic equation

\[ \lambda^3 + \eta_1\lambda^2 + \eta_2\lambda + \eta_3 = 0 \] (6)
where \( \eta_1 = \frac{\alpha}{R_c} + \delta + \gamma > 0, \quad \eta_2 = \frac{\alpha(\delta + \gamma)}{R_c} > 0, \)
and \( \eta_3 = ksn\beta(1 - R_c) > 0, \) for \( R_c < 1, \) and by Routh-Hurwitz criterion
(\( \eta_1 > 0, \eta_2 > 0, \eta_1\eta_2 > \eta_3 \) if and only if the real parts of the eigenvalues are negative) [43], if \( \eta_1\eta_2 - \eta_3 > 0, \) then \( F_1^* \) (the equilibrium point) is locally asymptotically stable. If \( \eta_1\eta_2 - \eta_3 < 0, \) \( F_1^* \) becomes unstable.

\[
\eta_1\eta_2 - \eta_3 = \frac{\alpha}{R_c} + \delta + \gamma\left(\frac{\alpha(\delta + \gamma)}{R_c}\right) - ksn\beta(1 - R_c)
\]
\[
= \frac{1}{R_c^2}(\alpha + \delta R_c + \gamma R_c)(\alpha \delta + \alpha \gamma) + ksn\beta(R_c - 1)
\]
\[
= \frac{1}{R_c^2}(\alpha^2 \delta + \alpha^2 \gamma + \alpha \delta^2 R_c + 2\alpha \delta \gamma R_c + \alpha \gamma^2 R_c + ksn\beta R_c^3 - ksn\beta R_c^2)
\]
\[
= k^2n^2\beta^2s^2\left(\alpha^2 \delta + \alpha^2 \gamma + \frac{\alpha^2 \delta^2 \gamma}{kn\beta s} + \frac{2\alpha^2 \delta \gamma^2}{kn\beta s} + \frac{\alpha^2 \gamma^3}{kn\beta s} + \frac{\alpha^3 \delta \gamma^3}{kn\beta s} - \frac{\alpha^2 \delta^2 \gamma^2}{kn\beta s}\right)
\]
\[
= \frac{1}{\delta^2 \gamma^2}(k^2n^2\beta^2s^2\delta + k^2n^2\beta^2s^2\gamma + kn\beta s\delta^2 \gamma + kn\beta s\delta^2 \gamma + kn\beta s\delta^2 \gamma + kn\beta s\delta^2 \gamma + \alpha \delta^2 \gamma^3) > 0
\]

\( \eta_1\eta_2 > \eta_3. \) This implies that the seropositivity equilibrium point \( F_1^* \)
\((T^*, T_1^*, V^*, V_1^*)\) is locally asymptotically stable.

**Theorem 5.** The seropositivity equilibrium point (4) is globally asymptotically stable for the system (1) in the positive 4-dimensional region
\( D_1^* = \{T(t), T_1(t), V(t), V_1(t)\}. \)

Proof. To show global stability, Li and Muldowney’s proof [Proof of Theorem 2.1, Li and Muldowney] [18] states that it suffices to show that the system is competitive in the region \( D_1^*. \)

Let the diagonal matrix \( H \) be as follows:

\[
H = \text{diag}(-1, -1, 1, 1), \quad \text{and from above } J = \begin{bmatrix}
-\frac{\alpha}{R_c} & 0 & -\frac{\delta \gamma}{n\beta} & 0 \\
\alpha(\frac{1}{R_c} - 1) & -\delta & \frac{\delta \gamma}{n\beta} & 0 \\
0 & n\beta & -\gamma & 0 \\
0 & n(1 - \beta) & 0 & -\gamma
\end{bmatrix}
\]

Hence \( HJH \) has nonpositive off-diagonal elements and the system is competitive, which implies a seropositive steady state \( F_1^* \) is globally asymptotically stable.
Also it is easy to prove $F_0^*$ is globally asymptotically stable. This proof will be left to the reader.

3. Numerical Simulations

The following numerical simulations use a similar set of parameter values to [6, 17, 44]. More specifically, $\alpha = 0.01 day^{-1}$, $s = 0.01 day^{-1}$, $n = 250 day^{-1}$, $\delta = 0.7 day^{-1}$, $k = 0.125, \gamma = 2, \beta = \theta = 0.1$, then $R = 0.0448 < 1$ is healthy (see parameters page 7 [6]). For $s = 5, \alpha = 0.03, k = 0.0014453, n = 480, \delta = 0.32, \gamma = 1.8, N = 480, \beta = 0.32$, so $R = 0.1556770 < 1$ which means this sample is also healthy [44, p. 521]. For the last example see page 10 [17], if $s = 160, \alpha = 0.16, k = 0.002, n = 480, \delta = 1.85, \gamma = 1.8, N = 480, \beta = 0.32$ $R = 0.010839843 < 1$ is healthy; also, the graph of stability for $x(t), y(t), z(t)$ in page 10 and 11.

4. Summary and Discussions

Several 3D and 4D nonlinear dynamical systems have been proposed by researchers, (see, for example Nowak [26], Perelson [31], Perelson, Kirschner, and De Boer [30], etc. In this paper basic productive number $R_0$ is defined in terms of the system (1) parameters. It can be used to interpret the stability of $CD4^+ T$ helper cells during chronic lymphadenopathy and sub-clinical immune dysfunction periods respectively. As the parameter $s$ increases, $\lim_{s \to \infty} \frac{\alpha \delta y}{kn \beta s}$ implies $R\to 0$ and the immune system kills the viruses out. It is shown that, if $R < 1$, then the system (1) has free equilibrium and it is globally asymptotically stable; if $R > 1$, then it is unstable, which implies that the death rate of the infected $T$ cells is greater than their supply $\frac{\alpha \delta n \beta s}{k \gamma} > s$.

From the theoretical and numerical results summarized above $R_0 = \frac{\alpha \delta y}{kn \beta s}$, determining the stability dynamic of the system (1) increases $s$ (the supply of $CD4^+ T$ helper cells) bringing $R_0$ lower than 1, making the infection equilibrium globally asymptotically stable, and the immune system then controls the virus.

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References


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