

# Analysis of stability about the CD4+ T-cells dynamics with nonlinear infection rate

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## Abstract

In this paper, we analyze mathematical models for the infection of human immunodeficiency virus-type 1(HIV-1) with target cells between initial infection. Assuming that the infection among the cells can be approximated, we consider the classical mathematical model with nonlinear infection rate. We prove that, if  $R_0 \leq 1$ , the HIV infection is cleared from the T-cells population; if  $R_0 > 1$  the HIV infection persists.

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## 1 Introduction

The natural history of HIV infection and immunodeficiency that characterizes AIDS typically falls into three stages. After infection with HIV-1, the amount of virus measured in blood typically increases to high levels and flu-like symptoms appear [2, 4]. After a few weeks, or in some cases months, this

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initial high level viremia disappears and, viral load stabilizes at some lower values. Next, a variable but usually long period of clinical latency ensues, during which the virus persists at a relatively stable level and the CD4+ T-cell count gradually falls. The period, during which the patient is asymptomatic, can last many years. In the final stages of the disease, the viral load usually increases rapidly and the CD4+ T-cell count declines to a point at which the immune system fails to provide protection against opportunistic infections. Death usually occurs due to one of these infections.

In 1993, Perelson, Kirschner and De Boer proposed an ordinary differential equation (ODE) model of cell-free viral spread of human immunodeficiency virus (HIV) in a well-mixed compartment such as the bloodstream. Their model consists of four components: uninfected healthy CD4+ T-cells, latently infected CD4+ T-cells, actively infected CD4+ T-cells, and free virus [1, 3, 5].

## 2 Model

The body is believed to produce CD4+ T-cells from prursors in the bone marrow and thymus at a constant rate  $s$ , and T-cells have a natural turn-over rate  $\alpha$ , and  $r$  is their growth rate (thus  $r > \alpha$  in general). Then the CD4+ T-cells dynamics can be written by the following logistic equation:

$$\dot{T} = s - \alpha T + rT\left(1 - \frac{T}{T_{max}}\right), \quad (2.1)$$

where  $T$  is the concentration of CD4+ T-cells and  $T_{max}$  is their carrying capacity. If the population ever reaches  $T_{max}$  it should decrease, thus we impose the constraint  $T_{max}\alpha > s$ . The equation (2.1) has a single stable steady state given by

$$\hat{T} = \frac{T_{max}}{2r}\left(r - \alpha + \sqrt{(r - \alpha)^2 + \frac{4rs}{T_{max}}}\right) \quad (2.2)$$

In HIV infection, the most important determinant of a sustained virological response is the clearance of infected cells during the period of viral inhibition. The various models proposed to describe the fall in HIV differ principally in their underlying assumptions regarding the nature and efficacy of the inhibition of viral replication that is imposed upon the virus- host system by nucleoside analogue therapy, the behavior of infected cell population after the commencement of therapy and ultimately the residual effect of this population on the

level of viraemia. Thus, in this paper, we investigate the model with nonlinear infection rate, which is given by the following form:

$$\begin{cases} \dot{T} = s - \alpha T + rT\left(1 - \frac{T+I}{T_{max}}\right) - \frac{kT(t-\tau)V(t-\tau)}{a+bT(t-\tau)} + \rho I, \\ \dot{I} = \frac{kT(t-\tau)V(t-\tau)}{a+bT(t-\tau)} - \beta I + \rho I, \\ \dot{V} = N\beta I + dV, \end{cases} \quad (2.3)$$

under the initial values

$$\begin{aligned} T(\xi) &= \varphi_1(\xi), \quad I(\xi) = \varphi_2(\xi), \quad V(\xi) = \varphi_3(\xi), \quad \xi \in [-\tau, 0], \\ \varphi_1(0) &\geq 0, \quad \varphi_2(0) \geq 0, \quad \varphi_3(0) \geq 0, \end{aligned}$$

where,  $T$ ,  $I$  and  $V$  denote the number of susceptible CD4+ T cells, infected CD4+ T cells, and free HIV virus particles, respectively. Parameter  $\alpha$ ,  $\beta$ , and  $d$  are natural death rate of the uninfected T cells, infected T cells, and virus particles, respectively and  $\tau$  are assuming only positive values,  $\rho$  is the rate of "cure". Because of the viral burden on the HIV infected T cells, we suppose that  $\alpha \leq \beta$ . 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 (2.3) but using a simplified logistic growth  $rT(1 - \frac{T}{T_{max}})$  for susceptible CD4+ T cells has been proposed in [1], for the model (2.3), we show that, if  $R_0 \leq 1$  the basic reproduction number, the infection-free equilibrium  $E^0$  is globally asymptotically stable, the virus is cleared and no HIV infection. If  $R_0 > 1$ ,  $E^0$  becomes unstable and the HIV infection persists in the T-cells population. Then, a unique chronic infection equilibrium  $E^0$  exists.

### 3 Local Stability and Permanence

The non-negative equilibria of the system (2.3) are  $E_0(\hat{T}, 0, 0)$ ,  $E^*(T^*, I^*, V^*)$ , where

$$\hat{T} = \frac{T_{max}}{2r} \left( r - \alpha + \sqrt{(r - \alpha)^2 + \frac{4rs}{T_{max}}} \right),$$

$$\begin{cases} T^* = \frac{ad(\rho+\beta)}{kN\beta-bd(\beta+\rho)}, \\ I^* = \frac{s-\alpha T^*+rT^*(1-\frac{T^*}{T_{max}})}{\beta+r\frac{T^*}{T_{max}}}, \\ V^* = \frac{N\beta(s-\alpha T^*+rT^*(1-\frac{T^*}{T_{max}}))}{d(\beta+r\frac{T^*}{T_{max}})}, \end{cases}$$

Let  $E^0(T^0, I^0, V^0)$  be any arbitrary equilibrium. Then the characteristic equation about  $E^0$  is given by

$$\begin{vmatrix} -\alpha + r - \frac{2eT^0}{T_{max}} - \frac{rI^0}{T_{max}} - \frac{k\alpha V^0 e^{-\lambda\tau}}{(a+bT^0)^2} - \lambda & -\frac{rT^0}{T_{max}} + \beta & -\frac{kT^0 e^{-\lambda\tau}}{a+bT^0} \\ \frac{k\alpha V^0 e^{-\lambda\tau}}{(a+bT^0)^2} & -\beta - \rho - \lambda & \frac{kT^0 e^{-\lambda\tau}}{a+bT^0} \\ 0 & N\beta & -d - \lambda \end{vmatrix} = 0.$$

For equilibrium  $E_0(\hat{T}, 0, 0)$  reduces to

$$\left(-\alpha + r - \frac{2r\hat{T}}{T_{max}} - \lambda\right)[\lambda^2 + (\beta + \rho + d)\lambda + \rho d + \beta d - N\beta \frac{k\hat{T}e^{-\lambda\tau}}{a + b\hat{T}}] = 0.$$

Obviously,  $E_0(\hat{T}, 0, 0)$  is locally asymptotically stable for  $\hat{T} < T^*$  and is a saddle point. Let

$$R_0 = \frac{\hat{T}}{T^*} = \frac{T_{max}[kN\beta - bd(\beta + \rho)](r - \alpha + \sqrt{(r - \alpha)^2 + \frac{4rs}{T_{max}}})}{2rad(\beta + \rho)},$$

which is called the basic reproductive number of the model (2.3).

When  $R_0 < 1$ , the uninfected steady state  $E_0$  is stable and the infected steady state  $E^*$  doesn't exist.

When  $R_0 = 1$ , one eigenvalue is 0 and it is simple.

When  $R_0 > 1$ ,  $E_0$  becomes unstable and  $E^*$  exist.

Thus, the basic reproductive number  $R_0$  determines the dynamical properties of system (2.3) over a long period of time.

**Remark 3.1.** If  $R_0 < 1$ ,  $E_0$  is locally asymptotically stable. If  $E_0$  is locally stable. If  $R_0 > 1$ ,  $E_0$  is a saddle point with a two-dimensional stable manifold and a one-dimensional unstable manifold.

In case of positive delay, the characteristic equation around the point  $E^0(T^0, I^0, V^0)$  is given by

$$\begin{aligned} P(\lambda) + Q(\lambda)e^{-\lambda\tau} &= 0, \\ P(\lambda) &= \lambda^3 + p_1\lambda^2 + p_2\lambda + p_3, \\ Q(\lambda) &= q_1\lambda^2 + q_2\lambda + q_3, \end{aligned}$$

where

$$\begin{aligned} p_1 &= \alpha - r + \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}} + \frac{kaV^0}{(a + bT^0)^2} + d + \rho, \\ p_2 &= \left(\alpha - r + \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}}\right)\left(\frac{kaV^0}{(a + bT^0)^2} + d + \rho\right) + \frac{kadV^0}{(a + bT^0)^2} + \rho d, \\ p_3 &= d\left(\alpha - r + \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}}\right)\left(\frac{kaV^0}{(a + bT^0)^2} + \rho\right), \\ q_1 &= \frac{kaV^0}{(a + bT^0)^2}, \\ q_2 &= \frac{kaV^0}{(a + bT^0)^2}\left(d + 2\rho - \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}}\right) - N\rho\frac{kT^0}{a + bT^0}, \\ q_3 &= \frac{kaV^0}{(a + bT^0)^2}\left(2\rho - \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}}\right) + \left(\alpha - r + \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}}\right)N\beta\frac{kT^0}{a + bT^0} \end{aligned}$$

The steady state is stable in the absence of delay ( $\tau = 0$ ), if the roots of

$$P(\lambda) + Q(\lambda) = 0, \quad \lambda^3 + (p_1 + q_1)\lambda^2 + (p_2 + q_2)\lambda + p_3 + q_3 = 0,$$

where

$$\begin{aligned} p_1 + q_1 &= \alpha + \frac{\rho I^0}{T^0} + \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}} + \rho + d + \frac{2kaV^0}{(a + bT^0)^2} = \beta + s + M_0 > 0, \\ p_2 + q_2 &= \left(\alpha + \frac{\beta I^0}{T^0} + \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}}\right) + \left(\rho + d + \frac{2kaV^0}{(a + bT^0)^2}\right) \\ &\quad + N\beta\frac{kT^0}{a + bT^0}\left(\frac{dkaV^0}{(a + bT^0)^2} + \rho d\right) + \frac{kaV^0}{(a + bT^0)^2}\left(\frac{kaV^0}{a + bT^0} + d + 2\rho - \frac{rI^0}{T_{max}}\right) \\ p_3 + q_3 &= \left(\alpha + \frac{\beta I^0}{T^0} + \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}}\right)\left(\frac{kaV^0}{(a + bT^0)^2} + \rho\right) + \frac{kaV^0}{(a + bT^0)^2}\left(\frac{kaV^0}{(a + bT^0)^2}\right) \\ &\quad + 2\rho - \frac{rI^0}{T_{max}} + N\beta\left(\alpha + \frac{\beta I^0}{T^0} + \frac{2rT^0}{T_{max}} + \frac{rI^0}{T_{max}}\right) \\ (p_2 + q_2)(p_1 + q_1) - (p_3 + q_3) &> 0, \end{aligned}$$

**Theorem 3.1.** *If*

$$(i) R_0 > 1, \quad (ii) M_0 \geq 0, \quad (iii) (p_2 + q_2)(p_1 + q_1) - (p_3 + q_3) > 0,$$

*then the positive equilibrium  $E^*(T^*, I^*, V^*)$  is locally asymptotically stable.*

*It is to see that solution of the system (2.3) always exists and stays positive and bounded. In fact, it is obvious for system (2.3), we have*

$$\lim_{t \rightarrow \infty} T(t) \leq \hat{T} = \frac{T_{max}}{2r} \left[ r - \alpha + \sqrt{(r - \alpha)^2 + \frac{4rs}{T_{max}}} \right]$$

*Then there is a  $t_1 \geq 0$  such that for any sufficiently small  $\varepsilon_0$ , we get*

$$T(t) \leq \hat{T} + \varepsilon_0,$$

*for  $t > t_1$ .*

**Theorem 3.2.** *There exists an  $M > 0$  such that for any positive solution  $(T(t), I(t), V(t))$  of the system (2.3),  $I(t) < M$ ,  $V(t) < M$ , for all large  $t$ .*

**Proof.** Let

$$L_1(t) = T(t) + I(t).$$

Calculating the derivative of  $L_1(t)$  along the solutions of the system (2.3), we can find

$$\begin{aligned} \dot{L}_1(t) &= s - \alpha T(t) + rT(t) \left( 1 - \frac{T(t) + I(t)}{T_{max}} \right) - \beta I(t) \\ &\leq -\alpha T(t) - \beta I(t) + rT(t) - \frac{rT(t)^2}{T_{max}} + s \leq -\alpha L_1(t) + M_1, \end{aligned}$$

here  $M_1 = \frac{rT_{max} + 4s}{4}$ . Recall that  $T(t) \leq \hat{T} + \varepsilon_0$ , for all  $t > t_1$ .

Then there exists an  $M_2 > 0$ , depending only on the parameters of the model (2.3), such that  $L_1(t) < M_2$ , for  $t > t_1$ . Then  $I(t)$  has an ultimately above bound. It follows from the third equation of (2.3) that  $V(t)$  has an ultimately above bound. Say, their maximum is  $M$ . Then, the proof of Theorem 3.2 is completed.  $\square$

## 4 Estimation of the length of delay to preserve stability

Firstly, we give the following lemma.

**Lemma 4.1.** (Nyquist criterion). *If  $L$  is the arc length of a curve encircling the right half-plane, the curve  $\bar{P}_J(L)$  will encircle the origin a number of times equal to the difference between the number of poles and the number of zeroes of  $\bar{P}_J(L)$  in the right half-plane.*

We consider the system (2.3) and the space of all real valued continuous functions defined on  $[-\tau, 0]$  satisfying the initial conditions (2.3) on  $[-\tau, 0]$ . We linearize the system (2.3) about its interior equilibrium  $E^0(T^0, I^0, V^0)$  and get

$$\begin{cases} \dot{T} = (-\alpha + r - \frac{2rT^0}{T_{max}} - \frac{rI^0}{T_{max}})T - \frac{kaV^0T(t-\tau)}{(a+bT^0)^2} + (\rho\rho - \frac{rI^0}{T_{max}})I - \frac{kT^0V(t-\tau)}{a+bT^0}, \\ \dot{I} = \frac{kaV^0T(t-\tau)}{(a+bT^0)^2} - (\beta + \rho)I - \frac{kT^0V(t-\tau)}{a+bT^0}, \\ \dot{v} = N\beta I - dV, \end{cases} \quad (4.1)$$

Taking Laplace transform of the system given by (4.1), we get

$$\begin{aligned} & (\xi + \alpha - r + \frac{rI^0}{T_{max}} + \frac{kaV^0e^{-\lambda\tau}}{(a+bT^0)^2})L_T(\xi) \\ &= \frac{kaV^0e^{-\lambda\tau}}{(a+bT^0)^2}K_1(\xi) + (\rho - \frac{rI^0}{T_{max}})L_I(\xi) - \frac{kT^0e^{-\lambda\tau}}{a+bT^0}L_V(\xi) - \frac{kT^0e^{-\lambda\tau}}{a+bT^0}K_2(\xi) + T(0), \\ & (\xi + \beta + \rho)L_I(\xi) \\ &= \frac{kaV^0e^{-\lambda\tau}}{(a+bT^0)^2}L_T(\xi) + \frac{kaV^0e^{-\lambda\tau}}{(a+bT^0)^2}K_1(\xi) - \frac{kT^0e^{-\lambda\tau}}{a+bT^0}L_V(\xi) - \frac{kT^0e^{-\lambda\tau}}{a+bT^0}K_2(\xi) + I(0), \\ & (d + \xi)L_V(\xi) = N\beta L_I(\xi) + V(0), \end{aligned} \quad (4.2)$$

where

$$K_1(\xi) = \int_0^\infty e^{-\xi\tau}T(t)dt, K_2(\xi) = \int_0^\infty e^{-\xi\tau}I(t)dt,$$

and  $L_T, L_I, L_V$  are the Laplace transform of  $T(t), I(t)$  and  $V(t)$ , respectively. Using Nyquist criterion, it can be shown that the conditions for local

asymptotic stability of  $E^*(T^*, I^*, V^*)$  are given by

$$\begin{cases} \operatorname{Im}H(iw) > 0, \\ \operatorname{Re}H(iw) > 0, \end{cases} \quad (4.3)$$

where  $H(\xi) = w\xi^3 + p_1\xi^2 + p_2\xi + p_3 + e^{-(\xi\tau)}(q_1\xi^2 + q_2\xi + q_3)$  and  $W_0$  is the smallest positive root of (4.3). Now substituting  $\lambda = iw (w > 0)$  into (4.3) and separating the real and imaginary parts we obtain the following

$$p_3 - P_1(w_0)^2 = (q_1w_0 - q_3w_0) \cos(w_0\tau) - q_2w_0 \sin(w_0\tau),$$

$$w_0p_2 + q_1w_0 - (w_0)^3 > -(q_1w_0 - q_3) \sin(w_0\tau) + q_2w_0 \cos(w_0\tau), \quad (4.4)$$

if satisfied simultaneously, are sufficient conditions to guarantee stability. We shall utilize them to get an estimate on the length of delay. Our aim is to find an upper bound  $w_+$  on  $w_0$ , independent of  $\tau$  and then to estimate  $\tau$  so that (4.3) holds for all values of  $w$ ,  $w \leq w \leq w_+$  and hence in particular at  $w = W_0$ . We rewrite (4.4) as

$$p_1w^2 = p_3 + (q_1w - q_3) \cos(w\tau) - q_2w \sin(w\tau). \quad (4.5)$$

Maximizing  $p_3 + (q_1w - q_3)\cos(w\tau) - q_2w \sin(w\tau)$  subject to  $|\sin(w_0\tau)| \leq 1$ ,  $|\cos(w_0\tau)| \leq 1$  we obtain

$$p_1w^2 \leq p_3 + |q_1w^2 - q_3| + q_2w. \quad (4.6)$$

Hence, if

$$w_+ = \sqrt{\frac{p_3 + |q_1w^2 - q_3| + q_2w}{p_1}}, \quad (4.7)$$

then clearly from (4.7) we have  $w_0 \leq w_+$ . From(4.4) we obtain

$$(w_0)^2 < p_2 + q_1 + q_1 \sin(w_0\tau) - \frac{q_3}{w_0} \sin(w_0\tau) - q_2 \cos(w_0\tau). \quad (4.8)$$

As  $E^*$  is locally asymptotically stable for  $\tau = 0$ , therefore sufficiently small  $\tau > 0$ , (4.8) will continue to hold. Substituting 4.5 in 4.8 and rearranging we get,

$$(q_1w^2 - q_3 - p_1q_2) \cos(w_0\tau) + \left(\frac{p_1q_3}{w_0} - q_2w_0 - p_1q_1(w_0)^2\right) \sin(w_0\tau) \leq p_1p_2 - q_3, \quad (4.9)$$



Using the bounds

$$(q_1 w_0^2 - q_3 - p_1 q_2) \cos(w_0 \tau) \leq (q_1 w_0^2 - q_3 - p_1 q_2) \tau^2,$$

$$\frac{p_1 q_3}{w_0} - q_2 w_0 - p_1 q_1 w_0^2 \leq \left( \frac{p_1 q_3}{w_0} - q_2 w_0 - p_1 q_1 w_0^2 \right) \tau,$$

we obtain from (4.9)

$$K_1 \tau^2 + K_2 \tau < K_3,$$

where

$$K_1 = q_1 w_0^2 - q_3 - p_1 q_2, \quad K_2 = \frac{p_1 q_3}{w_0} - q_2 w_0 - p_1 q_1 w_0^2, \quad K_3 = p_1 p_2 - q_3.$$

Hence, if  $\tau_+ = \frac{1}{2K_1}(-K_2 + \sqrt{(K_2)^2 + 4K_1 K_3})$ , then stability is preserved for  $0 \leq \tau \leq \tau_+$ .

## References

- [1] Rebecca Culshaw and Ruan Shigui, A delay-differential equation model of HIV infection of CD4+ T-cells, *Mathematical Biosciences*, **165**, (2000), 27-39.
- [2] D. Ho, A. Neumann, A. Perelson, W. Chen, J. Leonard and M. Markowitz, Rapid turnover of plasma virions and CD4+ lymphocytes in HIV-1 infection, *Nature*, **373**, (1995), 123-126.
- [3] A.S. Perelson, P. Essunger, Y.Z. Cao, M. Vesanen, A. Hurley, K. Saksela, M. Markowitz and D.D. Ho, Decay characteristics of HIV-1 infected compartments during combination therapy, *Nature*, **387**, (1997), 188-191.
- [4] A.S. Perelson and P. Nelson, Mathematical analysis of HIV-1 dynamics in vivo, *SIAM Review*, **41**(1), (1999), 3-44.
- [5] Lewin Sharon, Walters Tomos and Locarnini Stephen, Hepatitis B treatment: rational combination chemotherapy based on viral kinetic and animal model studies, *Antiviral Research*, **55**(3), (2002), 381-396.