HIV Infection in T-lymphocytes and Drug Induced CTL Response of a Time Delayed Model

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Abstract—**Drug therapy response of HIV-1 infected immune system is an important area of research by now. Today, a greater knowledge of drug induced CTL response allows us to better understand of cell mediated immune mechanism and humoral immune mechanism for viral infections. Moreover excessive stimulation of CTL in the immune system by different drugs leads to protective effects during natural infection with Human immunodeficiency virus of type-1. This paper concerns an application of drug therapy response to a mathematical model related to HIV-1 infection dynamics including a time delay in the removal of infected CD4$^+$T cells or analogously in the process of viral replication. The model is analysed analytically as well as numerically. Our results show that delay affects considerably the attainability of the reduction of viral load in the HIV-1 infected system.**

Keywords*—*Asymptotic Stability, CD4$^+$T cells, Cell Lysis, CTL, Immunodeficiency Virus of type-1, RTI, Time Delay, Time Series Solutions.

1 Introduction

Extensive research on the area of HIV-1 infection invading the human immune system started in early nineties of the last century [1]-[3]. Though considerable knowledge have been gathered till date regarding the implications of genetic variation of immune cells, HIV-1 pathogenesis and probable therapies treating the infected individuals, many of the issues still remain unsolved. Recent effort in this direction relates to the retroviral therapies used to treat HIV-1 patients making them to survive for a longer period against the odds of probable opportunistic diseases. Actually retroviral therapy when given to an individual patient make a portion of the immune cells to be toxic thereby introducing toxicity in the immune system of the individual. It is thus important to maintain an optimum controlled level of drug injection for an individual patient. This very issue of optimal drug therapy together with the dynamical evolution of CD4$^+$T lymphocytic immune cells needs proper understanding. In this communications we make an attempt to understand bearings of drug response on the dynamical behaviour of the lymphocytic immune cells populations specifically CD4$^+$T cells together with that of viral load.

It has been observed clinically that patients infected with immunodeficiency virus type-1 (HIV-1), if treated with a combination of inhibitor-drugs lamivudine and zidovudine shows a 10 to 100 fold reduction of viral load and nearly 25% increase in the healthy CD4$^+$T cells count. Sustenance of such drug receiving patients is observed to be more than one year [4], [5]. The longer sustenance is admitted to be consequences of the diminishing rate of infections of the uninfected T-cells. Obviously leads to the conjecture that the drug effectively drives the virus to state of near extinction.

In this paper we consider a mathematical model of HIV-1 infection to CD4$^+$T cells including the mentioned inhibitor drug. The system response to the drug-stimulation by generating Cytotoxic T-Lymphocyte(CTL) and this CTL's in-turn attack the actively infected CD4$^+$T cells and kill them. Note that there exists a finite time lag between a CD4$^+$T cells getting actively infected and its subsequent death. Such realistic time lag has been incorporated in the model under consideration. We analyze the dynamics of such a model to understand how the HIV-1-infected immune system responds to varied levels of drugs applied under the systematic therapy procedure.

Formulation of the mathematical model

Let $x(t)$ and $y(t)$ be the uninfected and infected (virus producing cells) portions of the hosts CD4$^+$T immune cells at a time t. Our focus here is to construct first a simple model for viral dynamics. For this purpose the following assumptions are made.
(A1): Infectible CD4$^+$T cells are produced at a constant rate λ and are removed on the system through the natural death rate d. A variable denoting free virus load in the system becomes relevant while considering short term viral dynamics. However when one is interested in

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drug induced changes at the steady state the variable corresponding to free virus can be omitted. At the steady state it is inherently assumed that the free virus populations is proportional to the virus-producing $CD4^+T$ cells which are already infected. Note that infected $CD4^+T$ cells produce free virus by their replication through the process of cell lysis.
(A2): The process of infection to the infectible $CD4^+T$ cells follows the law of mass action under mixing homogeneity. This means that the number of new infection at the steady state is proportional to $x(t)y(t)$.
(A3): A per capita death rate of infected $CD4^+T$ cells is considered and is denoted by a parameter a.
Based on the above assumption we can write down a simple model for virus dynamics as

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xy \\ \frac{dy}{dt} &= \beta xy - ay \end{aligned} \tag{1.1}$$

where β is the rate of contact between uninfected $CD4^+T$ cells with the virus producing T- cells. Although it can be seen in the literature that the rate at which uninfected $CD4^+T$ cells are converted into virus producing (infected) portion is smaller than β, we consider here the rate to be same as β. The argument in support of such enforcement goes as-at steady state the condition of mixing homogeneity is well set and the law of mass action holds perfectly. Whenever a HIV-1 infected patient is subjected to RTI (Reverse Transcriptase Inhibitors) drug, the virus replications within the virus producing T-cells faces a reduction. Such effect may be incorporated in the two variable simple virus dynamics model by reducing the numerical value of the parameter β (rate of infection). However, mere reduction of β in the basic viral dynamics model fails to explain the strong suppression of equilibrium virus load observed during long term drug therapy. Therefore it is imperative to include another variable in the basic viral dynamics model (1.1), in order to make the long term immune response of the model at per with those observed in reality. We include a variable z to represent the density of the Cytotoxic-T-Lymphocyte (CTL) responses against virus infected cells. The basic virus dynamics model with this inclusion becomes

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xy \\ \frac{dy}{dt} &= \beta xy - ay - pyz \\ \frac{dz}{dt} &= ky - bz \end{aligned} \tag{1.2}$$

Here p is the killing rate of the virus producing cells by CTL, k is the rate of stimulation (production) of CTL and b denotes the base line mortality rate of CTL. The basic viral dynamics model including CTL response assumes an instantaneous death of infected $CD4^+T$ cells. But in reality the infected T-cells are observed to have a latency period. During this latency period replication or reproduction of virus takes place within the infected cells. Thus, we consider a delay in the death term of infected (virus producing) T-cells. The average effect of such delay can be incorporate through a memory function or delay kernel, which under suitable conditions, yields model equations including a delay factor τ (≥ 0) as

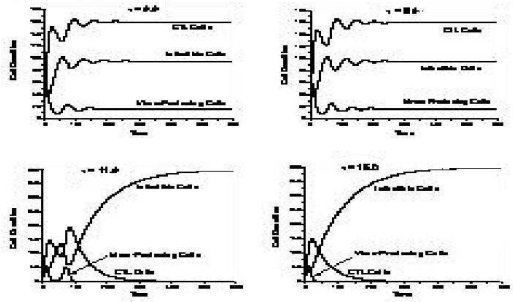

Figure 1: Time series solutions of model variables for different values of delay factor τ. $p = 0.001$ changes in the time series solutions with the increase of τ. Various model parameters are as in Table 1.

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \beta xy \\ \frac{dy}{dt} &= \beta xy - ay(t-\tau) - pyz \\ \frac{dz}{dt} &= ky - bz \end{aligned} \tag{1.3}$$

under the initial condition: $x(\theta) \geq 0$, $y(\theta) \geq 0$, $z(\theta) \geq 0$, $\theta \in (-\infty, 0]$

2 Local stability analysis

Right hand side of the equation (1.3) is a smooth function of x, y, z (variables) and the parameter, as long as the quantities are non-negative, so local existence and uniqueness properties holds in the positive octant. The modal equation (1.3) has the following equilibria on all the co-ordinate planes, $E_0(0,0,0)$, $E_1(\frac{\lambda}{d},0,0)$, and $E^*(x^*,y^*,z^*)$

where $x^* = \frac{(ab\beta - dkp) + \sqrt{(ab\beta - dkp)^2 + 4\beta^2 bpk\lambda}}{2b\beta^2}$

$y^* = \frac{\lambda - dx^*}{\beta x^*}, \qquad z^* = \frac{k(\lambda - dx^*)}{\beta b x^*}$

E^* exists provided $k < \frac{ab\beta}{pd}$, $x^* < \frac{\lambda}{d}$.
Here we are interested to investigate the local stability of the interior equilibrium E^* of the delay-induced system (1.3). Let $m(t) = x(t) - x^*$, $n(t) = y(t) - y^*$, $q(t) = z(t) - z^*$ are the perturbed variables. The linearized form of the system (1.3) at $E^*(x^*,y^*,z^*)$ is given by

$$\begin{aligned} \frac{dm}{dt} &= -dm - \beta m y^* - \beta n x^* \\ \frac{dn}{dt} &= \beta m y^* + \beta n x^* - an(t-\tau) - pnz^* - pqy^* \\ \frac{dq}{dt} &= kn - bq \end{aligned} \tag{2.1}$$

The characteristic equation of system (2.1) is given by

$$\rho^3 + (A + ae^{-\rho\tau})\rho^2 + (B + Ce^{-\rho\tau})\rho + D + Ee^{-\rho\tau} = 0 \tag{2.2}$$

where, $A = b + d + \beta y^* + pz^* - \beta x^*$, $B = bd + dpz^* + \beta by^* + \beta py^* z^* + bpz^* + pky^* - \beta dx^* - \beta bx^*$, $C = a(d + b + \beta y^*)$, $D = dbpz^* + dpky^* + \beta bpy^* z^* + \beta pky^{*2} - \beta dbx^*$, $E = abd + \beta aby^*$.

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Now to determine the nature of the stability, we require the sign of the real parts of the roots of the system (2.2).

$$\text{Let} \quad \Phi(\rho,\tau) = \rho^3 + (A + ae^{-\rho\tau})\rho^2 + (B + Ce^{-\rho\tau})\rho + D + Ee^{-\rho\tau} = 0 \tag{2.3}$$

For $\tau = 0$, i.e. for non-delayed system
$\Phi(\rho, 0) = \rho^3 + (A + a)\rho^2 + (B + C)\rho + D + E = 0$ From Routh-Hurwitz condition, the necessary and sufficient condition for locally asymptotic stability of the steady state is, $(A + a)(B + C) - (D + E) > 0$ and the non-delayed system is locally asymptotically stable around the positive interior equilibrium if
$y^* > x^*$, and $\theta > \max(\theta_1, \theta_2, \theta_3, \theta_4)$

$$\theta_1 = \tfrac{\beta x^*}{z^*},\ \theta_2 = \tfrac{\beta^2 x^* y^*}{dz^*},\ \theta_3 = \tfrac{\beta d^2 x^*}{abz^*},\ \theta_4 = \tfrac{\beta^2 b x^* y^*}{adz^*} \tag{2.4}$$

Substituting $\rho = u(\tau) + iv(\tau)$ in (2.2) and separating real and imaginary parts we obtain the following transcendental equations:

$$\begin{aligned} &u^3 - 3uv^2 + A(u^2 - v^2) + a(u^2 - v^2)e^{-u\tau}\cos v\tau \\ &+2auve^{-u\tau}\sin v\tau + Bu + Cue^{-u\tau}\cos v\tau \\ &+Cve^{-u\tau}\sin v\tau + D + Ee^{-u\tau}\cos v\tau = 0 \end{aligned} \tag{2.5}$$

$$\begin{aligned} &3u^2v - v^3 + 2Auv + 2auve^{-u\tau}\cos v\tau - \\ &a(u^2 - v^2)e^{-u\tau}\sin v\tau + Bv + Cve^{-u\tau}\cos v\tau \\ &-Cue^{-u\tau}\sin v\tau - Ee^{-u\tau}\sin v\tau = 0 \end{aligned} \tag{2.6}$$

3 Sufficient Conditions for Nonexistence of Delay Induced Instability

To find the conditions for nonexistence of delay induced instability, we now use the following theorem of Gopalsamy [6].

Theorem 3.1: A set of necessary and sufficient conditions for the equilibrium E^* to be asymptotically stable for all $\tau \geq 0$ is the following: (i) The real parts of all the roots of $\phi(\rho, 0) = 0$ are negative. (ii) For real v and $\tau \geq 0$, $\phi(iv, \tau) \neq 0$, where $i = \sqrt{-1}$.

Proof: Here $\phi(\rho, 0) = 0$ has roots whose real parts are negative provided (2.4) holds. Now for $v = 0$

$$\phi(0,\tau) = dbpz^* + dpky^* + \beta bpy^*z^* + \beta pk(y^*)^2 - \beta dbx^* - ab(d + \beta y^*) \neq 0 \tag{3.1}$$

and for $v \neq 0$

$$\phi(iv,\tau) = -iv^3 - Av^2 - av^2e^{-iv\tau} + iBv + iCve^{-iv\tau} + D + Ee^{-iv\tau} = 0 \tag{3.2}$$

Separating real and imaginary parts we get

$$Av^2 - D = Cv\sin v\tau + (E - av^2)\cos v\tau \tag{3.3}$$

$$-v^3 + Bv = (E - av^2)\sin v\tau - Cv\cos v\tau \tag{3.4}$$

Squaring and adding the above two equation, we get

$$(Av^2 - D)^2 + (-v^3 + Bv)^2 = a^2v^4 + (C^2 - 2aE)v^2 + E^2 \tag{3.5}$$

Let the right hand side of (3.5) be denoted by $f(v)$. Now for arbitrary real v , we get from (3.5)

$$f(v) \leq a^2v^4 + (C^2 - 2aE)v^2 + E^2 \tag{3.6}$$

Therefore a sufficient condition for the non existence of a real number v satisfying $\phi(iv, \tau) = 0$ can now be obtained from (3.5) and (3.6) as
$v^6 + (A^2 - 2B - a^2)v^4 + (B^2 - 2AD - C^2 + 2aE)v^2 + D^2 - E^2 \geq 0$
The inequality we can write in the form of

$$v^6 + Pv^4 + Qv^2 + R > 0 \tag{3.7}$$

$$P = A^2 - 2B - a^2,\ \ Q = B^2 + 2aE - 2AD - C^2,\ \ R = D^2 - E^2.$$

The sufficient condition can be obtained as if

$$p > \tfrac{2\beta x^*}{z^*},\quad a^{-1} > b^{-1} + d^{-1},\quad \text{and}\ \ pk > \tfrac{bdx^*}{y^{*2}} \tag{3.8}$$

Therefore condition (i) and (ii) of the above theorems are satisfied if (3.5) holds.

4 Estimation of the length of Delay to Preserve Stability

In this section we assume that in absence of delay, E^* is locally asymptotically stable. This is guaranteed if (2.4) holds. By continuity and for sufficiently small $\tau > 0$, all eigenvalues of (2.3) have negative real parts provided one can guarantee that no eigenvalue with positive real part bifurcates from infinity (which could happen since it is a retarded system). For stability analysis we use the Nyquist criterion [7]. To do this, we consider the system (2.1) and the space of real valued continuous functions defined on $[\tau, \infty)$ satisfying the initial conditions.
Let $\bar{m}(L)$, $\bar{n}(L)$, and $\bar{q}(L)$ be the Laplace transform of $m(t)$, $n(t)$, and $q(t)$ respectively. Taking the Laplace transformation of system (2.1), we have

$$\begin{aligned} &(L - A_1)\bar{m}(L) = A_2\bar{n}(L) + m(0) \\ &(L - B_2 - B_3e^{-L\tau})\bar{n}(L) = B_1\bar{m}(L) + B_4\bar{q}(L) + B_3e^{-L\tau}K_1(L) + n(0) \\ &(L - C_2)\bar{q}(L) = C_1\bar{n}(L) + q(0) \end{aligned} \tag{4.1}$$

where

$$K_1(L) = \int_{-\tau}^{0} e^{-L\delta}n(\delta)d\delta$$

$$K_2(L) = \int_{-\tau}^{0} e^{-L\delta}V(\delta)d\delta;\ \ t - \tau = \delta$$

$$\begin{aligned} &A_1 = -\delta_1 = -(d + \beta y^*) \quad A_2 = -\delta_2 = -\beta x^* \\ &B_1 = \delta_3 = \beta y^* \ \ B_2 = \delta_4 = \beta x^* - pz^* \\ &B_3 = -\delta_5 = -a \ \ B_4 = -\delta_6 = -py^* \\ &C_1 = k \qquad C_2 = -\delta_7 = -b \end{aligned} \tag{4.2}$$

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Rearranging we get

$$[L^3 + (\delta_1 + \delta_7 - \delta_4 + \delta_5 e^{-L\tau})L^2 + (\delta_2\delta_3 - \delta_1\delta_4 + \delta_1\delta_7 - \delta_4\delta_7 + k\delta_6 + \delta_1\delta_5 e^{-L\tau} + \delta_5\delta_7 e^{-L\tau})L + (\delta_2\delta_3\delta_7 - \delta_1\delta_4\delta_7 + k\delta_1\delta_6 + \delta_1\delta_5\delta_7 e^{-L\tau})]\bar{q}(L) = k\delta_3 m(0) + K(L+\delta_1)[n(0) - \delta_5 e^{-L\tau}K_1(L)] + [(L+\delta_1)(L - \delta_4 + \delta_5 e^{-L\tau}) + \delta_2\delta_3]q(0) \tag{4.3}$$

The inverse Laplace transform of $\bar{q}(L)$ will have terms which exponentially increase with time, if $\bar{q}(L)$ has poles with positive real parts. Since E^* needs to be locally asymptotically stable, it is necessary and sufficient that all poles of $\bar{q}(L)$ have negative real parts. We shall employ the Nyquist criterion which states that if L is the arc length of a curve encircling the right half- plane, the curve $\bar{q}(L)$ will encircle the origin a number of times equal to the difference between the number of poles and the number of zeroes of $\bar{q}(L)$ in the right half-plane. Let

$$F(L) = L^3 + [\chi_1 + \delta_5 e^{-L\tau}]L^2 + [\chi_2 + \delta_5\chi_3 e^{-L\tau}]L + \chi_4 + \delta_5\chi_5 e^{-L\tau} \tag{4.4}$$

$$\begin{aligned} \chi_1 &= \delta_1 + \delta_7 - \delta_4 \\ \chi_2 &= \delta_2\delta_3 - \delta_1\delta_4 + \delta_1\delta_7 - \delta_4\delta_7 + k\delta_6 \\ \chi_3 &= \delta_1 + \delta_7 \\ \chi_4 &= \delta_2\delta_3\delta_7 + k\delta_1\delta_6 - \delta_1\delta_4\delta_7 \\ \chi_5 &= \delta_1\delta_7 \end{aligned} \tag{4.4.1}$$

Then conditions for local asymptotic stability of E^*[7] is

$$Im\ F(im_0) > 0 \tag{4.5.1}$$

$$Re\ F(im_0) = 0 \tag{4.5.2}$$

where m_0 is the smallest positive root of equation (4.5.2)

$$F(im_0) = -im_0{}^3 - \chi_1 m_0{}^2 - \delta_5 m_0{}^2\cos m_0\tau + i\chi_2 m_0 + im_0{}^2\delta_5\sin m_0\tau + im_0\delta_5\chi_3\cos m_0\tau + \chi_4 + \delta_5\chi_5\cos m_0\tau + m_0\delta_5\chi_3\sin m_0\tau - i\delta_5\chi_5\sin m_0\tau > 0 \tag{4.6}$$

Now (4.5.1) and (4.5.2) becomes

$$-m_0{}^3 + \chi_2 m_0 > \delta_5(\chi_5 - m_0{}^2)\sin m_0\tau - m_0\delta_5\chi_3\cos m_0\tau \tag{4.7.1}$$

$$\chi_1 m_0{}^2 - \chi_4 = m_0\delta_5\chi_3\sin m_0\tau + \delta_5(\chi_5 - m_0{}^2)\cos m_0\tau \tag{4.7.2}$$

To get an estimation on the length of delay, we shall utilize the following conditions:

$$-m^3 + \chi_2 m > \delta_5(\chi_5 - m^2)\sin m\tau - m\delta_5\chi_3\cos m\tau \tag{4.8.1}$$

$$\chi_1 m^2 - \chi_4 = m\delta_5\chi_3\sin m\tau + \delta_5(\chi_5 - m^2)\cos m\tau \tag{4.8.2}$$

Therefore, E^* will be stable if the inequality (4.8.1) holds at $m = m_0$, where m_0 is the first positive root of equation (4.8.2). We shall now estimate an upper bound m_+ of m_0, independent of τ and then to estimate τ so that (4.8.1) holds for all values of m, $0 \le m \le m_+$, and hence in particular at $m = m_0$. The unique positive solution of $\chi_1 m^2 - \chi_4 = \delta(\chi_5 - m^2)$, denoted by m_+, is always greater than or equal to m_0. Since the right hand side of (4.8.2) is always less than or equal to $\sqrt{m^2\delta_5^2\chi_3^2 + \delta_5^2\chi_5^2 + \delta_5^2 m^4}$, the unique positive solution of $\chi_1 m^2 - \chi_4 = \delta_5\sqrt{m^2\chi_3^2 + \chi_5^2 + m^4}$ denoted by m_+ is always greater than or equal to m. By straight forward calculation, one can determined that

$$m_+ = \sqrt{\frac{(\delta_5{}^2\chi_3^2 + 2\chi_1\chi_4) + \sqrt{(\delta_5{}^2\chi_3^2 + 2\chi_1\chi_4)^2 - 4(\chi_1^2 - \delta_5^2)(\chi_4^2 - \delta_5^2\chi_5^2)}}{2(\chi_1^2 - \delta_5^2)}} \tag{4.9}$$

We see that m_+ is independent of τ. Now we need an estimation on τ so that (4.8.1) holds for all $0 \le m \le m_+$. Now rearranging (4.8.1) we get,

$$m^2 < \chi_2 + \delta_5\chi_3\cos m\tau - \delta_5(\tfrac{\chi_5}{m} - m)\sin m\tau \tag{4.10}$$

Note that at $\tau = 0$, (4.8.2) can be written as

$$m^2 = \tfrac{\chi_4 + \delta_5\chi_5}{\chi_1 + \delta_5} < \chi_2 + \delta_5\chi_3 \tag{4.11}$$

Hence (4.10) is valid for $\tau = 0$, $m = m_0$ By continuity it will hold for small $\tau > 0$ at $m = m_0$. Now substituting m^2 from (4.8.2) into (4.10) we get,

$$\delta_5\{m\chi_3 + (\tfrac{\chi_5}{m} - m)\chi_1\}\sin m\tau + \delta_5(\chi_5 - \chi_1\chi_3 - \chi_2)\cos m\tau + \delta_5{}^2\chi_3\sin^2 m\tau + \tfrac{\delta_5}{2}(\tfrac{\chi_5}{m} - m)\sin 2m\tau < \chi_1\chi_2 - \chi_4 + \delta_5{}^2\chi_3 \equiv \eta \tag{4.12}$$

We denote the l.h.s of (4.12) by $\nu(\tau, m)$, then we have $\nu(\tau, m) \le \delta_5\{m\chi_3 + (\tfrac{\chi_5}{m} - m)\chi_1\}m\tau + \delta_5(\chi_5 - \chi_1\chi_3 - \chi_2) + \delta_5{}^2\chi_3 m^2\tau^2 + \delta_5(\tfrac{\chi_5}{m} - m)m\tau \le \psi(\tau, m_+)$
Now if $\psi(\tau, m_+) < \eta$, then $\nu(\tau, m_0) < \eta$. Let τ_+ denote the unique positive root of $\psi(\tau, m_+) = \eta$ i.e. $\delta_5^2\chi_3 m^2\tau^2 + \delta_5(m^2\chi_3 + \chi_1\chi_5 - m^2\chi_1 + \chi_5 - m^2)\tau + \delta_5(\chi_5 - \chi_1\chi_3 - \chi_2) - \eta = 0$

$$\tau_+ = \tfrac{-\alpha + \sqrt{(\alpha^2 - 4\xi\theta)}}{2\xi} \tag{4.13}$$

where,

$$\xi = m^2\delta_5^2\chi_3, \quad \alpha = m^2\delta_5\chi_3 + \delta_5(\chi_5 - m^2)(\chi_1 + 1), \quad \theta = \delta_5(\chi_5 - \chi_1\chi_3 - \chi_2) - \eta \tag{4.14}$$

Then for $\tau < \tau_+$, the Nyquist criterion holds and τ_+ gives the estimate for the length of the delay τ for which stability is preserved.

5 Criterion for Preservation of Stability, Instability and Bifurcation Results:

Let us consider ρ and hence u and v as functions of τ. We are interested in the change of stability of E^* which will occur at the values of τ for which $u = 0$ and $v \neq 0$. Let $\hat{\tau}$ be such that for which $u(\hat{\tau}) = 0$ and $v(\hat{\tau}) = \hat{v} \neq 0$. Then (2.5) and (2.6) become

$$-A\hat{v}^2 - a\hat{v}^2\cos\hat{v}\hat{\tau} + C\hat{v}\sin\hat{b}\hat{\tau} + D + E\cos\hat{v}\hat{\tau} = 0 \tag{5.1}$$

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$$-\hat{v}^3 + a\hat{v}^2 \sin\hat{v}\hat{\tau} + B\hat{v} + C\hat{v}\cos\hat{v}\hat{\tau} - E\sin\hat{v}\hat{\tau} = 0 \tag{5.2}$$

Now eliminating $\hat{\tau}$ we get

$$\hat{v}^6 + (A^2 - 2B - a^2)\hat{v}^4 + (B^2 - C^2 - 2AD + 2aE)\hat{v}^2 + D^2 - E^2 = 0 \tag{5.3}$$

To analyze the change in the behavior of the stability of E^* with respect to τ, we examine the sign of $\frac{du}{d\tau}$ as u crosses zero. If this derivative is positive (negative) then clearly a stabilization (destabilization) can not take place at that value of $\hat{\tau}$. We differentiate (2.5) and (2.6) w.r.t. τ, then setting $\tau = \hat{\tau},\ u = 0$, and $v = \hat{v}$ we get

$$\begin{aligned} X\tfrac{du}{d\tau}(\hat{\tau}) + Y\tfrac{dv}{d\tau}(\hat{\tau}) &= g \\ -Y\tfrac{du}{d\tau}(\hat{\tau}) + X\tfrac{dv}{d\tau}(\hat{\tau}) &= h \end{aligned} \tag{5.4}$$

$$\begin{aligned} X &= -3\hat{v}^2 + B + C\cos\hat{v}\hat{\tau} + 2a\hat{v}\sin\hat{v}\hat{\tau} \\ &\quad - \hat{\tau}[(E - a\hat{v}^2)\cos\hat{v}\hat{\tau} + C\hat{v}\sin\hat{v}\hat{\tau}] \\ Y &= -2A\hat{v} + C\sin\hat{v}\hat{\tau} - 2a\hat{v}\cos\hat{v}\hat{\tau} \\ &\quad + \hat{\tau}[C\hat{v}\cos\hat{v}\hat{\tau} - (E - a\hat{v}^2)\sin\hat{v}\hat{\tau}] \\ g &= [(E - a\hat{v}^2)\sin\hat{v}\hat{\tau} - C\hat{v}\cos\hat{v}\hat{\tau}]\hat{v} \\ h &= [C\hat{v}\sin\hat{v}\hat{\tau} + (E - a\hat{v}^2)\cos\hat{v}\hat{\tau}]\hat{v} \end{aligned} \tag{5.5}$$

Solving (5.4), we get

$$\tfrac{du}{d\tau}(\hat{\tau}) = \tfrac{gX - hY}{X^2 + Y^2} \tag{5.6}$$

$\frac{du}{d\tau}(\hat{\tau})$ has the same sign as $gX - hY$. From (5.5) after simplification and solving (5.1) and (5.2), we get

$$gX - hY = \hat{v}^2[3\hat{v}^4 + 2(A^2 - 2B - a^2)\hat{v}^2 + (B^2 - C^2 + 2aE - 2AD)] \tag{5.7}$$

Let $F(z) = z^3 + P_1 z^2 + P_2 z + P_3$

$$P_1 = A^2 - 2B - a^2,\ P_2 = B^2 - C^2 + 2aE - 2AD,\ P_3 = D^2 - E^2 \tag{5.8}$$

which is the left hand side of (5.3) with $\hat{v}^2 = z$.

$$\text{Therefore, } F(\hat{v}^2) = 0 \tag{5.9}$$

$$\begin{aligned} &\text{Now, } \tfrac{dF}{dz}(\hat{v}^2) = 3\hat{v}^4 + 2P_1\hat{v}^2 + P_2 = \tfrac{gX - hY}{\hat{v}^2} \\ &\Rightarrow \tfrac{dF}{dz}(\hat{v}^2) = \tfrac{X^2 + Y^2}{\hat{v}^2} \cdot \tfrac{du}{d\tau}(\hat{\tau}) \\ &\Rightarrow \tfrac{du}{d\tau}(\hat{\tau}) = \tfrac{\hat{v}^2}{X^2 + Y^2} \cdot \tfrac{dF}{dz}(\hat{v}^2) \end{aligned} \tag{5.10}$$

Hence the criterion of instability (stability) of E^* are— (1) If the polynomial $F(z)$ has no positive root (being contradiction to the existence of $\hat{v} > 0$ be real) there can be no change of stability. (2) If $F(z)$ is increasing (decreasing) at all of its positive roots, instability (stability) is preserved. Now in this case, if (i) $P_3 < 0$, $F(z)$ has unique positive real root and then it must increase at that point [since $F(z)$ is a cubic in z, $Lt_{z\to\infty} F(z) = \infty$]. (ii) $P_3 > 0$, then (1) is satisfied, i.e. there can be no change of stability. (iii)If $P_2 < 0$, $P_3 > 0$ then minimum of $F(z)$ will exist at

$$z_m = \tfrac{-P_1 + \sqrt{P_1^2 - 3P_2}}{3} \tag{5.11}$$

$$\text{and if } F(Z_m) > 0 \tag{5.12}$$

$$\text{i.e, } 2{P_1}^3 - 9P_1P_2 + 27P_3 > 2({P_1}^2 - 3P_2)^{\frac{3}{2}} \tag{5.12.1}$$

since $27P_3 - 3P_1P_2 > 27P_3$

$$\text{Hence } 2P_1(P_1^2 - 3P_2) + 27P_3 - 3P_1P_2 > 27P_3 + 2{P_1}^3 \tag{5.13}$$

Thus for (5.12) to hold it is sufficient that

$$27P_3 + 2{P_1}^3 > 2({P_1}^2 - 3P_2)^{\frac{3}{2}}$$

$$P_2 > \tfrac{{P_1}^2 - (\frac{27P_3 + 2{P_1}^3}{2})^{\frac{2}{3}}}{3} \tag{5.14}$$

Therefore, we get the following theorem:

Theorem 5.1: *If $P_3 < 0$ and if E^* is unstable for $\tau = 0$, it will remain unstable for $\tau > 0$.*

Theorem 5.2: *If $P_3 < 0$ and if E^* is asymptotically stable for $\tau = 0$, it is impossible that it remains stable for $\tau > 0$. Hence there exists a $\hat{\tau} > 0$, such that for $\tau < \hat{\tau}$, E^* is asymptotically stable and for $\tau > \hat{\tau}$, E^* is unstable and as τ increases together with $\hat{\tau}$, E^* bifurcates into small amplitude periodic solutions of Hopf type [8]. The existence of unique $\hat{\tau}$ is given by*

$$\hat{\tau} = \tfrac{1}{\hat{v}} \arctan[\tfrac{(a\hat{v}^2 - E)(\hat{v}^3 - B\hat{v}) + C\hat{v}(A\hat{v}^2 - D)}{C\hat{v}(\hat{v}^3 - B\hat{v}) - (a\hat{v}^2 - E)(A\hat{v}^2 - D)}] + \tfrac{n\pi}{\hat{v}},\ n = 0, 1, 2, ... \tag{5.15}$$

Our required $\hat{\tau}$ is given by $n = 0$ in (5.15) and hence the Hopf bifurcation criteria is satisfied.

6 Numerical simulation

Table 1. Values of parameters used for models dynamics calculations.

Parameter	Definition	Default Value
λ	Constant rate of production of $CD4^+T$	10.0 $mm^{-3}day^{-1}$ [9],[10]
d	Death rate of Uninfected $CD4^+T$ cells	0.01 day^{-1} [9]
β	Rate of contact between x and y	0.002 $mm^{-3}day^{-1}$ [4]
a	Death rate of virus producing cells	0.24 day^{-1} [10]
p	Killing rate of Virus producing cells	0.001 $mm^{-3}day^{-1}$ [4]
k	Rate of simulation of CTL	0.2 day^{-1} [4]
b	Death rate of CTL	0.02 day^{-1} [4]

Numerical solutions of the model equation (1.3), we considered for the default value of model parameters as in Table 1. Initial values of model variables are set to $x(0) = 50$, $y(0) = 50$, and $z(0) = 2$. The variation of p is also restricted by the condition that $\frac{pk}{b} \sim 0.01 - 0.05$.

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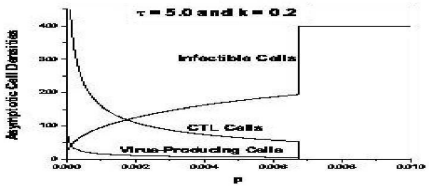

Figure 2: The phase diagram for model variables as a function of the parameter k with $\tau = 5.0$ and $p = 0.001$. Various model parameters are as in Table 1.

From Figure 1 we find that small values of delay factor enhances and elongate the initial oscillations in the time series solutions of model variables. But there exist a threshold delay beyond which oscillations in variables smeared away and with increasing τ such smearing becomes progressively fast. In Figure 2, we present the phase diagram of model variables as a function of the parameter p with $\tau = 5.0$ and $k = 0.2$. Here we find a threshold value of p beyond which asymptotic stable solutions for y and z die-down and the same for x rises to its global stable value.

7 Discussion and conclusion

We have considered a basic mathematical model to represent the virus dynamics of a HIV-1 infected individual including its response to RTI therapies. The RTI drugs actually impair the HIV-1 infected cells by inhibiting reverse transcription of viral RNA into DNA, thereby reducing the rate of infection of uninfected T-cells. Our focus is to explore the effect of delay on the sustainable reduction of virus load in the system.

In our analytical studies on the HIV-1 dynamics we focus on the qualitative aspects of the HIV-1 dynamics within the model. Our calculations reveal that the existence and uniqueness of the solutions of dynamical variables x, y, and z locally holds in the positive octant. Through the local stability analysis we obtain sufficient conditions for the nonexistence of delay induced instability. The conditions obtained point towards the existence of asymptotic stability of interior equilibrium. We have estimated the length of delay for which the stability of the system remains preserved. We find that delay assuming values within the estimated length, Nyquist criteria holds. When the delay is set to the value beyond the estimated length, stable equilibrium solutions are seen bifurcate into small amplitude periodic solutions of Hopf type.

Numerical calculations reveal that delay affects considerably the attainability of the reduction of viral load in the HIV-1 infected system. Note that in the present model the reduction of the infected proportion of T-cells actually means the reduction of viral load.

From discussion of the analytical and numerical solutions of the model it is clear that delay in the death rate of virus producing T-cells enhances oscillations in the model variables, but asymptotically solutions are always stable. Further for definite set of choice of parameters p, k, and τ the system moves to globally stable regime where sustainability of the reduction of the virus load is undoubtedly assured. Thus we can predict that if the application of RTI drugs are improvised at a optimum level in such a manner so as to match the parameters, killing rate of infected T-cells by CTL (p) at 0.001 mm^3 /virus stimulation rate of CTL (k at 0.2) and delay in the death rate of infected T-cells (τ) at around 11 days then the possibility of eradication of HIV-1 in an individual and thereby restoration of healthy immune system would also be possible.

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