Modeling the dynamics of HIV and $CD4^+$ T cells during primary infection

Prashant Kr. Srivastava *, Peeyush Chandra

Department of Mathematics and Statistics, Indian Institute of Technology Kanpur, Kanpur-208016, India

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ABSTRACT

A mathematical model for the dynamics of HIV primary infection is proposed and analysed for the stability of infected state. Further, as there is a time delay for infected $CD4^+$ T cells to become actively infected, a model is proposed to consider this time delay. The local stability of the delay model is discussed and results are shown numerically. It is found that the delay has no effect on the dynamics of HIV in the proposed model.

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1. Introduction

HIV is a retrovirus that targets the $CD4^+$ T lymphocytes, which are the most abundant white blood cells of the immune system. Although HIV infects other cells also, it wreaks the most havoc on the $CD4^+$ T cells by causing their decline and destruction, thus decreasing the resistance of the immune system. A number of mathematical models have been proposed to understand HIV dynamics, disease progression, anti-retroviral response etc. [1–4].

In 1989, Perelson [3] developed a simple model for the primary infection with HIV. Perelson et al. [4] extended the model and discussed some of the model's behaviour. They defined the model by considering four categories: uninfected $CD4^+$ T cells, latently infected $CD4^+$ T cells, productively infected $CD4^+$ T cells and virus population. Rong et al. [5] further modified the model by incorporating anti-retroviral effects to study the evolution of drug resistance. They considered three classes of $CD4^+$ T cells: uninfected cells, infected cells in eclipse phase and productively infected cells. The model depends on the observation that for a virus, when it enters a resting $CD4^+$ T cell, viral RNA may not be completely reverse transcribed into DNA [6]. If the cell is activated shortly following infection, the reverse transcription can proceed to completion. However, the un-integrated virus harbored in the resting cell may decay with time and partial DNA transcripts are labile and degrade quickly [7]. Hence a proportion of resting infected cells revert to the uninfected cells [8].

In this paper, we simplify the model for primary infection proposed by Rong et al. [5] by considering only three categories: uninfected $CD4^+$ T cells, infected $CD4^+$ T cells and virus population. The existence and local stability of the infected steady state are studied. We also discuss the global stability of infected steady state. We then incorporate a delay into the model to describe the time delay between the infection of $CD4^+$ T cell and the emission of virus particles on a cellular level as proposed by Herz et al. [9]. Numerical simulations are carried out to illustrate the results.

2. The primary infection model

In the model we considered the three populations; uninfected $CD4^+$ T cell $T(t)$, infected $CD4^+$ T cell $T^*(t)$, and the virus population $V(t)$. Following Rong et al. [5] and Essunger & Perelson [8], we assume here that a fraction of infected $CD4^+$ T

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* Corresponding author. Fax: +91 512 259 7500.
 E-mail addresses: pksri@iitk.ac.in (P.Kr. Srivastava), peeyush@iitk.ac.in (P. Chandra).

cells return to the uninfected class. In view of this, the following model is proposed.

$$\frac{dT}{dt} = s - kVT - dT + bT^*, \tag{1}$$

$$\frac{dT^*}{dt} = kVT - (b + \delta)T^*, \tag{2}$$

$$\frac{dV}{dt} = N\delta T^* - cV, \tag{3}$$

with $T(0) = T_0$, $T^*(0) = 0$ and $V(0) = V_0$.

Here, s is inflow rate of $CD4^+$ T cells and d its natural death rate. The parameter k represents rate of infection of T cells, δ represents death rate of infected T cells and includes the possibility of death by bursting of infected T cells, hence $\delta \geq d$. b is the rate at which infected cells return to uninfected class. c is death rate of virus and N is the average number of viral particles produced by an infected cell.

The above system has the following two steady states:

(1) $E_1 = \left(\frac{s}{d}, 0, 0\right)$ and

(2) $E_2 = (\overline{T}, \overline{T^*}, \overline{V})$ which exists whenever $R_0 = \frac{N\delta ks}{cd(b + \delta)} > 1$,

where $\overline{T} = \frac{(b+\delta)c}{N\delta k}$, $\overline{T^*} = \frac{1}{\delta}\left(s - \frac{cd(\delta+b)}{N\delta k}\right)$, and $\overline{V} = \frac{N\delta\overline{T^*}}{c}$.

Adding the first two equations of the system we get,

$$\dot{T} + \dot{T^*} = s - dT - \delta T^* \leq s - d(T + T^*) \quad (\text{since } d \leq \delta).$$

So both the uninfected and infected T cell populations are always bounded. Also from the third equation of the system it is easy to see that V is bounded. So we have a bounded set

$$\Gamma = \{(T(t), T^*(t), V(t)) \in \mathbb{R}_+^3 : 0 \leq T + T^* \leq s/d, V \leq K\},$$

for some $K \geq 0$, which is positively invariant with respect to system (1)–(3).

3. Local stability

Theorem 1. *The non-infected steady state E_1 is globally asymptotically stable in Γ if $R_0 \leq 1$ and is unstable if $R_0 > 1$.*

Proof. Define a Lyapunov function of the system (1)–(3)as

$$L = \frac{N\delta}{b + \delta}T^* + V. \tag{4}$$

Its derivative along a solution of system (1)–(3),

$$\dot{L} = \left(\frac{N\delta kT}{c(b + \delta)} - 1\right)cV. \tag{5}$$

It is clear from (4) that for $R_0 \leq 1$, $\dot{L} \leq 0$ as $T \leq \frac{s}{d}$. Furthermore, if M is the set of solutions of the system where $\dot{L} = 0$, then the Lyapunov–Lasalle Theorem [10] implies that all paths in Γ approach the largest positively invariant subset of the set M. Here, M is the set where $V = 0$. On the boundary of Γ where $V = 0$, we have $T^* = 0$, $\dot{T} = s - dT$. So $T \rightarrow \frac{s}{d}$ as $t \rightarrow \infty$. Hence all solution paths in Γ approach the non-infected steady state E_1 when $R_0 \leq 1$.

It can be easily seen from the Jacobian matrix of the system at E_1 that one root of characteristic equation is positive if $R_0 > 1$. Thus the non-infected steady state will be unstable whenever $R_0 > 1$. □

Theorem 2. *The infected steady state E_2 is locally asymptotically stable, whenever it exists. i.e. when $R_0 > 1$.*

Proof. The Jacobian matrix of the system at non-infected steady state E_2 is

$$J = \begin{pmatrix} -k\overline{V} - d & b & -k\overline{T} \\ k\overline{V} & -(b + \delta) & k\overline{T} \\ 0 & N\delta & -c \end{pmatrix}.$$

The characteristic equation of the system then becomes

$$\lambda^3 + A\lambda^2 + B\lambda + C = 0, \tag{6}$$

where

$$A = c + d + \delta + k\overline{V} + b,$$
$$B = (d + k\overline{V})(c + \delta) + bd,$$
$$C = c\delta k\overline{V}.$$

Clearly $A > 0, B > 0, C > 0$ and $AB - C > 0$ whenever $R_0 > 1$. Hence all inequalities of the Routh–Hurwitz criterion are satisfied. Therefore the infected steady state E_2 is locally asymptotically stable whenever it exists.   □

4. Global stability

Lemma 3. *E_1 is the only omega limit point of the system on the boundary of Γ when $R_0 > 1$. Further, it cannot be the omega limit point of any orbit which starts in the interior. In this case the system is uniformly persistent.*

Proof. For the function L, defined by Eq. (4), we note from Eq. (5) that its derivative along a solution of the system $\dot{L} > 0$ when $R_0 > 1$, for T sufficiently close to $\frac{s}{d}$ except for $V = 0$. Hence when $R_0 > 1$, the trajectories starting near the non-infected steady state E_1 must leave a neighborhood of E_1 except those on invariant T axis. Hence T cannot be the omega limit point of any orbit starting in the interior of Γ.

Since the maximal invariant set on the boundary $\partial\Gamma$ is T axis which is isolated, the hypothesis (H) of [11] holds for the system. Thus when $R_0 > 1$, E_1 becomes unstable and hence system is uniformly persistent [12] in the interior of Γ.   □

Now we discuss the global stability of E_2 for model (1)–(3) using the approach developed by Li and Muldowney [13], which we briefly summarize here.

Let the map $x \mapsto f(x)$ from an open subset $D \subset \mathbb{R}^n$ to $\mathbb{R}^n$ be such that the solution $x(t)$ to the differential equation

$$x' = f(x) \tag{7}$$

is uniquely determined by its initial value $x(0) = x_0$. We denote this solution by $x(t, x_0)$. Further, we assume that

(H_1) D is simply connected;
(H_2) $\bar{x}$ is the only equilibrium point of (7) in D, and
(H_3) there is a compact absorbing set $E \subset D$.

A set E is called absorbing in D for system (7) if $x(t, E_1) \subset E$ for each compact set $E_1 \subset E$ for sufficiently large t.
For a square matrix B, the *Lozinskiĭ measure* [14] with respect to induced matrix norm $\|.\|$ is defined as

$$\mu(B) = \lim_{h \to 0} \frac{\|I + hB\| - 1}{h}.$$

For $x \in D$, consider a map $x \mapsto Q(x)$ where $Q(x)$ is an $\binom{n}{2} \times \binom{n}{2}$ matrix valued C^1 function and $Q^{-1}(x)$ exists; define $B = Q_f Q^{-1} + QJ^{[2]}Q^{-1}$. The matrix Q_f is obtained by replacing each entry q_{ij} of Q by its derivative in the direction of f, and $J^{[2]}$ is second additive compound matrix [15] of the Jacobian matrix J of system (7). For *Lozinskiĭ measure* μ on $\mathbb{R}^{\binom{n}{2} \times \binom{n}{2}}$, define a quantity $\bar{q}_2$ as

$$\bar{q}_2 = \limsup_{t \to \infty} \sup_{x_0 \in E} \frac{1}{t} \int_0^t \mu(B(x(s, x_0)))\mathrm{d}s. \tag{8}$$

The following result is established in Li and Muldowney [13].

Theorem 4. *For the system (7), assume that assumptions (H_1), (H_2), and (H_3) hold. Then the unique equilibrium $\bar{x}$ is globally asymptotically stable in D if there exist a function $Q(x)$ and a Lozinskiĭ measure μ such that $\bar{q}_2 < 0$.*

Now in the same light of above discussion, we shall proceed as follows:
The Jacobian matrix J of the system (1)–(3) is given as,

$$J = \begin{pmatrix} -kV - d & b & -kT \\ kV & -(b + \delta) & kT \\ 0 & N\delta & -c \end{pmatrix}$$

and the corresponding associated second compound matrix $J^{[2]}$ is given as,

$$J = \begin{pmatrix} -kV - d - b - \delta & kT & kT \\ N\delta & -kV - d - c & b \\ 0 & kV & -c - b - \delta \end{pmatrix}.$$

Set the function

$$Q = Q(T, T^*, V) \equiv \operatorname{diag}\left(1, \frac{T^*}{V}, \frac{T^*}{V}\right),$$

then

$$Q_f Q^{-1} = \operatorname{diag}\left(0, \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V}, \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V}\right)$$

and

$$B = Q_f Q^{-1} + Q J^{[2]} Q^{-1}.$$

Now

$$Q J^{[2]} Q^{-1} = \begin{bmatrix} -d - kV - \delta - b & kT\dfrac{V}{T^*} & kT\dfrac{V}{T^*} \\[2mm] N\delta\dfrac{T^*}{V} & \dfrac{\dot{T}^*}{T^*} - \dfrac{\dot{V}}{V} - d - c - kV & b \\[2mm] 0 & kV & \dfrac{\dot{T}^*}{T^*} - \dfrac{\dot{V}}{V} - b - c - \delta \end{bmatrix}$$

$$\equiv \begin{bmatrix} B_{11} & B_{12} \\ B_{21} & B_{22} \end{bmatrix}.$$

where $B_{11} = [-d - kV - \delta - b]$, $B_{12} = \left(kT\dfrac{V}{T^*} \quad kT\dfrac{V}{T^*}\right)$, $B_{21} = \begin{bmatrix} N\delta\dfrac{T^*}{V} \\ 0 \end{bmatrix}$ and $B_{22} = \begin{bmatrix} \dfrac{\dot{T}^*}{T^*} - \dfrac{\dot{V}}{V} - d - c - kV & b \\[2mm] kV & \dfrac{\dot{T}^*}{T^*} - \dfrac{\dot{V}}{V} - b - c - \delta \end{bmatrix}.$

Now we define *Lozinskiĭ measure* as follows

$$\mu(B) \leq \max\{g_1, g_2\} \tag{9}$$

where $g_1 = \mu(B_{11}) + \|B_{12}\|$ and $g_2 = \|B_{21}\| + \mu(B_{22})$ (here, $\|B_{12}\|$ and $\|B_{21}\|$ are with respect to vector norm).

We have

$$\mu(B_{11}) = -d - kV - \delta - b,$$

$$\mu(B_{22}) = \max\left\{\frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - d - c - kV + kV, \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - b - c - \delta + b\right\}$$

$$= \frac{\dot{T}^*}{T^*} - \frac{\dot{V}}{V} - c - d. \quad \text{since } d \leq \delta.$$

Now $\dfrac{\dot{T}^*}{T^*} = \dfrac{kTV}{T^*} - (b + \delta)$ and $\dfrac{N\delta T^*}{V} = \dfrac{\dot{V}}{V} + c$.

Hence,

$$g_1 = \frac{\dot{T}^*}{T^*} - d - kV,$$

$$g_2 = \frac{\dot{T}^*}{T^*} - d.$$

Therefore we shall finally get

$$\mu(B) \leq \frac{\dot{T}^*}{T^*} - d \tag{10}$$

for sufficiently large t. Now, let $(T(t), T^*(t), V(t))$ be any solution starting in the compact absorbing set $E \subset \Gamma$ and let $\bar{t}$ be sufficiently large such that $(T(t), T^*(t), V(t)) \in E$ for all $t \geq \bar{t}$ and that system is persistent. Then along each solution $(T(t), T^*(t), V(t))$ such that $(T(0), T^*(0), V(0)) \in E$ we have for $t > \bar{t}$

$$\frac{1}{t}\int_0^t \mu(B)\mathrm{d}s \leq \frac{1}{t}\int_0^{\bar{t}} \mu(B)\mathrm{d}s + \frac{1}{t}\ln\left(\frac{T^*(t)}{T^*(\bar{t})}\right) - \left(\frac{t - \bar{t}}{t}\right)\eta. \tag{11}$$

The boundedness of $T^*(t)$ and definition of $\bar{q}_2$ finally gives $\bar{q}_2 < 0$.

5. The delay model

Here the delay in activation is considered. i.e. the time lag is considered from infection of cells to the cells becoming actively infected [9]. Hence, we have the following model,

$$\frac{\mathrm{d}T(t)}{\mathrm{d}t} = s - kV(t)T(t) - dT(t) + bT^*(t), \tag{12}$$

$$\frac{\mathrm{d}T^*(t)}{\mathrm{d}t} = kV(t-\tau)T(t-\tau) - (b+\delta)T^*(t), \tag{13}$$

$$\frac{\mathrm{d}V(t)}{\mathrm{d}t} = N\delta T^*(t) - cV(t), \tag{14}$$

with initial conditions $T(0) = T(\theta)$, $V(0) = V(\theta)$, and $T^*(0) = 0$; where $\theta \in [-\tau, 0]$.

Again we find an uninfected steady state $E_1 = (\frac{s}{d}, 0, 0)$ and infected steady state $E_2 = (\overline{T}, \overline{T^*}, \overline{V})$ where $\overline{T}$, $\overline{T^*}$, and $\overline{V}$ are the same as those in Section 2. It is easy to see through characteristic equation that the steady state E_1, which was unstable for primary infection model for $R_0 > 1$, remains unstable in this case also for all τ provided $R_0 > 1$.

Now we shall study the stability of infected steady state E_2. The linearized system is given by

$$\frac{\mathrm{d}Y(t)}{\mathrm{d}t} = J_1 Y(t) + J_2 Y(t-\tau), \tag{15}$$

where $J_1 = \begin{pmatrix} -d - k\overline{V} & b & -k\overline{T} \\ 0 & -(b+\delta) & 0 \\ 0 & N\delta & -c \end{pmatrix}$, $J_2 = \begin{pmatrix} 0 & 0 & 0 \\ k\overline{V} & 0 & k\overline{T} \\ 0 & 0 & 0 \end{pmatrix}$ and $Y(.) = (T(.),\ T^*(.),\ V(.))^{\mathrm{T}}$. The characteristic equation of the linearized system (15) is given by

$$\lambda^3 + A_2\lambda^2 + A_1\lambda + A_0 + (B_1\lambda + B_0)\mathrm{e}^{-\lambda\tau} = 0, \tag{16}$$

where

$$A_2 = c + d + \delta + k\overline{V} + b,$$
$$A_1 = (d + k\overline{V})(c + b + \delta) + c(b + \delta),$$
$$A_0 = (d + k\overline{V})(cb + c\delta),$$
$$B_1 = -k(N\delta\overline{T} + b\overline{V}),$$
$$B_0 = -k(dN\delta\overline{T} + bc\overline{V}).$$

Clearly when $\tau = 0$ all the roots of Eq. (16) have negative real part and for $\tau \neq 0$, it has infinitely many roots. By Rouché's Theorem [16] and continuity in τ, Eq. (16) has roots with positive real part if and only if it has purely imaginary root i.e. it will have all the roots with negative real part if it does not have any purely imaginary root. Now to see if Eq. (16) has purely imaginary roots or not, we put $\lambda = \mathrm{i}\omega$ in Eq. (16) and separate the real and imaginary parts, which gives

$$\omega^3 - A_1\omega = B_1\omega\cos\omega\tau + B_0\sin\omega\tau, \tag{17}$$

$$-A_2\omega^2 + A_0 = B_1\omega\sin\omega\tau - B_0\cos\omega\tau. \tag{18}$$

Squaring and adding Eqs. (17) and (18) we get

$$(\omega^3 - A_1\omega)^2 + (-A_2\omega^2 + A_0)^2 = B_1^2\omega^2 + B_0^2. \tag{19}$$

Putting $\omega^2 = m$ in (19) we get following cubic equation:

$$m^3 + \alpha m^2 + \beta m + \gamma = 0, \tag{20}$$

where $\alpha = A_2^2 - 2A_1$, $\beta = A_1^2 - B_1^2 - 2A_2A_0$ and $\gamma = A_0^2 - B_0^2$. It may be noted that Eq. (20) will have all the roots with negative real part iff the Routh–Hurwitz criterion is satisfied and hence (16) will have no purely imaginary root.

It is easy to show that $\alpha > 0$, $\gamma > 0$, hence the Routh–Hurwitz criterion is satisfied if

$$\alpha\beta - \gamma > 0. \tag{21}$$

Hence Eq. (20) will have all the roots with negative real parts provided condition (21) is satisfied and thus Eq. (19) will not have any real root. Now this shows that for any value of τ the characteristic equation will always have roots in negative half-plane only. Hence we have following theorem:

Theorem 5. *The infected steady state E_2 is locally asymptotically stable for the delay system* (12)–(14) *for all $\tau > 0$, provided $R_0 > 1$ and condition* (21) *is satisfied.*
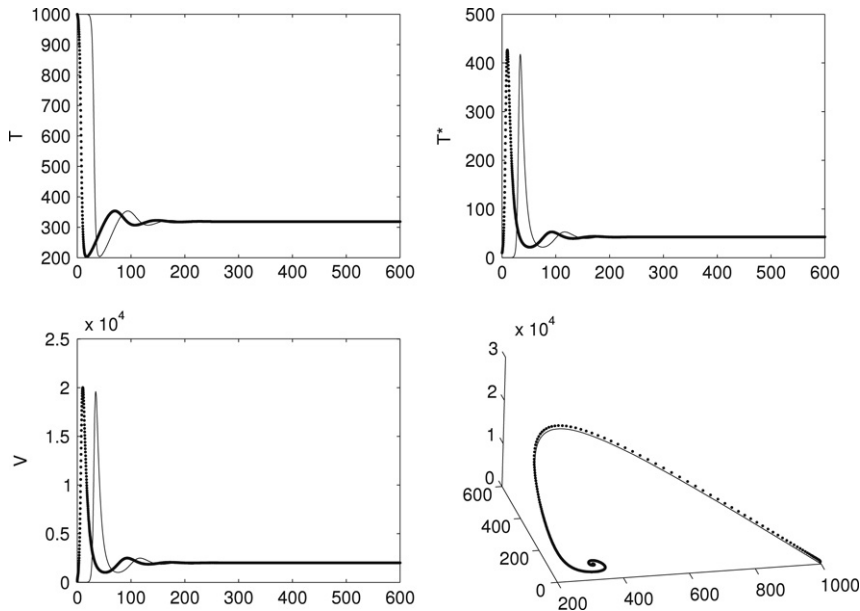
Fig. 1. Global stability of ODE model, for initial values I_1 (in solid line) and I_2 (in dashdot).
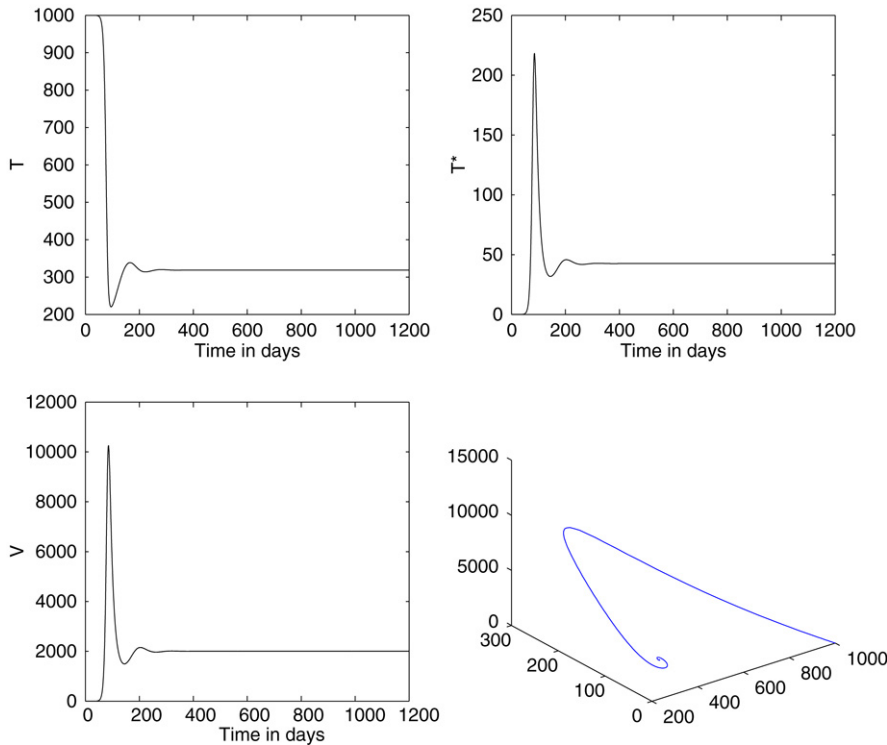

Fig. 2. Stability of delay model for $\tau = 3$.

6. Numerical simulation

We solved the primary infection model numerically using Matlab. We used the following data set: $s = 10$ mm^{-3} day^{-1}, $b = 0.2$ day^{-1}, $k = 0.000024$ mm^3 day^{-1}, $d = 0.01$ day^{-1}, $\delta = 0.16$ day^{-1}, $c = 3.4$ day^{-1}, and $N = 1000$. For this set of data $R_0 = 3.137$ and we find that the system goes to infected steady state $(318.75, 42.57, 2003.9)$. The results are plotted in Fig. 1 in solid line for the initial value $I_1 = (1000, 0, 0.001)$ and in dashdot for the initial value $I_2 = (1000, 10, 10)$. The delay model is also solved with initial value I_1 and for $\tau = 3$ and we found that system goes to infected steady state same as above. The results are plotted in Fig. 2.

7. Conclusion

It is observed that the proposed primary infection model has two steady states: uninfected and infected. It is found that the infection is cleared out when $R_0 \leq 1$ i.e. the uninfected steady state is globally stable, whereas the infection persists and the steady state is globally stable when $R_0 > 1$. It is clear from the definition of R_0 that R_0 decreases as the reverting rate, b of infected cells increases, hence R_0 can be low for a high parametric value of b. We investigated the effect of delay in infection i.e. the time taken by cells from the infected state to become actively infected. It was found in Theorem 5 that the system remains stable for all values of τ. This shows that there is no effect of delay on the activation of infection in $CD4^+$ T cells.

Acknowledgement

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