Asian Journal of Pharmaceutical Research and Health Care, *Vol 12(4), 198-212, 2020*
ISSN (Online) : 2250-1460
DOI: 10.18311/ajprhc/2020/25775

A Study on an HIV Pathogenesis Model with Different Growth rates of Uninfected and Infected *CD4⁺T* cells

Bhagya Jyoti Nath[1*], Kaushik Dehingia[2] and Hemanta Kumar Sarmah[2]

[1]Department of Mathematics, Barnagar College, Sorbhog – 781317, Barpeta, Assam, India; bhagyajyotinath13@gmail.com
[2]Department of Mathematics, Gauhati University, Guwahati – 781014, Assam, India; kaushikdehingia17@gmail.com, nsarmah@hotmail.com

Abstract

The objective of this paper is to discuss the dynamics of an HIV pathogenesis model with full logistic target cell growth of uninfected T cells and cure rate of infected T cells. Local and global dynamics of both infection-free and infected equilibrium points are rigorously established. It is found that if basic reproduction number $R_0 \leq 1$, the infection is cleared from T cells and if $R_0>1$, the HIV infection persists. Also, we have carried out numerical simulations to verify the results. The existence of non-trivial periodic solution is also studied by means of numerical simulation. Therefore, we find a parameter region where infected equilibrium point is globally stable to make the model biologically significant. From the overall study, it is found that proliferation of T cells cannot be ignored during the study of HIV dynamics for better results and we can focus on a treatment policy which can control the parameters of the model in such a way that the basic reproduction number remains less than or equal to one.

Keywords: HIV, Local and Global Stability, Periodic Solution, Treatment
2010 AMS classification: 34A34, 34D23, 37C25

1. Introduction

Acquired Immunodeficiency Syndrome (AIDS) which is caused by Human Immunodeficiency Virus (HIV) is one of the major threats for human community. Since the first patient was identified in 1981, HIV has claimed more than 32 million lives up to November 2019 and the epidemic continues to spread[1]. According to the literatures of biology, HIV mainly targets a host's $CD4^+T$ cells which results the gradual depletion of $CD4^+T$ cells pool[2]. Due to this, host's immune system becomes weak and leads to AIDS, which is the most advanced stage of HIV infection.

Mathematical model have played an important role in the study of epidemic. Different within-host HIV pathogenesis models have developed by the researchers to qualitatively investigate the dynamics of $CD4^+T$ cells and viruses[3–12]. It is believed that $CD4^+T$ cells are produced at a constant rate from precursors in bone marrow and thymus. With this assumption, there are many mathematical models in the literature describing the interaction between three populations: Uninfected $CD4^+T$ cells, infected $CD4^+T$ and virus[10,12]. However, the fact is that the T-cells start dividing when stimulated by antigen or mitogen. The understanding of T cells' proliferation is still under investigation. As the multiplication rate of T cells is density-dependent so T cell increases with decrease of multiplication rate[14,15]. Based on these, a simplified logistic term $rT\left(1-\frac{T}{T_{max}}\right)$ is used in

**Author for correspondence*

different literatures[7,8,16,17]. Since in presence of HIV, there are two types of T-cells: Uninfected and infected T cells, therefore total T cell concentration is given by $T+T^*$. Perelson *et al.*,[7] mentioned that it is reasonable to use full logistic term $rT\left(1-\frac{T+T^*}{T_{max}}\right)$, but ignored this arguing that proportion of infected cell is very small. Later, this full logistic term $rT\left(1-\frac{T+T^*}{T_{max}}\right)$ is used by many researchers in their study[5,18–20]. In all of these literatures, they have only considered the proliferation of uninfected $CD4^+T$ cells. Also, in these logistic terms, T represents the concentration of uninfected $CD4^+T$ cells, T^* represents the concentration of infected $CD4^+T$ cells, the multiplying rate and the maximum carrying capacity of T cells are r and T_{max} respectively.

Rong *et al.*,[6] modified basic HIV model by including eclipse phase, a class of infected cells which are not yet producing virus and also considered that cells in this phase revert to uninfected class at constant rate. Srivastava and Chandra[10] mentioned that when a virus enters a resting $CD4^+T$ cell, viral RNA may not be completely reverse transcribed into DNA[21]. Reverse transcription can be completed if the cell is activated shortly after infection. But, with time the un-integrated virus which harbour in the resting cell may decay and partial DNA copies are labile and damage quickly[22]. As a result, an amount of resting infected cells reverts to the uninfected class[4]. With this basis, Srivastava and Chandra[10] first considered a simplified model similar to basic model, to account for the observation that a fraction of infected cells revert back to uninfected class as the reverse transcription may not be completed in the eclipse phase for all infected cells[11].

In the view of significance of proliferation of T-cells and cure rate of infected T-cells, in this paper, a mathematical model for HIV infection which incorporates full-logistic growth term of uninfected T cells and recovery rate of infected T cells is studied. In the next section, we discuss some preliminaries which are required for stability analysis of the equilibrium points. In Sections 3 and 4, we discuss the model and positive invariance, boundedness, equilibrium points of the model. Sections 5 and 6 include local and global behaviour analysis of both the stationary points. In Section 7, we have carried out numerical simulations to verify our results. Finally in Section 8, we have given conclusion of the whole study.

2. Preliminaries

In this section, we will discuss some preliminaries which are used in the later part of this paper.

Result 1

[23]Consider the characteristic equation:

$$|\lambda I - A| = \lambda^n + b_1\lambda^{n-1} + \ldots + b_{n-1}\lambda + b_n = 0$$

determining the n eigen values λ of the real $n \times n$ matrix A. Then all the eigen values λ have negative parts if

$$\Delta_1 > 0, \Delta_2 > 0, \Delta_3 > 0, \ldots, \Delta_n > 0$$

where

$$\Delta_k = \begin{vmatrix} b_1 & 1 & 0 & 0 & 0 & 0 & \cdots & 0 \\ b_3 & b_2 & b_1 & 1 & 0 & 0 & \cdots & 0 \\ b_5 & b_4 & b_3 & b_2 & b_1 & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ b_{2k-1} & b_{2k-2} & b_{2k-3} & b_{2k-4} & b_{2k-5} & b_{2k-6} & \cdots & b_k \end{vmatrix}$$

The above result is well known as Routh-Hurwitz theorem which is used to check the local behaviours at each stationary points of our model.

The Global behaviour of the diseased stationary point in terms of parameter r is discussed using the Li and Muldowney criterion[24]. This global stability criterion is discussed below:

Let, $\mathcal{O}$ be an open set in $\mathbb{R}^n$, $f: x \in \mathcal{O} \mapsto f(x) \in \mathbb{R}^n$ be a C^1 function. Consider, $x(t)$ be a solution to the differential equation

$$x' = f(x) \tag{1}$$

which is uniquely determined by its initial value $x(0) = x_0$. Here $x(t, x_0)$ is the solution of (1).

For the system (1), a set H is called an absorbing in $\mathcal{O}$ if for sufficiently large $t, x(t, H_1) \subset H$, for each compact set $H_1 \subset \mathcal{O}$.

Then Li and Muldowney[24] considered the following assumptions:

(i) There is a unique equilibrium point $\bar{x}$ of the system in $\mathcal{O}$.
(ii) There exists a compact absorbing set $H \subset \mathcal{O}$.

For any $n \times n$ matrix M, second additive compound matrix is a $\binom{n}{2} \times \binom{n}{2}$ matrix which is denoted by $M^{[2]}$. For

a 3 × 3 matrix $M = (m_{ij})$, its second additive compound matrix is given by:

$$M^{[2]} = \begin{bmatrix} m_{11}+m_{22} & m_{23} & -m_{13} \\ m_{32} & m_{11}+m_{33} & m_{12} \\ -m_{31} & m_{21} & m_{22}+m_{33} \end{bmatrix}$$

For a complete discussion of compound matrix and its application in differential equations, see[26,27].

For a square matrix M, the Lozinskiĭ measure[25] with respect to the induced norm $|.|$ is defined as:

$$\mu(M) = \lim_{h\to 0} \frac{|I+hM|-1}{h}$$

For $x \in \mathcal{O}$, consider $Q: x \mapsto Q(x)$ be a $\binom{n}{2}\times\binom{n}{2}$ matrix-valued function that is C^1 and $Q^{-1}(x)$ exists, also consider μ be the Lozinskiĭ measure on $\mathbb{R}^{l\times l}$, where $l = \binom{n}{2}$. Define a quantity $\overline{q_2}$ as

$$\overline{q_2} = \lim_{t\to\infty} sup sup_{x_0\in E} \frac{1}{t}\int_0^t \mu\left(M\left(x(s,x_0)\right)\right)ds$$

where

$$M = Q_f Q^{-1} + QJ^{[2]}Q^{-1}$$

Here, the matrix Q_f is directional derivative in the direction of f. Again, $J^{[2]}$ represents the second additive compound matrix of J which is the Jacobian matrix of the system (1). The following result is established by Li and Muldowney[24].

Result 2

[24]Let $\mathcal{O}$ be simply connected domain and the above conditions (*i*) and (*ii*) satisfy for the system (1). If a function $Q(x)$ and a Lozinskiĭ measure μ exists for which $\overline{q_2} < 0$, then the unique equilibrium point $\bar{x}$ will be globally asymptotically stable in $\mathcal{O}$.

3. The model

In model (2) we consider three compartments: Uninfected *CD4⁺T* cell *T(t),* infected *CD4⁺T* cell *T*(t)* and the virus population *V(t)*. With these three populations, Wang and Li[5] discussed an HIV infection model with full logistic growth of healthy T cells. They studied local and global behaviors of existing stationary points. Similarly, Srivastava and Chandra[10] discussed a primary infection model with cure rate which means a fraction of infected cells revert back to uninfected class. Motivated by these works, we consider a model with both of the full logistic growth term and cure rate, which is given by the following system of ordinary differential equations:

$$\begin{aligned} \frac{dT}{dt} &= s + rT\left(1-\frac{T+T^*}{T_{max}}\right) - kVT - \alpha T + bT^*, \\ \frac{dT^*}{dt} &= kVT - (\beta+b)T^*, \\ \frac{dV}{dt} &= N\beta T^* - \gamma V. \end{aligned} \tag{2}$$

In this model, parameter s represents the inflow rate of healthy *CD4⁺T* cells and α is the natural turnover rate of uninfected *CD4⁺T* cells. $k > 0$ is the infection rate of uninfected *CD4⁺T* cells and thus the mass-action term kVT describes the incidence of infection of uninfected *CD4⁺T* cells. In model (2), we considered that healthy *CD4⁺T* cells can also be created by proliferation and this proliferation is described by the term $rT\left(1-\frac{T+T^*}{T_{max}}\right)$. Proliferation of infected *CD4⁺T* is not considered in this study. In the second equation, β is the natural turnover rate of infected *CD4⁺T* cells and b denotes the returning rate of infected *CD4⁺T* cells to the uninfected class. We consider $\alpha \le \beta$ because of virus burden on the infected cells. N represents the average number of virus particles produced by an infected cell during its life time and γ is the natural turnover rate of virus particles.

4 Positively Invariance, Boundedness and Equilibrium Points of the Model

The dynamics of healthy *CD4⁺T* cells, for the infection-free state are administrated by the equation,

$$\frac{dT}{dt} = s + rT\left(1-\frac{T}{T_{max}}\right) - \alpha T$$

From this, it can be shown that the T cell concentrations stabilizes at a level T_0 which is given by,

$$T_0 = \frac{T_{max}}{2r}\left[(r-\alpha)+\sqrt{(r-\alpha)^2+\frac{4sr}{T_{max}}}\right] \quad (3)$$

We consider the exact solutions $T(t)$, $T^*(t)$ and $V(t)$ of the model (2) have initial values $T(0) \geq 0$, $T^*(0) \geq 0$ and $V(0) \geq 0$. For a biologically feasible model, we need to show that exact solutions are positive for $t > 0$.

If not, we assume that there is a contradiction: we have a first t_1 such that

$$T(t_1)=0, T'(t_1)<0, T^*(0)\geq 0, V(0)\geq 0, 0<t<t_1$$

there exists a first t_2 such that

$$T^*(t_2)=0, T^{*'}(t_2)<0, T(0)\geq 0, V(0)\geq 0, 0<t<t_2$$

and there exists a first t_3 such that

$$V(t_3)=0, V'(t_3)<0, T(0)\geq 0, T^*(0)\geq 0, 0<t<t_3$$

Applying the first case in the first equation of model (2), we get

$$T'(t_1)=s+bT^*(t_1)>0$$

which is a contradiction to the first case. Thus, $T(t) \geq 0$ for all $t > 0$. Now applying the second case in the second equation of model (2), we get

$$T^{*'}(t_2)=kV(t_2)T(t_2)\geq 0$$

which is again a contradiction to second case. Thus, $T^*(t) \geq 0$ for all $t > 0$. In the same way, it can be shown that $V(t) \geq 0$ for all $t > 0$.

Thus, for these initial values the exact solutions $T(t)$, $T^*(t)$ and $V(t)$ lie in the non-negative octant for $t > 0$.

Therefore it is clear that, the non-negative octant $\mathbb{R}^3_+ = \{(T,T^*,V): T(t)\geq 0, T^*(t)\geq 0, V(t)\geq 0\}$ is positively invariant with respect to the model (2). Also, we can find a bounded region which will be also positively invariant with respect to the model (2). We add the first two equations of our model (2) to get

$$T'+T^{*'}=s+rT\left(1-\frac{T+T^*}{T_{max}}\right)-\alpha T-\beta T^* \quad (4)$$

Since, $T(t) \leq T_0$ if $T(0) \leq T_0$ and $\alpha \leq \beta$, equation (4) implies

$$T'+T^{*'}\leq s+rT_0-\alpha(T+T^*)$$

Therefore, $T+T^* \leq \frac{s+rT_0}{\alpha}+Ce^{-\alpha t} \to \frac{s+rT_0}{\alpha}$ as $t\to\infty$

. Here C is a constant. Thus, $T + T^*$ is bounded which indicates boundedness of T^* (say bounded by M). As T^* bounded so from the third equation of system (2) we have V is also bounded (say by K). Hence we have a set

$$\phi=\{(T,T^*,V)\in\mathbb{R}^3_+ : T\leq T_0, T^*\leq M, V\leq K\}$$

which is positively invariant w.r.t. the model (2).

Using next generation matrix method[28,29], we have calculated the basic reproduction number (R_0) of our model (2) which is $R_0=\frac{kN\beta T_0}{\gamma(b+\beta)}$. Basic reproduction number indicates the number of newly infected $CD4^+T$ cells that arise from any one infected cell when almost all cells are uninfected[11].

4.1 Proposition 1

If $R_0 \leq 1$ there exists only one equilibrium point which is infection-free equilibrium point $E_0 = (T_0, 0, 0)$ in ϕ and if $R_0 > 1$, there exits two equilibrium point in ϕ: infection-free equilibrium point E_0 and a unique infected equilibrium point $E^* = (\overline{T}, \overline{T^*}, \overline{V}) \in \text{int}(\phi)$, the interior of ϕ, where

$$\overline{T}=\frac{(\beta+b)\gamma}{N\beta k},\ \overline{T^*}=\frac{\gamma}{N\beta}\overline{V},\ \overline{V}=\frac{sp^2+(r-\alpha)\left(1+\frac{b}{\beta}\right)p\gamma-\frac{r\left(1+\frac{b}{\beta}\right)^2\gamma^2}{T_{max}}}{k\gamma\left\{p+\frac{r\gamma\left(1+\frac{b}{\beta}\right)}{\beta T_{max}}\right\}}$$

where $p = kN$.

The model discussed in[5] has the following infected equilibrium point for $R_{0_1}=\frac{kNT_0}{\gamma}>1$:

$$\overline{T}=\frac{\gamma}{Nk},\ \overline{T^*}=\frac{\gamma}{N\beta}\overline{V},\ \overline{V}=\frac{sp^2+(r-\alpha)p\gamma-\frac{r\gamma^2}{T_{max}}}{k\gamma\left(p+\frac{r\gamma}{\beta T_{max}}\right)}$$

Similarly, without considering full logistic growth term, the model discussed in[10] has the following infected equilibrium point for $R_{0_2}=\frac{N\beta ks}{\gamma\alpha(b+\beta)}>1$

$$\overline{T}=\frac{(\beta+b)}{N\beta k},\ \overline{T^*}=\frac{1}{\beta}\left(s-\frac{\gamma\alpha(\beta+b)}{N\beta k}\right),\ \overline{V}=\frac{N\beta}{\gamma}\overline{T^*}$$

Thus, comparing the infected equilibrium points of model (2) and the model in[10], it is observed that full logistic growth terms does not affect the healthy cell count $(\overline{T})$ while affects infected cell $(\overline{T})$ count and the viral load $(\overline{V})$. Similarly, comparing the model (2) with model in[5], it is observed that healthy and infected *CD4⁺T* cells count along with viral load are affected by the transfer of a proportion of infected T cells to uninfected class.

5 Stability of the Infection-free Equilibrium Point

From the proposition 1, it is clear that if $R_0 \le 1$, there exits only infection free equilibrium point E_0. In this section, we discuss the stability of the infection free equilibrium point E_0 in terms of basic reproduction number R_0.

The Jacobian matrix $J(E_0)$ of the model (2) at infection-free equilibrium point E_0 is given by:

$$J(E_0)=\begin{bmatrix} -\alpha+r\left(1-\frac{T_0}{T_{max}}\right)-\frac{rT_0}{T_{max}} & -\frac{rT_0}{T_{max}}+b & -kT_0 \\ 0 & -\beta-b & kT_0 \\ 0 & N\beta & -\gamma \end{bmatrix}$$

The characteristic equation of $J(E_0)$ is given by:

$$(\lambda-a_1)(\lambda^2+a_2\lambda+a_3)=0$$

where

$$a_1=-\alpha+r\left(1-\frac{T_0}{T_{max}}\right)-\frac{rT_0}{T_{max}}, a_2=\beta+\gamma+b \text{ and } a_3=(\beta+b)\gamma-N\beta kT_0$$

Therefore, one eigen value of the Jacobian matrix $J(E_0)$ is:

$$-\alpha+r\left(1-\frac{T_0}{T_{max}}\right)-\frac{rT_0}{T_{max}}=-\frac{s}{T_0}-\frac{rT_0}{T_{max}}<0$$

It is clear that, $a_2 > 0$. Therefore, using Routh-Hurwitz criterion the point E_0 is locally asymptotically stable if $a_3 > 0$.

$$a_3=(\beta+b)\gamma-N\beta kT_0=(\beta+b)\gamma\left\{1-\frac{N\beta kT_0}{(\beta+b)\gamma}\right\}=(\beta+b)\gamma(1-R_0) \quad (5)$$

From equation (5), if $R_0 < 1$ then the stationary point E_0 shows locally asymptotically stable behaviour. For $R_0 = 1$, we have local stability at E_0 as one eigen value is zero and E_0 is unstable for $R_0 > 1$.

Now, we will check the global stability of the infection-free equilibrium point E_0 using Lyapunov's second method.

Define the Lyapunov function for the model (2):

$$L=\frac{N\beta}{(\beta+b)}T^*+V \quad (6)$$

Calculating derivative of L:

$$\frac{dL}{dt}=\frac{N\beta}{(\beta+b)}\frac{dT^*}{dt}+\frac{dV}{dt} \quad (7)$$

With the help of second and third equations of the model, we get:

$$\frac{dL}{dt}=V\gamma\left\{\frac{N\beta kT}{(\beta+b)\gamma}-1\right\}\le V\gamma\left\{\frac{N\beta kT_0}{(\beta+b)\gamma}-1\right\}=V\gamma(R_0-1) \quad (8)$$

From Equation (8), we have $\frac{dL}{dt}\le 0$ if $R_0 \le 1$. Also $\frac{dL}{dt}=0$ only in two cases: case 1: $R_0 = 1$ and $T = T_0$, case 2: $V = 0$. Let the set of solutions where $\frac{dL}{dt}=0$ is denoted by S then Lyapunov-Lasalle theorem[13] suggests that all trajectories of the model (2) in the region ϕ go towards the positively invariant subset of S. On the boundary of ϕ, where virus is not present we have:

$$T^*=0, \frac{dT}{dt}=s+rT\left(1-\frac{T}{T_{max}}\right)-dT$$

Therefore, $T \to T_0$ when $t \to \infty$. Thus, all solutions in ϕ move towards E_0 when $R_0 \le 1$.

When $R_0 > 1$, it is observed from the Jacobian matrix $J(E_0)$ that one eigen value is positive. Therefore, infection-free equilibrium point E_0 is unstable when $R_0 > 1$.

Therefore, we can conclude that if $R_0 \le 1$ the equilibrium point which is infection-free is also globally asymptotically stable otherwise it is going to be unstable.

6 Stability of the Infected Equilibrium Point

Proposition 1 states that if $R_0 > 1$, there exits two equilibrium points infection-free and infected equilibrium point. Here, we discuss the stability behaviour of infected equilibrium point E^*.

The Jacobian matrix $J(E^*)$ at E^* is given by:

$$J(E^*)=\begin{bmatrix} -\bar{a} & -\frac{r\bar{T}}{T_{max}}+b & -k\bar{T} \\ k\bar{V} & -\beta-b & k\bar{T} \\ 0 & N\beta & -\gamma \end{bmatrix}$$

where $\bar{a}=r-\left(1-\frac{\bar{T}+\bar{T}^*}{T_{max}}\right)+\frac{r\bar{T}}{T_{max}}+\kappa\bar{v}=\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}+\frac{b\bar{T}^*}{\bar{T}}>0.$

Now for the Jacobian matrix $J(E^*)$ the characteristic polynomial is as follows:

$$P(\lambda)=\lambda^3+A\lambda^2+B\lambda+C$$

where $A=\bar{a}+\beta+b+\gamma$

$$B=\bar{a}(\beta+b+\gamma)+(\beta+b)\gamma-N\beta k\bar{T}-k\bar{V}\left(-\frac{r\bar{T}}{T_{max}}+b\right)$$

$$=\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(\beta+b+\gamma)+\frac{b\gamma\bar{T}^*}{\bar{T}}+\frac{k\bar{V}\bar{T}r}{T_{max}}$$

$$C=\bar{a}(\beta+b)\gamma-\bar{a}N\beta k\bar{T}-\left(-\frac{r\bar{T}}{T_{max}}+b\right)k\bar{V}\gamma+k^2\bar{T}\bar{V}N\beta$$

$$=\left(\beta+\frac{r\bar{T}}{T_{max}}\right)k\bar{V}\gamma$$

It is clear that $A > 0$, $B > 0$ and $C > 0$. Therefore by Routh-Hurwitz criterion the infected equilibrium point E^* whenever exits is locally asymptotically stable if the inequality $AB - C > 0$ is satisfied.

$$AB-C=(\bar{a}+b+\beta+\gamma)\left\{\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta+\gamma)+\frac{b\gamma\bar{T}^*}{\bar{T}}+\frac{k\bar{V}\bar{T}r}{T_{max}}\right\}-\left(\beta+\frac{r\bar{T}}{T_{max}}\right)k\bar{V}\gamma$$

$$=(\bar{a}+b+\gamma)\left\{\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta+\gamma)+\frac{b\gamma\bar{T}^*}{\bar{T}}+\frac{k\bar{V}\bar{T}r}{T_{max}}\right\}$$
$$+\beta\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta)+\beta\gamma\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)+\frac{\beta b\gamma\bar{T}^*}{\bar{T}}+\frac{\beta k\bar{V}\bar{T}r}{T_{max}}$$
$$-\beta k\bar{V}\gamma-\frac{r\bar{T}k\bar{V}\gamma}{T_{max}}$$

$$=(\bar{a}+b)\left\{\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta+\gamma)+\frac{b\gamma\bar{T}^*}{\bar{T}}+\frac{k\bar{V}\bar{T}r}{T_{max}}\right\}$$
$$+\gamma\left\{\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta+\gamma)+\frac{b\gamma\bar{T}^*}{\bar{T}}\right\}$$
$$+\beta\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta)+\frac{\beta b\gamma\bar{T}^*}{\bar{T}}$$
$$+\frac{\beta k\bar{V}\bar{T}r}{T_{max}}+\beta\gamma\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}-k\bar{V}\right) \quad (9)$$

Using first equation of the model (2):

$$\frac{s}{\bar{T}}-k\bar{V}=\alpha-r+r\left(\frac{\bar{T}+\bar{T}^*}{T_{max}}\right)-\frac{b\bar{T}^*}{\bar{T}} \quad (10)$$

Using (10) in (9), we get:

$$AB-C=(\bar{a}+b)\left\{\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta+\gamma)+\frac{b\gamma\bar{T}^*}{\bar{T}}+\frac{k\bar{V}\bar{T}r}{T_{max}}\right\}$$
$$+\gamma\left\{\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta+\gamma)+\frac{b\gamma\bar{T}^*}{\bar{T}}\right\}+\beta\left(\frac{s}{\bar{T}}+\frac{r\bar{T}}{T_{max}}\right)(b+\beta)$$
$$+\frac{\beta k\bar{V}\bar{T}r}{T_{max}}+\beta\gamma\left\{\alpha-r+r\left(\frac{2\bar{T}+\bar{T}^*}{T_{max}}\right)\right\}$$

Thus, $AB-C>0$ if $\alpha-r+r\left(\frac{2\bar{T}+\bar{T}^*}{T_{max}}\right)\geq 0.$

Therefore, the infected equilibrium point $E^*=(\bar{T},\bar{T}^*,\bar{V})$ is locally asymptotically stable for the model (2) if $R_0 > 1$ and

$$\alpha-r+r\left(\frac{2\bar{T}+\bar{T}^*}{T_{max}}\right)\geq 0.$$

From the local stability analysis of infected equilibrium point E^*, we can observe that the recovery or cure rate of infected T cells to uninfected T-cells b does not affect the

global stability of E^* but global stability of E^* is dependent on proliferation rate r. Therefore we will check the global stability of the infected equilibrium point in terms of parameter r and we will find a range of r where infected equilibrium point is globally asymptotically stable.

We know that if the T-cell population reaches $T_{\max}$ it should decrease. Therefore we have a constraint $s < \alpha T_{\max}^{3}$. Also, due to viral burden on infected T-cells we have $\alpha \le \beta$. Therefore, $s < \beta T_{\max}$, We have considered $p \in (0, 1)$ such that:

$$s < p\beta T_{\max} \tag{11}$$

Now, we add the first two equations of model (2) to get:

$$\left(T+T^*\right)' = s + rT\left(1-\frac{T+T^*}{T_{max}}\right) - \alpha T - \beta T^* \ge s - \beta\left(T+T^*\right).$$

Solving the differential inequality we get:

$$T\left(t\right)+T^*\left(t\right) \ge \frac{s}{\beta} + C_1 e^{-\beta t}$$

Here, C_1 is arbitrary constant. Using initial value conditions, we have

$$T\left(t\right)+T^*\left(t\right) \ge \frac{s}{\beta} + \left[T\left(0\right)+T^*\left(0\right)-\frac{s}{\beta}\right]e^{-\beta t} \ge \frac{ps}{\beta},$$

for any $p \in (0, 1)$ and sufficiently large t. Therefore we have the following result which will be used in finding global stability criteria for infected equilibrium point:

Result 3

Let $p \in (0, 1)$ be as in (11) and then there exists $\bar{t} > 0$

such that all solutions in the compact absorbing set H to (2) satisfy:

$$T\left(t\right)+T^*\left(t\right) \ge \frac{ps}{\beta}, t \ge \bar{t} \tag{12}$$

From the definition of ϕ it is clear that interior of ϕ is simply connected and also from proposition 1, if $R_0 > 1$ we have the unique equilibrium point E^* in int(ϕ). Also global stability behaviour at E_0 implies that there exists an absorbing compact set $H \subset \phi$ for model (2). Therefore, assumptions (*i*) and (*ii*) of the result 2 are satisfied for model (2).

For a general solution ($T(t)$, $T^*(t)$, $V(t)$) the associated Jacobian matrix J of the model (2) is:

$$J = \begin{bmatrix} -a & -\frac{rT}{T_{max}} + b & -kT \\ kV & -\beta - b & kT \\ 0 & N\beta & -\gamma \end{bmatrix}$$

where $a = \alpha - r\left(1-\frac{T+T^*}{T_{max}}\right) + \frac{rT}{T_{max}} + kV$.

The matrix $J^{[2]}$ related to the Jacobian matrix J is below:

$$J^{[2]} = \begin{bmatrix} -\left(a+\beta+b\right) & kT & kT \\ N\beta & -\left(a+\gamma\right) & -\frac{rT}{T_{max}} + b \\ 0 & kV & -\left(\beta+b+\gamma\right) \end{bmatrix}$$

Consider, the function:

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

Let, f denote the vector field on the model, then:

$$Q_f Q^{-1} = diag\left\{0, \frac{T^{*'}}{T^*} - \frac{V'}{V}, \frac{T^{*'}}{T^*} - \frac{V'}{V}\right\}.$$

Now, $M = Q_f Q^{-1} + QJ^{[2]}Q^{-1}$

$$= \begin{bmatrix} -\left(a+\beta+b\right) & kT\frac{V}{T^*} & kT\frac{V}{T^*} \\ N\beta\frac{T^*}{V} & \frac{T^{*'}}{T^*} - \frac{V'}{V} - a - \gamma & -\frac{rT}{T_{max}} + b \\ 0 & kV & \frac{T^{*'}}{T^*} - \frac{V'}{V} - \beta - b - \gamma \end{bmatrix}$$

$$= \begin{bmatrix} M_{11} & M_{12} \\ M_{21} & M_{22} \end{bmatrix}$$

where

$$M_{11} = \left[-a-\beta-b\right], M_{12} = \left[kT\frac{V}{T^*} \quad kT\frac{V}{T^*}\right], M_{21} = \left[N\beta\frac{T^*}{V} \quad 0\right]^T$$

and

$$M_{22}=\begin{bmatrix}\frac{T^{*'}}{T^*}-\frac{V'}{V}-a-\gamma & -\frac{rT}{T_{max}}+b\\ kV & \frac{T^{*'}}{T^*}-\frac{V'}{V}-\beta-b-\gamma\end{bmatrix}$$

Let, (u, v, w) be a vector in $\mathbb{R}^3$, consider a norm in $\mathbb{R}^3$ as $|u, v, w| = \max\{|u|, |v| + |w|\}$ and let μ be the corresponding Lozinskiĭ measure. Then we have,

$$\mu(M)\le \max\{g_1, g_2\} \tag{13}$$

where $g_1 = \mu_1(M_{11}) + |M_{12}|$ and $g_2 = |M_{21}| + \mu_1(M_{22})$. Here, Lozinskiĭ measure w.r.t. $l_1$norm is μ_1 and matrix norms w.r.t. the l_1 vector norm are $|M_{12}|, |M_{21}|$.

Thus,

$$\mu_1(M_{11})=-a-\beta-b, |M_{12}|=kT\frac{V}{T^*}, |M_{21}|=N\beta\frac{T^*}{V}$$

and $\mu_1(M_{22})$ can be calculated as follows,

$$\mu_1(M_{22})=max\begin{Bmatrix}\frac{T^{*'}}{T^*}-\frac{V'}{V}-a-\gamma+kV, \frac{T^{*'}}{T^*}-\frac{V'}{V}\\ -\beta-b-\gamma+\left|-\frac{rT}{T_{max}}+b\right|\end{Bmatrix}$$

$$\le\frac{T^{*'}}{T^*}-\frac{V'}{V}-\gamma+max\left\{-a+kV, -\beta-b+\frac{rT}{T_{max}}+b\right\}$$

$$=\frac{T^{*'}}{T^*}-\frac{V'}{V}-\gamma+max\left\{-Z, -\beta+\frac{rT}{T_{max}}\right\}$$

where

$$Z=a-kV=\alpha-r\left(1-\frac{T+T^*}{T_{max}}\right)+\frac{rT}{T_{max}}$$

$$\ge\alpha-r\left(1-\frac{ps}{\beta T_{max}}\right), t\ge\bar{t} \tag{14}$$

From the model (2), we get:

$$\frac{T^{*'}}{T^*}=\frac{kVT}{T^*}-\beta-b \text{ and } \frac{V'}{V}=\frac{N\beta T^*}{V}-\gamma$$

Substituting these values in the expressions of g_1 and g_2, we get:

$$g_1=-a-\beta-b+kT\frac{V}{T^*}=\frac{T^{*'}}{T^*}-a<\frac{T^{*'}}{T^*}-Z \tag{15}$$

$$g_2\le N\beta\frac{T^*}{V}+\frac{T^{*'}}{T^*}-\frac{V'}{V}-\gamma+max\left\{-Z, -\beta+\frac{rT}{T_{max}}\right\}$$

$$<\frac{T^{*'}}{T^*}-min\left\{Z, \beta-\frac{rT_0}{T_{max}}\right\} \tag{16}$$

Therefore, from (13), (15), (16), for sufficiently large t, we have:

$$\mu(M)\le\frac{T^{*'}}{T^*}-\eta$$

where $\eta=min\left\{\alpha-r\left(1-\frac{ps}{\beta T_{max}}\right), \beta-\frac{rT_0}{T_{max}}\right\}>0$.

Let, $\bar{t}$ be sufficiently large such that $(T(t), T^*(t), V(t))\in H$ for all $t\ge\bar{t}$ and $(T(t), T^*(t), V(t))$ is a solution which originate in the absorbing compact set $H\subset\phi$ and satisfies (12). Then along each solution $(T(t), T^*(t), V(t))$ for which $(T(0), T^*(0), V(0))\in H$ and $t\ge\bar{t}$, we have:

$$\frac{1}{t}\int_0^t\mu(M)ds\le\frac{1}{t}\int_0^{\bar{t}}\mu(M)ds+\frac{1}{t}ln\frac{T^*(t)}{T^*(\bar{t})}-\frac{t-\bar{t}}{t}\eta. \tag{17}$$

Consequently,

$$\overline{q_2}=\lim_{t\to\infty}sup sup_{x_0\in E}\frac{1}{t}\int_0^t\mu\left(M(x(s,x_0))\right)ds\le-\frac{\eta}{2}<0.$$

Thus, by Li and Muldowny[24] infected equilibrium point if exits is globally asymptotically stable if $r<min\left\{\frac{\alpha\beta T_{max}}{\beta T_{max}-ps}, \frac{\beta T_{max}}{T_0}\right\}$. Also in absence of HIV infection, T cell concentration stabilizes at T_0. Therefore, α cannot be greater than r. Hence, a range of parameter r where the infected equilibrium point E^* is globally asymptotically stable is:

$$\alpha\le r<min\left\{\frac{\alpha\beta T_{max}}{\beta T_{max}-ps}, \frac{\beta T_{max}}{T_0}\right\}$$

Thus, the infected equilibrium point E^* whenever exits is asymptotically stable in interior of ϕ if r satisfies:

$$r\left(1-\frac{ps}{\beta T_{max}}\right)<\alpha \text{ and } \frac{rT_0}{T_{max}}<\beta$$

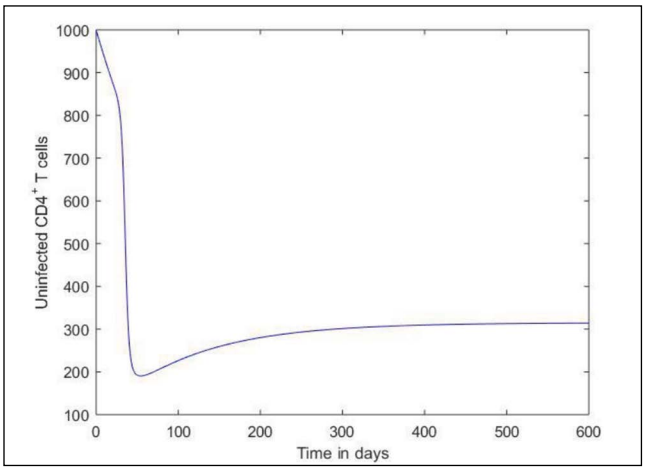
where $0 < p < 1$ and satisfies (11). Also a range of parameter r in which E^* is globally asymptotically stable is:

$$\alpha \le r < min\left\{\frac{\alpha\beta T_{max}}{\beta T_{max} - ps}, \frac{\beta T_{max}}{T_0}\right\}$$

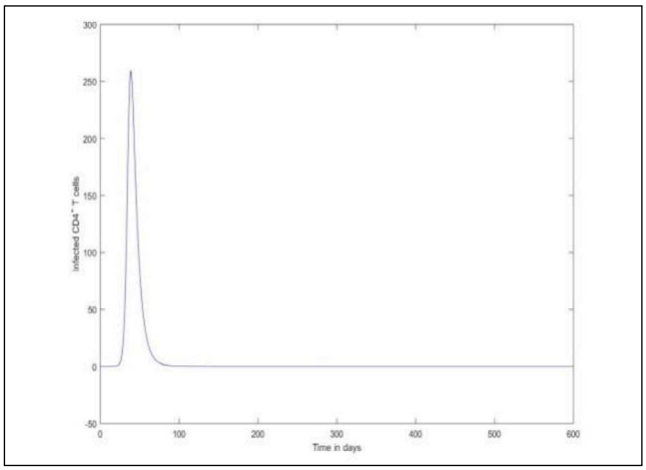
7. Numerical Simulation

In this section, we further investigate the dynamical behaviour of our model (2) using numerical simulation. Also verification of the already analysed analytic results will be done using numerical simulation. We have used MATLAB for these simulation works. For simulation, we will use the parameters which are also used in[10]. Specifically, $s = 10mm^{-3}\ day^{-1}$, $k = 0.000024mm^{-3}\ day^{-1}$, $\alpha = 0.01day^{-1}$, $b = 0.2day^{-1}$, $\beta = 0.16day^{-1}$, $\gamma = 3.4day^{-1}$ and $N = 1000$. Consider, T_{max} the shut-off level of T-cells in the body as 1500mm^{-3}[3,7]. To study the dynamical behaviour and verify the analytic results of the model, we use the parameters in the range which was found realistic with initial values $I = (1000,0,0.001)$.

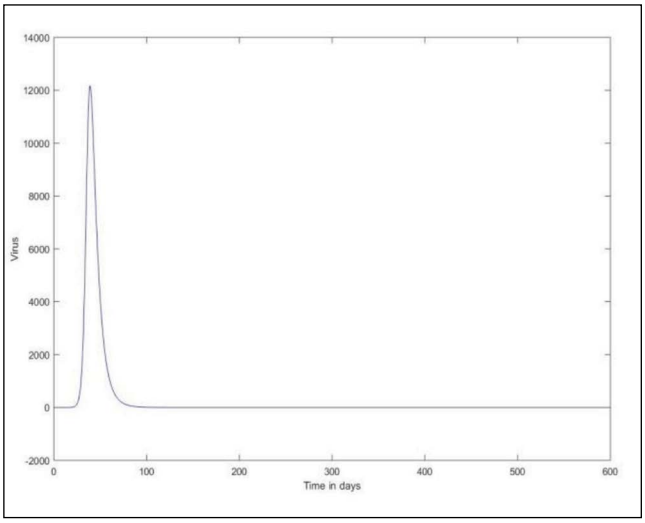
- For parameter values $s = 2.9mm^{-3}day^{-1}$, $r = 0.001$, $k = 0.000024mm^{-3}\ day^{-1}$, $\alpha = 0.01day^{-1}$, $b = 0.2day^{-1}$, $\beta = 0.16day^{-1}$, $\gamma = 3.4day^{-1}$, $T_{max} = 1500$ and $N = 1000$, we get basic reproduction number $R_0 = 0.98785 < 1$. Thus, analytic result of stability states that disease will die out. Figure 1(a)-(c) demonstrate the behaviours of different compartments of the model (2). Also, Figure 1(d) confirmed the global stability of the infection-free equilibrium $E_0(314.878, 0, 0)$ for these parameter values.



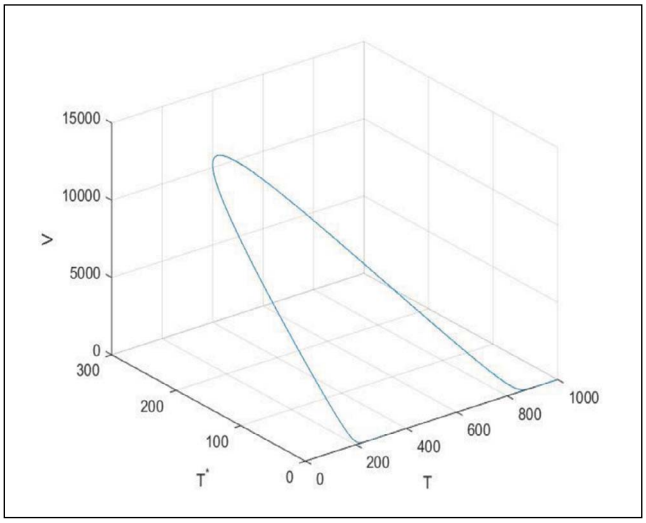
(a)



(b)



(c)



(d)

Figure 1: Global dynamics of $E_0(314.878,0,0)$ for initial value (1000, 0, 0.001).

- For parameter values

$$s = 2.9\,mm^{-3}day^{-1}, r = 0.02, k = 0.000024\,mm^{-3}day^{-1},\ \alpha = 0.01\,day^{-1},\ b = 0.2\,day^{-1}, \beta = 0.16\,day^{-1}, \gamma = 3.4\,day^{-1}, T_{max} = 1500$$

and N = 1000, we get basic reproduction number R_0 = 3.05392 > 1. Thus, proposition 1 states that infected equilibrium will exist. Figure 2(a)-(c) demonstrate the behaviours of different compartments of the model (2) in presence of virus. Also, Figure 2(d) confirmed the global stability of the infected equilibrium E^*(318.75, 28.8147, 1355.99) for these parameter values.

From the earlier discussion, it is clear that stability of the infected equilibrium point is dependent on the parameter r. Global stability result for infected equilibrium point provides a range of r where infected equilibrium is globally asymptotically stable. But from the discussion in[5], it is observed that E^* is globally asymptotically stable for small and large r and periodic solution exists for intermediate value of r.

For this model (2), if we consider the parameter values as considered in[5]. Specifically, $s = 0.1mm^{-3}day^{-1}$, $k = 0.0027mm^{-3}day^{-1}$, $\alpha = 0.02day^{-1}$, $\beta = 0.3day^{-1}$, $\gamma = 2.4day^{-1}$, T_{max} = 1500, N = 10. Without considering recovery or cure rate in[5], they carried out numerical simulations for r = 0.05, r = 0.8 and r = 3 and found global stability of infected equilibrium point for r = 0.05 and r = 3 whereas for$r$ = 0.8 they found stable periodic solution. Now, if we consider recovery or cure rate b = 0.002 then it is observed that the model (2) also has periodic solution (Figure 3). But, if we consider, b = 0.2 keeping all other parameters same, then the infection will be stale and the infected

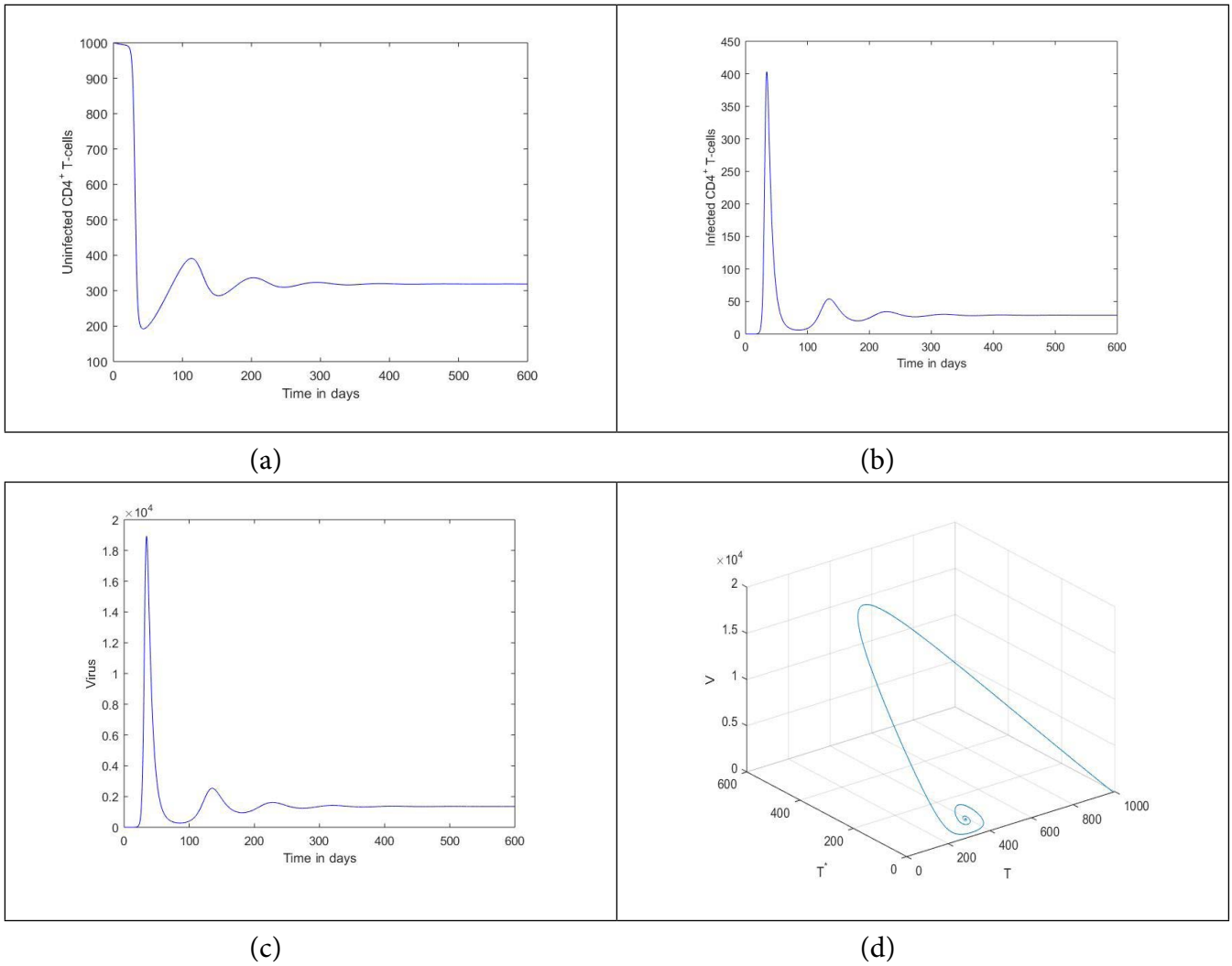


Figure 2: Global dynamics of E^*(318.75, 28.8147, 1355.99) for initial value (1000, 0, 0.001).

equilibrium point E^* will become globally asymptotically stable without any periodic solution (Figure 4). Therefore, recovery or cure rate affects the range of r where infected equilibrium point E^* is unstable.

Also, from simulation in[5], they observed that if the infected equilibrium point E^* is stable and the solutions converge to equilibrium point as damped oscillation and they found that damping factor and viral load at chronic stage depend on full logistic growth rate r. Here, we find that damping factor and viral load is also dependent on cure rate b. When $r = 0.05$, $b = 0.002$ the damping oscillation is visible up to 5000 days (Figure 5) but for $r = 0.05$, $b = 0.2$ the damping oscillation disappear after 500 days (Figure 6). Also, the viral load when $r = 0.05$, $b = 0.002$ persists at $10.3865 mm^{-3}$ (Figure 5) while it is $15.6296 mm^{-3}$ for $r = 0.05$, $b = 0.2$ (Figure 6).

8. Conclusion

In this paper, we have studied a differential equation in-host HIV model with full-logistic growth term $rT\left(1-\frac{T+T^*}{T_{max}}\right)$ for the growth of healthy T-cells and recovery or cure rate for infected T-cells. This assumes that the growth of healthy T-cells slows down during the course of infection and a portion of infected cells revert back to uninfected class. In the study, the basic reproduction number (R_0) is found to be threshold parameter. It is found that if $R_0 \leq 1$, the infection-free equilibrium point is globally stable otherwise unstable. Biologically, disease dies out if $R_0 \leq 1$. Also, if $R_0 > 1$, a unique infected equilibrium E^* exists. During numerical simulation, it is observed that E^* can be unstable for some values of r.

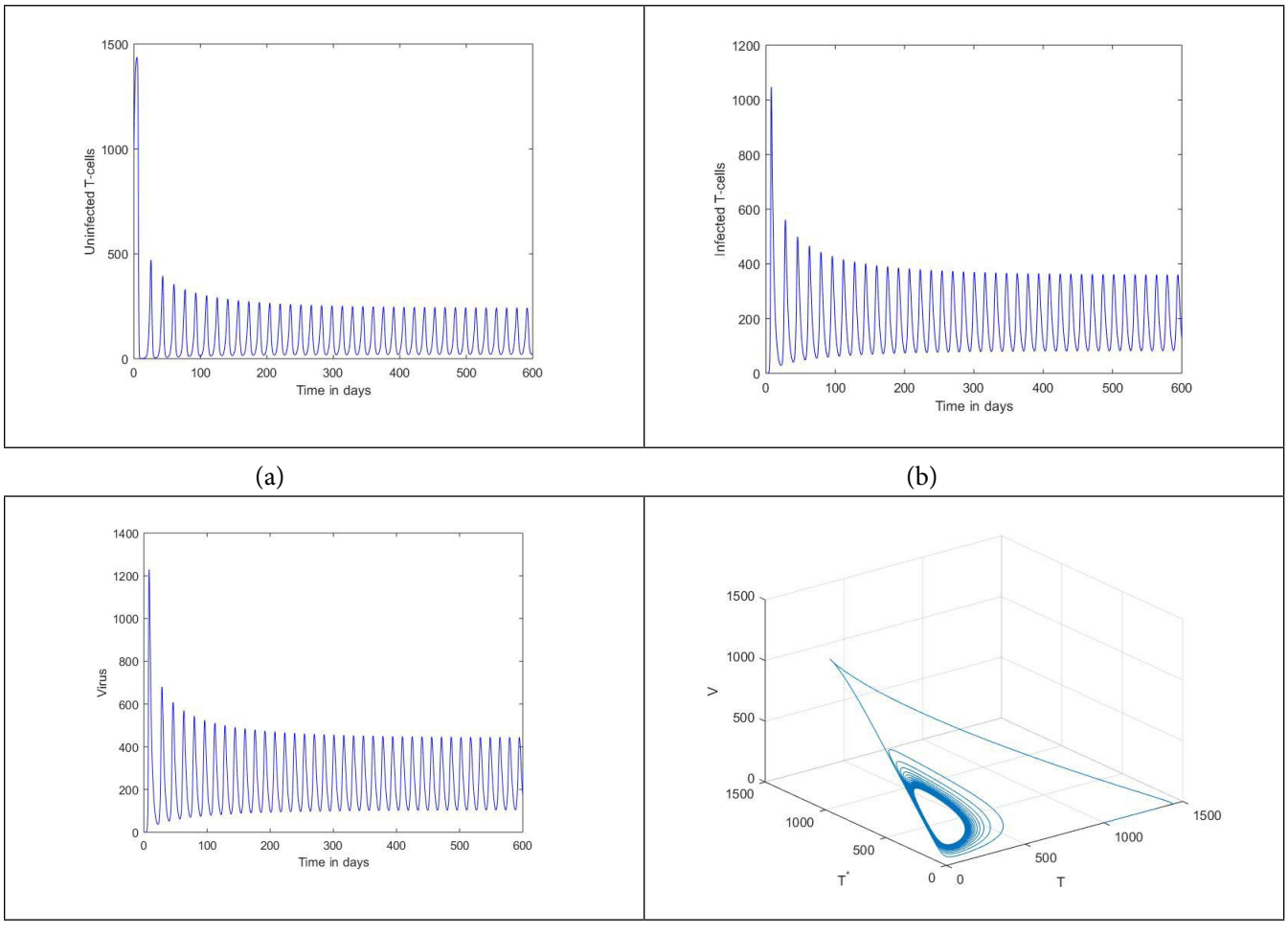


Figure 3: A periodic solution is shown when $r = 0.8$, b = 0.002.

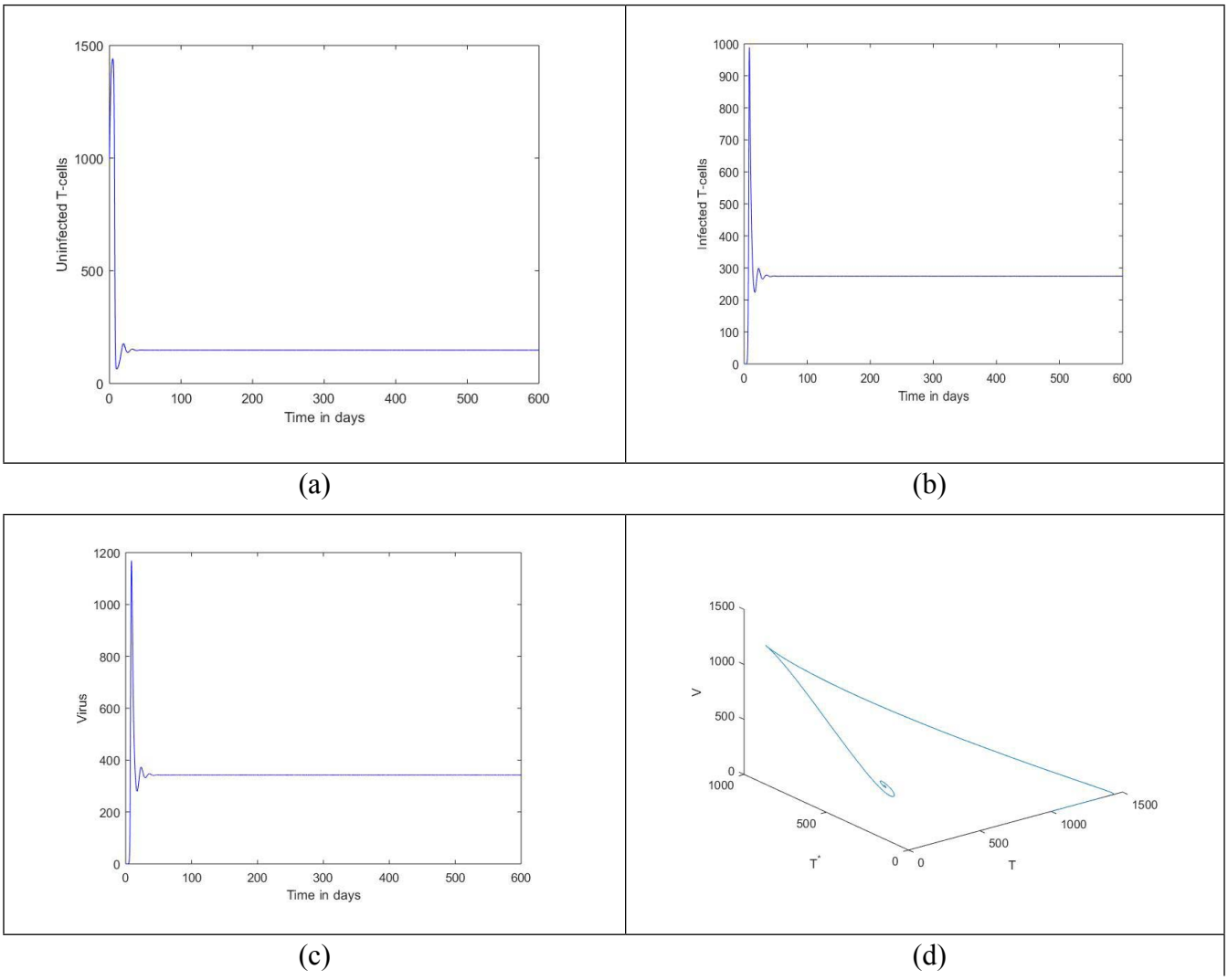


Figure 4: The periodic solution shown in Figure 3 does not exist for $r = 0.8$, $b = 0.2$.

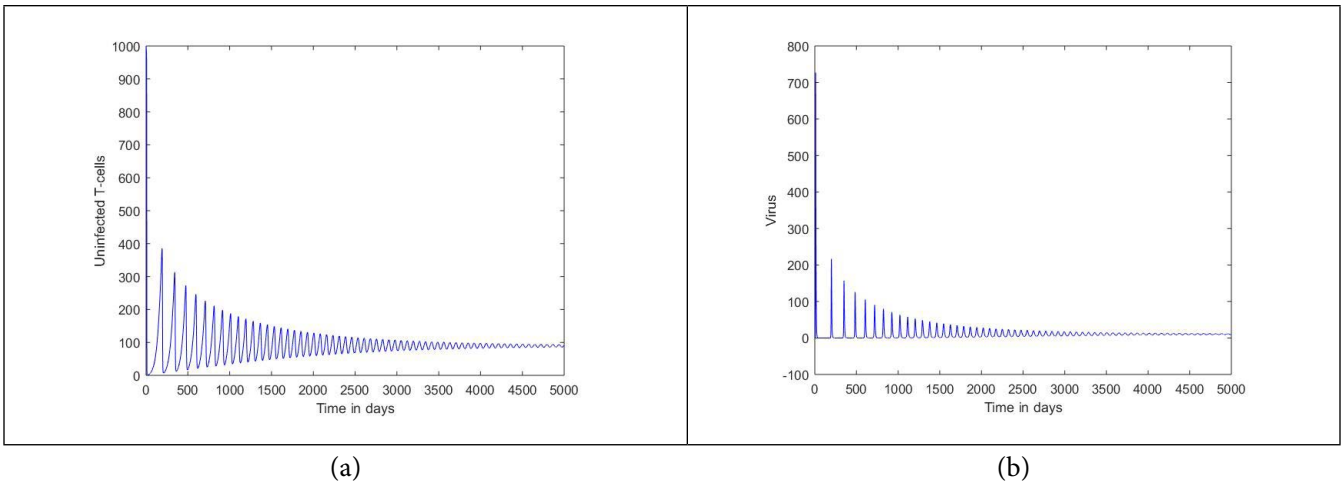
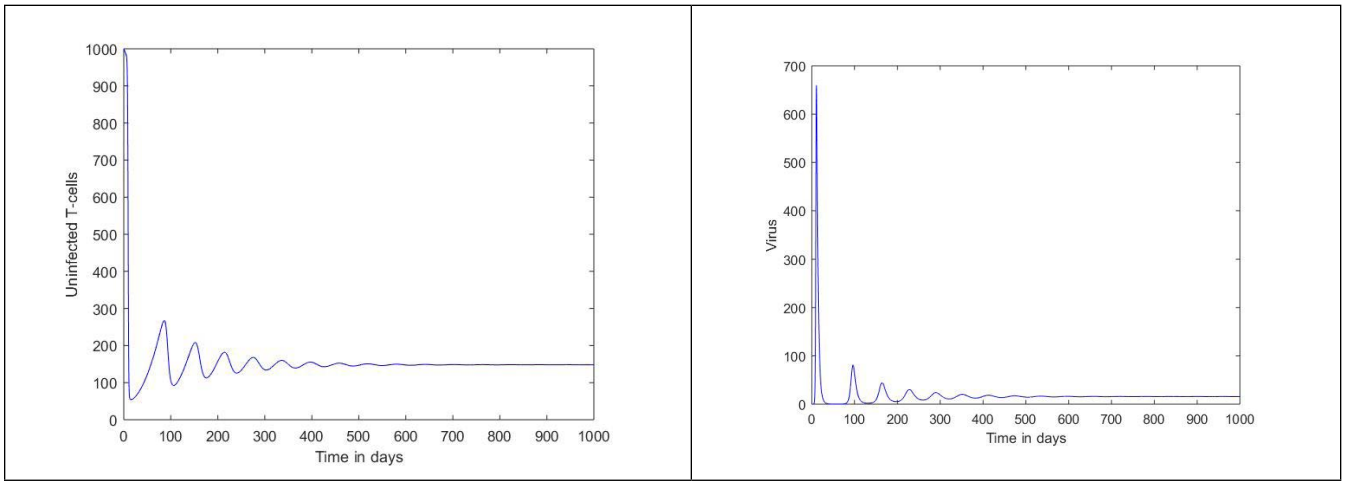


Figure 5: For $r = 0.05$, $b = 0.002$ infected equilibrium is globally stable with damping oscillations.



(a) (b)

Figure 6: For $r = 0.05$, $b = 0.2$ infected equilibrium is globally stable with damping oscillations.

Comparing the model (2) and the model which was discussed in Srivastava and Chandra[10] without considering proliferation of healthy T-cells; it is observed that inclusion of full-logistic growth term in model (2) leads to periodic solution for some range of parameter r. Though consideration of full logistic growth term makes the model more realistic but such oscillations are not observed in clinical data on HIV patients. Therefore, it is clear that the model (2) will be relevant if we find a range for r for which no such oscillations exists. Therefore, we have find a range of r where E^* is globally stable to make the model (2) biologically significant. Actually, in a model like (2), we ignore many features associated with HIV infection due to which we get such oscillations. Therefore, with the parameter range of r, the model (2) is more realistic and biologically significant as compared to the model in[10].

Now, comparing the model (2) and the model which was discussed in Wang and Li[5] without considering cure rate, the basic reproduction number for model in[5], $R_{0_1} = \frac{kNT_0}{\gamma}$. Obviously, basic reproduction number of model (2), $R_0 \leq R_{0_1}$. Thus it is observed that although the threshold behaviour and dynamical behaviour of model (2) is similar to that of model in[5], but in our model (2) we get lesser basic reproduction number as compared to model in[5]. This indicates that infection speed in model (2) with cure rate is slower than the model in[5] and we can comment that HIV can be controlled by increasing cure rate.Therefore, model (2) is more relevant as compared to the model discussed in Wang and Li[5].

Thus, from this study we have obtained a biologically feasible model (2) for HIV dynamics in human body in which we have incorporated full logistic term for proliferation of uninfected T cells and cure rate to obtain better results. Stability analysis of the model implies that if any treatment policy can lower the basic reproduction number less than or equal to one then HIV will be cleared out. From the expression of basic reproduction number, it is clear that it depends on different parameters of the model. Therefore, to control HIV infection, we can apply a treatment policy which can control the parameters to lower the basic reproduction number less than or equal to one. Also, there are different factors like inter-cellular delays, modes of transmissions etc. understanding of which will help to propose new treatment policy to control HIV infection. Better understanding of the effects of different factors on the dynamics of a more realistic model helps in applying optimal control strategy to maximize uninfected T cell population by blocking the infection new T cells by using minimum drug therapies. It is our future work to study the effect of different delays and treatment therapies to control HIV infection in human body.

9. References

1. World Health Organisation HIV/AIDS Key facts. 2020 Jul https://www.who.int/newsroom/fact-sheets/detail/hiv-

2. Douek DC, Brenchley JM, Betts MR, Ambrozak DR, Hill BJ, Okamoto Y, Casazza JP, Kuruppu J, Kunstman K, Wolinsky S, Grossman Z. HIV preferentially infects HIV-specific *CD4*$^+$ T cells. Nature. 2002 May; 417(6884):95–8. PMid: 11986671. https://doi.org/10.1038/417095a
3. Perelson AS, Kirschner DE, Boer R De. Dynamics of HIV infection of *CD4*$^+$ T cells. Math Biosci. 1993; 114:81–125. https://doi.org/10.1016/0025-5564(93)90043-A
4. Essunger P, Perelson AS. Modelling HIV infection *CD4*$^+$ T - subpopulations. J Theoret Biol. 1994; 170:367–91. PMid: 7996863. https://doi.org/10.1006/jtbi.1994.1199
5. Wang L, Li MY. Mathematical analysis of the global dynamics of a model for HIV infection of *CD4*$^+$ T cells. Math Biosci. 2006; 200:44–57. PMid: 16466751. https://doi.org/10.1016/j.mbs.2005.12.026
6. Rong L, Gilchrist MA, Feng Z, Perelson AS. Modeling within host HIV-1 dynamics and the evolution of drug resistance: Trade-offs between viral enzyme function and drug susceptibility. J Theoret Biol. 2007; 247(4):804–18. PMid: 17532343 PMCid: PMC2265667. https://doi.org/10.1016/j.jtbi.2007.04.014
7. Perelson AS, Nelson Patrick W. Mathematical Analysis of HIV-1 dynamics in Vivo. SIAM Review. 1999; 41(1):3–44. https://doi.org/10.1137/S0036144598335107
8. Leenheer P. De, Smith HL. Virus dynamics: A global analysis. SIAM J Appl Math. 2003; 63:1313–27. https://doi.org/10.1137/S0036139902406905
9. Gao T, Wang W, Liu X. Mathematical analysis of an HIV model with impulsive antiretroviral drug doses. Math Comput Simul. 2011 Dec; 82(4):653–65. https://doi.org/10.1016/j.matcom.2011.10.007
10. Srivastava PK, Chandra P. Modeling the dynamics of HIV and *CD4*$^+$ T cells during primary infection. Nonlinear Anal Real World Appl. 2010 Apr; 11(2):612–8. https://doi.org/10.1016/j.nonrwa.2008.10.037
11. Chandra P. Mathematical modeling of HIV dynamics: In Vivo. Mathematics Student-India. 2009; 78(1):7.
12. Nowak MA, May RM. Virus dynamics. UK: Oxford University Press; 2000.
13. LaSalle JP. The stability of dynamical systems. SIAM; 1976. PMCid: PMC1411100. https://doi.org/10.21236/ADA031020
14. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature. 1995; 373:123–6. PMid: 7816094. https://doi.org/10.1038/373123a0
15. Sachsenberg N, Perelson AS, Yerly S, Schockmel GA, Leduc D, Hirschel B, Perrin L. Turnover of *CD4*$^+$ and *CD8*$^+$ T lymphocytes in HIV-1 infection as measured by ki-67 antigen. J Exp Med. 1998; 187:1295–303. PMid: 9547340 PMCid: PMC2212238. https://doi.org/10.1084/jem.187.8.1295
16. Fan X, Brauner CM,Wittkop L. Mathematical analysis of a HIV model with quadratic logistic growth term. Discrete and Continuous Dynamical Systems Series-B. 2012; 17(7):2359–85. https://doi.org/10.3934/dcdsb.2012.17.2359
17. Song X, Neumann AU. Global stability and periodic solution of the viral dynamics. J Math Anal Appl. 2007 May; 329(1):281–97. https://doi.org/10.1016/j.jmaa.2006.06.064
18. Wang X, Song X. Global stability and periodic solution of a model for HIV infection of *CD4*$^+$ T cells. Appl Math Comput. 2007 Jun; 189(2):1331–40. https://doi.org/10.1016/j.amc.2006.12.044
19. Culshaw RV, Ruan S. A delay-differential equation model of HIV infection of *CD4*$^+$ T-cells. Math Biosci. 2000 May; 165(1):27–39. https://doi.org/10.1016/S0025-5564(00)00006-7
20. Merdan M, Gokdogan A, Yildirim A. On the numerical solution of the model for HIV infection of *CD4*$^+$ T cells. Comput Math. Appl. 2011 Jul; 62(1):118–23. https://doi.org/10.1016/j.camwa.2011.04.058
21. Zack JA, Arrigo SJ, Weitsman SR, Go AS, Haislip A, Chen IS. HIV-1 entry into quiescent primary lymphocytes: molecular analysis reveals a labile, latent viral structure. Cell. 1990 Apr; 61(2):213–22. https://doi.org/10.1016/0092-8674(90)90802-L
22. Zack JA, Haislip AM, Krogstad P, Chen IS. Incompletely reverse-transcribed human immunodeficiency virus type 1 genomes in quiescent cells can function as intermediates in the retroviral life cycle. J Virol. 1992 Mar; 66(3):1717–25. PMid: 1371173 PMCid: PMC240919. https://doi.org/10.1128/JVI.66.3.1717-1725.1992
23. Gradshteyn IS, Ryzhik IM. Routh-Hurwitz theorem, Tables of Integrals, Series and Products. San Diego: Academic Press; 2000.
24. Li MY, Muldowney JS. A geometric approach to global-stability problems. SIAM J Math Anal. 1996 Jul; 27(4):1070–83. https://doi.org/10.1137/S0036141094266449
25. Coppel WA. Stability and asymptotic behaviour of differential equations. Health, Boston; 1965.
26. Fiedler M. Additive compound matrices and inequalities for eigen values of stochastic matrices. Czech. Math J. 1974; 24(3): 392–402. https://doi.org/10.21136/CMJ.1974.101253
27. Muldowney JS. Compound matrices and ordinary differential equations. Rocky Mount. J Math. 1990 Oct: 857-72. https://doi.org/10.1216/rmjm/1181073047

28. Van den Driessche P, Watmough J. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math Biosci. 2002 Nov; 180(1-2):29–48. https://doi.org/10.1016/S0025-5564(02)00108-6

29. Bani-Yaghoub M, Gautam R, Shuai Z, Van Den Driessche P, Ivanek R. Reproduction numbers for infections with free-living pathogens growing in the environment. J Biol Dyn. 2012 Mar; 6(2):923–40. PMid: 22881277. https://doi.org/10.1080/17513758.2012.693206