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Analysis of HIV Infection of $CD4^+$ T-Cells with Distributed Delays

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Abstract

In this study, we introduce a Distributed delay to the model to describe the time delays between infection of a $CD4^+$ T-cells, and the emission of viral particles on a cellular level. We begin by determining the existence and stability of the equilibrium. Further We investigate the global stability of the infection-free equilibrium and give sufficient condition for the local stability of the infected steady state is asymptotically stable for all delays. Finally, the numerical simulations are presented to illustrate the analytical results.
Key words : Distributed Delay ; HIV-1; Global Stability; Local stability.

MSC (2010): 92D25, 34C23, 37B25.

1. INTRODUCTION

In recent years, there has been a lot of interest in mathematical modelling of HIV/AIDS infection, in order to predict the evolution of this modern plague. Since the discovery of the human immunodeficiency virus type 1 (HIV-1) in the early 1980s, the disease has spread in successive waves to most regions around the globe. It is reported that HIV has infected more than 60 million people, and over a third of them subsequently died [1]. Considerable scientific effort has been devoted to the understanding of viral pathogenesis, host/virus interactions, immune response to infection, and antiretroviral therapy [2]. HIV primarily

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attacks a host's $CD4^{+}T-$ cells (the main driver of the immune response). The amount of viruses in the blood is a good predictor of the stage of the disease. The amount of $CD4^{+}T-$ cells in a typical healthy person's peripheral blood ranges between $800/mm3$ and $1200/mm3$. When this value falls below 200, an HIV-positive patient is diagnosed with Acquired Immune Deficiency Syndrome (AIDS). HIV differs from most viruses in that it is a retrovirus: Viruses do not have the ability to reproduce independently, and they must be rely on a host to aid reproduction. Most viruses carry copies of their DNA and insert this into the host cell's DNA. Thus, when the host cell is stimulated for reproduction, it reproduces copies of the virus. T cells divide and increase in population once stimulated by antigen or mitogen. Chronic HIV infection causes gradual depletion of the $CD4^{+}T-$ cell pool, and thus progressively compromises the host's immune response, leading to humoral and cellular immune function loss (the marker of the onset of AIDS), making the host susceptible to opportunistic infections.

In 1993, Perelson, Krischner and De Boer [3] proposed an ODE model of cell-free viral spread of human immunodeficiency virus (HIV) in a well-mixed compartment such as the bloodstream. Their model consists of four components: uninfected healthy $CD4^{+}T-$ cells, latently infected $CD4^{+}T-$ cells, actively infected $CD4^{+}T-$ cells and free virus [4]. This model has been important in the field of mathematical modelling of HIV infection and many other models have been proposed which take the model of Perelson, Krischner and De Boer [3].

In [5] Liming Cai and Xuezhi Li have been simplify their model into one consisting of only three components: the healthy $CD4^{+}T-$ cells, infected $CD4^{+}T-$ cells and free virus and introduce a discrete time delay to the model to describe the times between infection of a $CD4^{+}T-$ cells and the emission of viral particles on a cellular level.Many Mathematical model, used the proliferation process of T-cells have been received in the literature. In addition researchers extend the basic models by adding $CD4^{+}$ T- cells simples logistic proliferation term $rT\left(1-\frac{T(t)}{T_{max}}\right)CD4^{+}$T-cells, full logisitic proliferation term $rT\left(1-\frac{T(t)+I(t)}{T_{max}}\right)$, where r is the maximum proliferation rate of $CD4^{+}$ T-cells, T, I respectively represent the concentration of susceptible $CD4^{+}$T-cells, infected $CD4^{+}$T-cells, and T_{max} is the maximum level of $CD4^{+}$T-cells concentration of the body, and injected T-cells at time t. Inspired by their work, in many authors have studied stability properties for delay differential equations and applied the results obtained to analyze the stability of the equilibria for the model of HIV-1 infection. To our knowledge, no works are contributed to the analysis for HIV infection of $CD4^{+}T-$ cells with two independent delays or two proportional delay terms. Motivated by this situation, we introduce a HIV infection model with independent time delays proposed by Culshaw and Ruan [6]. Here τ_1 and τ_2 are two time delays were included in our model. The first delay "τ_1" is the time between viral entry latent infection. The second delay "τ_2" is the time between cell infection and viral production. So, we assume that CD4+ T cells (healthy and infected) are governed by a full Logistic growth term. Therefore, we shall establish a mathematical model as follows

In this paper, we consider the effect of disturbed delays on the global dynamics of model 1.

$$T(\theta) = \phi_1(\theta) > 0, I(\theta) = \phi_2(\theta) > 0, V(\theta) = \phi_3(\theta) > 0, (-\tau \leq \theta \leq 0) \tag{1}$$

To this end, we consider the following more general delay differential equation model.

$$\left.\begin{aligned} T'(t) &= S - \mu_1 T + rT\left(1 - \frac{T+I}{T_{max}}\right) - KTV \\ I'(t) &= \int_0^\infty f_1(S)e^{-\delta_1 S} KT(t-S)V(t-S)dS - \mu_2 I + rT\left(1 - \frac{T+I}{T_{max}}\right) \\ V'(t) &= N\mu_2 \int_0^\infty f_2(S)e^{-\delta_2 S} I(t-S)dS - \mu_3 V \end{aligned}\right\} \tag{2}$$

When T(t), I(t) represent, respectively, the concentration of healthy $CD4^+$ T cells and infected $CD4^+$ T cells at time t; V(t) represents the concentration of free HIV at time t. Parameters s,$r, \tau, k, N, \mu_i; (\mu_i = 1, 2, 3)$ are positive constants. s is the growth rate of T-cells and T_{max} is their carrying capacity.$\mu_i (i = 1, 2, 3)$ are the nature death rates of the uninfected T-cells, infected T-cells and the virus particles, respectively.

It is reasonable to assume that $\mu_1 \leq \mu_2$, i.e., the infected T cells have a relatively shorter life than the uninfected T cells due to an HIV viral burden. k is the constant rate between virus and uninfected T cells. N is number of virus produced by infected CD4$^+$ T cells during its lifetime . T_{max} is the maximum level of $CD4^+$T-cells concentration in the body.

If the population ever reaches T_{max}, it should be decrease, thus we impose the constraint $\mu_1 T_{max}$. The terms $rT\left(1 - \frac{T+I}{T_{max}}\right)$and $rI\left(1 - \frac{T+I}{T_{max}}\right)$ are the logistic functions represents the proliferation of healthy and infected $CD4^+$T-cells respectively. τ denotes the time delays between the viral entry into target cell and the production of new virus particles.

In this paper, our primary goal is to carry out a complete mathematical analysis of system (2) and establish its global dynamics. It is well known by the fundamental theory of functional differential equations [Y kuang, 1993] [8] system (2) admits a unique solution (T(t),I(t),V(t)) satisfying the initial condition (3). It is easy to show that all solutions of system (2) with initial condition (3) are defined on $[0, +\infty)$ and remain positive for all $t \geq 0$.

Let us assume that the probability distribution function $f_i(s)$ satisfy $f(s) > 0$, and

$$\int_0^\infty f_i(s)ds = 1, \qquad \int_0^\infty f(u)e^{lu}du < \infty\ , \ \ i = 1, 2.$$

where $l > 0$.

The initial conditions of system (2) are

$$T(\theta) = \phi_1(\theta) > 0,\ I(\theta) = \phi_2(\theta) > 0,\ V(\theta) = \phi_3(\theta) > 0,\ (\tau \leq \theta \leq 0)\ , \tag{3}$$

where $\phi = (\phi_1, \phi_2, \phi_3) \in \mathcal{C}([-\tau, 0], \Re^3_{+0})$, the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\Re^3_{+0}$. Where $\Re^3_{+0} = \{(T, I, V) : T, I, V > 0\}$.
By a biological meaning, we further assume that $\phi_i(0) > 0$ for $i = 1, 2, 3$, with standard argument given [9]. It is easy to show the solution $T(t), I(t), V(t)$ with initial condition (3) exists and is unique for all $t \geq 0$.

Denote $\eta_1 = \int\limits_0^\infty f_1(S)e^{-\delta_1 S}dS$, then $0 < \eta_1 \leq 1$,
$\eta_2 = \int\limits_0^\infty f_2(S)e^{-\delta_2 S}dS$, then $0 < \eta_2 \leq 1$.

Lemma 1: *All the solution of system (2) with initial condition (3) are positive and ultimately bounded for all large t [3].*

$$\text{Let } \ \Omega = \left\{(T, I, V) \in R^3_+ : 0 < T \leq T_0, 0 < I \leq M_2, 0 < V \leq M_3\right\}$$

then Ω is the positive invariant set of system (2).

Next,we shall investigate the existence of equilibrium, of system (2).
The equilibrium of system (2) satisfy the following equation

$$\left.\begin{aligned} S-\mu_1 T+rT\left(1-\frac{T+I}{T_{max}}\right)-KTV &=0\\ \int_0^\infty f_1(S)e^{-\delta_1 S}KT(t-S)V(t-S)dS-\mu_2 I+rT\left(1-\frac{T+I}{T_{max}}\right) &=0\\ N\mu_2\int_0^\infty f_2(S)e^{-\delta_2 S}I(t-S)dS-\mu_3 V &=0 \end{aligned}\right\} \quad (4)$$

Clearly, the system (2) has always the infection free equilibrium $E_0(T_0,0,0)$, where

$$T_0=\frac{s}{\left[(\mu_1-r)+\frac{rT_0}{T_m}\right]}$$

From the third equation of (4), we have

$$I=\frac{\mu_3 V}{N\mu_2\eta_2}$$

Substituting this expression into the second equation of (4) and solving for T results in,

$$T=\left[\frac{\mu_3 T_m((\mu_2-r)}{N\mu_2\eta_1\eta_2 kT_m-r\mu_3}+\frac{r^2\mu_3}{N\mu_2\eta_2(N\mu_2\eta_1\eta_2 kT_m-r\mu_3)}\right]V \quad (5)$$

Rewriting the first equation of (4) as

$$s=T\left[\mu_1-r\left(1-\frac{T+I}{T_{max}}\right)+kV\right] \quad (6)$$

substituting and after straight forward computation, we obtain

$$s=(A+BV)(C+DV)$$

where

$$A=\frac{\mu_3 T_m(\mu_2-r)}{N\mu_2\eta_1\eta_2 kT_m-r\mu_3}$$
$$B=\frac{r\mu_3^2}{N\eta_2\mu_2(N\mu_2\eta_1\eta_2 kT_m-r\mu_3)}$$
$$C=(\mu_1-r)+\frac{\mu_3 r(\mu_2-r)}{N\mu_2\eta_1\eta_2 kT_m-r\mu_3}$$
$$D=\frac{N\mu_3\eta_1\eta_2 k^2 T_m+rk(N\mu_2 I-\mu_3)}{N\mu_2\eta_1\eta_2 kT_m-r\mu_3}$$

The critical number N_{crit} is defined by,

$$N_{crit} = \frac{\mu_3}{k\mu_2 T_0}\left(\frac{s}{T_0} + \mu_2 - \mu_1\right) > 0$$

It is easy to verify that the equation $s = (A + BV)(C + DV)$ has a unique positive root if and if only if $N > N_{crit}$.
Thus we also obtain

$$T^* = A + BV^* > 0 \text{ and } I^* = \tfrac{\mu_3}{N\mu_2}V^*.$$

2. STABILITY ANALYSIS

2.1. Local Stability

In this section, we study the local stability of the infection - free equilibrium and the infected equilibrium points.

Theorem 1:[10] *If $N \le N_{crit}$, then system (2) has only the uninfected equilibrium $E_0(T_0, 0, 0)$; if $N > N_{crit}$, the system (2) has the two equilibria; the infected free equilibria E_0 and the chronic infection equilibrium $E^*(T^*, I^*, V^*)$.*

Theorem 2:[11] *If $N < N_{crit}$,then system (2) has only the uninfected equilibrium $E_0(T_0, 0, 0)$ is asymptotically stable; if $N = N_{crit}$, then E_0 is locally stable; if $N > N_{crit}$, then E_0 is unstable.*

In the following, we shall investigate the geometric properties of the equilibra of (2). Let $E^*(T^*, I^*, V^*)$ be an arbitrary equilibrium. Thus, linerarizing the system(2)
at the equilibrium $E^*(T^*, I^*, V^*)$. We obtain the charateristic equation about E^*,

$$\begin{vmatrix} \lambda + M_1 & \frac{rT^*}{T_{max}} & kT^* \\ -kV^* e^{-\lambda\tau_1}\eta_1 + \frac{rI^*}{T_{max}} & \lambda + M_2 & -kT^* e^{-\lambda\tau_1} \\ 0 & -N\mu_2 e^{-\lambda\tau_2}\eta_2 & \lambda + \mu_3 \end{vmatrix} = 0 \tag{7}$$

where

$$M_1 = \left(\mu_1 + \tfrac{rI^* + 2rT^*}{T_{max}} + kV^* - r\right), \quad M_2 = \left(\mu_2 + \tfrac{2rI^* + rT^*}{T_max} - r\right)$$

The characteristic equation (7) reduces to

$$\Delta(\lambda,\tau_1,\tau_2) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 e^{-\lambda\tau_1} + a_4\lambda e^{-\lambda\tau_1}\eta_1 + a_5 e^{-\lambda(\tau_1+\tau_2)} - a_6\lambda e^{-\lambda(\tau_1+\tau_2)} - a_7 e^{-\lambda\tau_2} + a_8 = 0 \quad (8)$$

where

$$\begin{aligned}
a_1 &= \left(\frac{s}{T^*} + \frac{r\,(T^*+I^*)}{T_m} + \frac{kT^*V^*}{I^*} + \mu_3\right) > 0\\
a_2 &= \frac{s}{T^*}\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right) + (T^*+I^*)\,\frac{r\mu_3}{T_m}\\
a_3 &= \frac{rkT^*v^*\mu_3}{T_m}\eta_1\\
a_4 &= \frac{rkT^*v^*}{T_m}\eta_1\\
a_5 &= \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1 - \left(\frac{s}{T^*} + \frac{rT^*}{T_m}\right)\frac{kT^*V^*\mu_3}{I^*}\right]\\
a_6 &= \left[\frac{kT^*V^*\mu_3}{I^*}\right]\\
a_7 &= \left[\frac{rkT^*V^*\mu_3}{I^*}\right]\\
a_8 &= \left[\frac{sr\mu_3I^*}{T^*T_m} + \left(\frac{s}{T^*} + \frac{rT^*}{T_m}\right)\frac{kT^*V^*\mu_3}{I^*}\right]
\end{aligned}$$

where $\eta_1 = \int\limits_0^\infty f_1(s)e^{-\delta_1 s}ds$

when $\tau_1 = \tau_2 = 0$ in (8), we can write as $\lambda^3 + a_1\lambda^2 + \overline{a_2}\lambda + \overline{a_3} = 0$

since $\overline{a_2} = a_2 + a_4 - a_6$

$$\begin{aligned}
\overline{a_2} &= \frac{s}{T^*}\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right) + (T^*+I^*)\,\frac{r\mu_3}{T_m} + \frac{rkT^*v^*}{T_m}\eta_1 - \left[\frac{kT^*V^*\mu_3}{I^*}\right]\\
&= \frac{s}{T^*}\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right) + (T^*+I^*)\,\frac{r\mu_3}{T_m} + kT^*V^*\left(\frac{r}{T_m}\eta_1 - \left[\frac{\mu_3}{I^*}\right]\right) > 0
\end{aligned}$$

since $\overline{a_3} = a_3 + a_5 - a_7 + a_8$

$$\overline{a_3} = \frac{rkT^*v^*\mu_3}{T_m}\eta_1 + \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1 - \left(\frac{s}{T^*} + \frac{rT^*}{T_m}\right)\frac{kT^*V^*\mu_3}{I^*}\right] - \left[\frac{rkT^*V^*\mu_3}{I^*}\right]$$
$$+ \left[\frac{sr\mu_3 I^*}{T^*T_m} + \left(\frac{s}{T^*} + \frac{rT^*}{T_m}\right)\frac{kT^*V^*\mu_3}{I^*}\right]$$
$$= \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1\right] + \left[\frac{sr\mu_3 I^*}{T^*T_m}\right] + \left[\frac{rkT^*V^*\mu_3}{I^*}(\eta_1 - 1)\right]$$

Hence $a_1 > 0$, $\overline{a_2} > 0$, $\overline{a_3} > 0$, by directly calculating, we obtain

$$b = a_1\overline{a_2} - \overline{a_3}$$

$$= \left(\frac{s}{T^*} + \frac{r(T^*+I^*)}{T_m} + \frac{kT^*V^*}{I^*} + \mu_3\right)\frac{s}{T^*}\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right)$$
$$+ (T^*+I^*)\frac{r\mu_3}{T_m} + kT^*V^*\left(\frac{r}{T_m}\eta_1 - \left[\frac{\mu_3}{I^*}\right]\right) - \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1\right] - \left[\frac{sr\mu_3 I^*}{T^*T_m}\right]$$
$$- \left[\frac{rkT^*V^*\mu_3}{I^*}(\eta_1 - 1)\right]$$

$$= \left(\frac{r\mu_3}{T_m}\right)a_1(T^*+I^*) + \frac{s}{T^*}\left(\frac{s}{T^*} + \frac{rT^*}{T_m} + \frac{kT^*V^*}{I^*} + \mu_3\right)\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right)$$
$$+ kT^*V^*\left(\frac{r}{T_m}\eta_1 - \left[\frac{\mu_3}{I^*}\right]\right) - \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1\right] - \left[\frac{sr\mu_3 I^*}{T^*T_m}\right]$$
$$- \left[\frac{rkT^*V^*\mu_3}{I^*}(\eta_1 - 1)\right] - \left(\frac{rI^*}{T_m}\right)\frac{s}{T^*}\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right)$$

$$= \left(\frac{r\mu_3}{T_m}\right)a_1(T^*+I^*) + \frac{s}{T^*}\left(\frac{s}{T^*} + \frac{rT^*}{T_m} + \frac{kT^*V^*}{I^*} + \mu_3\right)\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right)$$
$$+ kT^*V^*\left(\frac{r}{T_m}\eta_1 - \left[\frac{\mu_3}{I^*}\right]\right) - \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1\right] - \left[\frac{rkT^*V^*\mu_3}{I^*}(\eta_1 - 1)\right] - \left[\frac{sr\mu_3 I^*}{T^*T_m}\right]$$
$$+ \left(\frac{rI^*}{T_m}\right)\frac{s}{T^*}\left(\frac{kT^*V^*}{I^*}\right) + \frac{s}{T^*}\left[\frac{rI^*}{T_m}\right]^2 + \left[\frac{sr\mu_3 I^*}{T^*T_m}\right]$$

$$= \left(\frac{r\mu_3}{T_m}\right) a_1 \left(T^* + I^*\right) + \frac{s}{T^*}\left(\frac{s}{T^*} + \frac{rT^*}{T_m} + \frac{kT^*V^*}{I^*} + \mu_3\right)\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right)$$
$$+ kT^*V^*\left(\frac{r}{T_m}\eta_1 - \left[\frac{\mu_3}{I^*}\right]\right) - \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1\right] - \left[\frac{rkT^*V^*\mu_3}{I^*}\left(\eta_1 - 1\right)\right]$$
$$+ \left(\frac{rskV^*}{T_m}\right) + \frac{s}{T^*}\left[\frac{rI^*}{T_m}\right]^2$$

$$= \left(\frac{r\mu_3}{T_m}\right) a_1 \left(T^* + I^*\right) + \frac{s}{T^*}\left(\frac{s}{T^*} + \frac{rT^*}{T_m} + \frac{kT^*V^*}{I^*} + \mu_3\right)\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right)$$
$$- \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1\right] + \frac{rs}{T_mT^*}\left[kT^*V^* + \frac{(rI^*)^2}{T_m}\right] + kT^*V^*\left(\frac{r}{T_m}\eta_1 - \left[\frac{\mu_3}{I^*}\right] + \frac{r\mu_3}{T_m}\eta_1 - \frac{r\mu_3}{T_m}\right)$$

If $\tau_1 = \tau_2 = 0$,by Routh-Hurwitz criterion, we have following theorem.

Theorem 3: *For non-delay case, the unqiue non-trivial infection steady state E^* of system (2) is locally asymptotically stable, when $N_{crit} > N$.*

2.2. Sufficient Conditions for Non Existence of Delay Induced Instability

To find the conditions for non existence of delay induced instability, we now use the following theorem.

Theorem 4: *A set of necessary and sufficient conditions for the equilibrium $\overline{E}$ to be asymptotically stable for all $\tau_1, \tau_2 \geq 0$ is the following.*

(i) The real parts of all the roots of $\Delta(\lambda, 0) = 0$ are negative.

(ii) For all real ω and $\tau_1, \tau_2 \geq 0$, $\Delta(i\omega, \tau_1, \tau_2) \neq 0$, where $i = \sqrt{-1}$

Proof:
Here $\Delta(\lambda, 0) = 0$ has roots whose real parts are negative.

Therefore, the condition (i) is easily satisifed.

we now verify the condition(ii) of theorem (5).

Firstly, when $\omega_0 = 0$, we have $\Delta(0, \tau) = a_3 + a_5 + a_7 \neq 0$

Secondly, when $\omega_0 \neq 0$, we have

$$\Delta\left(\lambda, \tau_1, \tau_2\right) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau_1} + a_4\lambda e^{-\lambda\tau_1} \tag{9}$$
$$+ a_5e^{-\lambda(\tau_1+\tau_2)} + a_6\lambda e^{-\lambda(\tau_1+\tau_2)} + a_7e^{-\lambda\tau_2} + a_8 = 0$$

where

$$a_1 = \left(\frac{s}{T^*} + \frac{r\left(T^* + I^*\right)}{T_m} + \frac{kT^*V^*}{I^*} + \mu_3\right) > 0$$
$$a_2 = \frac{s}{T^*}\left(\frac{kT^*V^*}{I^*} + \frac{rI^*}{T_m} + \mu_3\right) + \left(T^* + I^*\right)\frac{r\mu_3}{T_m}$$
$$a_3 = \frac{rkT^*v^*\mu_3}{T_m}\eta_1$$
$$a_4 = \frac{rkT^*v^*}{T_m}\eta_1$$
$$a_5 = \left[\frac{k^2T^*(V^*)^2\mu_3}{I^*}\eta_1 - \left(\frac{s}{T^*} + \frac{rT^*}{T_m}\right)\frac{kT^*V^*\mu_3}{I^*}\right]$$
$$a_6 = \left[\frac{kT^*V^*\mu_3}{I^*}\right]$$
$$a_7 = \left[\frac{rkT^*V^*\mu_3}{I^*}\right]$$
$$a_8 = \left[\frac{sr\mu_3I^*}{T^*T_m} + \left(\frac{s}{T^*} + \frac{rT^*}{T_m}\right)\frac{kT^*V^*\mu_3}{I^*}\right]$$

where

$$\eta_1 = \int\limits_0^\infty f_1(S)e^{-\delta_1 S}dS$$

Case 1 :

$$\boxed{\tau_1 = \tau_2 = 0}$$

Substuite the delay value in (9), the charactersitic equation becomes,

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau_1} + a_4\lambda e^{-\lambda\tau_1} + a_5e^{-\lambda(\tau_1+\tau_2)} - a_6\lambda e^{-\lambda(\tau_1+\tau_2)} - a_7e^{-\lambda\tau_2} + a_8 = 0$$
$$\lambda^3 + a_1\lambda^2 + \left(a_2 + a_4 - a_6\right)\lambda + \left(a_3 + a_5 - a_7 + a_8\right) = 0$$

By Routh-Hurwitz Criterian,that all the eigen values of the characteristic equation (6) has negative real part $\Leftrightarrow a_1 > 0, (a_2 + a_4 - a_6) > 0, (a_3 + a_5 - a_7 + a_8) > 0.$

Therefore, E^* is locally asymptotically stable.

Case 2:

$$\boxed{\tau_1 \neq 0, \tau_2 = 0 (\tau_1 > 0)}$$

The charactersitic equation becomes,

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + (a_3 + a_5)\,e^{-\lambda\tau_1} + (a_4 - a_6)\,\lambda e^{-\lambda\tau_1} + (a_8 - a_7) = 0 \qquad (10)$$

Let $\lambda = i\omega_1 (\omega_1 > 0)$
From the equation (10), becomes

$$-\,i\omega_1^3 - a_1\omega_1^2 + ia_2\omega_1 + (a_3 + a_5)\,e^{-i\omega_1\tau_1} + i\omega_1\tau_1\,(a_4 - a_6)\,e^{-i\omega_1\tau_1} + a_8 - a_7 = 0$$
$$i\omega_1^3 + a_1\omega_1^2 - ia_2\omega_1 - (a_3 + a_5)\,e^{-i\omega_1\tau_1} - i\omega_1\tau_1\,(a_4 - a_6)\,e^{-i\omega_1\tau_1} - a_8 + a_7 = 0$$

Separate the real and imaginary parts, we get

$$a_1\omega_1^2 + a_7 - a_8 = (a_3 + a_5)\cos\omega_1\tau_1 + (a_4 - a_6)\,\omega_1\sin\omega_1\tau_1$$
$$\omega_1^3 - a_2\omega_1 = (a_3 + a_5)\sin\omega_1\tau_1 + (a_4 - a_6)\,\omega_1\cos\omega_1\tau_1$$

Squaring and adding both equation, we obtain

$$(a_1\omega_1^2 + a_7 - a_8)^2 + \left(\omega_1^3 - a_2\omega_1\right)^2$$
$$= (a_3 + a_5)^2\left[\cos^2\omega_1\tau_1 + \sin^2\omega_1\tau_1\right] + (a_4 - a_6)^2\,\omega_1^2\left[\cos^2\omega_1\tau_1 + \sin^2\omega_1\tau_1\right]$$
$$(a_1\omega_1^2 + a_7 - a_8)^2 + \left(\omega_1^3 - a_2\omega_1\right)^2 = (a_3 + a_5)^2 + (a_4 - a_6)^2\,\omega_1^2$$
$$a_1^2\omega_1^4 + a_7^2 + a_8^2 - 2a_1a_7\omega_1^2 - 2a_1a_8\omega_1^2 + \omega_1^6 + a_1^2\omega_1^2 - 2a_2\omega_1^3\omega_1 - (a_3 + a_5)^2$$
$$-\,(a_4 - a_6)^2\,\omega_1^2 = 0$$

$$\omega_1^6 + (a_1^2 - 2a_2)\omega_1^4 + (a_2^2 - 2a_1a_7 - a_6^2 - a_6^2 - 2a_4a_6 - 2a_1a_8 - a_4^2)\omega_1^2 + (a_7^2 - 2a_3a_5 - a_3^2 - a_5^2 + a_8^2) = 0 \qquad (11)$$

Let

$$\rho = \omega^2,$$
$$b_1 = a_1^2 - 2a_2,$$
$$b_2 = a_2^2 - 2a_1a_7 - a_6^2 - a_4^2 - 2a_4a_6 - 2a_1a_8,$$
$$b_3 = a_7^2 + 2a_3a_5 - a_5^2 + a_8^2 - 2a_4a_6 - a_3^2$$

Then equation (11) becomes,

$$G(\rho) = \rho^3 + b_1\rho^2 + b_2\rho + b_3 = 0. \qquad (12)$$

We claim Equation (12) has no any positive roots for $b_2, b_3 > 0$. In fact, we notice that,

$$\frac{dg(\rho)}{dt} = 3\rho^2 + 2b_1\rho + b_2.$$

Let,

$$\frac{dg(\rho)}{dt} = 0 \Rightarrow 3\rho^2 + 2b_1\rho + b_2 = 0. \tag{13}$$

Then the root of equation (13) are given by,

$$\rho(1,2) = \left\{ \frac{-b_1 \pm \sqrt{b_1^2 - 3b_2}}{3} \right\}.$$

If $b_2 > 0$, then $(b^2 1 - 3b_2) < b_1^2$ (i.e) $\sqrt{(b_1^2 - 3b_2)} < b_1$.

Hence ρ_1, ρ_2 are both negative, equation (13) has no positive root.

Therefore, if $G(0) = b_3 > 0$, then equation (13) has no positive root. For any time delay $\tau_1, \tau_2 > 0$, the infected equilibrium,$E^* = (T^*, I^*, V^*)$ is locally asymptotically stable for $\tau_1 > 0, \ \ \tau_2 = 0$

Case 3:

$$\boxed{\tau_1 = 0, \ \ \tau_2 \neq 0 \ \ (\tau_2 > 0)}$$

The charactersitic equation becomes,

$$\lambda^3 + a_1\lambda^2 + (a_2 + a_4)\lambda + (a_5 - a_7) e^{-\lambda\tau_2} - a_6\lambda e^{-\lambda\tau_2} + (a_3 + a_2) = 0 \tag{14}$$

Let $\lambda = i\omega_2(\omega_2 > 0)$

From the equation (14), becomes

$$\Rightarrow -i\omega_2^3 - a_1\omega_2^2 i\omega_2 + (a_5 + a_7) e^{-i\omega_2\tau_2} + i\omega_2 a_6 e^{-i\omega_2\tau_2} - a_3 - a_8 = 0$$

Separate the real and imaginary parts, we get

$$a_1\omega_2^2 - (a_3 + a_8) = (a_5 - a_7)\cos\omega_2\tau_2 + a_6\omega_2 \sin\omega_2\tau_2$$
$$\omega_2^3 - (a_2 + a_4)\omega_2 = -(a_5 - a_7)\sin\omega_2\tau_2 + a_6\omega_1 \cos\omega_2\tau_2$$

Squaring and adding both equation, we obtain

$$a_1\omega_2^4 + a_3^2 + a_8^2 - 2a_1a_3\omega_2^2 - 2a_1a_8\omega_2^2 + (a_2 + a_4)^2\omega_2^2 - 2\omega_2^3 (a_2 + a_4)\omega_2$$
$$- \left(a_7^2 + a_5^2 - 2a_3a_7\right) - a_6^2\omega_2^2 + \omega_2^6 = 0$$

$$\omega_2^6 + \left(a_1^2 - 2a_2 - 2a_4\right)\omega_2^4 + \left[a_2^2 - 2a_1a_8 + a_4^2 - 2a_1a_3 - a_6^2 - 2a_2a_4\right]\omega_2^2 \\ + \left[a_3^2 + 2a_3a_7 + a_8^2 + a_7^2 - a_5^2\right] = 0 \tag{15}$$

Let

$$\rho = \omega_2^2,$$
$$b_1 = a_1^2 - 2a_2,$$
$$b_2 = a_2^2 + 2a_2a_4 + a_4^2 - 2a_1a_3 - 2a_1a_8,$$
$$b_3 = a_3^2 + 2a_3a_8 + a_7^2 + a_8^2 - a_5^2$$

Then equation (15) becomes,

$$G(\rho) = \rho^3 + b_1\rho^2 + b_2\rho + b_3 = 0. \tag{16}$$

We claim Equation (16) has no any positive roots for $b_2, b_3 > 0$. In fact, we notice that Now,

$$\frac{dg(\rho)}{dt} = 3\rho^2 + 2b_1\rho + b_2.$$

Let,

$$\frac{dg(\rho)}{dt} = 0 \Rightarrow 3\rho^2 + 2b_1\rho + b_2 = 0. \tag{17}$$

Then the root of equation (17) are given by,

$$\rho(1,2) = \left\{\frac{-b_1 \pm \sqrt{b_1^2 - 3b_2}}{3}\right\}.$$

If $b_2 > 0$, then $(b^21 - 3b_2) < b_1^2$ (i.e) $\sqrt{(b_1^2 - 3b_2)} < b_1$.
Hence ρ_1, ρ_2 are both negative, equation (14) has no positive root.

Therefore, if $G(0) = b_3 > 0$, then equation (14) has no positive root. For any time delay $\tau_1, \tau_2 > 0$, the infected equilibrium,$E^* = (T^*, I^*, V^*)$ is locally asymptotically stable for $\tau_1 = 0, \ \ \tau_2 > 0$

Case 4:

$$\boxed{\tau_1 \neq 0, \tau_2 \neq 0}$$

The charactersitic equation becomes,

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau_1} + a_4\lambda e^{-\lambda\tau_1} + a_5e^{-\lambda(\tau_1+\tau_2)} + a_6\lambda e^{-\lambda(\tau_1+\tau_2)} + a_7e^{-\lambda\tau_2} + a_8 = 0$$

Let $\tau_1 = \tau_2 = \tau > 0$

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3e^{-\lambda\tau} + a_4\lambda e^{-\lambda\tau} + a_5e^{-\lambda(2\tau)} + a_6\lambda e^{-\lambda(2\tau)} + a_7e^{-\lambda\tau} + a_8 = 0$$

Let $\lambda = i\omega(\omega > 0)$

$$i\omega^3 + a_1\omega^2 - a_2i\omega - a_3e^{-i\omega\tau} - a_4i\omega e^{-i\omega\tau} - a_5e^{-i\omega(2\tau)} + a_6i\omega e^{-i\omega(2\tau)} + a_7e^{-i\omega\tau} - a_8 = 0$$

Separate the real and imaginary parts, we have

$a_1\omega^2 - a_8 = a_3\cos\omega\tau + a_5\sin\omega(2\tau) + a_4\omega\sin\omega\tau - a_6\omega\sin\omega(2\tau) - a_7\cos\omega\tau$

$\omega^3 - a_2\omega = -a_3\sin\omega\tau - a_5\cos\omega(2\tau) - a_4\omega\cos\omega\tau + a_6\omega\sin\omega(2\tau) + a_7\cos\omega\tau$

Squaring and adding both equation, we obtain

$$\left(a_1\omega^2 + a_8\right)^2 + \left(\omega^3 - a_2\omega\right)^2 = a_3^2 + a_4^2\omega^2 + a_5^2 + a_6^2\omega^2 + a_7^2$$

$$\omega^6 + \left(a_1^2 - 2a_2\right)\omega^4 + \left(a_2^2 - 2a_1a_8 - a_4^2 - a_6^2\right)\omega^2 + \left(a_8^2 - a_3^2 - a_7^2 - a_5^2\right) \quad (18)$$

Let $\rho = \omega_2^2$,
$b_1 = a_1^2 - 2a_2$,
$b_2 = a_2^2 - 2a_1a_8 - a_4^2 - a_6^2$,
$b_3 = a_8^2 - a_3^2 - a_7^2 - a_5^2$

Then the equation (18) becomes,

$$G(\rho) = \rho^3 + b_1\rho^2 + b_2\rho + b_3 = 0.$$

by case(i), we get $\Delta\left(i\omega_2, \tau\right) \neq 0$,for any $\tau > 0$.

Therefore $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable for $\tau_2 > 0, \;\; \tau_1 = 0$

Hence the condition (i) and (ii) of theorem (3) are satisfied if the system (2) holds. □

3. GLOBAL STABILITY ANALYSIS

In this section, we construct a suitable Liapunov function to study the global dynamics of the infection - free equilibrium and chronic infection equilibrium for system (2).

Theorem 5: *If $N \leq N_{crit}$, then the infection - free equilibrium, $E_0(T_0, 0, 0)$ of system (2) is globally asymptotically stable in Ω.*

Proof:
Define a Liapunov functional

$$W(t) = T(t) - T_0 \ln \frac{T(t)}{T_0} + I(t) - V(t) + \frac{1}{\eta_1} \int_0^{\infty} f_1(s) e^{-\delta_1 s} k \int_0^{\tau_1} T(t-\omega) V(t-\omega) d\omega ds$$
$$+ \frac{N \mu_2 k T_0}{\mu_3} \int_0^{\infty} f_2(s) e^{-\delta_2 s} \int_0^{\tau_2} I(t-\omega) d\omega$$

Here W(t) is well-defined, continuous and positive defined for all $(T, I, V) > 0$ and $\theta \in [0, \rho]$. Also, the global minimum $W(=0)$ occurs at the infection free steady state E_0. Thus every solutions tends to the viral free steady state E_0. Further, a function W(t) along the trajectories of (2) satisfies.

$$\frac{dW}{dt} = (T - T_0) \left[\frac{s}{T} + r \left(1 - \frac{T+I}{T_m} \right) - \mu_1 - kV \right] + \int_0^{\infty} f_1(s) e^{-\delta_1 s} k T(t-\tau_1) V(t-\tau_1) ds - \mu_2 I$$
$$+ rI \left(1 - \frac{T+I}{T_m} \right) - N\mu_2 \int_0^{\infty} f_2(s) e^{-\delta_2 s} I(t-\tau_2) ds - \mu_3 V +$$
$$\frac{1}{\eta_1} \int_0^{\infty} f_1(s) e^{-\delta_1 s} \left[-kT(t-\tau_1) V(t-\tau_1) + kTV \right] + \frac{N \mu_2 k T_0}{\mu_3} \int_0^{\infty} f_2(s) e^{-\delta_2 s} \left[I(t-\tau_2) - I(t) \right]$$

$$= (T - T_0) \left[\frac{s}{T} + r \left(1 - \frac{T+I}{T_m} \right) - \mu_1 - kV \right] + rI \left(1 - \frac{T+I}{T_m} \right) + \eta_1 k T(t-s) V(t-s) - \mu_2 I$$
$$- N \mu_2 \eta_2 I(t-s) - \mu_3 V + \left[-kT(t-s) V(t-s) + kTV \right] + \frac{N \mu_2 k T_0 \eta_2}{\mu_3} \left[I(t-s) - I(t) \right]$$

Since

$$\eta_1 = \int_0^{\infty} f_1(S) e^{-\delta_1 S} dS$$
$$\eta_2 = \int_0^{\infty} f_2(S) e^{-\delta_2 S} dS$$

$$= (T - T_0)\left[\frac{s}{T} + r\left(1 - \frac{T+I}{T_m}\right) - \mu_1\right] - kTV + kT_0V + rI\left(1 - \frac{T+I}{T_m}\right)$$
$$+ \eta_1 kT(t-s)V(t-s) - \mu_2 I - N\mu_2\eta_2 I(t-s) - \mu_3 V - kT(t-s)V(t-s) + kTV$$
$$+ \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t-s) - \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t)$$

$$= (T - T_0)\left[\frac{s}{T} + r\left(1 - \frac{T+I}{T_m}\right) - \mu_1\right] + kT_0V + rI\left(1 - \frac{T+I}{T_m}\right) + \eta_1 kT(t-s)V(t-s) - \mu_2 I$$
$$- N\mu_2\eta_2 I(t-s) - \mu_3 V - kT(t-s)V(t-s) + \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t-s) - \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t)$$

Using this equation,

$$r - \mu_1 = \frac{rT_0}{T_m} - \frac{s}{T_0}$$

$$\frac{dW}{dt} = (T - T_0)\left[-\frac{s(T-T_0)}{TT_0} - \frac{r\,(T-T_0)}{T_m} - \frac{rI}{T_m}\right] + kT_0V + rI\left(1 - \frac{T_0}{T_m}\right) - \mu_2 I$$
$$- \frac{r}{T_m}(T - T_0)\,I - \frac{rI^2}{T_m} - \mu_3 V + \eta_1 kT(t-s)V(t-s)$$
$$- N\mu_2\eta_2 I(t-s) - kT(t-s)V(t-s) + \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t-s) - \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t)$$

$$= \left[-\frac{s\,(T-T_0)^2}{TT_0} - \frac{r\,(T-T_0)^2}{T_m} - \frac{2r\,(T-T_0)\,I}{T_m}\right] + kT_0V + rI\left(1 - \frac{T_0}{T_m}\right) - \mu_2 I - \frac{rI^2}{T_m} - \mu_3 V$$
$$- kT(t-s)V(t-s)[1-\eta_1] - N\mu_2\eta_2 I(t-s) + \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t-s) - \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t-s)$$

$$= \left[-\frac{s\,(T-T_0)^2}{TT_0}\right] - \left[\frac{r}{T_m}(T - T_0) + I\right]^2 + kT_0V + rI\left(1 - \frac{T_0}{T_m}\right) - \mu_2 I - \mu_3 V$$
$$- kT(t-s)V(t-s)[1-\eta_1] - N\mu_2\eta_2 I(t-s) + \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t-s) - \frac{N\mu_2 kT_0\eta_2}{\mu_3}I(t-s)$$

Using this equation,

$$r\left(1 - \frac{T_0}{T_m}\right) = \mu_1 - \frac{s}{T_0}$$

$$= \left[-\frac{s\,(T-T_0)^2}{TT_0}\right] - \left[\frac{r}{T_m}\,(T-T_0)+I\right]^2 + \left[\mu_1 - \frac{s}{T_0} - \mu_2 - \frac{N\mu_2 kT_0\eta_2}{\mu_3}\right] I$$
$$- kT(t-s)V(t-s)[1-\eta_1] - N\mu_2\eta_2 I(t-s)\left[1-\frac{kT_0}{\mu_3}\right]$$
$$= \left[-\frac{s\,(T-T_0)^2}{TT_0}\right] - \left[\frac{r}{T_m}\,(T-T_0)+I\right]^2 - \frac{\mu_2 kT_0\eta_2}{\mu_3}\left[\frac{\mu_3}{\mu_2 kT_0\eta_2}\left(\frac{s}{T_0}-\mu_1+\mu_2\right)-N\right] I$$
$$- kT(t-s)V(t-s)[1-\eta_1] - N\mu_2\eta_2 I(t-s)\left[1-\frac{kT_0}{\mu_3}\right]$$
$$= \left[-\frac{s\,(T-T_0)^2}{TT_0}\right] - \left[\frac{r}{T_m}\,(T-T_0)+I\right]^2 - \frac{\mu_2 kT_0\eta_2}{\mu_3}\left[N_{crit}-N\right] I - kT(t-s)V(t-s)[1-\eta_1]$$
$$- N\mu_2\eta_2 I(t-s)\left[1-\frac{kT_0}{\mu_3}\right]$$

Since

$$N_{crit} = \frac{\mu_3}{\mu_2 kT_0\eta_2}\left(\frac{s}{T_0}-\mu_1+\mu_2\right)$$

Rewritten $\frac{dW}{dt}$ interms of the critical number,we get

$$\frac{dw}{dt} = \left[-\frac{s\,(T-T_0)^2}{TT_0}\right] - \left[\frac{r}{T_m}\,(T-T_0)+I\right]^2 - \frac{\mu_2 kT_0\eta_2}{\mu_3}\left[N_{crit}-N\right] I$$
$$- kT(t-s)V(t-s)[1-\eta_1] - N\mu_2\eta_2 I(t-s)\left[1-\frac{kT_0}{\mu_3}\right]$$

If $N \leq N_{crit}$, then $\frac{dW}{dt} \leq 0$, from corollary [12], E_0 is asymptotically stable. Also, $N = N_{crit}$, $\frac{dW}{dt} = 0$ implies that $T(t) = T_0$ and $I(t) = 0$. While in the case $N < N_{crit}$, $\frac{dL}{dt} = 0$ if and only if $T(t) = T_0$ and $I(t) = 0$. It is easy to show that $E_0(T_0, 0, 0)$ is the largest invariant set $\{(T(t), I(t), V(t)) : \frac{dL}{dt} = 0\}$. By the classical Liapunov - Lasalle invariance principle [13], E_0 is globally asymptotically stable. This complete the proof. □

In the following, we consider the global asymptotic stability of chronic infection equilibrium $E^*(T^*, I^*, V^*)$. We construct an Liapunov functional for chronic infection equilibrium using suitable combinations of the Liapunov functions given in [14].

$$g(x) := x - 1 - \ln\ x$$

Thus, the function g has a global minimum at 1 and satisfies $g(1) = 0$.

Theorem 6: *If $N > N_{crit}$ and $r \leq \mu_1 + \frac{r}{T_m}[T^* + I^*]$,then the unique chronic infection equilibrium $E_0 = (T_0, 0, 0)$ of system(2) is globally asymptotically stable in $\tau \geq 0$.*

Proof:

We define a Lyapunav functional as follows.

$$L(t) = L_1(t) + L_2(t) + L_3(t)$$

where

$$L_1(t) = \left(T(t) - T^* \ln \frac{T(t)}{T^*}\right) + \left(I(t) - I^* \ln \frac{I(t)}{I^*}\right) + \frac{kT^*V^*}{N\mu_2\eta_2 I^*}\left(V(t) - V^* \ln \frac{V(t)}{V^*}\right) \tag{19}$$

$$L_2(t) = \frac{kT^*V^*}{\eta_1}\int_0^\infty f1(s)e^{-\delta_1 s}\int_0^{\tau_1}\left(\frac{T(t-\omega)V(t-\omega)}{T^*V^*} - 1 - \ln\frac{T(t-\omega)V(t-\omega)}{T^*V^*}\right)d\omega \ \ ds \tag{20}$$

$$L_3(t) = \frac{kT^*V^*}{\eta_2}\int_0^\infty f2(s)e^{-\delta_2 s}\int_0^{\tau_2}\left(\frac{I(t-\omega)}{I^*} - 1 - \ln\frac{I(t-\omega)}{I^*}\right)d\omega \ \ ds \tag{21}$$

At infected steady state, we have

$$\left.\begin{aligned} r - \mu_1 &= \frac{-s}{T^*} + kV^* + \frac{r}{T_m}(T^* + I^*) \\ r - \mu_2 &= \frac{-kT^*V^*}{I^*}\eta_1 + \frac{r}{T_m}(T^* + I^*) \\ \mu_3 V^* &= \eta_2 N\mu_2 I^* \end{aligned}\right\} \tag{22}$$

The derivative of $U_1(t)$ with respect to t along the solution of (19), we get

$$\begin{aligned}\frac{dL_1}{dt} &= \left(\frac{T-T^*}{T}\right)\frac{dT}{dt} + \frac{1}{\eta_1}\left(\frac{I-I^*}{I}\right)\frac{dI}{dt} + \frac{kT^*V^*}{N\mu_2 I^*\eta_2}\left(\frac{V-V*}{V}\right)\frac{dV}{dt} \\ &= (T-T^*)\left(\frac{s}{T} - \frac{r}{T_m}(T+I) - kV + r - \mu_1\right) + \left(\frac{I-I^*}{\eta_1}\right) \\ &\left(\int_0^\infty f_1(s)e^{-\delta_1 s}\frac{kT(t-\tau_1)V(t-\tau_1)}{I} - \frac{r}{T_m}(T+I) + r - \mu_2\right) + \frac{kT^*V^*}{N\mu_2 I^*\eta_2}\left(1 - \frac{V^*}{V}\right) \\ &\left(N\mu_2\int_0^\infty f_2(s)e^{-\delta_2 s}I(t-\tau_2) - \mu_3 V\right)\end{aligned}$$

Using the equation (22) , we get

$$\begin{aligned}\frac{dL_1}{dt} =& (T-T^*)\left[\left(\frac{-s}{TT^*}(T-T^*)-k\left(V-V^*\right)\right)-\frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]\right]\\ &+\frac{(I-I^*)}{\eta_1}\left[\int\limits_0^\infty f_1(s)e^{-\delta_1 s}\left(\frac{kT(t-\tau_1)V(t-\tau_1)}{I}-\frac{kT^*V^*}{I^*}\right)\right]ds\\ &-\frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]+\frac{kT^*V^*}{N\mu_2\eta_2 I^*}\left(N\mu_2\int\limits_0^\infty f_2(s)e^{-\delta_2 s}I(t-\tau_2)ds\right)\\ &-\frac{kT^*V^*}{N\mu_2 I^*\eta_2}\left(\frac{V^*}{V}\right)\left(\int\limits_0^\infty f_2(s)e^{-\delta_2 s}N\mu_2 I(t-\tau_2)-\mu_3 V\right)\end{aligned}$$

$$\begin{aligned}=&\left\{\left(\frac{-s}{TT^*}(T-T^*)^2\right)-\frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]^2\right\}+\left\{-kTV+kTV^*+kT^*V-kT^*V^*\right\}\\ &+\frac{1}{\eta_1}\left[\int\limits_0^\infty f_1(s)e^{-\delta_1 s}kT(t-\tau_1)V(t-\tau_1)ds\right]-kT^*V^*\left(\frac{I}{I^*}\right)-kT(t-\tau_1)V(t-\tau_1)\left(\frac{I^*}{I}\right)\\ &+kT^*V^*+\frac{kT^*V^*}{\eta_2 I^*}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}I\left(t-\tau_2\right)ds-\frac{kT^*V^*}{\eta_2 I^*}\left(\frac{V^*}{V}\right)\left(I(t-\tau_2)\int\limits_0^\infty f_1(s)e^{-\delta_1 s}ds\right)\\ &-kT^*V-\frac{kT^*V^*}{N\mu_2\eta_2 I^*}\left(\frac{V^*}{V}\right)\left[\frac{N\mu_2\eta_2 I^*}{V^*}\right]-kT^*V+kT^*V^*\end{aligned}$$

$$\begin{aligned}=&\left\{\left(\frac{-s}{TT^*}(T-T^*)^2\right)-\frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]^2\right\}\\ &+\frac{kT^*V^*}{\eta_1}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}ds\\ &\left(1+\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}-\frac{I}{I^*}-\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\frac{I^*}{I}+\frac{T}{T^*}-\frac{TV}{T^*V^*}\right)\\ &+\frac{kT^*V^*}{\eta_2 I^*}\int\limits_0^\infty f_2(s)e^{-\delta_2 s}I\left(t-\tau_2\right)ds-\frac{kT^*V^*}{\eta_2 I^*}\left(\frac{V^*}{V}\right)\int\limits_0^\infty f_2(s)e^{-\delta_2 s}I\left(t-\tau_2\right)ds\end{aligned}$$

We can rewritten $\frac{dL_1}{dt}$ as,

$$\frac{dL_1}{dt} = \left\{ \left(\frac{-s}{TT^*}(T-T^*)^2 \right) - \frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]^2 \right\}$$
$$+ \frac{kT^*V^*}{\eta_1} \int_0^\infty f_1(s)e^{-\delta_1 s}$$
$$\left[\left(1 + \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} - \frac{I}{I^*} - \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\frac{I^*}{I} + \frac{T}{T^*} - \frac{TV}{T^*V^*} \right) ds \right]$$
$$+ \frac{kT^*V^*}{\eta_2 I^*} \int_0^\infty f_2(s)e^{-\delta_1 s} I\left(t-\tau_2\right) ds - \frac{kT^*V^*}{\eta_2 I^*} \left(\frac{V^*}{V}\right) \int_0^\infty f_2(s)e^{-\delta_1 s} I\left(t-\tau_2\right) ds$$

$$= \left\{ \left(\frac{-s}{TT^*}(T-T^*)^2 \right) - \frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]^2 \right\}$$
$$+ \frac{kT^*V^*}{\eta_1} \int_0^\infty f_1(s)e^{-\delta_1 s}$$
$$\left[\left(3 - \frac{T^*}{T} - \frac{TV}{T^*V^*} + \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} - \frac{I}{I^*} - \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\frac{I^*}{I} \right) ds \right]$$
$$+ \frac{kT^*V^*}{\eta_1} \left[\int_0^\infty f_1(s)e^{-\delta_1 s} \left(\frac{T}{T^*} + \frac{T^*}{T} - 2 \right) \right] + \frac{kT^*V^*}{\eta_2 I^*} \int_0^\infty f_2(s)e^{-\delta_1 s} I\left(t-\tau_2\right) ds$$
$$- \frac{kT^*V^*}{\eta_2 I^*} \left(\frac{V^*}{V}\right) \int_0^\infty f_2(s)e^{-\delta_1 s} I\left(t-\tau_2\right) ds$$

$$= -\left(s - kT^*V^*\right) \left[\frac{(T-T^*)^2}{TT^*} \right] - \frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]^2$$
$$+ \frac{kT^*V^*}{\eta_1} \int_0^\infty f_1(s)e^{-\delta_1 s}$$
$$\left[\left(3 - \frac{T^*}{T} - \frac{TV}{T^*V^*} + \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} - \frac{I}{I^*} - \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\frac{I^*}{I} \right) ds \right]$$
$$+ \frac{kT^*V^*}{\eta_2 I^*} \int_0^\infty f_2(s)e^{-\delta_1 s} I\left(t-\tau_2\right) ds - \frac{kT^*V^*}{\eta_2 I^*} \left(\frac{V^*}{V}\right) \int_0^\infty f_2(s)e^{-\delta_1 s} I\left(t-\tau_2\right) ds$$

Using the equation,

$$\left(\frac{s-kT^*V^*}{T^*}\right)=(\mu_1-r)+\frac{r}{T_m}\left(T^*+I^*\right)$$

We get,

$$\frac{dL_1}{dt}=-\left\{(\mu_1-r)+\frac{r}{T_m}\left(T^*+I^*\right)\right\}\left[\frac{(T-T^*)^2}{T}\right]-\frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]^2$$
$$+\frac{kT^*V^*}{\eta_1}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}$$
$$\left(3-\frac{TV}{T^*V^*}+\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}-\frac{T^*}{T}-\frac{I}{I^*}-\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\left[\frac{I^*}{I}\right]\right)ds$$
$$+\frac{kT^*V^*}{\eta_2 I^*}\int\limits_0^\infty f_2(s)e^{-\delta_2 s}I\left(t-\tau_2\right)ds-\frac{kT^*V^*}{\eta_2 I^*}\left(\frac{V^*}{V}\right)\int\limits_0^\infty f_2(s)e^{-\delta_2 s}I\left(t-\tau_2\right)ds$$

Since the $L_2(t)$ equation,

$$L_2(t)=\frac{kT^*V^*}{\eta_1}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}\int\limits_0^{\tau_1}\left(\left[\frac{T(t-\omega)V(t-\omega)}{T^*V^*}-1-\ln\frac{T(t-\omega)V(t-\omega)}{T^*V^*}\right)\right]d\omega\ \ ds$$

It is easy to see that,the derivative of L_2

$$\frac{dL_2}{dt}=\frac{kT^*V^*}{\eta_1}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}\left\{\frac{d}{dt}\int_0^{\tau_1}\left(\frac{T(t-\omega)V(t-\omega)}{T^*V^*}-1-\ln\frac{T(t-\omega)V(t-\omega)}{T^*V^*}\right)d\omega\right\}ds$$
$$=\frac{kT^*V^*}{\eta_1}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}\left\{\int_0^{\tau_1}\frac{d}{dt}\left(\frac{T(t-\omega)V(t-\omega)}{T^*V^*}-1-\ln\frac{T(t-\omega)V(t-\omega)}{T^*V^*}\right)d\omega\right\}ds$$
$$=-\frac{kT^*V^*}{\eta_1}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}\left\{\int\limits_0^{\tau_1}\frac{d}{d\omega}\left[\frac{T(t-\omega)V(t-\omega)}{T^*V^*}-1-\ln\frac{T(t-\omega)V(t-\omega)}{T^*V^*}\right]d\omega\right\}ds$$
$$=-\frac{kT^*V^*}{\eta_1}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}\left\{\left[\frac{T(t-\omega)V(t-\omega)}{T^*V^*}-1-\ln\frac{T(t-\omega)V(t-\omega)}{T^*V^*}\right]_{\omega=0}^{\tau_1}\right\}ds$$

$$=-\frac{kT^*V^*}{\eta_1}\int\limits_0^\infty f_1(s)e^{-\delta_1 s}\left[\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}+\frac{TV}{T^*V^*}+\ln\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}-\ln\frac{TV}{T^*V^*}\right]ds$$

Consider

$$\ln\frac{T(t-s)V(t-s)}{T^*V^*}+\ln\frac{T^*V^*}{TV}=\ln\left(\frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I}+\frac{IV^*}{I^*V}+\frac{T^*}{T}\right)$$

$$\frac{dL_2}{dt} = -\frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}$$
$$\left[\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} + \frac{TV}{T^*V^*} + \ln\frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I} + \ln\frac{IV^*}{I^*V} + \ln\frac{T^*}{T}\right]ds$$

Since $L_3(t)$ the equation,

$$L_3(t) = \int_0^{\tau_1}\left(\frac{I(t-\omega)}{I^*} - 1 - \ln\frac{I(t-\omega)}{I^*}\right)d\omega$$

The dervative of L_3 along solution of system (2), we get

$$\frac{dL_3}{dt} = \frac{d}{dt}\left[\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\int_0^{\tau_2}\left(\frac{I(t-\omega)}{I^*} - 1 - \ln\frac{I(t-\omega)}{I^*}\right)d\omega\right]ds$$
$$= \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\frac{d}{dt}\int_0^{\tau_2}\left(\frac{I(t-\omega)}{I^*} - 1 - \ln\frac{I(t-\omega)}{I^*}\right)d\omega\right]ds$$
$$= \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\int_0^{\tau_2}\frac{d}{dt}\left(\frac{I(t-\omega)}{I^*} - 1 - \ln\frac{I(t-\omega)}{I^*}\right)d\omega\right]ds$$
$$= \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[-\int_0^{\tau_2}\frac{d}{d\omega}\left(\frac{I(t-\omega)}{I^*} - 1 - \ln\frac{I(t-\omega)}{I^*}\right)d\omega\right]ds$$
$$= \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left(-\left[\frac{I(t-\omega)}{I^*} - 1 - \ln\frac{I(t-\omega)}{I^*}\right]_{\omega=0}^{\tau_2}\right)ds$$
$$= \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[-\frac{I(t-\tau_2)}{I^*} + \frac{I}{I^*} + \ln\frac{I(t-\tau_2)}{I^*} + \ln\frac{I}{I^*}\right]ds$$

Consider,

$$\ln\frac{I(t-\tau_2)}{I^*} + \ln\frac{I}{I^*} = \ln\frac{I(t-\tau_2)V^*}{I^*V} - \ln\frac{IV^*}{I^*V}$$

$$\frac{dL_3}{dt} = \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[-\frac{I(t-\tau_2)}{I^*} + \frac{I}{I^*} + \ln\frac{I(t-\tau_2)V^*}{I^*V} - \ln\frac{IV^*}{I^*V}\right]ds$$

Since

$$\frac{dL}{dt} = \frac{dL_1}{dt} + \frac{dL_2}{dt} + \frac{dL_3}{dt}$$

We obtain,

$$\frac{dL}{dt} = -\left\{(\mu_1 - r) + \frac{r}{T_m}(T^* + I^*)\right\}\left[\frac{(T-T^*)^2}{T}\right] - \frac{r}{T_m}\left[(T-T^*) + (I-I^*)\right]^2$$

$$+ \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}$$

$$\left(3 - \frac{TV}{T^*V^*} + \frac{T(t-\tau_2)V(t-\tau_2)}{T^*V^*} - \frac{T^*}{T} - \frac{I}{I^*} - \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\left[\frac{I^*}{I}\right]\right) ds$$

$$+ \frac{kT^*V^*}{\eta_2 I^*}\int_0^\infty f_2(s)e^{-\delta_2 s} I(t-\tau_2)\, ds - \frac{kT^*V^*}{\eta_2 I^*}\left(\frac{V^*}{V}\right)\int_0^\infty f_2(s)e^{-\delta_2 s} I(t-\tau_2)\, ds$$

$$+ \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}$$

$$\left[-\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} + \frac{TV}{T^*V^*} + \ln\frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I} + \ln\frac{IV^*}{I^*V} + \ln\frac{T^*}{T}\right] ds$$

$$+ \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[-\frac{I(t-\tau_2)}{I^*} + \frac{I}{I^*} + \ln\frac{I(t-\tau_2)V^*}{I^*V} - \ln\frac{IV^*}{I^*V}\right] ds$$

$$= -\left\{(\mu_1 - r) + \frac{r}{T_m}(T^* + I^*)\left[\frac{(T-T^*)^2}{T}\right]\right\} - \frac{r}{T_m}\left[(T-T^*) + (I-I^*)\right]^2$$

$$+ \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}$$

$$\left(3 - \frac{TV}{T^*V^*} + \frac{T(t-\tau_2)V(t-\tau_2)}{T^*V^*} - \frac{T^*}{T} - \frac{I}{I^*} - \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\left[\frac{I^*}{I}\right]\right) ds$$

$$+ \frac{kT^*V^*}{\eta_2 I^*}\int_0^\infty f_2(s)e^{-\delta_2 s} I(t-\tau_2)\, ds - \frac{kT^*V^*}{\eta_2 I^*}\left(\frac{V^*}{V}\right)\int_0^\infty f_2(s)e^{-\delta_2 s} I(t-\tau_2)\, ds$$

$$+ \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}$$

$$\left[-\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*} + \frac{TV}{T^*V^*} + \ln\frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I} + \ln\frac{IV^*}{I^*V} + \ln\frac{T^*}{T}\right] ds$$

$$+\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[-\frac{I(t-\tau_2)}{I^*}\right]ds+\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\frac{I}{I^*}\right]ds$$

$$+\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\ln\frac{I(t-\tau_2)V^*}{I^*V}-\ln\frac{IV^*}{I^*V}\right]ds$$

$$=-\left\{(\mu_1-r)+\frac{r}{T_m}(T^*+I^*)\left[\frac{(T-T^*)^2}{T}\right]-\frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]^2\right\}$$

$$+\frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}\left(3-\frac{I}{I^*}-\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\left[\frac{I^*}{I}\right]\right)ds$$

$$+\frac{kT^*V^*}{\eta_2 I^*}\int_0^\infty f_2(s)e^{-\delta_2 s}I\left(t-\tau_2\right)ds-\frac{kT^*V^*}{\eta_2 I^*}\left(\frac{V^*}{V}\right)\int_0^\infty f_2(s)e^{-\delta_2 s}I\left(t-\tau_2\right)ds$$

$$-\frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}\left[\ln\frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I}+\ln\frac{IV^*}{I^*V}+\ln\frac{T^*}{T}\right]ds$$

$$+\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[-\frac{I(t-\tau_2)}{I^*}\right]ds+\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\frac{I}{I^*}\right]ds$$

$$+\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\ln\frac{I(t-\tau_2)V^*}{I^*V}-\ln\frac{IV^*}{I^*V}\right]ds$$

$$\frac{dL}{dt}=-\left\{(\mu_1-r)+\frac{r}{T_m}(T^*+I^*)\left[\frac{(T-T^*)^2}{T}\right]+\frac{r}{T_m}\left[(T-T^*)+(I-I^*)\right]^2\right\}$$

$$+\frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}\left(3-\frac{T^*}{T}-\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\left[\frac{I^*}{I}\right]\right)$$

$$+\frac{kT^*V^*}{\eta_2 I^*}\int_0^\infty f_2(s)e^{-\delta_2 s}I\left(t-\tau_2\right)ds-\frac{kT^*V^*}{\eta_2 I^*}\left(\frac{V^*}{V}\right)\int_0^\infty f_2(s)e^{-\delta_2 s}I\left(t-\tau_2\right)ds$$

$$-\frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}\left[\ln\frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I}+\ln\frac{IV^*}{I^*V}+\ln\frac{T^*}{T}\right]$$

$$+\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[-\frac{I(t-\tau_2)}{I^*}\right]ds+kT^*V^*\left[\frac{I}{I^*}\right]$$

$$+\frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\ln\frac{I(t-\tau_2)V^*}{I^*V}\right]+kT^*V^*\ln\frac{IV^*}{I^*V}$$

$$\frac{dL}{dt} = -\left\{(\mu_1 - r) + \frac{r}{T_m}(T^* + I^*)\left[\frac{(T-T^*)^2}{T}\right] + \frac{r}{T_m}\left[(T-T^*) + (I-I^*)\right]^2\right\}$$
$$+ \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}$$
$$\left(3 - \frac{T^*}{T} - \frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\left[\frac{I^*}{I}\right] - \ln\frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I} - \ln\frac{T^*}{T}\right) ds$$
$$- \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\frac{I(t-\tau_2)V^*}{I^*V}\ln\frac{I(t-\tau_2)V^*}{I^*V}\right] ds$$

$$= -\left\{(\mu_1 - r) + \frac{r}{T_m}(T^* + I^*)\left[\frac{(T-T^*)^2}{T}\right]\right\} - \frac{r}{T_m}\left[(T-T^*) + (I-I^*)\right]^2$$
$$- \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}\left[\frac{T^*}{T} - 1 - \ln\frac{T^*}{T}\right] ds$$
$$- \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}\left[\frac{T(t-\tau_1)V(t-\tau_1)}{T^*V^*}\left[\frac{I^*}{I}\right] - 1 - \ln\frac{T(t-\tau_1)V(t-\tau_1)I^*}{T^*V^*I}\right] ds$$
$$- \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[\frac{I(t-\tau_2)V^*}{I^*V} - 1 - \ln\frac{I(t-\tau_2)V^*}{I^*V}\right] ds$$

$$\frac{dL}{dt} = -\left\{(\mu_1 - r) + \frac{r}{T_m}(T^* + I^*)\left[\frac{(T-T^*)^2}{T}\right]\right\} - \frac{r}{T_m}\left[(T-T^*) + (I-I^*)\right]^2$$
$$- \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}\left[g\frac{T^*}{T}\right] ds - \frac{kT^*V^*}{\eta_1}\int_0^\infty f_1(s)e^{-\delta_1 s}\left[g\left(\frac{T(t-\tau_1)I^*V(t-\tau_1)}{T^*V^*I}\right)\right] ds$$
$$- \frac{kT^*V^*}{\eta_2}\int_0^\infty f_2(s)e^{-\delta_2 s}\left[g\left(\frac{I(t-\tau_2)V^*}{I^*V}\right)\right] ds$$

Notice that $T^*, I^*, V^* > 0$, we have that $\frac{dL}{dt} \leq 0$. By theorem 5.3.1 in [15], solutions limit to μ, the largest invarient subset $L'(t) = 0$. Using the similar argument as that in [15] and by Lasealle's on variable principle, the globl asymptotic stability of E^* follows.

Therefore, $E^*(T^*, I^*, V^*)$ is globally asymptotically stable for any $\tau_1, \tau_2 \geq 0$.This complte the proof. $\square$

4. NUMERICAL RESULTS

In this section, to verify the validity of the theoretical result of this paper, we perform numerical simulation for the model (2) with particular distribution function $f(s)$ as

$$f(s) = \delta(s - s_1, s_2),$$

where s is a positive constant and $\delta(s - s_1)$ is the dirac delta function. Then we can see that

$$\int_0^\infty f(s)ds = 1, \quad \eta_1 = \int_0^\infty \delta(s - s_1)e^{-ms}ds = e^{-ms_1}, \quad \eta_2 = \int_0^\infty \delta(s - s_2)e^{-ms}ds = e^{-ms_2}$$

$$\int_0^\infty \delta(s - s_1)e^{-\delta s}\phi(t - s)ds = e^{-\delta s_1}\phi(t - s_1),$$
$$\int_0^\infty \delta(s - s_2)e^{-\delta s}\phi(t - s)ds = e^{-\delta s_1}\phi(t - s_2),$$

for any function of ϕ, with such choice, model (2) leads to:

$$\left.\begin{aligned} T'(t) &= S - \mu_1 T + rT\left(1 - \frac{T + I}{T_{max}}\right) - KTV \\ I'(t) &= \int_0^\infty f_1(S)e^{-\delta_1 S}KT(t - S)V(t - S)dS - \mu_2 I + rT\left(1 - \frac{T + I}{T_{max}}\right) \\ V'(t) &= N\mu_2 \int_0^\infty f_2(S)e^{-\delta_2 S}I(t - S)dS - \mu_3 V \end{aligned}\right\} \quad (23)$$

For the system (23), we define the critical number is as:

$$N_{crit} = \frac{\mu_3}{k\mu_2\eta_2 T_0}\left(\frac{s}{T_0} + \mu_2 - \mu_1\right) > 0.$$

Here we note that, the derived N_{crit} depends on time delay parameter s_1. To conduct numerical results for system (23), we use the data given in Table 1. These secondary

Table 1: Variables and Parameters for viral spread

Parameter	Expansion	Values
T	Uninfected $CD4^{+}$T cell population size	$1000mm^{-3}$
I	Infected $CD4^{+}$T cell density	0
V	Initial density of HIV RNA	$10^{-3}\ mm^{-3}$
μ_1	Natural death rate of $CD4^{+}$T cells	$0.2\ day^{-1}$
μ_2	Blanket death rate of infected $CD4^{+}$T cells	$1\ day^{-1}$
μ_3	Death rate of free virus	$2.4\ day^{-1}$
k	Rate $CD4^{+}$T cells become infected with virus	$1 \times 10^{-4} mm^3 day^{-1}$
r	Growth rate of $CD4^{+}$T cell population	$0.95 day^{-1}$
N	Number of virions produced by infected $CD4^{+}$T cells	Varies
T_{max}	Maximal population level of $CD4^{+}$T cells	$1500mm^{-3}$
s	Source term for uninfected $CD4^{+}$T cells	$0.1\ day^{-1}\ mm^{-3}$
T_0	$CD4^{+}$T cell population for HIV-negative persons	$1000\ mm^{-3}$

parameter values were either determined experimentally or estimated from patient data. The average $CD4^{+}$T cells count in healthy human is $1000/mm^3$, which is taken as its initial value. Since there is no infected $CD4^{+}$T cells immediately after first effective contact between a healthy $CD4^{+}$T cell and a human immunodeficiency virus, so the initial value of infected $CD4^{+}$T cells is taken to be zero. The initial viral load is considered as $1 \times 10^{-3}/mm^3$. We therefore fix the initial value for each iteration as $(1000,\ 0,\ 1 \times 10^{-3})$. Thus the parameter values and initial condition of the system relate to real world scenarios.

For the default parameter values, we can conclude the critical value N_{crit} as $\frac{\mu_3}{k\mu_2 e^{-ms_1}T_0}\left(\frac{s}{T_0} + \mu_2 - \mu_1\right)$. The model system (23) will be globally asymptotically stable. In Figure 1 we choose $s = 0.1,\ N = 2$ and then choose $\tau = 0.1$. Then the system (23) results as asymptotically stable. In Figure 2 by increase 2 exhibits the hopf bifurcation. Similarly in Figure 4 by increasing the value of N as $N = 10$, and s as $s = 0.5$ and τ as $\tau = 0.7$, then the system (23) again exhibits the hopf bifurcation. Finally Figure 5 shows that the existence of the hopf bifurcation by choosing the values as $N = 10,\ s = 0.9$ and $\tau = 0.2$.

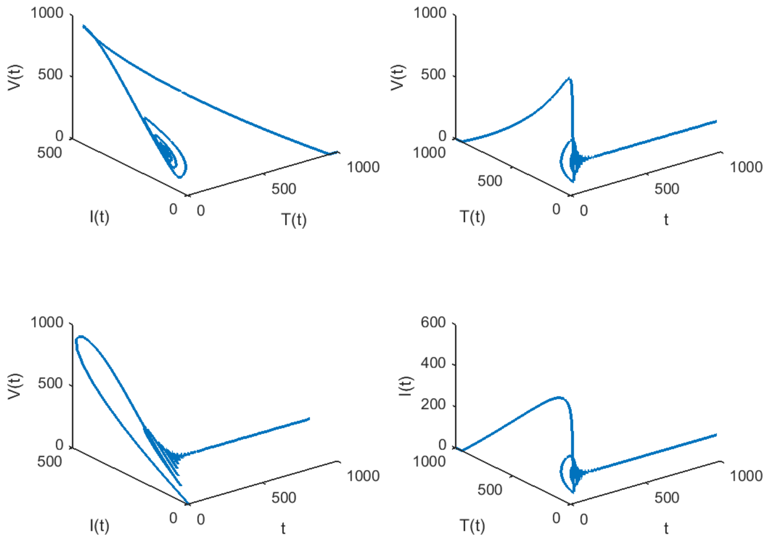

Figure 1: Equilibrium $\overline{E}$ is asymptotically stable for $\tau = 0.2,\ s = 0.1$ and $N = 2$

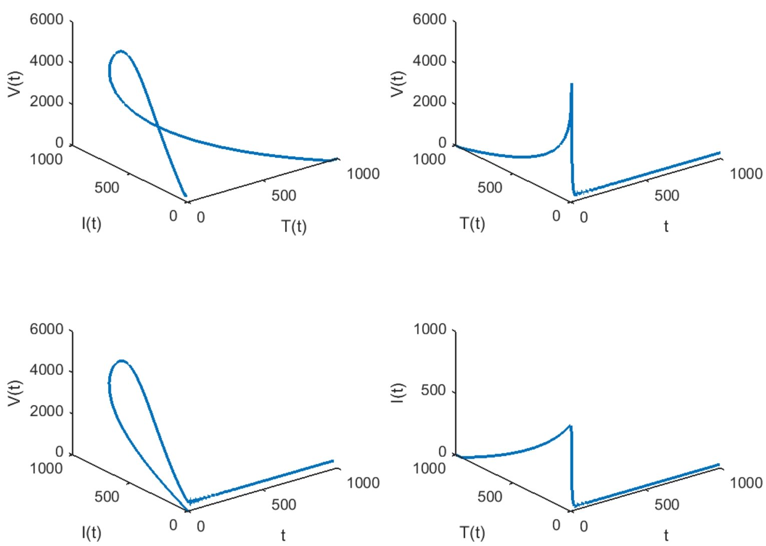

Figure 2: Equilibrium $\overline{E}$ is asymptotically stable for $\tau = 0.2,\ s = 0.1$ and $N = 10$

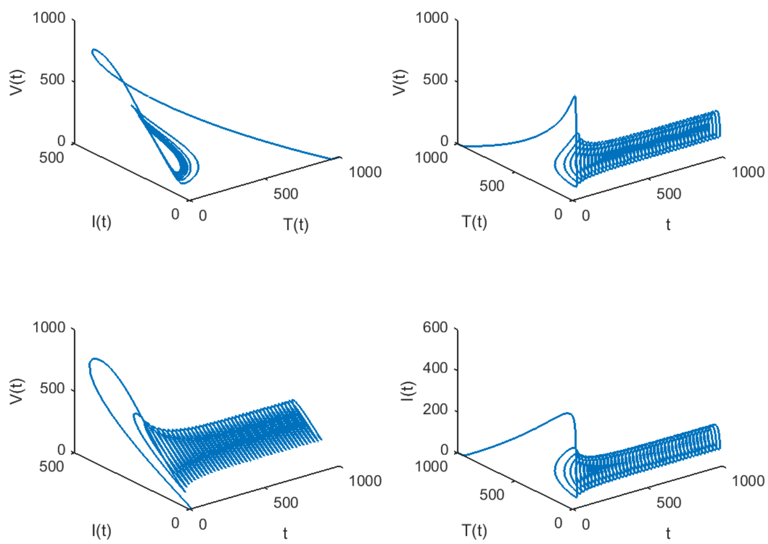

Figure 3: Hopf bifurcation occurs for $\tau = 0.7,\ s = 0.5$ and $N = 2$

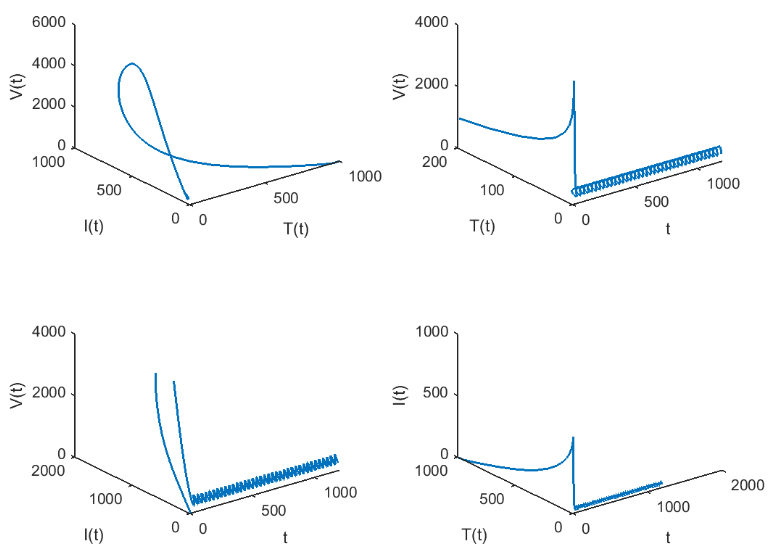

Figure 4: Hopf bifurcation occurs for $\tau = 0.7,\ s = 0.5$ and $N = 10$

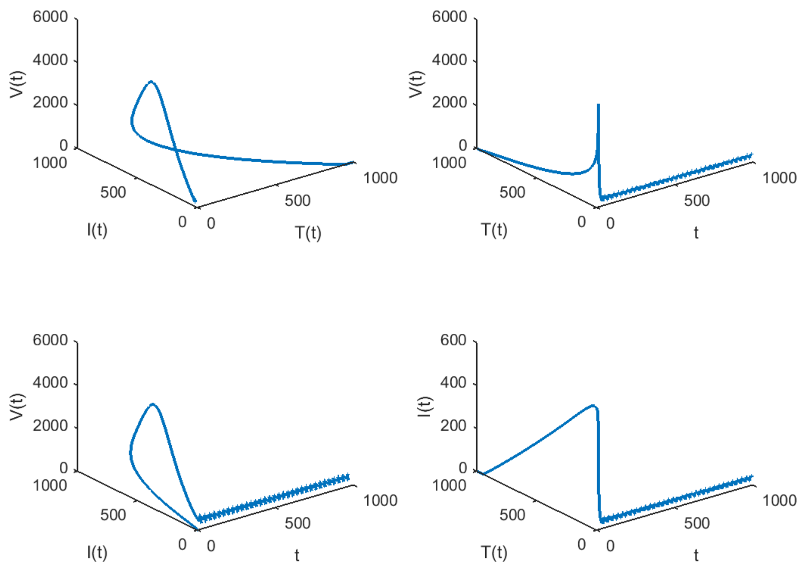

Figure 5: Hopf bifurcation occurs for $\tau = 0.2,\ s = 0.9$ and $N = 10$

5. RESULTS AND DISCUSSION

In this paper we incorporate distributed delays to make the model more realistic and our numerical simulation will explore the importance of discrete delay and distributed delay in the model. Our goal is the construction of Liapunov functional is to prove the global stability of the steady states of a virus dynamics model including distributed delays and full logistic proliferation term of $CD4^{+}$T cells (healthy and infected).

We obtain a critical number N_{crit} on the number of viral particles released per infectious cell in order for infection to be sustained. We obtained that if $N \leq N_{crit}$, we will have only infection free equilibrium, which is globally asymptotically stable and the virus is cleared of the cells population irrespective to the initial conditions. If $N \geq N_{crit}$, then the infection free equilibrium becomes unstable and a unique chronic infection equilibrium exists. We proved the global stability of the chronic infection equilibrium if the condition $r \leq \mu_1 + \frac{r}{T_{max}}[\overline{T}+\overline{I}]$ is satisfied. In this case viral infection is present in the cells population and will become a persistent infection. The result show that for the viral infection model with mitotic transmission the time delay has no effect on both global asymptotic properties of the infection free equilibrium and global asymptotic properties of the chronic infection of the equilibrium. The graphs are plotted to show the comparison of our results with the numerical approach.

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