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Mathematical Modeling of the Interaction between Langerhans Cells and the Spread of HIV Infection

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Abstract - *In this research work, we propose a system of nonlinear ordinary differential equation used to model the interaction between Langerhans cells and HIV infection. The model consists of five compartments, namely, susceptible Langerhans cells, infected Langerhans cells, susceptible T-cells, infected T-cells and free HIV particles. The biology of interactions of Langerhans cells with HIV and mathematical preliminaries which plays a crucial role in our entire research work was described. By presenting a theoretical framework related to the infection mechanism, a biologically meaning full assumption was considered. Furthermore, the positivity of the model solution, the equilibrium point (both virus free and endemic equilibrium) of the model was shown and its stability was investigated. Finally, by using a numerical simulation the developed model was studied and the results concluded that the numerical simulation matches the analytical solution as expected.*

Key Words: *Langerhans cells, T-cells, HIV, Stability and Numerical Simulation.*

1. INTRODUCTION

The term *Langerhans cell (LC)* was studied by a German medical student Paul Langerhans. He was 21 years old when he described in 1868 a new epidermal cell type which now bears his name. The cells have long dendrites, so Langerhans mistakenly regarded them as a component of the nervous system. A century later, Inga Silberberg discovered that these cells instead have a role in immunity, and later work showed they are a type of dendritic cell, a classic antigen-presenting cell. A network of epidermal LC laces through the skin and mucosa, including the anal and vaginal mucosa as well as the male foreskin [2].

An electron microscopic study showed that during sensitization to allergenic compounds, LC migrate from the skin through the lymph vessels and come into close contact with lymphocytes in the draining lymph nodes [3]. These findings suggested that LC play an important role in the development of the immune response to skin antigens and triggered various groups to investigate the possibility that it may function as the most peripheral arm of the immune system. Throughout the 1970s and early 1980s, it was established that the cell represented an essential element of the immune system playing a central role in the mechanisms of defense of the body in a wide range of pathological processes [4].

It is a well known fact that the CD4+ T-cells are targets of HIV and are also important for the establishment and maintenance of an adaptive immune response. CD8+ T-cells are the primary effectors cells in HIV infection, as they kill infected cells and produce non-lytic antiviral factors. In lymph node, LC activates CD4+ and CD8+ T-cells during its presentation of antigen. Originated from the bone marrow, LCs migrate to the peripheral epithelia (skin, mucous membrane) where they play a primordial role in the induction of an immune response and are especially active in stimulating naive T lymphocytes in the primary response through a specific cooperation with CD4+ T cells after migration to proximal lymph node. Also LC can repopulate from local and blood-borne precursors. Similar to other myeloid DC, LCs is able to bridge innate and adaptive immunity. They are able to interact directly with

microorganisms at the periphery to produce effectors cytokines and initiate or re-stimulate activation of T and B cells through antigen presentation [7, 8].

The immunocompetent cells which act as antigen-presenting cells, Langerhans cells, can be infected. Its infection by HIV is relevant to several reasons. Firstly, LCs of mucosal epithelia may be among the first cells to be infected following mucosal HIV expositor and, secondly, LCs may serve as reservoir for continued infection of CD4+ T cells, especially in lymph node where epidermal LCs migrate following antigenic activation [5].Additionally, many indirect and/or direct experimental data have shown that LCs may be a privileged target, reservoir, and vector of dissemination for the HIV for the inoculation sites (mucosa) to lymph nodes where the emigrated infected LCs could infect T lymphocytes. Apart from many plasma membrane determinants, LCs also expresses CD4+ molecules which make them susceptible targets and reservoirs for HIV. Once infected these cells due to their localization in areas at risk (skin, mucous membranes), their capacity to migrate from the epidermal compartment to lymph nodes, and their ability to support viral replication without major cytopathic effects could play a role of vector in the dissemination of virus from the site of inoculation to the lymph nodes and thereby contribute to the infection of T lymphocytes [6].

Infection of biopsies of human cervical and skin of primate foreskin tissue explants show that LC can be infected. Topical infection of human vaginal epithelial explants with HIV strongly suggested that LC and non-activated T-lymphocytes are the major cell types expressing HIV antigen in and emigrating from the explants and they are often associated during emigration with HIV antigen concentrated at their contact region. The latter suggests that LCs is transferring HIV to CD4 T cells. LC may also provided a mode of intracellular storage while transporting HIV to CD4 T cells in the sub mucosal lymphoid tissue and thence to draining lymph nodes [3].

Alternatively, another data suggest that LC has an anti-viral function by capturing HIV for degradation and thus initially impairing HIV transmission. This anti-viral function is dependent on viral load and LC phenotype, strongly suggesting that the role of LC in HIV transmission is also likely to be influenced by local conditions such as viral load, stage of the menstrual cycle, state of vaginal mucus and/or inflammation and co-infections. They are also of particular importance because HIV exploits it to enhance infection. Therefore, LC are the critical link between virus, CD4+ and CD8+ T-cells. After encountering antigen in the periphery, LC mature and travel to the lymph node (LN). LC maturation includes increasing antigen presentation on major histocompatibility complex (MHC) molecules, and up regulating co-stimulatory molecules.Mature LC prime CD4+ T-cells to become effector T-helper cells. Additionally, LC cross-present exogenous antigens on MHC to prime CD8+ T-cells differentiate into cytotoxic T lymphocytes (CTL). Thus it is essential for fighting intracellular pathogens like HIV. In contrast, LC may act as one of the primary initial targets for HIV infection. Since it is specialized by antigen presentation and belongs to the skin immune system, the virus can associated with it to travel to lymphoid tissue, where 98% of T-cells reside. During antigen presentation, it can facilitate infection of CD4+ T-cell. As part of the normal immune response, LCs captures virions at the site of transmissions in the mucosa (peripheral tissues) and migrates to the lymphoid tissue where they present to naive T cells and hence are responsible for large-scale infections of the CD4+ T cells. Generally, as a result of these roles of LC, in HIV infections, it plays a dual role of promoting immunity while also facilitating infections [2, 8, 9].

1.1. Mathematical Preliminaries

In this section we present some definitions and theorems required to analyze model systems in our research work.

Theorem 1.1 (Existence and Uniqueness Theorem): Assume D is an open subset of $\mathbb{R} \times \mathbb{R}^n$, and $f: D \longrightarrow \mathbb{R}^n$ is continuous. Then for each $t_0 \in \mathbb{R}$ and $x_0 \in \mathbb{R}^n$, the initial value problem (IVP)

$$x' = f(t,x), \quad x(t_0) = x_0 \qquad (1)$$

has a solution x. If in addition, f has continuous first order partial derivative with respect to $x_1, x_2, \dots, x_n$ in R^n, then equation (1) has a unique solution.

The proof is found on [10].

Definition 1.1: Let f is a real valued function defined on a domain D. The function f is said to be bounded on D if and only if there is a positive number M such that $|f(x,y)| \leq M$ for all $(x,y) \in D$.

Definition 1.2: A domain $\Omega \subseteq \mathbb{R}^n$ is said to be positively invariant for the system $\frac{dx}{dt} = f(x)$ if for all $x(t_0) \in \Omega$, then $x(t) \in \Omega$ for all $t \geq t_0$.

Routh-Hurwitz Criteria

Given a polynomial,

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + a_2\lambda^{n-2} + \cdots + a_{n-1} + a_n$$

where the coefficients a_i are real constants, for $i = 1,2, \dots, n$, define the n Hurwitz matrices using the coefficients a_i of the characteristic polynomial:

$$H_1 = [a_1], \quad H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, H_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix}, \text{ and } H_n = \begin{bmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 0 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \dots & 0 \\ 0 & 0 & 0 & 0 & \dots & a_n \end{bmatrix}$$

where $a_j = 0$ if $j > 0$.

All of the roots of the polynomial $P(\lambda)$ are negative or have negative real part if and only if the determinants of all Hurwitz matrices are positive: $\det H_j > 0$ for all $j = 1,2, \dots, n$.

When $n = 2$, we have $P_2(\lambda) = \lambda^2 + a_1\lambda + a_2$. Hence by Routh-Hurwitz criteria we have $\det H_1 = a_1 > 0$ and

$$\det H_2 = \det \begin{bmatrix} a_1 & 1 \\ 0j & a_2 \end{bmatrix} = a_1 a_2 > 0$$

Similarly, when $n = 5$:

$$a_i > 0 \text{ for } i = 1, 2, \dots, 5, \frac{a_1 a_2 - a_3}{a_1} > 0, a_3 - \frac{a_1(a_1 a_4 - a_5)}{a_1 a_2 - a_3} > 0, \; a_1 a_4 - a_5 - \frac{a_5(a_1 a_2 - a_3)^2}{a_3(a_1 a_2 - a_3) - a_1(a_1 a_4 - a_5)} > 0 \qquad (2)$$

2. MODEL FORMULATION AND ANALYSIS

Aspects of an organism's defense against viral and bacterial infections and the reaction of immune system to infection are the main problems in practical immunology. In addition to antiviral and antibacterial defense, the immune system plays a decisive role in tissue incompatibility reactions, antitumor immunity, autoimmune diseases, and allergies [6]. Therefore, the formulation of mathematical models of the interaction between Langerhans cells and the spread of HIV infection provides the tangible understanding on these systems and the HIV transmission with its life-span.

2.1. Model Formulation

In this section, we develop a model which describes the interaction between HIV and Langerhans cells as a system of nonlinear ordinary differential equation. For the model we denote by (L) the concentration of healthy Langerhans cells (or susceptible Langerhans cells), (L_I) the concentration of infected Langerhans cells, (T) the concentration of healthy T-cells (or susceptible T-cells), (T_I) the concentrations of infected T-cells and (V) the concentration of free HIV.

2.1.1. Assumptions of the Model

The main feature of the model is that the force of infection is obtained by averaging the probability of exposure of Langerhans cells and T-cells to HIV. For the model, the following assumptions have been taken:

(i) The amount of healthy Langerhans cells can increase due to newly recruited (produced) individuals. In converse, the number can decrease due to the natural death rate and infection rate.

(ii) The susceptible Langerhans cells become infected Langerhans cells when in contact with the free virus and it remove from the circulation by both natural death and virus induced death rate.

(iii) The number of healthy (susceptible) T-cells increases due to its constant rate of production in bone marrow, but the number can decreases due to its natural death rate, infection rate by free virus, infection rate by infected Langerhans cells and infection rate by infected T-cells.

(iv) The susceptible T-cells become infected T-cells when in contact with free virus and infected Langerhans cells; and the infected T-cells remove by its natural death rate and virus induced death rate.

(v) The effective antiviral immune response of healthy T-cells in collaborations of healthy Langerhans cell depends on the amount of virus present, the infected tissues and the chronicity of the infection.

(vi) An infected Langerhans cells and infected T-cells release hundreds of virions that can infect a healthy Langerhans cells and healthy T-cells.

The schematic diagram used for the development of model is shown in Figure (1).

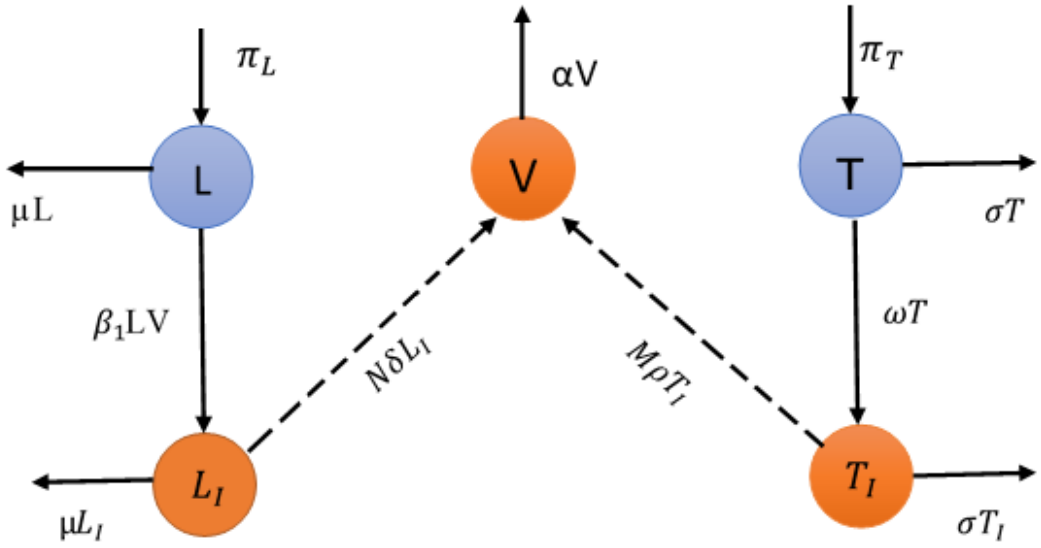

Figure 1: Model structure

Parameter description	Symbol
The constant rate of production of susceptible Langerhans cells from the bone marrow	π_L
Infection rate of susceptible Langerhans cells by free virus	β_1
Natural death rate of Langerhans cells	μ
Death rate of L_I due to virus (virus induced death rate)	δ
The constant rate of production of susceptible T-cells from the bone marrow	π_T
Natural death rate of T cells	σ
Infection rate of T-cells by free virus	β_2
Infection rate of T-cells by infected Langerhans cells	β_3
Infection rate of T-cells by infected T-cells	β_4
Death rate of infected T-cells due to virus (virus induced death)	ρ
Removal rate of free virus	α
Number of the virus particles assumed to produced by the infected Langerhans cells during its life time including any of its daughter cells	N
Number of the virus particles assumed to produced by the infected T-cells during its life time including any of its daughter cells	M

Table 1: The parameter description and its symbol

Depending on the assumptions stated and the schematic diagram of our model structure, we can formulate the governing model equations:

$$\begin{cases} \dfrac{dL}{dt} = \pi_L - \beta_1 VL - \mu L \\ \dfrac{dL_I}{dt} = \beta_1 VL - \mu L_I - \delta L_I \\ \dfrac{dT}{dt} = \pi_T - \sigma T - \beta_2 VT - \beta_3 L_I T - \beta_4 T_I T \\ \dfrac{dT_I}{dt} = \beta_2 VT + \beta_3 L_I T + \beta_4 T_I T - \sigma T_I - \rho T_I \\ \dfrac{dV}{dt} = \mathrm{N}\delta\mathrm{L_I} + \mathrm{M}\rho\mathrm{T_I} - \alpha\mathrm{V} \end{cases} \quad (3)$$

where $\frac{dL}{dt}$, $\frac{dL_I}{dt}$, $\frac{dT}{dt}$, $\frac{dT_I}{dt}$ and $\frac{dV}{dt}$ denote the rates of change of population densities of concentration of susceptible Langerhans cell (L), infected Langerhans cell (L_I), susceptible T-cells (T), infected T- cells (T_I) and free HIV (V) at a time t respectively. The descriptions of symbols of parameters are explained in Table 1. We also suppose that $\omega = \beta_2 V + \beta_3 L_I + \beta_4 T_I$ for the schematic diagram shown on Figure 1.

2.2. Model Analysis

In this section we study the basic properties of the solutions of system of equation (3). For this, we are going to show the existence and uniqueness of the solution, positivity of the solution, steady states and stability of the solution.

2.2.1. Existence and Uniqueness

Theorem 2.1: Suppose that a system of equation (3) is given with non negative initial value $X(t_0) = (L_0, L_{I_0}, T_0, T_{I_0}, V_0)$. Then it has a unique solution.

Proof: We proof Theorem 2.1 by using Theorem 1.1.

(i) Existence:

Let $(t, L, L_I, T, T_I, V) \subset \mathbb{R} \times \mathbb{R}^5$. Assume

$f_1(L, L_I, T, T_I, V) = \pi_L - \beta_1 VL - \mu L$

$f_2(L, L_I, T, T_I, V) = \beta_1 VL - \mu L_I - \delta L_I$

$f_3(L, L_I, T, T_I, V) = \pi_T - \sigma T - \beta_2 VT - \beta_3 L_I T - \beta_4 T_I T$

$f_4(L, L_I, T, T_I, V) = \beta_2 VT + \beta_3 L_I T + \beta_4 T_I T - \sigma T_I - \rho T_I$ and

$f_5(L, L_I, T, T_I, V) = \mathrm{N}\delta\mathrm{L_I} + \mathrm{M}\rho\mathrm{T_I} - \alpha\mathrm{V}$

Then all f_i are continuous in $(t, L, L_I, T, T_I, V) \subset \mathbb{R} \times \mathbb{R}^5$ for $i = 1, \ldots, 5$. By Theorem (1.1) for each $t_0 \in \mathbb{R}$ and $(L, L_I, T, T_I, V) \in \mathbb{R}^5$ there exist a solution of the system of equation (3) with the given initial values.

(ii) Uniqueness:

Since all f_i has a continuous first order partial derivatives with respect to L, L_I, T, T_I and V, by Theorem (1.1) the system of equation (3) with the given initial value has a unique solution.

2.2.2. Invariant Region

Since we are modeling interaction between Pathogens and healthy cells at cellular level, the variables and parameters are assumed to be positive for all $t \geq 0$. The system of equation (3) will therefore be analyzed in a suitable feasible region Ω of biological interest

$$\Omega = \left\{(L, L_I, T, T_I, V) \in \mathbb{R}^5_+ : L + L_I \leq \frac{\pi_L}{\mu}, T + T_I \leq \frac{\pi_T}{\sigma}\right\}.$$

We note that the model describes a population and therefore it is very important to prove that all the state variables (L, L_I, T, T_I and V) are non-negative for all time. More precisely if the system of equation (3) has non-negative initial data, then the solution will remain inside Ω for all time $t \geq 0$, i.e., the set Ω is positively invariant.

Theorem 2.2: The region Ω is positively invariant.

Proof: In our model we have three sub populations namely; Langerhans cells, T cells and virus. Considering the total population of Langerhans cells only we have

$$L_{tot} = L + L_I$$

Hence

$$\frac{dL_{tot}}{dt} = \frac{dL}{dt} + \frac{dL_I}{dt}$$
$$= (\pi_L - \beta_1 VL - \mu L) + (\beta_1 VL - \mu L_I - \delta L_I)$$
$$= \pi_L - \mu(\underbrace{L + L_I}_{L_{tot}}) - \delta L_I$$
$$= \pi_L - \mu L_{tot} - \delta L_I$$
$$\leq \pi_L - \mu L_{tot}, \quad \text{since } \delta, L_I \geq 0$$

$$\frac{dL_{tot}}{dt} + \mu L_{tot} \leq \pi_L \tag{4}$$

After multiplying both sides of equation (4) by its integrating factor $e^{\mu t}$, we get

$$(e^{\mu t})\left(\frac{dL_{tot}}{dt}\right) + (e^{\mu t})\mu L_{tot} \leq \pi_L e^{\mu t}$$

$$(L_{tot} e^{\mu t})' \leq \pi_L e^{\mu t} \tag{5}$$

Then integrate both sides of equation (5) with respect to t.

$L_{tot} e^{\mu t} \leq \frac{\pi_L}{\mu} e^{\mu t} + c_1$, where c_1 is a constant of integration.

$$L_{tot} \leq \frac{\pi_L}{\mu} + c_1 e^{-\mu t}$$

At $t = 0$ we have $L_{tot} = L_{tot}(0)$ which implies that $c_1 = L_{tot}(0) - \frac{\pi_L}{\mu}$.

Using this value of c_1 we get:

$$L_{tot} \leq \frac{\pi_L}{\mu} + (L_{tot}(0) - \frac{\pi_L}{\mu})e^{-\mu t}$$

As the number of Langerhans cells increases (i.e. $t \to \infty$) we have

$$\lim_{t\to\infty} L_{tot} \leq \frac{\pi_L}{\mu} := m_1$$

Similarly the total population of T cells is given by $T_{tot} = T + T_I$

Thus we have

$$\frac{dT_{tot}}{dt} = \frac{dT}{dt} + \frac{dT_I}{dt}$$
$$= (\pi_T - \sigma T - \beta_2 VT - \beta_3 L_I T - \beta_4 T_I T) + (\beta_2 VT + \beta_3 L_I T + \beta_4 T_I T - \sigma T_I - \rho T_I)$$

$$= \pi_T - \sigma\, T - \sigma\, T_I - \rho\, T_I = \pi_T - \sigma(\underbrace{T + T_I}_{T_{tot}}) - \rho\, T_I$$

$$\frac{dT_{tot}}{dt} \le \pi_T - \sigma\, T_{tot}, \text{ since } \rho\,, T_I \ge 0$$

$$\frac{dT_{tot}}{dt} + \sigma\, T_{tot} \le \pi_T \qquad (6)$$

Multiply both sides of equation (6) by its integrating factor $e^{\sigma\, t}$.

$$(e^{\sigma\, t})\frac{\mathrm{dT_{tot}}}{\mathrm{dt}} + (e^{\sigma\, t})\sigma\, \mathrm{T_{tot}} \le (e^{\sigma\, t})\pi_\mathrm{T}$$

$$(\, T_{tot} e^{\sigma\, t})' \le \pi_T e^{\sigma\, t} \qquad (7)$$

Then integrate both sides of equation (7) with respect to t.

$T_{tot} e^{\sigma t} \le \frac{\pi_T}{\sigma} e^{\sigma t} + c_2$, where c_2 is a constant of integration.

$$T_{tot} \le \frac{\pi_T}{\sigma} + c_2 e^{-\sigma t}$$

At $t = 0$ we have $T_{tot} = T_{tot}(0)$ so that we have $c_2 = T_{\mathrm{tot}}(0) - \frac{\pi_T}{\sigma}$. Therefore we have

$$T_{tot} \le \frac{\pi_T}{\sigma} + \left(T_{\mathrm{tot}}(0) - \frac{\pi_T}{\sigma}\right) e^{-\sigma t}$$

As the number of T cells increases (i.e. $t \to \infty$) we have

$$\lim_{t\to\infty} T_{tot} \le \frac{\pi_T}{\sigma} := m_2$$

Now, since $0 \le L_{tot} \le m_1$ and $0 \le T_{tot} \le m_2$, we have $L_I \le m_1$ and $T_I \le m_2$.

Thus the equations of the rate of change of virus sub population $\frac{dV}{dt} = N\delta\, L_I + M\rho T_I - \alpha V$ canbe rewritten as:

$$\frac{dV}{dt} \le N\delta m_1 + M\rho m_2 - \alpha\, V$$

$$\frac{dV}{dt} + \alpha V \le N\delta m_1 + M\rho m_2 \qquad (8)$$

Again to solve the first order linear differential inequality (8), we need to find it's integrating factor and solve it as we solve for L_{tot} and T_{tot}. Therefore, its solution is given as

$$V(t) \le \frac{N\, \delta m_1 + M\rho\, m_2}{\alpha} + \left(V(0) - \frac{N\, \delta m_1 + M\rho\, m_2}{\alpha}\right) e^{-\alpha t}$$

As time progress we have $\lim_{t\to\infty} V(t) \le \frac{N\, \delta m_1 + M\rho\, m_2}{\alpha} := m_3$

Now, since all solutions of L_{tot}, T_{tot} and V are bounded by Q where $Q = \max\{m_1, m_2, m_3\}$, we have

$$L, L_I, T, T_I, V \le Q$$

Therefore, all the solutions remain in the region Ω and thus we have proved that the region Ω is positively invariant.

Theorem 2.3: All the solutions of system of equation (3) are bounded.

Proof: In proof of Theorem 2.2 we have shown that

$\lim_{t\to\infty} L_{tot} \le \frac{\pi_L}{\mu} := m_1$, $\lim_{t\to\infty} T_{tot} \le \frac{\pi_T}{\sigma} := m_2$ and $\lim_{t\to\infty} V(t) \le \frac{N\, \delta m_1 + M\rho\, m_2}{\alpha} := m_3$

Then, we have

$0 \le L \le m_1, 0 \le L_I \le m_1\,, 0 \le T \le m_2, 0 \le T_I \le m_2$ and $0 \le V \le m_3$.

Therefore the Theorem is proved.

2.2.3. Steady States and Stability

In this section, we are going to determine the equilibrium point and stability properties of the system of equation (3).

Proposition 2.4: The reasonable initial conditions of the system (3) are:

$$L_0 = L(0) = \frac{\pi_L}{\mu}, L_{I_0} = L_I(0) = 0, T_0 = T(0) = \frac{\pi_T}{\sigma}, T_{I_0} = T_I(0) = 0, V_0 = V(0) = 0$$

Proof: In the absence of virus, since $L_I = 0, T_I = 0$ and $V = 0$, the rates of change of population densities of the system of equation (3) can be reduced to

$$\begin{cases} \frac{dL}{dt} = \pi_L - \mu L \\ \frac{dT}{dt} = \pi_T - \sigma T \end{cases} \quad (9)$$

Now, to get the steady state value of equation (3) in the absence of virus, we equate the right hand side of equation (9) to 0 as follows.

$\pi_L - \mu L = 0$ and $\pi_T - \sigma T = 0$ which implies $L = \frac{\pi_L}{\mu}$ and $T = \frac{\pi_T}{\sigma}$.

Thus, the reasonable initial conditions for infection by free virus of equation (3) can be

$$L(0) = L_0 = \frac{\pi_L}{\mu}, L_I(0) = 0, T(0) = T_0 = \frac{\pi_T}{\sigma}, T_I(0) = 0, V(0) = V_0 = 0$$

and the equilibrium point of uninfected system is $\left(\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0, 0\right)$.

Endemic Equilibrium (EE)

In the presence of virus we can find the critical point, endemic equilibrium point, of the system of equation (3) as follows:

Suppose that

$$f_1(L, L_I, T, T_I, V) = \pi_L - \beta_1 VL - \mu L \quad (10)$$

$$f_2(L, L_I, T, T_I, V) = \beta_1 VL - \mu L_I - \delta L_I \quad (11)$$

$$f_3(L, L_I, T, T_I, V) = \pi_T - \sigma T - \beta_2 VT - \beta_3 L_I T - \beta_4 T_I T \quad (12)$$

$$f_4(L, L_I, T, T_I, V) = \beta_2 VT + \beta_3 L_I T + \beta_4 T_I T - \sigma T_I - \rho T_I \quad (13)$$

$$f_5(L, L_I, T, T_I, V) = \mathrm{N}\delta\mathrm{L_I} + \mathrm{M}\rho\mathrm{T_I} - \alpha\mathrm{V} \quad (14)$$

Then we solve for $f_1 = 0, f_2 = 0, f_3 = 0, f_4 = 0$ and $f_5 = 0$ simultaneously.

From equation (10) and equation (11) we have

$$\frac{\pi_L}{\beta_1 V + \mu} = \frac{(\mu + \sigma)L_I}{\beta_1 V}$$

which can be rearranged as

$$\pi_L \beta_1 V - (\mu + \delta)L_I \beta_1 V = (\mu + \delta)\mu L_I \quad (15)$$

Again, from equation (12) and equation (13), we have

$$\frac{\pi_T}{\sigma + \beta_2 V + \beta_3 L_I + \beta_4 T_I} = \frac{(\sigma + \rho)T_I}{\beta_2 V + \beta_3 L_I + \beta_4 T_I}$$

After rearranging it, we obtain

$$\pi_T \beta_2 V - (\sigma + \rho)\beta_2 T_I V = (\sigma + \rho)T_I(\sigma + \beta_3 L_I + \beta_4 T_I) - \pi_T \beta_3 L T_I - \pi_T \beta_4 T_I \quad (16)$$

From equation (14, we have

$$V = \frac{N\delta L_I + M\rho T_I}{\alpha} \qquad (17)$$

Substituting equation (17) in equation (15) and bringing like term together gives:

$$L_I\left[\frac{N\pi_L\beta_1\delta}{\alpha} - \mu(\mu+\delta)\right] + T_I\left[\frac{M\pi_L\beta_1\rho}{\alpha}\right] = L_I^2\left[\frac{N\beta_1\delta\,(\mu+\delta)}{\alpha}\right] + L_IT_I\left[\frac{M\beta_1\rho(\mu+\delta)}{\alpha}\right].$$

If we let $a = \frac{N\pi_L\beta_1\delta}{\alpha} - \mu(\mu+\delta), b = \frac{M\pi_L\beta_1\rho}{\alpha}, c = \frac{N\beta_1\delta\,(\mu+\delta)}{\alpha}$ and $d = \frac{M\beta_1\rho(\mu+\delta)}{\alpha}$ we will have, $aL_I + bT_I = cL_I^2 + dL_IT_I$ (18)

Similarly, insert equation (17) into (16) and collect like term together. We obtain

$eL_I + fT_I = gT_IL_I + hT_I^2.$ (19)

Where $e = \frac{N\pi_T\beta_2\delta}{\alpha} + \pi_T\beta_3,\ f = \frac{M\pi_T\beta_2\rho}{\alpha} - \sigma(\sigma+\rho) + \pi_T\beta_4,\ g = \frac{N\beta_2\rho\,(\sigma+\rho)}{\alpha} + \beta_3(\delta+\rho)$ and $h = \frac{M\beta_2\rho\,(\delta+\rho)}{\alpha} + (\delta+\rho)\beta_4.$

Now, after rearranging and combining together the equations (18) and (19) we will obtain equation (20) below.

$T_I^4[gch^2 - dhg^2] + T_I^3[2hg(de-cf) - hg(de-ga) - g^2(gb-df)] + T_I^2[gcf^2 + (de-ga)(he+fg) - dhe^2 + 2eg(gb-df)] + T_I[fe(de-ga) - e^2(gb-df)] = 0$ (20)

Suppose

$k = gch^2 - dhg^2,\ l = 2hg(de-cf) - hg(de-ga) - g^2(gb-df),\ m = gcf^2 + (de-ga)(he+fg) - dhe^2 + 2eg(gb-df)$ and $n = fe(de-ga) - e^2(gb-df).$

Then, equation (20) become

$$kT_I^4 + lT_I^3 + mT_I^2 + nT_I = 0$$

but $T_I = 0$ is the trivial solution. Therefore, we will have the cubic polynomial

$$kT_I^3 + lT_I^2 + mT_I + n = 0\,.$$

We can solve this cubic polynomial using mat lab and only take the real and positive T_I and neglect the rest. So, we get

$$T_I = \frac{\left(-27k^8n+9k^7lm-2k^6l^3+3\sqrt{3}\sqrt{27k^{16}n^2-18k^{15}lmn+4k^{15}m^3+4k^{14}l^3n-k^{14}l^2m^2}\right)^{1/3}}{3\times 2^{1/3}k^3} - \frac{2^{\frac{1}{3}}\left(2187k^5c-729k^4l^2\right)}{2187k^3\left(-27k^8n+9k^7lm-2k^6lm+3\sqrt{3}\sqrt{27k^{16}n^2-18k^{15}lmn+4k^{15}m^3+4k^{14}l^3n-k^{14}l^2m^2}\right)^{1/3}} - \frac{l}{3k} \qquad (21)$$

Using this solutions of T_I, we can solve for L, L_I, T and V and obtain

$L_I = \frac{T_I(hT_I-f)}{e-gT_I}, V = \frac{N\delta\,L_I+M\rho\,T_I}{\alpha}, L = \frac{\pi_L}{\beta_1V+\mu}, T = \frac{(\sigma+\rho)T_I}{\beta_2V+\beta_3L_I+\beta_4T_I}$ (22)

Generally, we have seen that the system of equation (3) has two steady states:

The uninfected steady states (VFE) $\left(E_0 = \frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0, 0\right)$ and the infected steady state (EE) $E^* = (L^*, L_I^*, T^*, T_I^*, V^*)$ where $L^*, L_I^*, T^*, T_I^*, V^*$ are values of L, L_I, T, T_I, V given in equation (21) and (22) above.

2.2.4. Local Stability of Virus Free Equilibrium (VFE)

To discuss the local stability of virus free equilibrium, $\left(E_0 = \frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0,0\right)$, we consider the linearized system of equation (3) at E_0 .

Now we find the Jacobean matrix from equation (10)-(14) as follows.

$$J(L, L_I, T, T_I, V) = \begin{pmatrix} \frac{\partial f_1}{\partial L} & \frac{\partial f_1}{\partial L_I} & \frac{\partial f_1}{\partial T} & \frac{\partial f_1}{\partial T_I} & \frac{\partial f_1}{\partial V} \\ \frac{\partial f_2}{\partial L} & \frac{\partial f_2}{\partial L_I} & \frac{\partial f_2}{\partial T} & \frac{\partial f_2}{\partial T_I} & \frac{\partial f_2}{\partial V} \\ \frac{\partial f_3}{\partial L} & \frac{\partial f_3}{\partial L_I} & \frac{\partial f_3}{\partial T} & \frac{\partial f_3}{\partial T_I} & \frac{\partial f_3}{\partial V} \\ \frac{\partial f_4}{\partial L} & \frac{\partial f_4}{\partial L_I} & \frac{\partial f_4}{\partial T} & \frac{\partial f_4}{\partial T_I} & \frac{\partial f_4}{\partial V} \\ \frac{\partial f_5}{\partial L} & \frac{\partial f_5}{\partial L_I} & \frac{\partial f_5}{\partial T} & \frac{\partial f_5}{\partial T_I} & \frac{\partial f_5}{\partial V} \end{pmatrix}$$

$$= \begin{pmatrix} -\beta_1 V - \mu & 0 & 0 & 0 & -\beta_1 L \\ \beta_1 V & -(\mu+\delta) & 0 & 0 & \beta_1 L \\ 0 & -\beta_3 T & -\sigma - \beta_2 V - \beta_3 L_I - \beta_4 T_I & -\beta_4 T & -\beta_2 T \\ 0 & \beta_3 T & \beta_2 V + \beta_3 L_I + \beta_4 T_I & \beta_4 T - (\sigma+\rho) & \beta_2 T \\ 0 & N\delta & 0 & M\rho & -\alpha \end{pmatrix} \quad (23)$$

The Jacobean matrix of virus free equilibrium E_0 is

$$J\left(\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0,0\right) = \begin{pmatrix} -\mu & 0 & 0 & 0 & \frac{-\beta_1 \pi_L}{\mu} \\ 0 & -(\mu+\delta) & 0 & 0 & \frac{\beta_1 \pi_L}{\mu} \\ 0 & \frac{-\beta_3 \pi_T}{\sigma} & -\sigma & \frac{-\beta_4 \pi_T}{\sigma} & \frac{-\beta_2 \pi_T}{\sigma} \\ 0 & \frac{\beta_3 \pi_T}{\sigma} & 0 & \frac{\beta_4 \pi_T}{\sigma} - (\sigma+\rho) & \frac{\beta_2 \pi_T}{\sigma} \\ 0 & N\delta & 0 & M\rho & -\alpha \end{pmatrix}$$

Then, the linearized system is:

$$\begin{pmatrix} \frac{du}{dt} \\ \frac{dv}{dt} \\ \frac{dw}{dt} \\ \frac{dx}{dt} \\ \frac{dy}{dt} \end{pmatrix} = J\left(\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0,0\right) \begin{pmatrix} u \\ v \\ w \\ x \\ y \end{pmatrix} = \underbrace{\begin{pmatrix} -\mu & 0 & 0 & 0 & \frac{-\beta_1 \pi_L}{\mu} \\ 0 & -(\mu+\delta) & 0 & 0 & \frac{\beta_1 \pi_L}{\mu} \\ 0 & \frac{-\beta_3 \pi_T}{\sigma} & -\sigma & \frac{-\beta_4 \pi_T}{\sigma} & \frac{-\beta_2 \pi_T}{\sigma} \\ 0 & \frac{\beta_3 \pi_T}{\sigma} & 0 & \frac{\beta_4 \pi_T}{\sigma} - (\sigma+\rho) & \frac{\beta_2 \pi_T}{\sigma} \\ 0 & N\delta & 0 & M\rho & -\alpha \end{pmatrix}}_{=A} \begin{pmatrix} u \\ v \\ w \\ x \\ y \end{pmatrix}$$

If we let

$$a_{11} = \mu, a_{15} = a_{25} = \frac{\beta_1 \pi_L}{\mu}, a_{22} = \mu + \delta\,, a_{32} = a_{42} = \frac{\beta_3 \pi_T}{\sigma}, a_{33} = \sigma, a_{34} = \frac{\beta_3 \pi_T}{\sigma},$$

$$a_{35} = a_{45} = \frac{\beta_2 \pi_T}{\sigma}, a_{44} = \sigma + \rho - \frac{\beta_4 \pi_T}{\sigma}, a_{52} = N\delta\,, a_{54} = M\rho\,, a_{55} = \alpha$$

, we will have

$$A = \begin{pmatrix} -a_{11} & 0 & 0 & 0 & -a_{15} \\ 0 & -a_{22} & 0 & 0 & a_{15} \\ 0 & -a_{32} & -a_{33} & -a_{34} & -a_{35} \\ 0 & a_{32} & 0 & -a_{44} & a_{35} \\ 0 & a_{52} & 0 & a_{54} & -a_{55} \end{pmatrix}$$

Then, the Eigen polynomial of the coefficient matrix A is obtained as follows.

$$|A - \lambda I = 0 \Leftrightarrow \begin{vmatrix} -a_{11} - \lambda & 0 & 0 & 0 & -a_{15} \\ 0 & -a_{22} - \lambda & 0 & 0 & a_{15} \\ 0 & -a_{32} & -a_{33} - \lambda & -a_{34} & -a_{35} \\ 0 & a_{32} & 0 & -a_{44} - \lambda & a_{35} \\ 0 & a_{52} & 0 & a_{54} & -a_{55} - \lambda \end{vmatrix} = 0$$

$$\lambda^5 + b_1\lambda^4 + b_2\lambda^3 + b_3\lambda^2 + b_4\lambda + b_5 = 0 \qquad (24)$$

Where

$$b_1 = a_{11} + a_{12} + a_{33} + a_{44} + a_{55}$$

$$b_2 = a_{11}(a_{22} + a_{33} + a_{44} + a_{55}) + a_{22}a_{33} + (a_{22} + a_{33})(a_{44} + a_{55}) + a_{44}a_{55} + a_{54}a_{35} - a_{15}a_{52}$$

$$b_3 = a_{11}a_{22}a_{33} + a_{11}(a_{22} + a_{33})(a_{44} + a_{55}) + a_{11}a_{44}a_{55} + a_{11}a_{54}a_{35} - a_{11}a_{15}a_{52} + a_{22}a_{33}(a_{44} + a_{55}) + a_{44}\,a_{55}(a_{22} + a_{33}) + a_{54}a_{35}(a_{22} + a_{33}) - a_{15}a_{32}a_{54} + a_{15}a_{52}(a_{44} - a_{33})$$

$$b_4 = a_{11}a_{22}a_{33}(a_{44} + a_{55}) + a_{11}a_{44}a_{55}(a_{22} + a_{33}) + a_{11}a_{54}a_{35}(a_{22} + a_{33}) - a_{11}a_{15}a_{32}a_{54} + a_{11}a_{15}a_{52}(a_{44} - a_{33}) + a_{22}a_{33}a_{44}a_{55} + a_{22}a_{33}a_{54}a_{35} - a_{15}a_{32}a_{33}a_{54} + a_{15}a_{52}a_{33}a_{44}$$

$$b_5 = a_{11}a_{22}a_{33}(a_{44}a_{55} + a_{54}a_{35}) + a_{11}a_{15}a_{33}(a_{52}a_{44} - a_{32}a_{54})$$

By Routh-Hurwitz criterion, it follows that all eigenvalues of equation (24) have negative real parts if and only if it satisfies:

$$b_1 > 0 \text{ for } i = 1, \ldots, 5,\ \frac{b_1 b_2 - b_3}{b_1} > 0, b_3 - \frac{b_1(b_1 b_4 - b_5)}{b_1 b_2 - b_3} > 0 \qquad (25)$$

Note that equation (25) was obtained in section (1.7). If condition (25) holds, the virus free equilibrium $E_0 = \left(\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0, 0\right)$ is locally asymptotically stable.

2.2.5. Stability of Endemic Equilibrium

In similar fashion to the local stability of virus free equilibrium, the local stability of endemic equilibrium, $E^*(L^*, L_I^*, T^*, T_I^*, V^*)$, is obtained by linearizing system of equation (3) at E^*. Using equation (23), the Jacobian matrix of E^* is

$$J(E^*) = \begin{pmatrix} -\beta_1 V^* - \mu & 0 & 0 & 0 & -\beta_1 L^* \\ \beta_1 V^* & -(\mu + \delta) & 0 & 0 & \beta_1 L^* \\ 0 & -\beta_3 T^* & -\sigma - \beta_2 V^* - \beta_3 L_I^* - \beta_4 T_I^* & -\beta_4 T^* & -\beta_2 T^* \\ 0 & \beta_3 T^* & \beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^* & \beta_4 T^* - (\sigma + \rho) & \beta_2 T^* \\ 0 & N\delta & 0 & M\rho & -\alpha \end{pmatrix}.$$

The linearized system of equation (3) is

$$\begin{pmatrix} \frac{du\prime}{dt} \\ \frac{dv\prime}{dt} \\ \frac{dw\prime}{dt} \\ \frac{dx\prime}{dt} \\ \frac{dy\prime}{dt} \end{pmatrix} = \underbrace{\begin{pmatrix} -\beta_1 V^* - \mu & 0 & 0 & 0 & -\beta_1 L^* \\ \beta_1 V^* & -(\mu+\delta) & 0 & 0 & \beta_1 L^* \\ 0 & -\beta_3 T^* & -\sigma - \beta_2 V^* - \beta_3 L_I^* - \beta_4 T_I^* & -\beta_4 T^* & -\beta_2 T^* \\ 0 & \beta_3 T^* & \beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^* & \beta_4 T^* - (\sigma+\rho) & \beta_2 T^* \\ 0 & N\delta & 0 & M\rho & -\alpha \end{pmatrix}}_{=B} \begin{pmatrix} u' \\ v' \\ w' \\ x' \\ y' \end{pmatrix}$$

(26)

Then

$$|B-\lambda| = 0 \Leftrightarrow \begin{vmatrix} -b_{11}-\lambda & 0 & 0 & 0 & -b_{15} \\ b_{21} & -b_{22}-\lambda & 0 & 0 & b_{15} \\ 0 & -b_{32} & -b_{33}-\lambda & -b_{34} & -b_{35} \\ 0 & b_{32} & b_{43} & b_{44}-\lambda & b_{32} \\ 0 & b_{52} & 0 & b_{54} & -b_{55}-\lambda \end{vmatrix} = 0.$$

Where $b_{11} = \beta_1 V^* + \mu,\ b_{15} = \beta_1 L^*,\ b_{21} = \beta_1 V^*,\ b_{22} = \mu + \delta,\ b_{25} = b_{15}, b_{32} = \beta_3 T^*, b_{33} = \sigma + \beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^*, b_{34} = \beta_4 T^*,\ b_{35} = \beta_2 T^*,\ b_{42} = b_{32}, b_{43} = \beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^*,\ b_{44} = \beta_4 T^* - (\sigma + \rho), b_{45} = b_{35}, b_{52} = N\delta, b_{54} = M\rho,\ b_{55} = \alpha$

This implies

$$\lambda^5 + c_1\lambda^4 + c_2\lambda^3 + c_3\lambda^2 + c_4\lambda + c_5 = 0 \qquad (27)$$

Where

$c_1 = b_{33} + b_{55} + b_{22} + b_{11} - b_{44}$

$c_2 = b_{22}(b_{33} + b_{55} - b_{44}) + b_{33}(b_{55} - b_{44}) - b_{44}b_{55} - b_{54}b_{35} + b_{34}b_{43} - b_{15}b_{52} + b_{11}(b_{22} + b_{33} - b_{44} + b_{55})$

$c_3 = b_{22}b_{33}(b_{55} - b_{44}) + b_{22}(b_{34}b_{45} - b_{44}b_{55} - b_{54}b_{35}) - b_{33}(b_{44}b_{55} + b_{54}b_{35}) + b_{34}b_{43}b_{55} - b_{15}b_{33}b_{52} - b_{32}b_{54}b_{15} + b_{15}b_{52}b_{44} - b_{11}b_{22}(b_{44} - b_{33} - b_{55}) - b_{11}b_{33}(b_{44} - b_{55}) - b_{11}b_{44}b_{55} - b_{11}b_{54}b_{35} + b_{11}b_{34}b_{43} - b_{11}b_{15}b_{52} + b_{21}b_{15}b_{52}$

$c_4 = b_{22}b_{34}b_{43}b_{55} - b_{22}b_{33}(b_{44}b_{55} + b_{54}b\_35) - b_{15}b_{43}(b_{34}b_{52} - b_{32}b_{54}) + b_{15}b_{33}(b_{52}b_{44} - b_{32}b_{54}) + b_{11}b_{22}b_{33}(b_{55} - b_{44} + b_{11}b_{22}(b_{34}b_{43} - b_{44}b_{55} - b_{54}b_{35}) - b_{11}b_{33}(b_{44}b_{55} + b_{54}b_{35}) + b_{11}b_{34}b_{43}b_{55} - b_{11}b_{15}b_{33}b_{52} - b_{11}b_{32}b_{54}b_{15} + b_{11}b_{52}b_{44} + b_{21}b_{15}(b_{33}b_{52} + b_{33}b_{54} - b_{52}b_{44})$

$c_5 = b_{11}b_{22}(b_{34}b_{43}b_{55} - b_{33}(b_{44}b_{55} + b_{54}b_{35})) - b_{11}b_{15}b_{43}(b_{34}b_{52} - b_{32}b_{54}) - b_{11}b_{15}b_{33}(b_{32}b_{54} - b_{52}b_{44}) + b_{15}b_{21}(b_{43}(b_{34}b_{52} - b_{32}b_{54}) + b_{33}(b_{32}b_{54} - b_{52}b\_44))$

By Routh-Hurwitz criterion described in section (1.7), it follows that all eigenvalues of equation (27) have negative real parts if and only if it satisfies:

$$c_1 > 0, c_5 > 0, \frac{c_1c_2 - c_3}{c_1} > 0, c_3 - \frac{c_1(c_1c_4 - c_5)}{c_1c_2 - c_3} > 0, c_1c_4 - c_5 - \frac{c_5(c_1c_2 - c_3)^2}{c_3(c_1c_2 - c_3) - c_1(c_1c_4 - c_5)} \qquad (28)$$

Therefore, the endemic equilibrium point $E^* = (L^*, L_I^*, T^*, T_I^*, V^*)$ is locally asymptotically stable if condition (28) holds.

2.2.6. Global Stability

The global stability of obtained equilibrium can be analyzed by transforming the system of equations into a linear system and then choosing a suitable Lyapunov function to analyze each equilibrium point. By letting

$L = L^* + x_1 , L_I = L_I^* + x_2 , T = T^* + x_3, T_I = T_I^* + x_4, V = V^* + x_5$ where x_1, x_2, x_3, x_4 and x_5 are small perturbations about L^*, L_I^*, T^*, T_I^* and V^* respectively, the system of equation (3) is turned into a linear system which is of the form $\dot{x_i} = J(E_0)x_i$, where $J(E_0)$ is the Jacobian matrix of equations (3) and $i = 1, \ldots, 5$. Thus, the linear system of equation (3) is

$$\frac{dx_1}{dt} = -(\beta_1 V^* + \mu)x_1 - \beta_1 L^* x_5$$
$$\frac{dx_2}{dt} = \beta_1 V^* x_1 - (\mu + \delta)x_2 + \beta_1 L^* x^5$$
$$\frac{dx_3}{dt} = -\beta_3 T^* x_2 - (\sigma + \beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^*)x_3 - \beta_4 T^* x_4 - \beta_2 T^* x_5$$
$$\frac{dx_4}{dt} = \beta_3 T^* x_2 + (\beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^*)x_3 + \big(\beta_4 T^* - (\sigma + \rho)\big)x_4 + \beta_2 T^* x_5$$
$$\frac{dx_5}{dt} = N\delta\, x_2 + M\rho\, x_4 - \alpha\, x_5$$

Theorem: The equilibrium $E_0(L^*, 0, T^*, 0,0) = \left(\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0,0\right)$ is globally stable provided that $\delta(NL^* - 1) \leq \mu$ and $\rho(MT^* - 1) \leq \sigma$.

Proof:

We define a Lyapunov function as $Z(x_1, x_2, x_3, x_4, x_5) = \frac{x_1}{L^*} + \frac{x_2}{L^*} + \frac{x_3}{T^*} + \frac{x_4}{T^*} + x_5$, where L^*, T^* are components of the equilibrium point $E_0(L^*, 0, T^*, 0,0) = \left(\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0,0\right)$. Since $(x_1, x_2, x_3, x_4, x_5) \in \mathbb{R}_+^5, Z(x_1, x_2, x_3, x_4, x_5)$ is a positive definite function. Differentiating Z with respect to time t we get

$$\frac{dZ}{dt} = \frac{\partial Z}{\partial x_1}\frac{dx_1}{dt} + \frac{\partial Z}{\partial x_2}\frac{dx_2}{dt} + \frac{\partial Z}{\partial x_3}\frac{dx_3}{dt} + \frac{\partial Z}{\partial x_4}\frac{dx_4}{dt} + \frac{\partial Z}{\partial x_5}\frac{dx_5}{dt}$$
$$= [-(\beta_1 V^* + \mu)x_1 - \beta_1 L^* x_5]\frac{1}{L^*} + [\beta_1 V^* x_1 - (\mu + \delta)x_2 + \beta_1 L^* x^5]\frac{1}{L^*}$$
$$+ [-\beta_3 T^* x_2 - (\sigma + \beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^*)x_3 - \beta_4 T^* x_4 - \beta_2 T^* x_5]\frac{1}{T^*}$$
$$+ \left[\beta_3 T^* x_2 + (\beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^*)x_3 + \big(\beta_4 T^* - (\sigma + \rho)\big)x_4 + \beta_2 T^* x_5\right]\frac{1}{T^*}$$
$$+ [N\delta\, x_2 + M\rho\, x_4 - \alpha\, x_5]$$
$$= -\frac{\mu}{L^*}x_1 - \left(\frac{\mu + \sigma}{L^*} - N\sigma\right)x_2 - \frac{\sigma}{T^*}x_3 - \left(\frac{\sigma + \rho}{T^*} - M\rho\right)x_4 - \alpha x_5$$

Choosing

$$\frac{\mu+\sigma}{L^*} - N\sigma \geq 0, \frac{\sigma+\rho}{T^*} - M\rho, \qquad (29)$$

We have

$$\frac{dZ}{dt} = -\frac{\mu}{L^*}x_1 - \left(\frac{\mu + \sigma}{L^*} - N\sigma\right)x_2 - \frac{\sigma}{T^*}x_3 - \left(\frac{\sigma + \rho}{T^*} - M\rho\right)x_4 - \alpha x_5 \leq 0$$

Then, equation (29) can be rearranged as $\delta\,(NL^* - 1) \leq \mu$, $\rho(MT^* - 1) \leq \sigma$ so $E_0 = (L^*, 0, T^*, 0,0)$ is Lyapunov stable. Therefore, the theorem is proved.

3. NUMERICAL SIMULATION

In previous sections we have investigated analytically the properties of proposed model. Now, we shall investigate numerically the results of proposed model by means of numerical simulation. We solve our system of equation (3) by using an iterative method with Runge-Kutta fourth order scheme.

3.1. Implementation of Runge-Kutta Fourth Order Method for Numerical Solution

Firstly, we give a brief description of the Runge-Kutta method of order four (RK4) for the system of equations (3). We first develop a sets of k's used to make predictions of the dependent variable at the midpoint of the interval. These are then employed to make predictions at the end of the interval that are used to develop the values of k's at the end interval k_4. Finally, the k's values are combined into a set of increment functions and brought back to the beginning to make the final prediction [1]. The following illustrates these approaches.

We start with initial conditions $L(t_0) = L_0, L_I(t_0) = L_{I_0}, T(t_0) = T_0, T_I(t_0) = T_{I_0}, V(t_0) = V_0$.

We assume that the values $L_i, L_{I_i}, T_i, T_{I_i}$ and V_i has been computed. Now we calculate $L_{i+1}, L_{I_{i+1}}, T_{i+1}, T_{I_{i+1}}$ and V_{i+1} by Runge-Kutta fourth order method as:

$$L_{i+1} = L_i + \frac{1}{6}(k_{11} + 2(k_{21} + k_{31}) + k_{41})$$

$$L_{I_{i+1}} = L_{I_i} + \frac{1}{6}(k_{12} + 2(k_{22} + k_{32}) + k_{42})$$

$$T_{i+1} = T_i + \frac{1}{6}(k_{13} + 2(k_{23} + k_{33}) + k_{43})$$

$$T_{I_{i+1}} = T_{I_i} + \frac{1}{6}(k_{14} + 2(k_{24} + k_{34}) + k_{44})$$

$$V_{i+1} = V_i + \frac{1}{6}(k_{15} + 2(k_{25} + k_{35}) + k_{45})$$

With,

$$k_{1j} = hf_j(t_0, L_0, L_{I_0}, T_0, T_{I_0}, V_0)$$

$$k_{2j} = hf_j(t_0 + \frac{h}{2}, L_i + \frac{k_{11}}{2}, L_{I_i} + \frac{k_{12}}{2}, T_i + \frac{k_{13}}{2}, T_{I_i} + \frac{k_{14}}{2}, V_i + \frac{k_{15}}{2})$$

$$k_{3j} = hf_j(t_0 + \frac{h}{2}, L_i + \frac{k_{21}}{2}, L_{I_i} + \frac{k_{22}}{2}, T_i + \frac{k_{23}}{2}, T_{I_i} + \frac{k_{24}}{2}, V_i + \frac{k_{25}}{2})$$

$k_{4j} = hf_j(t_0 + h, L_i + k_{31}, L_{I_i} + k_{32}, T_i + k_{33}, T_{I_i} + k_{34}, V_i + k_{35})$ where f_j's are equations given in (10-14) for $j = 1, \ldots, 5$.

This gives us the next approximate values of L, L_I, T, T_I and V. Then t is set to $t_0 + h$ and the values of L, L_I, T, T_I and V are iterated with the above formula.

3.2. Values of Parameters and Initial Variables

Choosing variable and parameter values characteristic at the cellular level is difficult. In our model, if measurements have been attempted, the values taken may not be as accurate as we need for quantitative predictions. Thus one role of modeling is to point out where further quantitative measurements can improve our understanding of the AIDS disease process. For example, the number of CD4+ T cells in the peripheral blood is approximately $1000/mm^3$, although it fluctuates from time to

time depending on the total lymphocyte count [13]. As it is common in the clinical literature, we shall report all cell numbers per cubic milliliter. For our simulations, we declare the numerical parameters and variable by using similar procedure as for T cells above. We list these values in Table (2) and using these values we get Figure (2).

Parameters	**Approximated Values**
Initial population size of healthy Langerhans cells (L)	800mm^{-3}
Initial population size of infected Langerhans cells (L_I)	0.033mm^{-3}
Initial healthy T-cells (T) population size	$1000mm^{-3}$
Initial population size of infected T-cells (T_I)	$0.045mm^{-3}$
Initial HIV population size (V)	5mm^{-3}
The constant rate of production of susceptible Langerhans cells from the bone marrow (π_L)	19mm^{-3}
Infection rate of susceptible Langerhans cells by free virus ($\beta_1\}$)	$0.002\ day^{-1}$
Natural death rate of Langerhans cells (μ)	$0.002\ \text{day}^{-1}$
Death rate of L_I due to virus (δ)	$0.007\ \text{day}^{-1}$
The constant rate of production of susceptible T-cells from the bone marrow (π_T)	15mm^{-3}
Natural death rate of T cells (σ)	$0.001\ \text{day}^{-1}$
Infection rate of T-cells by free virus (β_2)	$0.0002\ \text{day}^{-1}$
Infection rate of T-cells by infected Langerhans cells (β_3)	$0.0004\ \text{day}^{-1}$
Infection rate of T-cells by infected T-cells (β_4)	$0.003\ \text{day}^{-1}$
Death rate of infected T-cells due to virus (ρ)	$0.008\ \text{day}^{-1}$
Number of the virus particles assumed to produced by the infected Langerhans cells during its life time including any of its daughter cells(N)	$2\ \text{day}^{-1}$
Number of the virus particles assumed to produced by the infected T-cells during its life time including any of its daughter cells(M)	$4\ \text{day}^{-1}$
virus death rate (α)	$0.8\ \text{day}^{-1}$

Table 2: The approximated values of variable and parameters declared in the numerical simulation

Figure 2 illustrates the dynamics of the disease for Healthy Langerhans cells, infected Langerhans cells, Healthy T-cells, infected T-cells and Free Virus with increasing time. The population of susceptible Langerhans cells decreases as time increases due to the presence of virus as shown in Figure 2(a). As we can see from Figure 2(b), (d) and (e), the Population of infected Langerhans cells, Infected T-cells and Free Viruses increases when time increases. On Figure 2(c), we observe that the population size of susceptible T-cells increases starting from its initial population size since the healthy T-cells defense viral infection, but as time increases it start to decrease. This is due to structure HIV virus. That means, HIV is an enveloped retrovirus. When it leaves a host cell it takes a part of that cell and duplicates itself along with host cells. Therefore, it starts to multiply itself within a short period of time including its

daughter cells so that it wins healthy T-cells. For the sake of easy comparison, we can observe all of this dynamical interaction on one plane in Figure 2(f).

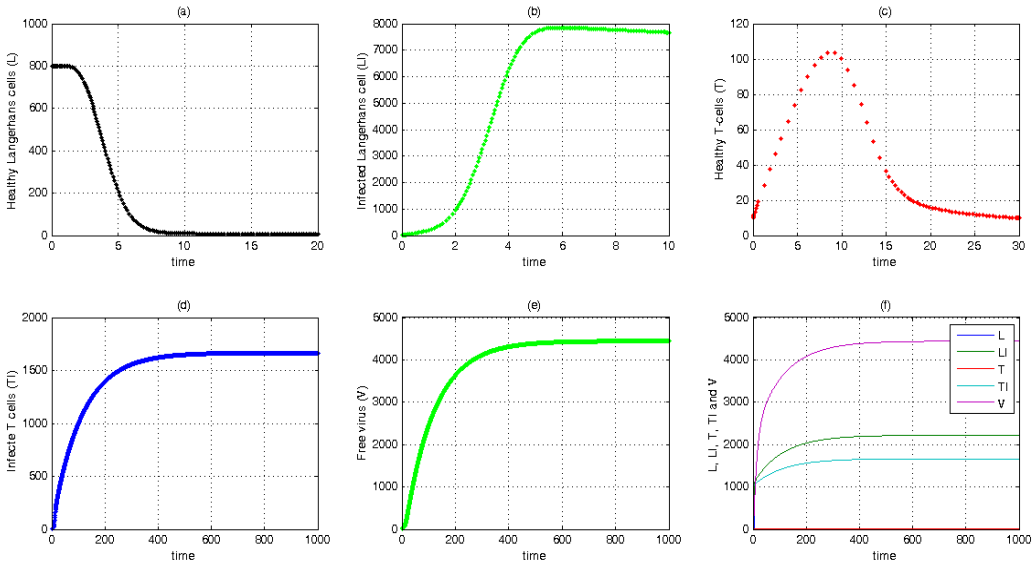

Figure 2: Dynamics of the model showing the virus progression in an increasing time t

4. CONCLUSION

Infectious diseases are a threat for our modern society due to the increased population density on Earth, so being able to understand and predict the dynamics of infectious diseases is extremely important.

In this research work, we have developed a model used to explain the interaction between host cells and HIV infection. The model was developed in accordance with previous models in the literature review, and in accordance of the biologically reasonable assumptions and parameters. It was shown that, the model has a biologically meaningful region in which we had carried out all our model analysis. Also, it was shown that the solution of the model systems exists and unique, positively invariant and non negative. The stability properties of both virus free and endemic equilibrium were determined; as the stability nature of solutions will assist us to determine the extent to which the disease will disappear from the population. In order to insights into the HIV/AIDS dynamics at cellular level, the numerical simulations of the model are carried out.

In addition, in this work we have improved the understanding of the interaction between Langerhans cells and HIV infection by explaining the most crucial point take place in developing our model system. Furthermore, by using the language of mathematics we have provided the tangible understanding on the viral pathogenesis and its life-span for the immunologist, for the researchers and for the clinicians to propose the new powerful tools on the stimulation of the immune system in order to increase its efficiency in the struggle against antigen invasion.

Generally, this study assists us to consolidate our knowledge on the dynamics of HIV - host cells interaction and it concretely simplifies the complexity to understand the interplay between the virus and host cells. At the future, it will be helpful to obtain good estimates for introduced parameter values especially, the reactivation rate of individually infected cells. Our work may require additional information to improve these findings by using future research studies, extensions, modifications and analysis of the model. Moreover, based on the parameter values, the equilibrium point may be created or destroyed or their stability may change. To understand these changes the model requires bifurcation

analysis by varying the values of these parameters. Thus, as a future prospect, it would be important to distinguish more clearly, on these analyses and provide a more reasonable fact on the interplay between Langerhans cells and HIV infections.

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