MATHEMATICAL MODELING OF THE INTERACTION BETWEEN LANGERHANS CELLS AND THE SPREAD OF HIV INFECTION

By

Lencha Tamiru Abdisa

A Thesis Submitted to Applied Mathematics Program

School of Applied Natural Science

Presented in Partial Fulfillment of the Requirement for the

Degree of Master's of Science in Applied Mathematics

Office of Graduate Studies

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Approval Page

This is certify that the thesis prepared by Lencha Tamiru entitled "**Mathematical Modeling of the Interaction between Langerhans cells and HIV Infection**" submitted in partial fulfillment of the requirement for the degree of Master of Science in **Mathematics** with the regulation of the University and meets the accepted standards with respect to originality.

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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 a mathematical preliminaries which plays a crucial role in our entire research work were described. Also, the existing model which focuses on representing the long term dynamics of the interaction between T-cells and HIV infection was studied to assist us in formulating our model system. By presenting a theoretical framework related to the infection mechanism, a biologically meaning full assumption were considered. Furthermore, the positivity of the model solution, the equilibrium point (both virus free and endemic equilibrium) of the model was shown and it's 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.

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

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Lencha Tamiru

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Notations and Abbreviations

AIDS	Acquired immune deficiency syndrome
APC	Antigen presenting cell
CTL	cytotoxic T lymphocytes
DC	Dendritic cell
HIV	Human immunodeficiency virus
L	Susceptible Langerhans cells
L_I	Infected Langerhans cells
LC	Langerhans cell
T	Susceptible T-cells
T_I	Infected T-cells
LN	Lymph node
MHC	Major histocompatibility complex
ODE	Ordinary differential equation
V	Free HIV virus
L_{tot}	Total population of Langerhans cells
T_{tot}	Total population of T-cells
VFE	Virus-free equilibrium
EE	Endemic equilibrium

Chapter 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 [1].

An electron microscopic studies 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 [2]. 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 [3].

1.1 Definition of terms

Dendritic cell [1]: A special type of cell that is a key regulator of the immune system, acting as a professional antigen-presenting cell (APC) capable of activating naive T cells

and stimulating the growth and differentiation of B cells.

Langerhans cell [2, 4]: A dendritic cell of the interstitial spaces of the mammalian epidermis functions as an antigen-presenting immune cells and binds antigen entering through the skin and transports it to the lymph nodes by sensing any kind of danger in the skin like the air traffic controllers of the immune system. They send out special agents − immune cells such as T cells and B cells to capture foreign invaders such as bacteria and viruses, and fight off injuries like cuts and scrapes. They constantly monitor the environment of the skin for unsafe situations and send immune cells on their missions to bring back information about any trespasser. Then the body can decide to amass a great force of inflammatory cells to fight off the attacker by creating an allergic reaction or forming scar tissue.

$CD4^+$ [5]: CD4 (cluster of differentiation 4) is a glycoprotein found on the surface of immune cells such as T helper cells, monocytes, macrophages, and dendritic cells.

$CD4^+$ T-helper cells [5]: CD4+ T helper cells are white blood cells that are an essential part of the human immune system. They are often referred to as $CD4^+$ cells, T-helper cells or T4 cells. They are called helper cells because one of their main roles is to send signals to other types of immune cells, including $CD8^+$ killer cells. $CD4^+$ cells send the signal and $CD8^+$ cells destroy and kill the infection or virus.

Lymph [5]: A clear yellowish, slightly alkaline, coagulable fluid, containing white blood cells in a liquid resembling blood plasma, that is derived from the tissues of the body and conveyed to the bloodstream by the lymphatic vessels.

lymph node [5]: A lymph node or lymph gland is an oval-shaped organ of the immune system, distributed widely throughout the body including the armpit and stomach and linked by lymphatic vessels.

Macrophages [2]: (Greek: big eaters, from Greek word (makros) = large, and (phagein) = to eat) are a type of white blood cell that engulfs and digests cellular debris, foreign substances, microbes, cancer cells, and anything else that does not have the types of proteins specific of healthy body cells on its surface in a process called phagocytosis.

Peripheral tissues [5]: are the tissues in the immune system and the skin or other tissues mucosal in nature that have potential to be exposed to bacteria and pathogens in the environment. These tissues are referred to as peripheral tissues because they are the tissues situated closest to the outside of the body.

Antigen-presenting cells [1]: are any of various cells (as a macrophage, B cells or

Langerhans cell) that take up an antigen and process it into a form recognized by and serving to activate a specific helper T cell.

plasma membrane [6]: The plasma membrane is the boundary between the cell and its environment. It regulates what enters and exits the cell. Cells must maintain an appropriate amount of molecules to function inside them. They must also have a way to keep things out or to allow things to enter. This is the job of the plasma membrane. The plasma membrane is like the guard at a gated community. The guard must inspect those who enter and those who leave to make sure that only the people and things needed in the community are there.

HIV Envelope Proteins [7]: HIV is an enveloped virus which makes it different from many other retroviruses. It doesn't just have a protein coat. Instead, when HIV leaves a host cell it takes part of that cell's plasma membrane with it. That bit of membrane becomes the HIV envelope. However, the HIV envelope isn't only made up of components from the host. It is also made up of HIV envelope proteins. HIV envelope proteins include gp 41, gp 120, and gp 160. GP stands for "glycoprotein". Glycoproteins have carbohydrate or sugar components as well as a protein backbone. The number after the gp refers to the proteins' length.

Cytotoxic T lymphocytes [8]: are lymphocytes that kill other ("target") cells. Targets may include virus-infected cells (e.g. HIV-infected CD4+ T cells) and cells infected with intracellular bacterial or protozoal parasites.

B cells [7]: (also known as B lymphocytes) are a type of white blood cell of the lymphocyte subtype. They function in the humoral immunity component of the adaptive immune system by secreting antibodies. Additionally, B cells present antigen (they are also classified as professional antigen-presenting cells (APCs)) and secrete cytokines.

Major histocompatibility complex [7]: The major histocompatibility complex (MHC) is a set of cell surface proteins essential for the acquired immune system to recognize foreign molecules in vertebrates, which in turn determines histocompatibility. The main function of MHC molecules is to bind antigens derived from pathogens and display them on the cell surface for recognition by the appropriate T-cells. MHC molecules mediate interactions of leukocytes, also called white blood cells (WBCs), which are immune cells, with other leukocytes or with body cells. The MHC determines compatibility of donors for organ transplant, as well as one's susceptibility to an autoimmune disease via crossreacting immunization.

Cytokines [8]: are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. They are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Cytokine is a general name; other names are defined based on their presumed function, cell of secretion, or target of action. For example, cytokines made by lymphocytes can also be referred to as lymphokines. Many of the lymphokines are also known as interleukins, since they are not only secreted by leukocytes but also able to affect the cellular responses of leukocytes. Those cytokines secreted by monocytes or macrophages are termed monokines and chemokines are cytokines with chemotactic activities.

1.2 Statement of the Problem

Many aspects of the complex interaction between HIV and human immune system remain elusive. The essence of this research focuses on these interactions by presenting the role of Langerhans cells(LC) in HIV infection. In patients infected with HIV, a large amount of virus is associated with LCs in lymphoid tissues. At that time, to assess the influence of LCs on HIV viral dynamics we need to present and analyses a mathematical model describing their interactions. For this, the study is intended to answer the following leading questions.

(i) What are the basic idea of the biological interplay between the Langerhans cells and HIV virus?

(ii) How mathematical model helps to visualize the specific roles of the Langerhans cells in HIV infections using ODE?

(iii) What are the steady states and stability conditions of the formulated ODE model?

(iv) What are the biological implication of the model solution?

1.3 Objective of the Study

1.3.1 General Objective

The main objective of the present study is to investigate the interaction between Langerhans cells and the spread of HIV infection using mathematical model.

1.3.2 Specific Objectives

The research is deliberate to explore the following specific objectives:

(i) Providing the basic idea of the biological interplay between the Langerhans cells and HIV virus.

(ii) Developing a mathematical model used to help visualize the specific roles of the Langerhans cells in the spread of HIV/AIDS.

(iii) Analyzing the steady states and stability of the formulated ODE model.

(iv) Investigating the biological implication of the model solution.

1.4 Significance and Beneficiaries of the Study

HIV is a devastating human pathogen that causes serious immunological diseases in human around the world. The virus is able to remain latent in an infected host for many years, allowing for the long-term survival and inevitably prolonging the infection process. The location and the mechanism of HIV latency are under investigation and remain important topics in the study of viral pathogenesis. Given that HIV is a blood-borne pathogen, a number of cell types have been proposed to be the sites of latency including resting memory $CD4^+$ T cells, peripheral blood monocytes, dendritic cells (particularly Langerhans cells), macrophages in the lymph nodes and haematopoietic stem cells in the bone marrow. Due to this we need the mathematical modeling approaches to analysis and updates the latest advances in the study of HIV interactions with Langerhans cells. The outcome of the study benefits the immunologist, the researchers and the clinicians to propose the new powerful tools for the stimulation of the immune system in order to increase its efficiency in the struggle against antigen invasion. Also it provides the tangible understanding on viral pathogenesis and its life-span.

1.5 Research Methodology

In this research work we develop a mathematical model which describes the interaction between Langerhans cells and the spread of HIV infections using a system of non-linear ordinary differential equations. Usually, non-linear ordinary differential equations are not solvable analytically. We try to determine the conditions for the local and global stability of the model using Jacobian matrix and Lyapunov functions respectively. The analytical solutions to the mathematical problems are supplemented by numerical simulations using a biologically meaningful system parameter values. We also try to analyze the proposed mathematical model numerically by using matlab.

1.6 The Biology of Langerhans Cells and it's Interactions with HIV

In this section, we study a biological interaction between Langerhans cells and HIV infection by focusing on the roles of the Langerhans cells(LC) and the modes of infections by HIV.

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 effector cells in HIV infection, as they kill infected cells and produce non-lytic antiviral factors. In lymph node, LC activate $CD4^+$ 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 are 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 restimulate activation of T and B cells through antigen presentation [9, 10].

The immunocompetent cells which act as an 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 [4]. 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 [10].

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 LC are transferring HIV to CD4 T cells. LC may also provided a mode of intracellular storage while transporting HIV to CD4 T cells in the submucosal lymphoid tissue and thence to draining lymph nodes [2].

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 exoginous 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 migrate 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 role of LC, in HIV infections, it plays a dual role of promoting immunity while also facilitating infections [1, 10, 11].

1.7 Mathematical Preliminaries

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

Theorem 1.7.1. *(Existence and Uniqueness Theorem): Assume $\mathcal{D}$ is an open subset of $\mathbb{R} \times \mathbb{R}^n$, $f : \mathcal{D} \to \mathbb{R}^n$ is continuous. Then for each $t_0 \in \mathbb{R}$ and $x_0 \in \mathbb{R}^n$, the initial value problem (IVP)*

$$x' = f(t, x), x(t_0) = x_0 \tag{1.1}$$

has a solution x. If in addition, f has continuous first order partial derivatives with respect to $x_1, x_2, ..., x_n$ in $\mathbb{R}^n$, then equation (1.1) has a unique solution.
The proof is found on [12].

Definition 1.7.1. Let f be a real valued function defined on a domain $\mathcal{D}$. The function f is said to be bounded on $\mathcal{D}$ if and only if there is a positive number M such that $|f(x, y)| \leq M$ for all $(x, y) \in \mathcal{D}$.

Definition 1.7.2. 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 $t \geq t_0$.

Steady State and Stability

Definition 1.7.3. (Equilibrium Solution): Consider the n-dimensional initial value autonomous system:

$$\begin{aligned} \frac{dX}{dt} &= F(X), \\ x(0) &= x_0. \end{aligned} \tag{1.2}$$

If $F(x) = 0$, we say that x is an equilibrium solution (steady-state solution, fixed point, or critical point) of the system. Furthermore, the steady state solutions are the condition under which the system does not change any more [12].

Definition 1.7.4. (Formal definition of equilibrium): A point x_e is called an equilibrium point of $\frac{dx}{dt} = f(t, x)$, or simply an equilibrium, at time t_0 if for all $t \geq t_0$,

$$f(t, x_e) = 0$$

Note that if x_e is an equilibrium of our system at t_0, then it is also an equilibrium for all $T \geq t_0$

A nonlinear system may have a number of equilibrium states, but the origin, $x = 0$, may or may not be it's equilibrium state. If the origin is not the equilibrium state, it is always possible to translate the origin of the coordinate system to that state. So, no loss of generality is lost in assuming that the origin is the equilibrium state of interest.

Stability of an equilibrium points relates to the tendency of the system to return to its position when slightly disturbed. A system is said to be at *equilibrium* if opposing forces in the system are balanced, and in turn the state of the system remains constant and unchanged. A system is said to be *stable* if its state returns to a state of equilibrium following some perturbation (e.g. an environmental disturbance). A system is *globally stable* if its state returns to the state of equilibrium following a perturbation of any magnitude, where as, a *locally stable* system indicates that displacements must occur in a defined neighborhood of the equilibrium in order for the system to return to the same state of the equilibrium.

Definition 1.7.5. Consider a non linear autonomous system

$$\begin{aligned} \frac{dx}{dt} &= f(x, y) \\ \frac{dy}{dt} &= g(x, y) \end{aligned}$$

such that the system has an isolated critical point $(0,0)$ and the function $f(x,y)$ and $g(x,y)$ have continuous first order partial derivatives for all $(x,y) \in \mathcal{D}$ containing the point $(0,0)$. Let $E(x,y)$ be a function with first order partial derivatives at all points (x,y) in a domain $\mathcal{D}$ containing the point $(0,0)$.

(i) The function $E(x,y)$ is said to be positive definite in $\mathcal{D}$ if and only if
$E(x,y) > 0$, $\forall (x,y) \in \mathcal{D} \backslash \{(0,0)\}$ and $E(0,0) = 0$
The function $E(x,y)$ is said to be positive semidefinite in $\mathcal{D}$ if and only if
$E(x,y) \geq 0$, $\forall (x,y) \in \mathcal{D} \backslash \{(0,0)\}$ and $E(0,0) = 0$

(ii) The function $E(x,y)$ is said to be negative definite in $\mathcal{D}$ if and only if
$E(x,y) < 0$, $\forall (x,y) \in \mathcal{D} \backslash \{(0,0)\}$ and $E(0,0) = 0$
The function $E(x,y)$ is said to be negative semidefinite in $\mathcal{D}$ if and only if
$E(x,y) \leq 0$, $\forall (x,y) \in \mathcal{D} \backslash \{(0,0)\}$ and $E(0,0) = 0$

(iii) Let $E(x,y)$ be a positive definite function in the domain $\mathcal{D}$ such that $\frac{dE}{dt} = E_x f(x,y) + E_y g(x,y)$ is negative semidefinite in $\mathcal{D}$. Then the function E is called Lyapunov function for the system in $\mathcal{D}$ and the system is globally stable in Lyapunov sense.

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 $i = 1, \cdots, n$, define the n Hurwitz matrices using the coefficients a_i of the characteristic polynomial:

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

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

$$detH_j > 0, \text{ for all } j = 1, 2, \cdots, n.$$

When $n = 2$, we have $P_2(\lambda) = \lambda^2 + a_1\lambda + a_2$. Hence by Routh-Hurwitz criteria we have $detH_1 = a_1 > 0$ and

$$detH_2 = det \begin{bmatrix} a_1 & 1 \\ 0 & a_2 \end{bmatrix} = a_1 a_2 > 0.$$

Similarly, when $n = 5$:

$$\begin{aligned} a_i > 0, \text{ for } i = 1, \cdots, 5, \ \frac{a_1 a_2 - a_3}{a_1} > 0, a_3 - \frac{a_1(a_1 a_4 - a_5)}{a_1 a_2 - a_3} > 0 \\ a_1 a_4 - a_5 - \frac{a_5(a_1 a_2 - a_3)^2}{a_3(a_1 a_2 - a_3) - a_1(a_1 a_4 - a_5)} > 0 \end{aligned} \tag{1.3}$$

Chapter 2

Literature Review

The recent pandemic of the human immunodeficiency virus (HIV) has produced global concern and a greater awareness towards the formulation of the mathematical model describing the transmission dynamics of the virus. Many models have been formulated to investigate these transmission dynamics. We now present a brief survey of some papers of mathematical models developed on the interaction between HIV/AIDS and host cells .

A mathematical modeling of population dynamics of HIV infection was considered in [13]. In this model, the total population is restricted within high risk population. By considering the epidemic characteristics of HIV/AIDS, the author classifies the high risk population into two groups: injecting drug users and people engaged in commercial sex which include female sex workers and clients of female sex workers. The infectives and AIDS are defined by their transmission modes. The conditions and thresholds for the existence of four equilibria are established. They also compute the reproduction number for each group independently, and show that when the reproduction numbers are less than unity, the disease-free equilibrium is globally stable. The local stability for other equilibria including two boundary equilibria and one positive equilibrium are figured out. When they omit the infectivity of AIDS patients, global stability of these equilibria are obtained. For the simulation, they carried out the parameter estimation and it shows that the HIV infection maintains a higher prevalence in injecting drug users.

The basic HIV model which contains three ordinary differential equations (ODE) representing the dynamics of healthy and infected CD4 + T lymphocytes and HIV load were presented in [14, 15, 16]. These model and the motivation behind its analysis are briefly reviewed. The paper also covers the process of introducing antiretroviral drugs into the

system and the equilibrium point of the model was derived. In introducing antiretroviral drugs they consider two major categories, namely,reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs). RTIs prevent new HIV infection by disrupting the conversion of viral RNA into DNA inside of T cells. PIs reduce the number of viruses particles produced by an actively-infected T cells. Additionally, the local and global asymptotic stability of the systems equilibria was analyzed.

Along with discovery and further understanding of T cells, the mathematical modeling of immune systems significantly increased from time to time. At the cellular level, a mathematical modeling of the interaction between HIV and CD4+ T cells was developed by [17, 18]. In this work the authors considered two models. The first has viral dynamics of only uninfected cells and virus-producing cells. In the first model, they calculate R_0, the basic reproductive number both with and without treatment. They show that for $R_0 \leq 1$ there is only the equilibrium with no virus-producing cells whereas for $R_0 > 1$ there is a unique equilibrium with both uninfected cells and virus-producing cells but they only take into account a key players in HIV infection. The second model examine the dynamics of uninfected cells, infected cells and virus. Here target cells correspond mostly to $CD4^+$ T cells expressing an appropriate co-receptor so as to be susceptible to infection. The model was shown to be able to describe the kinetics of acute HIV infection and the establishment of a steady-state. Only a small fraction of $CD4^+$ T cells in the periphery become infected with HIV and thus identifying the target cells in this model is not straightforward. However, the model is able to describe the kinetics of T-cell depletion by considering mostly T cells are target cells. Despite its ability to fit data, this model may be too simple in that it does not include any other explicit immune response.

Along with further discovery, the model consisting of only the healthy $CD4^+$ T-cells, infected $CD4^+$ T-cells and free viruses are studied by [19, 20, 21]. In this model, they were presented the existence and stability of the infected steady state. Then, they introduce a discrete time delay to the model to describe the time between infection of a $CD4^+$ T-cells and the emission of viral particles on a cellular level. They were also study the effect of the time delay on the stability of endemically infected equilibrium; criteria were given to ensure that the infected equilibrium is asymptotically stable for all delay. Last, it was observed that time delay does not induce instability and oscillations in the model.

In all we state above literature survey, all of the authors formulate the model which describe the dynamics of viral infection and human immune cells and analysis their model.

In similar manner, in our research work, we develop the mathematical modeling of the interaction between Langerhans cells and HIV infection along with $CD4^+$ T-cells. Since the Langerhans cells present antigen to other immune cells, it highly interrelated with target cells of infection, specially $CD4^+$ T-cells. Therefore, our work focuses on the generalization of effect of infected T-cells and infected Langerhans cells on free viral population size. Consequently, in the next chapter, we are going to develop and analyze a mathematical modeling of the interaction between Langerhans cells and HIV by considering the very interrelated cells, $CD4^+$ T-cells.

Chapter 3

Model Formulation and Analysis

Aspects of an organism's defence 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 defence, the immune system plays a decisive role in tissue incompatibility reactions, antitumour immunity, autoimmune diseases, and allergies [8]. Therefore, the formulation of mathematical models of the interaction between Langerhans cells and the spread of HIV infection provides the tangible understanding on these system and the HIV transmission with its life-span.

3.1 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.

3.1.1 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 increase due to it's constant rate of production in bone marrow, but the number can decreases due to it's 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 it's 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 are shown in figure (3.1) below.

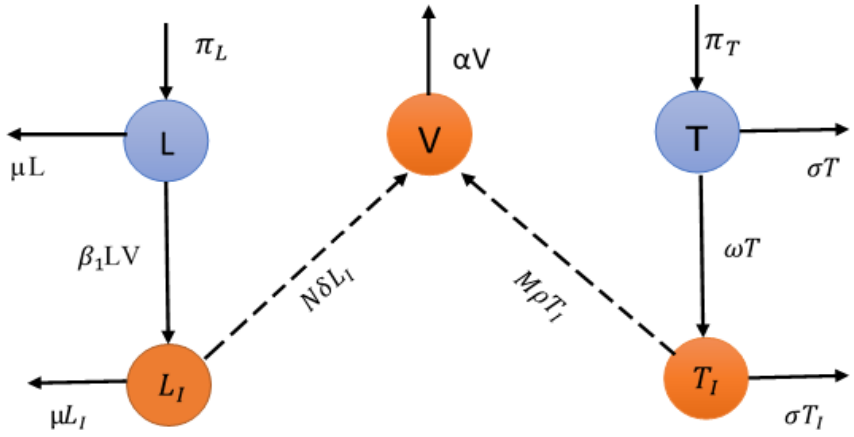

Figure 3.1: Model structure

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

$$\begin{cases} \frac{dL}{dt} = \pi_L - \beta_1 VL - \mu L \\ \frac{dL_I}{dt} = \beta_1 VL - \mu L_I - \delta L_I \\ \frac{dT}{dt} = \pi_T - \sigma T - \beta_2 VT - \beta_3 L_I T - \beta_4 T_I T \\ \frac{dT_I}{dt} = \beta_2 VT + \beta_3 L_I T + \beta_4 T_I T - \sigma T_I - \rho T_I \\ \frac{dV}{dt} = N\delta L_I + M\rho T_I - \alpha V \end{cases} \tag{3.1}$$

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 the 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 (3.1). We also suppose that $\omega = \beta_2 V + \beta_3 L_I + \beta_4 T_I$ for the schematic diagram shown on figure (3.1) above.

Parameter description	Symbol
The constant rate of production of susceptible Langerhans cells from the bone marrow	$\pi_{_L}$
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	$\pi_{_T}$
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 3.1: The parameter description and it's symbol

3.2 Model Analysis

In this section we study the basic properties of the solutions of system of equation (3.1). 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.

3.2.1 Existence and Uniqueness

Theorem 3.2.1. *Suppose that a system of equation (3.1) is given with non negative initial value* $X(t_0) = (L_0, L_{I0}, T_0, T_{I0}, V_0)$. *Then it has a unique solution.*

Proof. We proof this by using theorem (1.7.1).

(i) **Existence:**

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

$$f_1(L, L_I, T, T_I, V) = \pi_L - \beta_1 VL - \mu L,$$
$$f_2(L, L_I, T, T_I, V) = \beta_1 VL - \mu L_I - \delta L_I,$$
$$f_3(L, L_I, T, T_I, V) = \pi_T - \sigma T - \beta_2 VT - \beta_3 L_I T - \beta_4 T_I T,$$

$$f_4(L, L_I, T, T_I, V) = \beta_2 VT + \beta_3 L_I T + \beta_4 T_I T - \sigma T_I - \rho T_I \text{ and}$$
$$f_5(L, L_I, T, T_I, V) = N\delta L_I + M\rho T_I - \alpha V$$

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,...,5. By Theorem (1.7.1) 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 (3.1) 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 (1.7.1) the system of equation (3.1) with the given initial value has a unique solution. □

3.2.2 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 (3.1) 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 (3.1) 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 3.2.2. *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,

$$\begin{aligned}\frac{dL_{tot}}{dt} =& \frac{dL}{dt} + \frac{dL_I}{dt} \\ =& (\pi_L - \beta_1 VL - \mu L) + (\beta_1 VL - \mu L_I - \delta L_I) \\ =& \pi_{_L} - \mu(\underbrace{L + L_I}_{L_{tot}}) - \delta L_I \\ =& \pi_{_L} - \mu L_{tot} - \delta L_I \\ \leq& \pi_{_L} - \mu L_{tot}, \text{ since } \delta, L_I \geq 0 \\ & \frac{dL_{tot}}{dt} + \mu L_{tot} \leq \pi_{_L} \end{aligned} \tag{3.2}$$

After multiplying both sides of equation (3.2) by it's integrating factor $e^{\mu t}$, we get

$$\begin{aligned}(e^{\mu t})(\frac{dL_{tot}}{dt}) + (e^{\mu t})\mu L_{tot} &\leq \pi_{_L} e^{\mu t} \\ (L_{tot}e^{\mu t})' &\leq \pi_{_L} e^{\mu t} \end{aligned} \tag{3.3}$$

Then integrate both sides of equation (3.3) with respect to t.

$$\begin{aligned}L_{tot}e^{\mu t} &\leq \frac{\pi_{_L}}{\mu} e^{\mu t} + c_1, \text{where } c_1 \text{ is a constant of integration.} \\ L_{tot} &\leq \frac{\pi_{_L}}{\mu} + c_1 e^{-\mu t}\end{aligned}$$

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

$$\begin{aligned}\frac{dT_{tot}}{dt} &= \frac{dT}{dt} + \frac{dT_I}{dt} \\ &= (\pi_T - \sigma T - \beta_2 VT - \beta_3 L_I T - \beta_4 T_I T) + (\beta_2 VT + \beta_3 L_I T + \beta_4 T_I T - \sigma T_I - \rho T_I) \\ &= \pi_{_T} - \sigma T - \sigma T_I - \rho T_I = \pi_{_T} - \sigma(\underbrace{T + T_I}_{T_{tot}}) - \rho T_I \end{aligned}$$

$$\frac{dT_{tot}}{dt} \leq \pi_{_T} - \sigma T_{tot}, \text{ since } \rho, T_I \geq 0$$

$$\frac{dT_{tot}}{dt} + \sigma T_{tot} \leq \pi_{_T} \tag{3.4}$$

Multiply both sides of equation (3.4) by it's integrating factor $e^{\sigma t}$.

$$(e^{\sigma t})\frac{dT_{tot}}{dt} + \sigma T_{tot}(e^{\sigma t}) \leq \pi_{_T} e^{\sigma t}$$

$$\left(T_{tot}e^{\sigma t}\right)' \leq \pi_{_T} e^{\sigma t} \tag{3.5}$$

Then integrate both sides of equation (3.5) with respect to t.

$$T_{tot}e^{\sigma t} \leq \frac{\pi_{_T}}{\sigma}e^{\sigma t} + c_2, \text{where } c_2 \text{ is a constant of integration.}$$

$$T_{tot} \leq \frac{\pi_{_T}}{\sigma} + c_2 e^{-\sigma t}$$

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

$$T_{tot} \leq \frac{\pi_{_T}}{\sigma} + \left(T_{tot}(0) - \frac{\pi_{_T}}{\sigma}\right) e^{-\sigma t}$$

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

$$\lim_{t\to\infty} T_{tot} \leq \frac{\pi_{_T}}{\sigma} := m_2$$

Now, since $0 \leq L_{tot} \leq m_1$ and $0 \leq T_{tot} \leq m_2$, we have $L_I \leq m_1$ and $T_I \leq m_2$. Thus the equation of the rate of change of virus sub population

$$\frac{dV}{dt} = N\delta L_I + M\rho T_I - \alpha V$$

can be rewritten as:

$$\begin{aligned} \frac{dV}{dt} &\leq N\delta m_1 + M\rho m_2 - \alpha V \\ \frac{dV}{dt} + \alpha V &\leq N\delta m_1 + M\rho m_2 \end{aligned} \tag{3.6}$$

Again to solve the first order linear differential inequality (3.6), we need to find it's integrating factor and solve it as we solve for L_{tot} and T_{tot}. Therefore, it's solution is given as

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

As time progress we have

$$\lim_{t\to\infty} V(t) \leq \frac{N\delta m_1 + M\rho m_2}{\alpha} := m_3$$

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

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

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

□

Theorem 3.2.3. *All the solutions of system of equation (3.1) are bounded.*

Proof. In proof of Theorem (3.2.2) we have shown that

$$\lim_{t\to\infty} L_{tot} \leq \frac{\pi_{_L}}{\mu} := m_1, \quad \lim_{t\to\infty} T_{tot} \leq \frac{\pi_{_T}}{\sigma} := m_2 \quad \text{and} \quad \lim_{t\to\infty} V(t) \leq \frac{N\delta m_1 + M\rho m_2}{\alpha} := m_3$$

Then, we have

$$0 \leq L \leq m_1, 0 \leq L_I \leq m_1, 0 \leq T \leq m_2, 0 \leq T_I \leq m_2 \quad \text{and} \quad 0 \leq V \leq m_3.$$

Therefore we have proved the Theorem.

□

3.2.3 Steady States and Stability

In this section, we are going to determine the equilibrium point and stability properties of the system of equation (3.1).

Proposition 3.2.4. *The reasonable initial conditions of the system (3.1) are:*

$$L_0 = L(0) = \frac{\pi_{_L}}{\mu}, L_{I0} = L_I(0) = 0, T_0 = T(0) = \frac{\pi_{_T}}{\sigma}, T_{I0} = T_I(0) = 0, V_0 = V(0) = 0$$

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 (3.1) can be reduced to

$$\begin{aligned} \frac{dL}{d} &= \pi_{_L} - \mu L \\ \frac{dT}{dt} &= \pi_{_T} - \sigma T \end{aligned} \tag{3.7}$$

Now, to get the steady state value of equation (3.1) in the absence of virus, we equate the right hand side of equation (3.7) to 0 as follows.

$$\pi_{_L} - \mu L = 0 \text{ and } \pi_{_T} - \sigma T = 0 \text{ which implies } L = \tfrac{\pi_{_L}}{\mu} \text{ and } T = \tfrac{\pi_{_T}}{\sigma}$$

Thus, the reasonable initial conditions for infection by free virus of equation (3.1) can be

$$L(0) = L_0 = \tfrac{\pi_{_L}}{\mu},\ L_I(0) = 0,\ T(0) = T_0 = \tfrac{\pi_{_T}}{\sigma},\ T_I(0) = 0\ ,\ V(0) = V_0 = 0$$

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 (3.1) as follows:
suppose that

$$f_1(L, L_I, T, T_I, V) = \pi_L - \beta_1 VL - \mu L \tag{3.8}$$

$$f_2(L, L_I, T, T_I, V) = \beta_1 VL - \mu L_I - \delta L_I \tag{3.9}$$

$$f_3(L, L_I, T, T_I, V) = \pi_T - \sigma T - \beta_2 VT - \beta_3 L_I T - \beta_4 T_I T \tag{3.10}$$

$$f_4(L, L_I, T, T_I, V) = \beta_2 VT + \beta_3 L_I T + \beta_4 T_I T - \sigma T_I - \rho T_I \tag{3.11}$$

$$f_5(L, L_I, T, T_I, V) = N\delta L_I + M\rho T_I - \alpha V \tag{3.12}$$

then we solve for $f_1 = 0, f_2 = 0, f_3 = 0, f_4 = 0$ and $f_5 = 0$ simultaneously.
From equation(3.8) and equation (3.9) we have

$$\frac{\pi_{_L}}{\beta_1 V + \mu} = \frac{(\mu_2 + \delta)L_I}{\beta_1 V}$$

which can be rearranged as

$$\pi_L \beta_1 V - (\mu + \delta)L_I \beta_1 V = (\mu + \delta)\mu L_I \tag{3.13}$$

Again, from equation (3.10) and equation (3.11), 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

$$\pi_T \beta_2 V - (\sigma + \rho)\beta_2 T_I V = (\sigma + \rho)T_I(\sigma + \beta_3 L_I + \beta_4 T_I) - \pi_T \beta_3 L T_I - \pi_T \beta_4 T_I. \tag{3.14}$$

From equation (3.12), we have

$$V = \frac{N\delta L_I + M\rho T_I}{\alpha}. \tag{3.15}$$

Substituting equation (3.15) in equation (3.13) and bringing like term together gives:

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

If we let

$$a = \frac{N\pi_{_L}\beta_1\delta}{\alpha} - \mu(\mu+\delta),$$
$$b = \frac{M\pi_{_L}\beta_1\rho}{\alpha},$$
$$c = \frac{N\beta_1\delta(\mu+\delta)}{\alpha} \quad \text{and}$$
$$d = \frac{M\beta_1\rho(\mu+\delta)}{\alpha}$$

we will have,

$$aL_I + bT_I = cL_I^2 + dL_IT_I \tag{3.16}$$

Similarly, insert equation (3.15) into (3.14) and collect like term together. We obtain

$$L_I[\frac{N\pi_{_T}\beta_2\delta}{\alpha} + \pi_{_T}\beta_3] + T_I[\frac{M\pi_{_T}\beta_2\rho}{\alpha} - (\sigma+\rho)\sigma + \pi_T\beta_4] = T_IL_I[\frac{N\beta_2\rho(\sigma+\rho)}{\alpha} + \beta_3(\delta+\rho)] + T_I^2[\frac{M\beta_2\rho(\delta+\rho)}{\alpha} + (\delta+\rho)\beta_4].$$

If we let

$$e = \frac{N\pi_{_T}\beta_2\delta}{\alpha} + \pi_{_T}\beta_3,$$
$$f = \frac{M\pi_{_T}\beta_2\rho}{\alpha} - \sigma(\sigma+\rho) + \pi_T\beta_4],$$
$$g = \frac{N\beta_2\rho(\sigma+\rho)}{\alpha} + \beta_3(\delta+\rho) \quad \text{and}$$
$$h = \frac{M\beta_2\rho(\delta+\rho)}{\alpha} + (\delta+\rho)\beta_4$$

we will have,

$$eL_I + fT_I = gT_IL_I + hT_I^2 \tag{3.17}$$

Now, after rearranging and combining together the equations (3.16) and (3.17) we will obtain equation (3.18) below.

$$T_I^4[gch^2 - dhg^2] + T_I^3[2hg(de-cf) - hg(de-ga) - g^2(gb-df)]$$
$$+ T_I^2[gcf^2 + (de-ga)(he+fg) - dhe^2 + 2eg(gb-df)] + T_I[fe(de-ga) - e^2(gb-df)] = 0 \tag{3.18}$$

Suppose

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

then, equation (3.18) 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 matlab and only take the real and positive T_I and neglect the rest. So, we get

$$T_I = \frac{\left(-27k^8n + 9k^7lm - 2k^6l^3 + 3\sqrt{3}\sqrt{27k^{16}n^2 - 18k^{15}lmn + 4k^{15}m^3 + 4k^{14}l^3n - k^{14}l^2m^2}\right)^{\frac{1}{3}}}{3 \times 2^{\frac{1}{3}}k^3} - \frac{2^{\frac{1}{3}}\left(2187k^5c - 729k^4l^2\right)}{2187k^3\left(-27k^8n + 9k^7lm - 2k^6lm + 3\sqrt{3}\sqrt{27k^{16}n^2 - 18k^{15}lmn + 4k^{15}m^3 + 4k^{14}l^3n - k^{14}l^2m^2}\right)^{\frac{1}{3}}} - \frac{l}{3k} \tag{3.19}$$

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

$$L_I = \frac{T_I(hT_I - f)}{e - gT_I}, V = \frac{N\delta L_I + M\rho T_I}{\alpha}, L = \frac{\pi_{_L}}{\beta_1 V + \mu}, T = \frac{(\sigma + \rho)T_I}{\beta_2 V + \beta_3 L_I + \beta_4 T_I} \tag{3.20}$$

Generally,we have seen that the system of equation (3.1) has two steady states: the uninfected steady states(VFE) $E_0 = \left(\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0, 0\right)$ and the infected steady state (EE) $E^* = (L^*, L_I^*, T^*, T_I^*, V^*)$ where $L^*, L_I^*, T^*, T_I^*, V^*$ are those values of L, L_I, T, T_I, V given in equation (3.19) and (3.20) above.

Local Stability of Virus Free Equilibrium (VFE)

To discuss the local stability of virus free equilibrium, $E_0 = \left(\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0, 0\right)$, we consider the linearized system of equation (3.1) at E_0.

Now we find the Jacobian matrix from equation (3.8) − (3.12) as follows.

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

$$= \begin{pmatrix} -\beta_1 V - \mu & 0 & 0 & 0 & -\beta_1 L \\ \beta_1 V & -(\mu + \delta) & 0 & 0 & \beta_1 L \\ 0 & -\beta_3 T & -\sigma - \beta_2 V - \beta_3 L_I - \beta_4 T_I & -\beta_4 T & -\beta_2 T \\ 0 & \beta_3 T & \beta_2 V + \beta_3 L_I + \beta_4 T_I & \beta_4 T - (\sigma + \rho) & \beta_2 T \\ 0 & N\delta & 0 & M\rho & -\alpha \end{pmatrix} \tag{3.21}$$

The Jacobian 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.

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

$$\lambda^5 + b_1\lambda^4 + b_2\lambda^3 + b_3\lambda^2 + b_4\lambda + b_5 = 0 \tag{3.22}$$

where

$$\begin{aligned}
b_1 =& a_{11}+a_{12}+a_{33}+a_{44}+a_{55} \\
b_2 =& a_{11}(a_{22}+a_{33}+a_{44}+a_{55})+a_{22}a_{33}+(a_{22}+a_{33})(a_{44}+a_{55})+a_{44}a_{55}+a_{54}a_{35}-a_{15}a_{52} \\
b_3 =& a_{11}a_{22}a_{33}+a_{11}(a_{22}+a_{33})(a_{44}+a_{55})+a_{11}a_{44}a_{55}+a_{11}a_{54}a_{35}-a_{11}a_{15}a_{52}+a_{22}a_{33}(a_{44}+a_{55}) \\
& +a_{44}a_{55}(a_{22}+a_{33})+a_{54}a_{35}(a_{22}+a_{33})-a_{15}a_{32}a_{54}+a_{15}a_{52}(a_{44}-a_{33}) \\
b_4 =& a_{11}a_{22}a_{33}(a_{44}+a_{55})+a_{11}a_{44}a_{55}(a_{22}+a_{33})+a_{11}a_{54}a_{35}(a_{22}+a_{33})-a_{11}a_{15}a_{32}a_{54}+ \\
& a_{11}a_{15}a_{52}(a_{44}-a_{33})+a_{22}a_{33}a_{44}a_{55}+a_{22}a_{33}a_{54}a_{35}-a_{15}a_{32}a_{33}a_{54}+a_{15}a_{52}a_{33}a_{44} \\
b_5 =& a_{11}a_{22}a_{33}(a_{44}a_{55}+a_{54}a_{35})+a_{11}a_{15}a_{33}(a_{52}a_{44}-a_{32}a_{54})
\end{aligned}$$

By Routh-Hurwitz criterion, it follows that all eigenvalues of equation (3.22) have negative real parts if and only if it satisfies:

$$\begin{gathered} b_i > 0 \text{ for } i = 1, \cdots, 5,\ \frac{b_1b_2-b_3}{b_1} > 0, b_3 - \frac{b_1(b_1b_4-b_5)}{b_1b_2-b_3} > 0 \\ b_1b_4 - b_5 - \frac{b_5(b_1b_2-b_3)^2}{b_3(b_1b_2-b_3)-b_1(b_1b_4-b_5)} > 0 \end{gathered} \tag{3.23}$$

Note that equation (3.23) was obtained in section (1.7).
If condition (3.23) holds, the virus free equilibrium $E_0 = (\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0, 0)$ is locally asymptotically stable.

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 (3.1) at E^*. Using equation (3.21), the Jacobian matrix of E^* is

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

then the linearized system of equation (3.1) is

$$\begin{pmatrix} \frac{du'}{dt} \\ \frac{dv'}{dt} \\ \frac{dw'}{dt} \\ \frac{dx'}{dt} \\ \frac{dy'}{dt} \end{pmatrix} = \underbrace{\begin{pmatrix} -\beta_1 V^* - \mu & 0 & 0 & 0 & -\beta_1 L^* \\ \beta_1 V^* & -(\mu+\delta) & 0 & 0 & \beta_1 L^* \\ 0 & -\beta_3 T^* & -\sigma - \beta_2 V^* - \beta_3 L_I^* - \beta_4 T_I^* & -\beta_4 T^* & -\beta_2 T^* \\ 0 & \beta_3 T^* & \beta_2 V^* + \beta_3 L_I^* + \beta_4 T_I^* & \beta_4 T^* - (\sigma+\rho) & \beta_2 T^* \\ 0 & N\delta & 0 & M\rho & -\alpha \end{pmatrix}}_{=B} \begin{pmatrix} u' \\ v' \\ w' \\ x' \\ y' \end{pmatrix} \tag{3.24}$$

Then,

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

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

$$\lambda^5 + c_1\lambda^4 + c_2\lambda^3 + c_3\lambda^2 + c_4\lambda + c_5 = 0 \tag{3.25}$$

where

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

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

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

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

$c_5 = b_{11}b_{22}(b_{34}b_{43}b_{55} - b_{33}(b_{44}b_{55} + b_{54}b_{35})) - b_{11}b_{15}b_{43}(b_{34}b_{52} - b_{32}b_{54}) - b_{11}b_{15}b_{33}(b_{32}b_{54} - b_{52}b_{44})$
$+ b_{15}b_{21}(b_{43}(b_{3452} - b_{32}b_{54}) + b_{33}(b_{32}b_{54} - b_{52}b_{44}))$

By Routh-Hurwitz criterion described in section (1.7), it follows that all eigenvalues of equation (3.25) have negative real parts if and only if it satisfies:

$$\begin{aligned} c_1 > 0, c_5 > 0, \frac{c_1c_2 - c_3}{c_1} > 0, c_3 - \frac{c_1(c_1c_4 - c_5)}{c_1c_2 - c_3} > 0 \\ c_1c_4 - c_5 - \frac{c_5(c_1c_2 - c_3)^2}{c_3(c_1c_2 - c_3) - c_1(c_1c_4 - c_5)} > 0 \end{aligned} \tag{3.26}$$

Therefore, the endemic equilibrium point $E^* = (L^*, L_I^*, T^*, T_I^*, V^*)$ is locally asymptotically stable if condition (3.26) holds.

Global Stability

The global stability of obtained equilibrium can be analysed by transforming the system of equations (3.1) into a linear system and then choosing a suitable Lyapunov function to analyse 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 (3.1) 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 (3.1) and i=1, ..., 5. Thus, the linear system of equation (3.1) is

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

Theorem 3.2.5. *The equilibrium* $E_0(L^*, 0, T^*, 0, 0) = (\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0, 0)$ *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^* and T^* are components of the equilibrium point $E_0(L^*, 0, T^*, 0, 0) = (\frac{\pi_L}{\mu}, 0, \frac{\pi_T}{\sigma}, 0, 0)$ Since $(x_1, x_2, x_3, x_4, x_4) \in \mathbb{R}^5_+$, $Z(x_1, x_2, x_3, x_4, x_5)$ is a positive definite function. Differentiating Z with respect to time t we get

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

Choosing

$$\frac{\mu + \delta}{L^*} - N\delta \geq 0 \quad \text{and} \frac{\sigma + \rho}{T^*} - M\rho \geq 0 \tag{3.27}$$

we have

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

Then, equation (3.27) can be rearranged as
$\delta(NL^* - 1) \leq \mu$ and $\rho(MT^* - 1) \leq \sigma$. So $E_0 = (L^*, 0, T^*, 0, 0)$ is Lyapunov stable. Therefore, the theorem is proved. □

3.3 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 (3.1) by using an iterative method with Runge-Kutta fourth order scheme.

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 (3.1). 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. The following illustrates these approaches.

We start with initial conditions

$$est = 0, L(t_0) = L_0, L_I(_{t_0}) = L_{I_0}, T(t_0) = T_0, T_I(t_0) = T_{I_0}, V(t_0) = V_0.$$

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

$$\begin{aligned}
L_{i+1} &= L_i + \frac{1}{6}\left[k_{11} + 2(k_{21} + k_{31}) + k_{41}\right] \\
L_{Ii+1} &= L_{Ii} + \frac{1}{6}\left[k_{12} + 2(k_{22} + k_{32}) + k_{42}\right] \\
T_{i+1} &= T_i + \frac{1}{6}\left[k_{13} + 2(k_{23} + k_{33}) + k_{43}\right] \\
T_{Ii+1} &= T_{Ii} + \frac{1}{6}\left[k_{14} + 2(k_{24} + k_{34}) + k_{44}\right] \\
V_{i+1} &= V_i + \frac{1}{6}\left[k_{15} + 2(k_{25} + k_{35}) + k_{45}\right]
\end{aligned}$$

with,

$$\begin{aligned}
k_{1j} &= hf_j(t_0, L_0, L_{I0}, T_0, T_{I0}, V_0) \\
k_{2j} &= hf_j(t_0 + \frac{h}{2}, L_i + \frac{k_{11}}{2}, L_{Ii} + \frac{k_{12}}{2}, T_i + \frac{k_{13}}{2}, T_{Ii} + \frac{k_{14}}{2}, V_i + \frac{k_{15}}{2}) \\
k_{3j} &= hf_j(t_0 + \frac{h}{2}, L_i + \frac{k_{21}}{2}, L_{Ii} + \frac{k_{22}}{2}, T_i + \frac{k_{23}}{2}, T_{Ii} + \frac{k_{24}}{2}, V_i + \frac{k_{25}}{2}) \\
k_{4j} &= hf_j(t_0 + h, L_i + k_{31}, L_{Ii} + k_{32}, T_i + k_{33}, T_{Ii} + k_{34}, V_i + k_{35})
\end{aligned}$$

where f_j's are equations given in (3.8) − (3.12) for j=1,...,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.

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 [22]. 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 those values in table (3.2) and using these values we get figure (3.2) and (3.3) below.

Parameters	Approximated Values
Initial population size of healthy Langerhans cells (L)	$800mm^{-3}$
initial population size of infected Langerhans cells (L_I)	$0.033mm^{-3}$
intial 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 ($\pi_{_L}$)	$19mm^{-3}$
Infection rate of susceptible Langerhans cells by free virus (β_1)	0.002 day^{-1}
Natural death rate of Langerhans cells (μ)	0.002 day^{-1}
Death rate of L_I due to virus (δ)	0.007 day^{-1}
The constant rate of production of susceptible T-cells from the bone marrow($\pi_{_T}$)	$15mm^{-3}$
Natural death rate of T cells(σ)	0.001 day^{-1}
Infection rate of T-cells by free virus (β_2)	0.0002 day^{-1}
Infection rate of T-cells by infected Langerhans cells(β_3)	0.0004 day^{-1}
Infection rate of T-cells by infected T-cells(β_4)	0.003 day^{-1}
Death rate of infected T-cells due to virus(ρ)	0.008 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 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 day^{-1}
virus death rate(α)	0.8 day^{-1}

Table 3.2: The approximated values of variable and parameters declared in the numerical simulation

Figure 3.2 illustrates the dynamics of the disease for healthy Langerhans cells (a), infected Langerhans cells (b), Healthy T-cells (c) and infected T-cells (d) with increasing time. The population of susceptible Langerhans cells and susceptible T cells decreases as time increases due to the presence of virus as shown in (a) and (c). For (b) and (d), the reverse is true.

Figure (3.3) shows the dynamics of infection by comparing Virus versus time (e), healthy Langerhans cells versus virus (f), infected Langerhans cells versus virus (g) and healthy T cells versus virus (h). In (e) we observe that, at initial time t, the population size of free virus particle stays on it's initial number, but after a time being it increases rapidly. This is due to it's structure. That means, HIV is an enveloped retrovirus. When it leaves a host cell it takes a part of that cells and duplicate it self along with host cells. Therefore, it starts to multiply it self within a short period of time including it's daughter cells. In (f) we also observe that at the beginning of viral infection, the population size of susceptible Langerhans cells increases but after a moment due to the effects and increment of viral infection the graph bends back ward which shows the decreasement of the amount of healthy Langerhans cells. Similarly in h, the population size of susceptible T-cells decreases starting from its initial population size ($1000/mm^3$) but, since the healthy T-cells protect viral infection, the number of the virus does not increases as much as for healthy Langerhan cells in (f). The graph approaches to x label (healthy T-cells) when the population size of T-cells are large in amount and when the number of this cells become smaller and smaller, the graphs approaches to y label which shows the increment of viral infection. Thus, this justified the analytical results of disease free-equilibrium E_0. In (g), we observe that as population size of infected Langerhans cells increases, the population size of free virus particle also increases. For the sake of easy comparison, we can observe all of this dynamical interaction on one plane in figure (3.4).

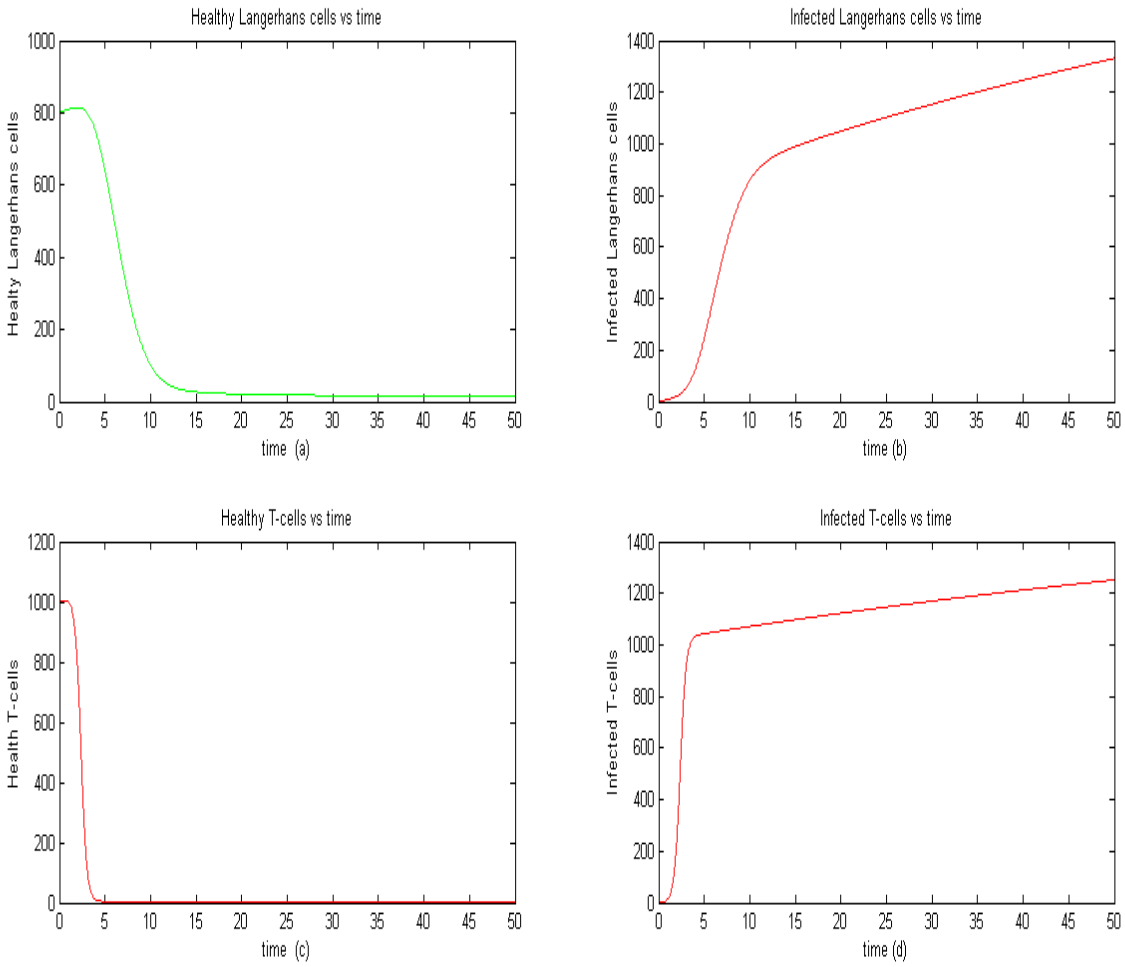

Figure 3.2: Dynamics of the model individual showing the virus progression in an increasing time t

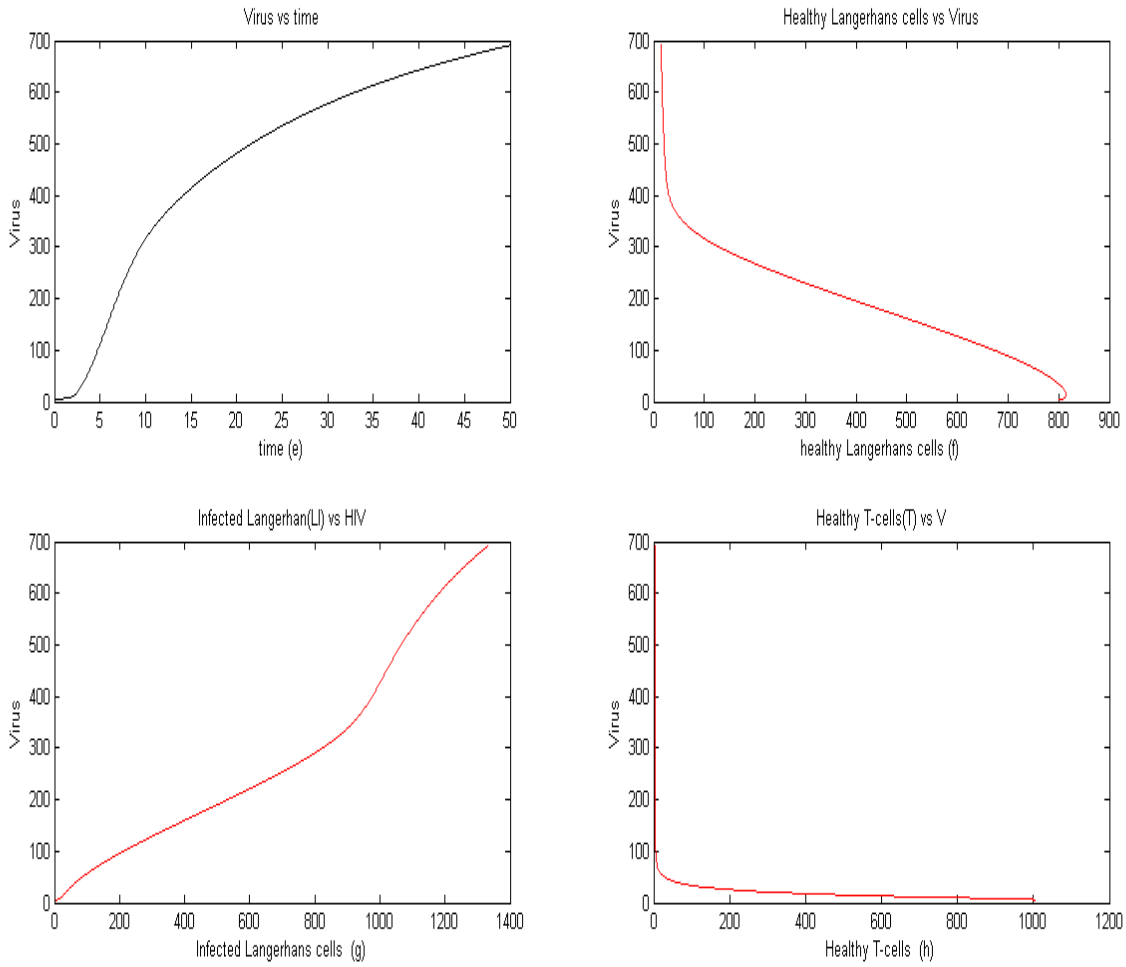

Figure 3.3: Dynamics of the model individual showing the interaction between the virus and healthy cells

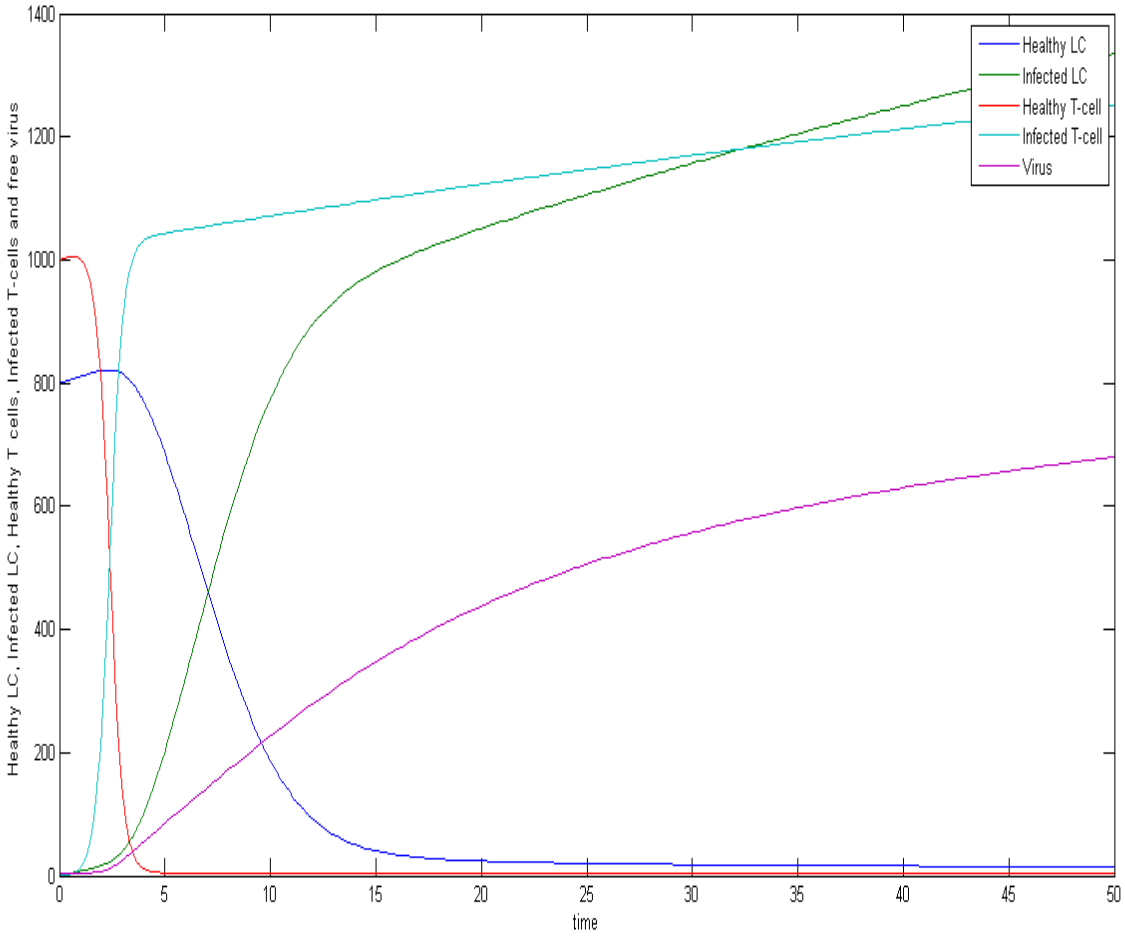

Figure 3.4: Graph of all model individual compartment on one plane

Chapter 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 meaning full 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 nonnegative. 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 assist us to consolidate our knowledge on the dynamics of HIV − host cells interaction and it concretely simplify 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 this 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 this 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 analysis and provide a more reasonable fact on the interplay between Langerhans cells and HIV infections.

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Appendix

For the numerical analysis of the model system, we have used the following matlab code.

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```
% Using Fourth order Runge-Kutta method to solve numerically the developed model on the↙
interaction between LC and HIV:
%            dx1/dt = p1-b1*x5*x1-m*x1
%            dx2/dt = b1*x5*x1-m*x2-d*x2
%            dx3/dt = p2-s*x3-b2*x5*x3-b3*x2*x3-b4*x4*x3
%            dx4/dt = b2*x5*x3+b3*x2*x3+b4*x4*x3-s*x4-r*x4
%            dx5/dt = n1*d*x2+n2*r*x4-a*x5
%  Study the behaviour of the solution by varying the step length dx.
% Clear screen and memory.        %
clear all;
format long e;
% Determine time step, desired length of simulation, and number of required iterations.
dt = 0.01;
Tmax = 50;
%N = floor(Tmax/dt);
N = Tmax/dt;
% Initial condition takes the form X=[L(0) LI(0) T(0) TI(0) V(0)]
X=[800 0.033 1000 0.045 5];
t=0;
% Parameter values for the interaction between Lc and HIV.
p1=20;
b1=0.002;
m=0.002;
d=0.007;
p2=15;
s=0.001;
b2=0.0002;
b3=0.0004;
b4=0.003;
r=0.008;
n1=2;
n2=4;
a=0.08;

F1=@(X1,X2,X3,X4,X5) p1-b1*X5*X1-m*X1;
F2=@(X1,X2,X3,X4,X5) b1*X5*X1-m*X2-d*X2;
F3=@(X1,X2,X3,X4,X5) p2-s*X3-b2*X5*X3-b3*X2*X3-b4*X4*X3;
F4=@(X1,X2,X3,X4,X5) b2*X5*X3+b3*X2*X3+b4*X4*X3-s*X4-r*X4;
F5=@(X1,X2,X3,X4,X5) n1*d*X2+n2*r*X4-a*X5;

for i=2:N+1
t=[t;(i-1)*dt];
k1=[F1(X(i-1,1),X(i-1,2),X(i-1,3),X(i-1,4),X(i-1,5)).*dt F2(X(i-1,1),X(i-1,2),X(i-1,3),X↙
(i-1,4),X(i-1,5)).*dt F3(X(i-1,1),X(i-1,2),X(i-1,3),X(i-1,4),X(i-1,5)).*dt F4(X(i-1,1),X↙
(i-1,2),X(i-1,3),X(i-1,4),X(i-1,5)).*dt F2(X(i-1,1),X(i-1,2),X(i-1,3),X(i-1,4),X(i-1,5)).↙
*dt];
```

```
k2=[F1(X(i-1,1)+(1/2).*k1(1,1),X(i-1,2)+(1/2).*k1(1,2),X(i-1,3)+(1/2).*k1(1,3),X(i-1,4)+↙
(1/2).*k1(1,4),X(i-1,5)+(1/2).*k1(1,5)).*dt F2(X(i-1,1)+(1/2).*k1(1,1),X(i-1,2)+(1/2).*k1↙
(1,2),X(i-1,3)+(1/2).*k1(1,3),X(i-1,4)+(1/2).*k1(1,4),X(i-1,5)+(1/2).*k1(1,5)).*dt F3(X↙
(i-1,1)+(1/2).*k1(1,1),X(i-1,2)+(1/2).*k1(1,2),X(i-1,3)+(1/2).*k1(1,3),X(i-1,4)+(1/2).*k1↙
(1,4),X(i-1,5)+(1/2).*k1(1,5)).*dt F4(X(i-1,1)+(1/2).*k1(1,1),X(i-1,2)+(1/2).*k1(1,2),X↙
(i-1,3)+(1/2).*k1(1,3),X(i-1,4)+(1/2).*k1(1,4),X(i-1,5)+(1/2).*k1(1,5)).*dt F5(X(i-1,1)+↙
(1/2).*k1(1,1),X(i-1,2)+(1/2).*k1(1,2),X(i-1,3)+(1/2).*k1(1,3),X(i-1,4)+(1/2).*k1(1,4),X↙
(i-1,5)+(1/2).*k1(1,5)).*dt];
k3=[F1(X(i-1,1)+(1/2).*k2(1,1),X(i-1,2)+(1/2).*k2(1,2),X(i-1,3)+(1/2).*k2(1,3),X(i-1,4)+↙
(1/2).*k2(1,4),X(i-1,5)+(1/2).*k2(1,5)).*dt F2(X(i-1,1)+(1/2).*k2(1,1),X(i-1,2)+(1/2).*k2↙
(1,2),X(i-1,3)+(1/2).*k2(1,3),X(i-1,4)+(1/2).*k2(1,4),X(i-1,5)+(1/2).*k2(1,5)).*dt F3(X↙
(i-1,1)+(1/2).*k2(1,1),X(i-1,2)+(1/2).*k2(1,2),X(i-1,3)+(1/2).*k2(1,3),X(i-1,4)+(1/2).*k2↙
(1,4),X(i-1,5)+(1/2).*k2(1,5)).*dt F4(X(i-1,1)+(1/2).*k2(1,1),X(i-1,2)+(1/2).*k2(1,2),X↙
(i-1,3)+(1/2).*k2(1,3),X(i-1,4)+(1/2).*k2(1,4),X(i-1,5)+(1/2).*k2(1,5)).*dt F5(X(i-1,1)+↙
(1/2).*k2(1,1),X(i-1,2)+(1/2).*k2(1,2),X(i-1,3)+(1/2).*k2(1,3),X(i-1,4)+(1/2).*k2(1,4),X↙
(i-1,5)+(1/2).*k2(1,5)).*dt];
k4=[F1(X(i-1,1)+k3(1,1),X(i-1,2)+k3(1,2),X(i-1,3)+k3(1,3),X(i-1,4)+k3(1,4),X(i-1,5)+k3↙
(1,5)).*dt F2(X(i-1,1)+k3(1,1),X(i-1,2)+k3(1,2),X(i-1,3)+k3(1,3),X(i-1,4)+k3(1,4),X(i-↙
1,5)+k3(1,5)).*dt F3(X(i-1,1)+k3(1,1),X(i-1,2)+k3(1,2),X(i-1,3)+k3(1,3),X(i-1,4)+k3(1,4),↙
X(i-1,5)+k3(1,5)).*dt F4(X(i-1,1)+k3(1,1),X(i-1,2)+k3(1,2),X(i-1,3)+k3(1,3),X(i-1,4)+k3↙
(1,4),X(i-1,5)+k3(1,5)).*dt F5(X(i-1,1)+k3(1,1),X(i-1,2)+k3(1,2),X(i-1,3)+k3(1,3),X(i-↙
1,4)+k3(1,4),X(i-1,5)+k3(1,5)).*dt];
Xtemp=[(1/6).*(k1(1,:)+2.*k2(1,:)+2.*k3(1,:)+k4(1,:))];
X=[X;X(i-1,:)+Xtemp];
end

% Plot results
% First plot: L(t) vs t , second plot: LI(t) vs t, third plot: T(t) vs t,
% fourth plot: TI(t) vs t, fifth plot:  V(t) vs t, sixth plot: L vs V
subplot(2,4,1)
plot(t(:),X(:,1),'g-')
title('Healthy Langerhans cells vs time')
xlabel('time  (a)')
ylabel('Healty Langerhans')

subplot(2,4,2)
plot(t(:),X(:,2),'r-')
title('Infected Langerhans cells vs time')
xlabel('time (b)')
ylabel('Infected Langerhans cells')
```

```
subplot(2,4,3)
plot(t(:),X(:,3),'r-')
title('Healthy T-cells vs time')
xlabel('time  (c)')
ylabel('Health T-cells')

subplot(2,4,4)
plot(t(:),X(:,4),'p-')
title('Infected T-cells vs time')
xlabel('time (d)')
ylabel('Infected T-cells')

subplot(2,4,5)
plot(t(:),X(:,5),'k-')
title('Virus vs time')
xlabel('time (e)')
ylabel('Virus')

subplot(2,4,6)
plot(X(:,1),X(:,5),'r-')
title('Healthy Langerhans cells vs Virus')
xlabel('healthy Langerhans cells (f)')
ylabel('Virus')

subplot(2,4,8)
plot(X(:,2),X(:,5),'r-')
title('Infected Langerhan(LI) vs HIV')
xlabel('Infected Langerhans cells  (g)')
ylabel('Virus')

subplot(2,4,7)
plot(X(:,3),X(:,5),'b-')
title('Healthy T-cells(T) vs V')
xlabel('Healthy T-cells  (h)')
ylabel('Virus')
```

Declaration

I here under signed declare that this thesis is my original work and has not been presented for a degree in any other university, and that all sources of material used for the thesis have been duly acknowledged.

(Name)	Signature