MATHEMATICAL MODEL OF THE INTERACTION BETWEEN CYTOTOXIC T LYMPHOCYTES AND HIV

ADAMA SCIENCE AND TECHNOLOGY UNIVERSITY
SCHOOL OF APPLIED NATURAL SCIENCES
APPLIED MATHEMATICS PROGRAM

By

Eshetu Dadi

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Abstract

In this thesis work we developed a mathematical model to describe the dynamics of the interaction between Cytotoxic T Lymphocytes and HIV. The resulting model is a system of non-linear ordinary differential equations. In this thesis, we prove existence and uniqueness as well as positivity and boundedness of the solutions to the system of differential equations. In addition, we derive the reproduction numbers, and analyze the local stability of the differential equation model. From the analytical solution and numerical simulations we observe that if the reproduction number is less than the solution converges to the disease free stead state, while if the reproduction number is greater than the solution converges to endemic equilibrium point and the infection cannot cleared.

Abbrevation

AIDS - Acquired Immunodeficiency Syndrome
CTL - Cytotoxic T Lymphocyte
CD_4 - Cluster of Differentiation
CD_8 - Cluster of Differentiation
DNA - Deoxyribonucleic Acid
HIV - Human Immunodeficiency Virus
RNA - Ribonucleic Acid.

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Chapter 1

Introduction

1.1 Background of the Study

Human Immunodeficiency Virus(HIV) is known as a pathogen causing the Acquired Immunodeficiency Syndrome(AIDS), which is the end stage of the infection. AIDS causes mortality, morbidity of millions of people and expenditure of enormous amounts of money in public health care and disease control. AIDS was first reported in the USA in 1981, by the center for Disease Control (CDC) which recorded a cluster of Pneumocystis carimi (a form of rare pneumonia) in five homosexual men in Los Angeles. In the initial stage, the CDC did not have an official name for the disease, often referring to it by way of the diseases that were associated with it, for example, lymphadenopathy-disease of the lymph nodes, and the disease after which the discoverers of HIV originally named the virus. The CDC later used the name Kaposis Sarcoma (a form of skin cancer) and opportunistic infections. By 1986 there was sufficient understanding of the retrovirus to lead to a new name, HIV, or human immunodeficiency virus. It is now accepted that AIDS is a disease of the human immune system caused by the human immunodeficiency virus (HIV)[1].
Moreover, HIV dynamics with the immune system is different from any other virus in that it affects the immune system directly by attacking the CD_4 T-cells, also known as helper T cells. CD_4 T-cells are cells in the immune system that plays a key role in identifying foreign bodies and infected cells in the body. These virions and infected cells are

consumed by a macrophage, which tags itself for destruction. The CD_4 T-cells identify these protein tags on the macrophage and produce cytokines that stimulates production of beta cells and Cytotoxic T Lymphocytes(CTL) cells, also known as killer T cells. Just as it's nickname implies CTL cells are the actual cells that connect with the macrophages and injects chemicals that denatures the foreign body and exterminates the infection[8].

HIV virions attaches to CD_4 T-cells through connecting particular co-receptors found on the CD_4 T-cells membrane, thus allowing them access into the cell. The virions then goes to fuse with the cell releasing its DNA and replication mechanics into the cell. From there, the virus replicates its DNA through reverse transcription where a reverse transcriptase and intergrase proteins regenerates the virus's DNA and incorporates it into the cell's DNA. The cell will unknowingly continue to reproduce it's own DNA along with the virus DNA. This process may remain asymptomatic for many years, ten year on average, allow the infection to spread and remain undetected. After the virus's DNA has been translated into protein strings, an enzyme known as protease will cut these long HIV protein chains into individual proteins that, combined with the virus's DNA, can assemble into a new virus. The virus will then push itself out of the host cell taking parts of its membrane along with it and go on to infect other cells.

The most intericate part of this cycle for HIV viruses in particular is by infect CD_4 T-cells, it reduced the number of CTL stimulations and thus weakens the body's immune response towards fighting off the virus. When the virus become pathogenic and the CD_4 T-cells of patient decline to $200/mm^3$ or below, the diagnosis of AIDS is given[1].

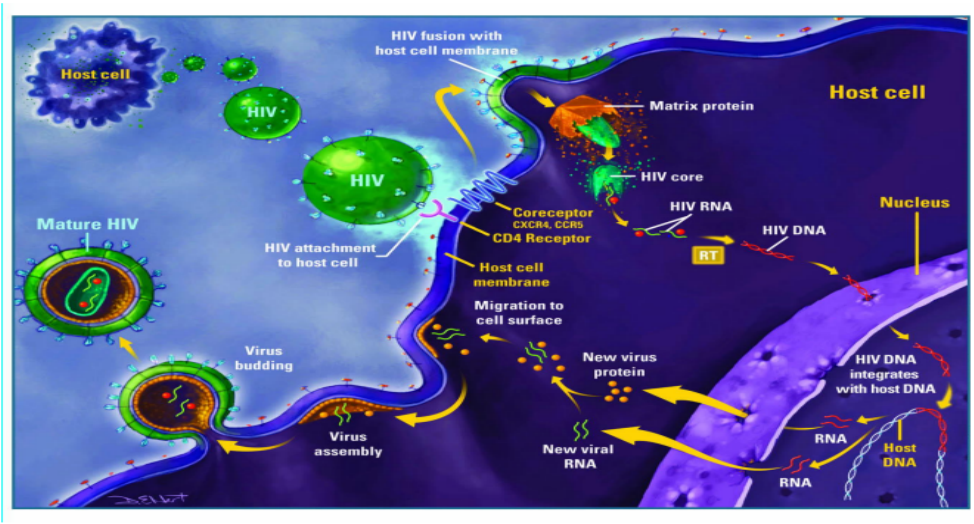

Figure 1.1: Life cycle of HIV virus [5].

Over the past two decades, hundreds of thousands of journal articles pertaining to HIV/AIDS have been publish. Among there are hundreds of mathematical and statistical models of various aspects of the disease.

Broadly speaking, we can classify the various mathematical models of HIV dynamics into one of two categories,

1.Epidemiological models, which attempt to assess the spread of infection through a population using quantitative and theoretical means, and

2.Immunological models, which examine the with in host cellular responses to an invader.

The utility of mathematical models to the HIV-immune system interaction is twofold.

(i) A good model can predict with a great deal of accuracy what will transpire in the very long term.

(ii) To help treatment with drug therapy at different regimes[5].

1.2 Statement of the Problem

The world has committed to ending the AIDS epidemic by 2030. AIDS is one of the most serious, deadly diseases in human history and become an important infectious disease in both the developed and developing countries. In just the last two years the number of people living with HIV on antiretroviral theraph has increased by about a third, reaching 17 million people 2 million more than the 15 million by 2015 target set by the United Nations General Assembly in 2011. In 2015 there were 2.1 million new HIV infections worldwide, adding upto a total of 36.7 million people living with HIV.

In many African countries, AIDS is already a major cause of death special in South Africa and Kenya. South Africa alone had nearly 3.4 million people on treatment, more than any other country in the world(global-AIDS update 2016). In 2014 estimated number of people living with HIV in Ethiopia was 769 600 with 15 700 new HIV infections and 35 600 AIDS related deaths(Ethiopia update sheet on HIV-AIDS programme 2014).

However, mathematical models based on a firm understanding of biological interactions, can provide non-intuitive insights into the dynamics of host response to infectious agents. In this research work we develop a mathematical model describing the interaction of Cytotoxic T lymphocytes to HIV Virus. So, this study is intended to answer the following basic questions:

1. What are the basic assumption to develop a mathematical model which describes the interaction between Cytotoxic T lymphocytes and HIV?

2. How mathematical models helps to visualize the role of Cytotoxic T lymphocytes on HIV infections?

3. What are the biological interpretation of the solutions of the mathematical model which describe the dynamics of the interaction between Cytotoxic T lymphocytes and HIV?

1.3 Objectives of the Study

1.3.1 General Objective

The general objective of this research work is to understand the dynamics of the interaction between Cytotoxic T lymphocytes and HIV.

1.3.2 Specific Objectives

The specific objectives of this study are to:

• develop a mathematical model that describe the interaction between Cytotoxic T lymphocytes and HIV.

• visualize the role of Cytotoxic T lymphocytes on HIV using ordinary differential equations.

• investigate the dynamics of the interaction between Cytotoxic T lymphocytes and HIV.

• interprate the solution of the model using numerical simulation

1.4 Significance of the Study

This study provides a reliable information on how we can use mathematical models to understand the dynamics of the interaction between Cytotoxic T lymphocytes and HIV. The study will also visualize the role of Cytotoxic T lymphocytes on HIV. Therefore, the result of this research work will help to:

1. understand the dynamics of the infection.
2. the scientific community to further investigate the problem.
3. design intervention strategies to policy makers.

1.5 Research Methodology

For effective achievement of the objectives, we first develop a mathematical model which describes the dynamics of the interaction between Cytotoxic T lymphocytes and HIV using a system of non linear ordinary differential equations by considering only three components: Concentration of healthy Cytotoxic T Lymphocytes, concentration of infected cells and concentration of free virus particles respectively at time t with resulting three system of ordinary differential equation.

Then we will determine uninfected steady state and infected steady state. Next, both local and global stability analysis of the equilibrium points of the model equation will be determined using Jacobian matrix and Lyapunove function respectively.

Finally, biological explanations for the mathematical results will be discussed. In addition to this, the analytical solutions of the model equation will be supplemented by numerical simulations by appropriately choosing the system parameter values using MATLAB.

Chapter 2

Literature Review

Mathematical modeling of infectious diseases began in the 1760 with Daniel Bernoulli's modeling of smallpox. Since then, mathematical models have been developed to simulate the spread of a wide range of other infectious diseases, such as bubonic plague, measles, tuberculosis, malaria and influenza to name but a few examples. These mathematical models have been developed to address a range of questions that cannot be answered through the use of traditional epidemiological methods.

Over the years mathematical models using differential equations have been used to gain an understanding of HIV viral dynamics. The models have evolved overtime, including more parameters as we gain more understanding of the disease. Yousfi [4] develop the mathematical model describing the interaction between the viruses, CD_4 T-cells and the Cytotoxic T Lymphocytes taking into account two saturated rates describing viral infection and CTL proliferation. The authors show how the cellular immune response can control the load of the HIV virus. Early models in virus dynamics focused only on CTL response. Perelson [6] suggested the following equation for CTL response:

$$\frac{dZ}{dt} = cyZ - bZ, \tag{2.0.1}$$

where CTLs proliferate in response to antigenic simulation with a rate y. In the absence of stimulation, CTLs decay at rate b. The parameter c denotes the CTL responsiveness, that is, the growth rate of specific CTLs after encountering infected cells. In this model,

there is a minimum level of infected cells y necessary to stimulate a CTL response. That is, the CTL response will increase only if $cy > b$. This simple model of CTL dynamics can be modified to consider the saturation of CTL expansion as the number of CTLs growths to relatively high numbers, which is expressed by the following equation [12]

$$\frac{dZ}{dt} = \frac{cyZ}{1+\epsilon Z} - bZ. \tag{2.0.2}$$

The parameter ϵ represents the saturation level. This model has similar dynamical properties as the previous simple model. The difference is the steady state levels of virus load and cells. If the saturation occurs at lower level of CTLs(high values of ϵ), this model is verified to a simple one given by Ciupe [2]

$$\frac{dZ}{dt} = cy - bZ. \tag{2.0.3}$$

Here, the rate of CTL expansion is simply proportional to the amount of antigen, but not the rate of CTLs. In this model, the CTL response never goes extinct provided there are antigens.

By a lytic mechanisms, CTL is assumed to kill infected cells which is expressed by Krakauer [11]

$$\frac{dY}{dt} = \beta xv - (d+\alpha)y - pyZ. \tag{2.0.4}$$

Infected cells are killed by CTL at a rate pyZ. The parameter p specifies the rate at which CTL kills infected cells. The CTL response also functions by non-lytic mechanisms. CTL decreases the rate at which uninfected target cells become infected, which is expressed by the following equations[9],

$$\begin{aligned} \frac{dx}{dt} &= \lambda - dx - \frac{\beta}{1+qZ}xv, \\ \frac{dy}{dt} &= \frac{\beta}{1+qZ}xv - (d+\alpha)y. \end{aligned} \tag{2.0.5}$$

The term qZ represents the suppression/inhibition of CTL on the viral infection. Similarly, the immune response may also reduce the rate of viral production [12]

$$\begin{aligned} \frac{dy}{dt} &= \beta xv - (d + \frac{\alpha}{1+qz})y, \\ \frac{dv}{dt} &= \frac{k}{(1+qZ)}y - uv. \end{aligned} \tag{2.0.6}$$

In this case, the CTL immune response follows the equation[12]

$$\frac{dz}{dt} = \frac{cyz}{(1+qz)(1+\epsilon z)} - bz. \tag{2.0.7}$$

Another important immune response in controlling virus infection is the antibody response. The antibody response is modeled in a similar way as the CTL response. The main difference is that antibody secreting B cells are activated by antigen specific CD_4 T-cells which recognize viral antigen on the surface of antigen presenting cells (APCs) such as macrophages or some dentritic cells. Since the amount of antigen presentation by the APCs is proportional to the abundance of free virus particles, the growth of this immune response must be proportional to v rather than y. Denoting the antibody response by Z, the model for Z is given as

$$\frac{dZ}{dt} = \frac{cvZ}{1+\epsilon z} - bZ. \tag{2.0.8}$$

Once the antibody response has developed, it removes free virus particles, which is given by equation [3]

$$\frac{dx}{dt} = ky - uv - pvZ. \tag{2.0.9}$$

Here, antibody response removes free virus particles at a rate p. However, in each of the above model they use uninfected cells as CD_4 T-cells as assumption but they use CTLs to clear the infected cells and free virus particles.

In this research work we investigate the complexity of the interplay between HIV and Cytotoxic T Lymphocytes. For more understanding on the behavior of the real situation Cytotoxic T Lymphocytes and HIV, we use Cytotoxic T Lymphocytes as uninfected cells by virus as assumption.

Chapter 3

Model Formulation and Analysis

We consider the dynamical model which describe the interaction between HIV and Cytotoxic T Lymphocytes as a system of three ordinary differential equations. For the model we use Z, I and V to denote the concentration of healthy Cytotoxic T Lymphocytes, the concentration of infected Cells, and concentration of free HIV respectively.
Then $\frac{dZ}{dt}$, $\frac{dI}{dt}$ and $\frac{dV}{dt}$ denotes the rate change of population densities of the concentration of healthy Cytotoxic T Lymphocytes, infected cells and free HIV virus respectively, at a time t respectively.

We assume that healthy CTL cells are produced in the thymus. While production of healthy CTL cells does decrease with the aging of the human body. When we considering removal of these cells, we note that healthy CTL cells do age and, in time, expire. Within the model, we assume that each health CTL cell functions for roughly the same amount of time, and thus, the death rate does not vary over the entire population. Instead, we assume the overall number of healthy CTL cells lost in a group over a certain period of time is proportional to the number of healthy CTL cells with in the group. The other mechanism through which the population of healthy CTL cells may decrease via infection. In considering such effects, we utilize an interaction term that arises from the widely used " mass action principle" to describe the transfer between populations when the virus infects healthy CTL cells. This mass action term represents the idea that the rate of interaction, or infection, is directly proportional to the product of the participating

populations, namely those of virus particles and healthy CTL cells. This completes the interactions for the healthy CTL cells. We note that the only way to increase the population of infected CTL cells is through HIV infection. Thus, our model will contain the same mass action term to describe the removal of the healthy CTL cells and the addition of infected CTL cells. Similar to the healthy CTL cells, infected CTL cells die-off at a rate population to the size of their current population. The virus, while produced from the infected CTL cells, does not cause the destruction of infected CTL cells. Thus, such a transition is not included with in the model.

While the virus production rate does differ from cell to cell, we can assume that the aggregate rate is proportional to the population of infected CTL cells. In contrast, there is a way in which the virus can be removed, or cleared from the body. This removal is known as viral clearance. It is the removal by the body of individual virus particles, and is performed at a rate proportional to the current amount of virus particles with in the body.

Based on the biological description above, we have the following system of three ODEs.

$$\begin{aligned} \frac{dZ}{dt} &= s - \alpha Z - kVZ, \\ \frac{dI}{dt} &= kVZ - aI, \\ \frac{dV}{dt} &= cI - dV, \end{aligned} \tag{3.0.1}$$

where the parameters, s and c the production rates of healthy CTL cells, infected CTL cells, respectively. The term kVZ is the interaction rate of healthy CTL cells and HIV. The parameters α, a, d are the death rates of healthy CTL cells, the infected CTL cells, and virions, respectively. It is important to note that all of the model parameters are assumed to be positive. In addition, there are two biologically reasonable assumptions we are able to make with regard to the values of parameters in relation to one another. Notably, it is biologically reasonable to assume that infected cells have a higher death rate than uninfected cells, namely a $\geqslant \alpha$.

S In order for an infection to take hold, the basic reproduction number R_0, defined as

the average number of secondary infections produced when one infected cell is introduced to a host population, when almost all cells are healthy, must be greater than one. For system (3.0.1)

$$R_0 = (kZ)(\tfrac{1}{a})(c)(\tfrac{1}{d}) = \tfrac{kZc}{ad}$$

where kZ is the rate at which the virus infects healthy cells and c is the rate one infected cell produces virus particles. Again, assuming the body is healthy and in equilibrium when the virus is first introduced to the body, $Z = \frac{s}{\alpha}$ initially, So

$$R_0 = \tfrac{skc}{\alpha ad}.$$

3.1 Existence, Positivity and Boundedness of solution

In order to retain the biological validity of the model, we must prove that solutions to the system of differential equations are positive and bounded for all time. Furthermore, the populations must remain finite since the human body can only be composed of a finite number of cells. In addition, boundedness and positivity illustrate that once infected, it is possible that the population of the virus will continue to exist beneath the detectable threshold without doing significant damage.

The next step in analyzing our model will be to prove positivity and boundedness for the system of differential equations. We do so by proving the following lemma.

Lemma(Positivity). Let $t_0 > 0$. In the model, if the initial conditions satisfy $Z(0) > 0$, $I(0) > 0$ and $V(0) > 0$ then for all $t \in [0, t_0]$ Z(t), I(t), V(t) will remain positive in $\mathbb{R}^3_+$.

proof:- We must prove that for all $t \in [0, t_0]$ Z(t), I(t), V(t) will be positive in $\mathbb{R}^3_+$. We know that all of the parameters used in the system are positive. Thus, we can place lower bounds on each of the equations given in the model. Thus,

$$\frac{dZ}{dt} = \text{s-}\alpha\ \text{Z(t)- kV(t)Z(t)} \geq \text{-}\alpha\ \text{Z(t)- kV(t)Z(t)}, \quad \text{if} \quad \text{V(t), Z(t)} \geq 0$$
$$\frac{dI}{dt} = \text{kV(t)Z(t) - aI(t)} \geq \text{- aI(t)}, \quad \text{if} \quad \text{I(t)} \geq 0$$
$$\frac{dV}{dt} = \text{cI(t) - dV(t)} \geq \text{- dV(t)}, \quad \text{if} \quad \text{V(t)} \geq 0$$

Using separation of variables we can resolve the inequalities and produce:

$$Z(t) \geq \exp^{-\alpha t - k\int V(t)dt} \geq 0$$
$$I(t) \geq \exp^{-at} \geq 0$$
$$V(t) \geq \exp^{-dt} \geq 0$$

Thus, for all for all $t \in [0, t_0]$ Z(t), I(t), V(t) will be positive and remain in $\mathbb{R}^3_+$.

Lemma(Boundedness). There exists Z_M, I_M, $V_M > 0$ such that for Z(t), I(t), V(t) $\limsup_{t\longrightarrow\infty}(Z(t)) \leqslant Z_M$, $\limsup_{t\longrightarrow\infty}(I(t)) \leqslant I_M$, $\limsup_{t\longrightarrow\infty}(V(t)) \leqslant V_M$ for all $t \in [0, t_0]$

Proof:- We must prove that for all $t \in [0, t_0]$ Z(t), I(t), V(t) will be bounded. We know that all of the constants used in the system are positive. Then now

$$\frac{dZ}{dt} + \frac{dI}{dt} = s - \alpha - aI$$

Since all of the constants are positive,

$$\frac{d(Z+I)}{dt} = s - min\{\alpha, a\}(Z+I)(t)$$

which implies

$$(Z+I)(t) \leq \frac{s}{min\{\alpha, a\}} + c_0 \exp^{-min\{\alpha,a\}}$$

taking the limsup of both sides,

$$\limsup_{t\longrightarrow\infty}(Z+I)(t) \leq \limsup_{t\longrightarrow\infty}(\frac{s}{min\{\alpha,a\}} + c_0\exp^{-min\{\alpha,a\}})$$
$$= \frac{s}{min\{\alpha,a\}}$$

So, choose

$$Z_M = I_M = \frac{s}{min\{\alpha,a\}}$$

Thus, (Z+I)(t) is bounded, so Z(t) and I(t) are bounded since

$$Z(t), I(t) \leq (Z+I)(t)$$
$$\text{so, } Z(t) \leq Z_M and I(t) \leq I_M \quad \text{for all } t \in [0,t_0].$$

Furthermore, since all of the constants are positive, we can place an upper bound on $\frac{dV}{dt}$ so,

$$\frac{dV}{dt} = cI(t) - dV(t) \leq cI(t)$$

Therefore, we can choose

$$V_M = cI_M.$$

Thus,

$$V(t) \leq cI_M = cI_M.$$

Hence, since I(t) is bounded for all $t \in [0,t_0]$, we know that V(t) is bounded for all $t \in [0,t_0]$.

Theorem 1.(Existence). Let $t_0 > 0$. In the model, if the initial conditions satisfy $Z(0) > 0$, $I(0) > 0$ and $V(0) > 0$ then for all $t \in [0,t_0]$ Z(t), I(t), V(t) the solution exist in $\mathbb{R}^3_+$.

Proof:- Existence and uniqueness. In the case of our model we have:

$$x = \begin{bmatrix} Z(t) \\ I(t) \\ V(t) \end{bmatrix} and\ f(x) = \begin{bmatrix} s - \alpha Z - kVZ \\ kVZ - aI \\ cI - dV \end{bmatrix}$$

Note that f has a continuous derivative on $\mathbb{R}^3$ and thus, f is locally Lipschitz in $\mathbb{R}^3$. Hence, by fundamental Theorem of Existence and Uniqueness, we know that there exists a unique, positive and bounded solution to the ordinary differential equations given(3.0.1).

3.2 Steady State

In order to fully understand the dynamics of the three component model, it is necessary to first determine equilibrium solutions. An equilibrium solution is a constant solution of the model equation (3.0.1) so that if the system begins at such a value, it will remain there for all time. In other words, the populations are unchanging; so, the rate of change for each population is zero.

In the absence of virus, the rate change of population densities of the concentration of healthy CTL from the system of ODE in (3.0.1) can be reduced to;

$$\frac{dZ}{dt} = s - \alpha Z \tag{3.2.1}$$

Now, to solve the steady state value(s) of the CTLs in the absence of virus, we equate the right hand side of equation (3.2.1) equal to zero as follows;

$$s - \alpha Z = 0$$
$$\Rightarrow Z = \frac{s}{\alpha} \quad \text{say,} \quad Z_0 = \frac{s}{\alpha}$$

Hence, the steady state of uninfected system is $E_0 = (Z_0, 0, 0)$.

Next, in the presence of virus we can find the steady state of the ODE model (3.0.1) as follows.

$$s - \alpha Z - kVZ = 0 \tag{3.2.2}$$

$$kVZ - aI = 0 \tag{3.2.3}$$

$$cI - dV = 0 \tag{3.2.4}$$

To find Z combine (3.2.3) and (3.2.4)

$$\text{kVZ - aI} = 0$$

$$\text{cI - dV} = 0$$

$$\text{then, } V = \tfrac{cI}{d} \text{ and kVZ} = \text{aI}$$

$$\Rightarrow Z = \frac{aI}{kV}, \text{ then substitute value of V gives}$$
$$Z = \frac{ad}{kc}.$$

After substituting this values of Z in (3.2.2) and (3.2.3) we respectively obtain;

$$s - \alpha(\frac{ad}{kc}) - kV(\frac{ad}{kc}) = 0 \tag{3.2.5}$$

$$kV(\frac{ad}{kc}) - aI = 0 \tag{3.2.6}$$

Then to compute the value(s) of I we add equation (3.2.5) and (3.2.6) and we get;

$$I = \frac{s}{a} - \frac{\alpha d}{kc}$$

In order to solve for V substituting the value of I in (3.1.4) and this gives;

$$V = \frac{cs}{ad} - \frac{\alpha}{k}$$

Depending on these interpretation system (3.0.1) has two steady states.The uninfected steady state $E_0 = (Z_0, 0, 0)$ and the infected steady state $\bar{E} = (\bar{Z}, \bar{I}, \bar{V})$, where

$$Z_0 = \frac{s}{\alpha},$$
$$\bar{Z} = \frac{ad}{kc},$$
$$\bar{I} = \frac{s}{a} - \frac{\alpha d}{kc}, \quad if \quad \frac{s}{a} - \frac{\alpha d}{kc} > 0 \text{ and}$$
$$\bar{V} = \frac{cs}{ad} - \frac{\alpha}{k}, \quad if \quad \frac{cs}{ad} - \frac{\alpha}{k} > 0$$

E_0 is characterized as a viral free equilibrium point; this means that $t \longrightarrow \infty$,the virus will be eliminated from the body. $\bar{E}$ describe the persistence of the virus, and the only equilibrium which describes the co-existence of virus and CTL as $t \longrightarrow \infty$.

3.3 Stability Analysis

3.3.1 Local Stability Analysis

For linear ODE, it is well known that the stability properties only depend up on the reproduction number of the system. However, our model is non linear, and thus we must rely on linearization to unify the local behavior of the linear and nonlinear systems.
We will investigate the local stability of the equilibrium points of the system of equation using Jacobian matrix.

$$J = \begin{pmatrix} \frac{\partial f}{\partial z} & \frac{\partial f}{\partial I} & \frac{\partial f}{\partial V} \\ \frac{\partial g}{\partial z} & \frac{\partial g}{\partial I} & \frac{\partial g}{\partial V} \\ \frac{\partial h}{\partial z} & \frac{\partial h}{\partial I} & \frac{\partial h}{\partial V} \end{pmatrix} = \begin{pmatrix} -\alpha - kV & 0 & -kZ \\ kV & -a & kZ \\ 0 & c & -d \end{pmatrix}$$

Then, by studying the linearized system we can investigate the stability of each equilibrium point E_0 and $\bar{E}$. As we will see below, this property depends only on a single number referred to as the reproduction number, denoted by R_0, which is the average number of secondary infections produced in an uninfected cell population, by an infected cell or free virus particle. Given by

$$R_0 = \frac{skc}{\alpha ad}$$

We now prove two theorems that demonstrate the relationship between the value of R_0 and the local asymptotic stability of equilibrium points.These results imply that one can simply examine the value of R_0 to determine whether the absence of virus or existence of virus occurs in the limit of the system as $t \longrightarrow \infty$.

Theorem 2. Equilibrium point E_0 given by

$$(\text{Z, I, V}) = (\frac{s}{\alpha}, 0, 0)$$

is locally asymptotically stable if $R_0 < 1$.

Proof:- We begin by computing J(E_0) and determining its corresponding eigenvalues, since these values are known to characterize the local asymptotic behavior of the associated linear system. Specifically, if every eigenvalue possesses negative real part, then the equilibrium point will be stable. On the other hand, if one or more of the eigenvalues possess positive real part, then the equilibrium point will be unstable. We remark that in the rare event that $R_0 = 1$, the equilibrium E_0 and $\bar{E}$ are identical.
Evaluating the Jacobian at $E_0 = (\frac{s}{\alpha}, 0, 0)$ results in

$$J(E_0) := \begin{bmatrix} -\alpha & 0 & \frac{-ks}{\alpha} \\ 0 & -a & \frac{ks}{\alpha} \\ 0 & c & -d \end{bmatrix}$$

The corresponding characteristic equation can be written as

$$(\lambda + \alpha)((\lambda + a)(\lambda + d) - \tfrac{ksc}{\alpha})$$

Thus, $\lambda = -\alpha < 0$ is negative eigenvalue of the system, the remaining quadratic equation is

$$\lambda^2 + \lambda(a + d) + ad - \tfrac{ksc}{\alpha} = 0$$

Then, using quadratic formula the other eigenvalues are

$$\lambda = \frac{-(a + d) \pm \sqrt{(a + d)^2 - 4(ad - \frac{ksc}{\alpha})}}{2}$$

since the first term under the square root is nonnegative, these eigenvalues have negative real part if and only if

$$4(ad - \tfrac{ksc}{\alpha}) > 0$$
$$\text{or } 4ad(1 - R_0) > 0$$

since all parameters are positive, we see that all eigenvalues possess negative real part if and only if $R_0 < 1$. Thus, in this case E_0 is a locally asymptotically stable equilibrium point if $R_0 < 1$.

R_0 has been incorporated within the stability analysis, we can rewrite the viral persistence equilibrium in terms of R_0, and notice that it possesses non positive population values for $R_0 \leqslant 1$. Hence,it should not be surprising that solutions do not tend to the viral persistence equilibrium for such values of R_0. However, as long as $R_0 > 1$, we find that viral persistence is stable.

Theorem 3 Equilibrium point $\bar{E}$ given by

$$(Z, I, V) = (\tfrac{s}{\alpha R_0}, \tfrac{s(R_0-1)}{aR_0}, \tfrac{\alpha(R_0-1)}{k})$$

is locally asymptotically stable if and only if $R_0 > 1$.

Proof:- The analysis for $\bar{E}$ is similar to that of E_0. We first find the Jacobian matrix at $\bar{E}$. The Jacobian matrix is given by

$$J(\bar{E}) = \begin{bmatrix} -\alpha - k(\frac{cs}{ad} - \frac{\alpha}{k}) & 0 & -k(\frac{ad}{kc}) \\ k(\frac{cs}{ad} - \frac{\alpha}{k}) & -a & k(\frac{ad}{kc} \\ 0 & c & -d \end{bmatrix} = \begin{bmatrix} \frac{-ksc}{ad} & 0 & \frac{-ad}{c} \\ \frac{-ksc}{ad} - \alpha & -a & \frac{ad}{c} \\ 0 & c & -d \end{bmatrix}$$

This results in the characteristic equation of the from

$$\lambda^3 + e_1\lambda^2 + e_2\lambda + e_3 = 0$$

$$\text{where } e_1 = d + a + \tfrac{ksc}{ad}, \quad e_2 = \tfrac{ksc}{a} + \tfrac{ksc}{d}, \quad e_3 = ksc - da\alpha$$

In the case of (3.0.1), it is possible to determine the signs of the solutions to the characteristic equation using a theorem of Routh Hurwitz. According to the Routh-Hurwitz criteria, all roots of this cubic equation possess negative real part if and only if $e_1e_2e_3 > 0$ and $e_1e_2 > e_3$. Hence, it is sufficient to show that $R_0 > 1$ if and only if the Routh-Hurwitz criteria are satisfied.

Then, $e_3 = ksc - da\alpha = da\alpha(R_0 - 1) > 0$ and since all the coefficients in the system are positive,$e_1e_2 > 0$. Additionally,

$$e_1e_2 = (d + a + \tfrac{ksc}{ad})(\tfrac{ksc}{a} + \tfrac{ksc}{a}) > d(\tfrac{ksc}{d}) = ksc > ksc - da\alpha = e_3.$$

Thus, $R_0 > 1$ implies that $\bar{E}$ is a locally asymptotically stable equilibrium point. The other direction follows trivially since $e_3 > 0$ implies $R_0 > 1$. Hence, this is both a necessary and sufficient condition due to the form of e_3, and the proof is completed.

Our analysis reveals one every important fact about the overall system, for starting values sufficiently close to equilibrium point, the long term behavior depends only on the value of R_0. If $R_0 > 1$ then the system tends towards an end state with a non-zero population of infected cells and virions(viral persistence), but if $R_0 \leq 1$ then the final equilibrium is a state with no virus or infection (viral extinction).

3.3.2 Global Stability Analysis

In this section, we investigate the global stability of the model(3.01).

Theorem 4: If $R_0 < 1$, then the disease-free equilibrium point E_0 is globally asymptotically stable.

Proof: Let us consider the following Lyapunov function

$$L(Z, I, V) = Z - Z_0 \ln(\tfrac{Z}{Z_0}) + I - I_0 \ln(\tfrac{I}{I_0}) + \tfrac{a}{c}(V - V_0 \ln(\tfrac{V}{V_0}))$$

By taking the derivatives of L(Z,I,V) we get

$$\dot{L}(Z, I, V) = \dot{Z}(1 - \tfrac{Z_0}{Z}) + \dot{I}(1 - \tfrac{I_0}{I}) + \tfrac{a}{c}\dot{V}(1 - \tfrac{V_0}{V})$$

By using the system (3.0.1) we have

$$\dot{L} = (s - \alpha Z - kVZ)(1 - \tfrac{s}{\alpha Z}) + (kVZ - aI) + \tfrac{a}{c}(cI - dV)$$

After some simplification we obtain that

$$\dot{L} = 2s - (\alpha Z + \tfrac{s^2}{\alpha Z}) + \tfrac{kVs}{\alpha}(1 - \tfrac{1}{R_0})$$

The V term is non positive,and $R_0 \leqslant 1$. Since

$$\alpha Z + \tfrac{s^2}{\alpha Z} \geq 2s$$

Thus, $\dot{L} < 0$ and E_0 is globally stable equilibrium point if $R_0 \leqslant 1$ by Lasalle's In variance theorem.

Theorem 5: If $R_0 > 1$, then the presence of virus equilibrium point $\bar{E}$ is globally asymptotically stable.

Proof: Let us consider the following Lyapunov function

$$L(Z, I, V) = Z - Z_0 \ln(\tfrac{Z}{Z_0}) + I - I_0 \ln(\tfrac{I}{I_0}) + \tfrac{a}{c}(V - V_0 \ln(\tfrac{V}{V_0}))$$

By taking the derivatives of L(Z,I,V) we get

$$\dot{L}(Z, I, V) = \dot{Z}(1 - \tfrac{Z_0}{Z}) + \dot{I}(1 - \tfrac{I_0}{I}) + \tfrac{a}{c}\dot{V}(1 - \tfrac{V_0}{V})$$

By using the system (3.0.1) we have

$$\dot{L} = (s - \alpha Z + kVZ)(1 - \tfrac{ad}{kcZ}) + (kVZ - aI)(1 - \tfrac{skc - \alpha ad}{akcI}) + \tfrac{a}{c}(cI - dV)(1 - \tfrac{csk - \alpha ad}{adkV})$$

After some simplification we obtain that

$$\dot{L} = s(3 - \tfrac{1}{R_0}) - (\alpha Z - \tfrac{s^2}{R_0 \alpha Z}) - \tfrac{ks}{a}(1 - \tfrac{1}{R_0})\tfrac{ZV}{I} - \tfrac{a\alpha}{k}(R_0 - 1)\tfrac{I}{V}$$

If $R_0 > 1$, then we have that all terms, but the first, are clearly non positive. This expression can be further rewritten as

$$\dot{L} = s(3(1 - \tfrac{1}{R_0} + \tfrac{2}{R_0})) - (\alpha Z + \tfrac{s^2}{R_0^2 \alpha Z}) - \tfrac{s^2}{R_0^2 \alpha Z}(1 - \tfrac{1}{R_0}) - \tfrac{ks}{a}(1 - \tfrac{1}{R_0})\tfrac{ZV}{I} - \tfrac{a\alpha}{k}(R_0 - 1)\tfrac{I}{V}$$

Using the arithmetic geometric inequality, we have that

$$\tfrac{-s^2}{R_0 \alpha Z}(1 - \tfrac{1}{R_0}) - \tfrac{ks}{a}(1 - \tfrac{1}{R_0})\tfrac{ZV}{I} - \tfrac{a\alpha}{k}(R_0 - 1)\tfrac{I}{V}$$

Also,

$$\alpha Z + \tfrac{s^2}{R_{0^2 \alpha Z}} \geqslant 2sR_0.$$

Thus, $\dot{L} < O$, and $\bar{E}$ is a globally stable equilibrium point by Lasalle's invariance theorem. If $R_0 \leqslant 1$, the disease free equilibrium point is a global attractor, and the infection cannot persist. If $R_0 > 1$, the endemic equilibrium point becomes a global attractor, and the infections persists indefinitely.

3.4 Backward Bifurcation Analysis

The backward bifurcation shows the coexistence of the disease free steady state with the stable endemic equilibrium point, when $R_0 < 1$. Let $\Phi = k$ be the bifurcation parameter. Introducing $x_1 = Z, x_2 = I, x_3 = V$, the system (3.0.1) becomes

$$\begin{aligned} \frac{dZ}{dt} &= s - \alpha x_1 - \Phi \frac{x_1 x_3}{x_1 + x_2 + x_3} = f_1 \\ \frac{dI}{dt} &= \Phi \frac{x_1 x_3}{x_1 + x_2 + x_3} - a x_2 = f_2 \\ \frac{dV}{dt} &= c x_2 - d x_3 = f_3 \end{aligned} \tag{3.4.1}$$

with $R_0 = 1$ corresponding to $\Phi = \Phi^\star = \frac{ad}{c}$. The disease free equilibrium is $X^\star = (\frac{s}{\alpha}, 0, 0)$.

The linearization matrix of system (3.4.1) around the disease free equilibrium when $\Phi = \Phi^\star$ is

$$D_x f = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} \\ \frac{\partial f_3}{\partial x_1} & \frac{\partial f_3}{\partial x_2} & \frac{\partial f_3}{\partial x_3} \end{pmatrix} = \begin{pmatrix} -\alpha & 0 & -\Phi^\star \\ 0 & -a & \Phi^\star \\ 0 & c & -d \end{pmatrix}$$

It is clear that 0 is a simple eigenvalue of $D_x f$. A right eigenvector associated with 0 eigenvalue is $w = [\frac{-a}{c\alpha}, \frac{1}{c}, \frac{1}{d}]'$, and the left eigenvector v satisfying v.w=1 is $v = (0, \frac{cd}{a+d}, \frac{ad}{a+d})$. Algebraic calculation show that

$\frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \frac{ad\alpha}{cs}, \frac{\partial^2 f_2}{\partial x_2 \partial x_3} = \frac{-ad\alpha}{cs}, \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \frac{-ad\alpha}{cs}, \frac{\partial^2 f_2}{\partial x_3 \partial x_2} = \frac{-ad\alpha}{cs}, \frac{\partial^2 f_2}{\partial^2 x_3} = \frac{-2ad\alpha}{cs}, \frac{\partial^2 f_2}{\partial^2 x_3 \partial \Phi^\star} =$ 1

The rest of the second derivatives appearing in the formula h and g in (3.4.1) are all zero. Hence

$$\begin{aligned} h &= \frac{-2a\alpha}{cs(a+d)}(d+c) < 0 \\ g &= v_2 w_3 = \frac{c}{a+d} > 0 \end{aligned}$$

since the coefficient of h is negative and also coefficient of g is automatically positive, it follows that the system (3.0.1) or (3.4.1) at $R_0 = 1$ is backward bifurcation.

Chapter 4

Numerical Simulation

In this chapter, we use numerical solutions to illustrate the theoretical results of model (3.0.1). The numerical values depend on the particular units that are chosen. Biological reasonable qualitative behavior of an infection is initiated when there is on infection cells and healthy CTL cells are at a steady-state.

The parameter values in all cases are:

$$s = 0.272, \alpha = 0.00136, k = 0.0000027, a = 0.33, c = 100, d = 2$$

only the parameter k is varied in the simulation. These parameter represent the interaction between CTL cells and HIV.

For numerical simulation of the model (3.0.1) we use initial conditions;

$$\text{Z(0)=20, I(0)=0.4, V(0)=0}$$

Figure 4.1 shows the solution dynamics of model (3.0.1) when the reproduction number $R_0 < 1$. In this case the only steady state is the Diseases free steady state E_0. The density of infectious cells and viruses will eventually decrease to 0, but the density of CTL cells converges to Z_0. In other words, the solutions converge to the disease free steady-state E_0, where the infection wipes out. The basic reproduction number is $R_0 = 0.0356$.

$$\text{Z(0)=100, I(0)=1, V(0)=4}$$

Next, for numerical simulation of the model (3.0.1) we use the initial conditions;

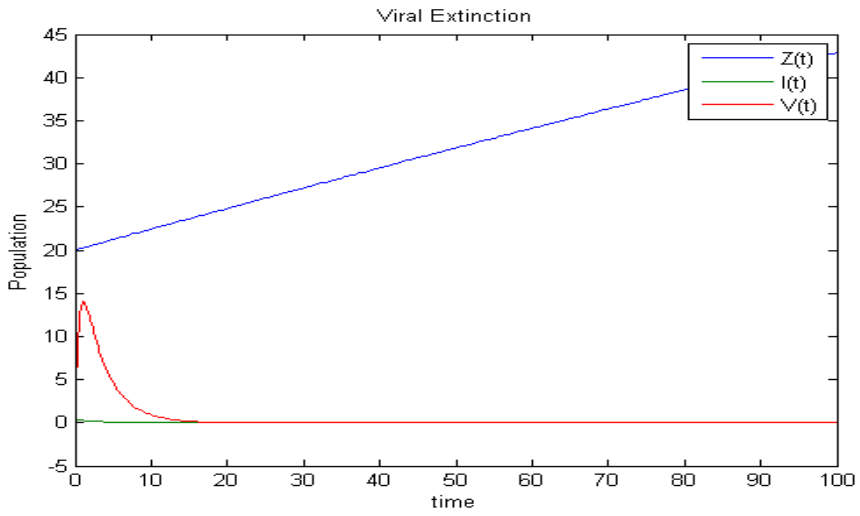

Figure 4.1: Viral Extinction

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Figure 4.2 shows the solution dynamics of model (3.0.1) when the reproduction number $R_0 > 1$. In this case the steady-state is viral persistence equilibrium point $\bar{E}$. Thus, the viruses continue to replicate. In other words, the solutions converges to the viral persistence equilibrium point $\bar{E}$. The basic reproduction number is $R_0 = 3.564$. Figure

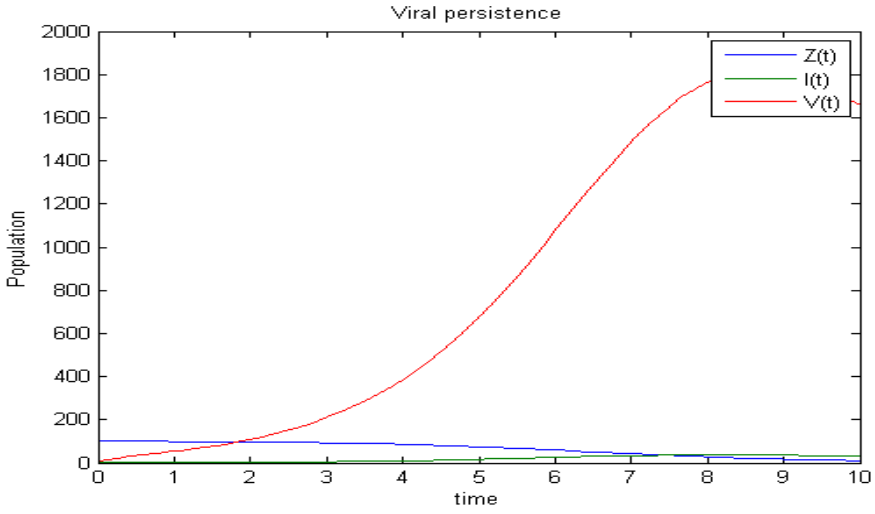

Figure 4.2: Viral Persistence

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4.3 shows the backward bifurcation phenomena, where the disease free state coexists with the stable endemic equilibrium point, when $R_0 < 1$. Thus, the occurrence of backward

bifurcation has an important implication for epidemiological control measures, since an epidemic may persist at steady state even if $R_0 < 1$. Figure 4.4 shows the solution

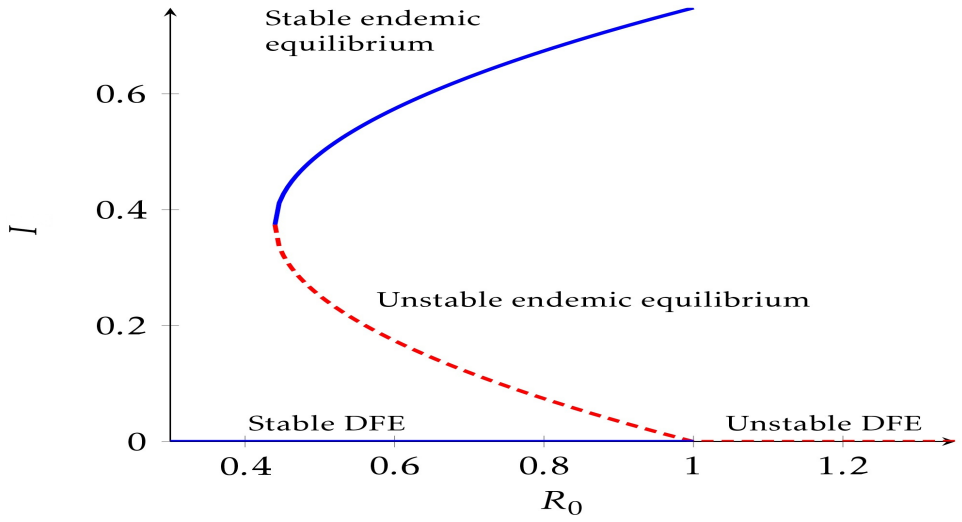

Figure 4.3: Backward bifurcation

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dynamics of model (3.0.1) when the reproduction number, R_0 is less than one. According to Theorem 4, E_0 is globally asymptotically stable. This implies the solution converges to disease free steady state E_0, then the infection is cleared.

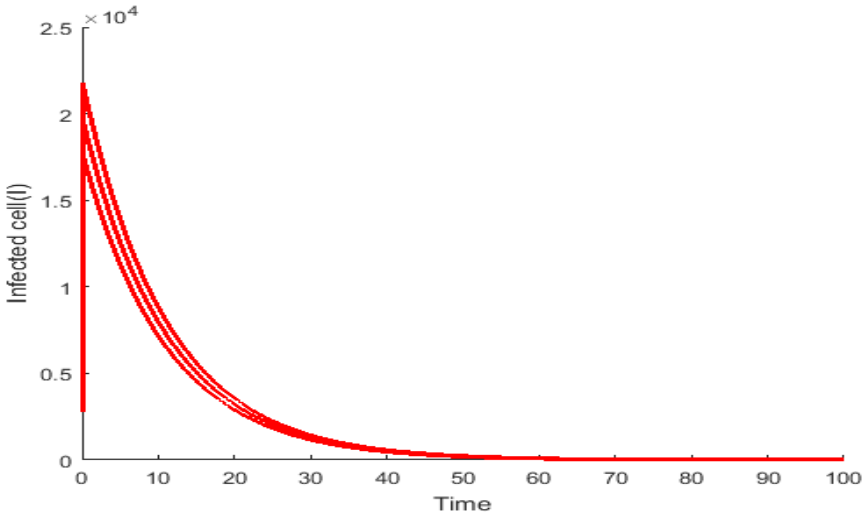

Figure 4.4: Global stability

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4.1 Result and Discussion

In this thesis we develop and analyze for HIV dynamics using reasonable biological assumption about both virus and CTL cells. The proposed model focused on the highly dynamic interaction between HIV particles, uninfected CTL cells and infected cells. Our finding illustrate that utilizing one determined threshold parameters, R_0 known as the viral reproduction number, as well as some small, biologically reasonable assumptions, allow to predict the local asymptotic stability of the system around the equilibrium point. Furthermore, we are able to classify equilibrium point based up on their persistence or extinction of . This is especially important when considering the notion of viral persistence and extinction as we are able to determine conditions which yield viral extinction and persistence. Our analysis highlights that if the value of the viral reproduction number, $R_0 \leq 1$, the equilibrium will be locally stable virus free equilibrium point, and if $R_0 > 1$ the equilibrium will be locally stable in the presence of virus equilibrium point. In addition to this, if $R_0 < 1$ the behavior is expected from most viral infections, and results from the fact that each infected cell will fail to produce an additional infected cell prior to death. However, $R_0 > 1$ we fully expect that the immune system activated and results of the ability of HIV virus to effectively evade immune detection.

Chapter 5

Conclusions and Recommendation

In this thesis, we have studied a mathematical model that describe the interaction between Cytotoxic T Lymphocyte and HIV. By analyzing the corresponding characteristic equations, the local stability of an infection-free equilibrium point and infection equilibrium point are discussed. By constructing suitable Lyapunov functions and Lasalles Invariant principle, the global stability are also established, it is proved that if the basic reproduction number, R_0 is less than or equal to one, the infection-free equilibrium point is globally asymptotically stable, if R_0, is more than one, the infection equilibrium point is globally asymptotically stable.

Furthermore, our work in this thesis reveals that the model we developed effectively addresses the dynamics of HIV infection. Thus, there is potential to further the analysis that we conducted in this thesis to incorporate a time delay, which would more accurately model the true dynamics of the system.

Appendix

Theorem 6. (Fundamental Existence and Uniqueness theorem)

Suppose the function $f : \mathbb{R}^n_+ \to \mathbb{R}^n$ is continuously differentiable. Then x(t) is a solution of the differential equation $\frac{dx}{dt} = f(x)$ on an interval I if x(t) is differentiable on I and if for all $t \in I, \quad x(t) \in \mathbb{R}^n$ and $\frac{dx}{dt} = f(x(t))$ and given $x_0 \in \mathbb{R}^n$, x(t) is a solution of the initial value problem [7];

$$\frac{dx}{dt} = f(x) \quad x(t_0) = x_0$$

Remark: The above is a well known theorem and ensures that the solutions exists and unique in the neighborhood of x_0, i.e., the function is locally Lipschitz [7].

Theorem 7.(Poincare-Perron)

Let A be a constant matrix in the system $\frac{dx}{dt} = Ax$ with eigenvalues $\lambda_i, i = 1, 2, ..., n$

i. If the system is stable, then $Re\lambda_i \leq 0$, i=1,2,...,n

ii. If either $Re\lambda_i < 0$, i=1,2,...,n or if $Re\lambda_i \leq 0$, i=1,2,...,n and there is no zero repeated eigenvalue; then the system is uniformly stable.

iii. The system is asymptotically stable if and only if $Re\lambda_i < 0$, i=1,2,...,n; note that it is also uniformly stable by (ii).

iv. If $Re\lambda_i > 0$, i=1,2,...,n the solution is unstable.

Remark: If any of the eigenvalues have a positive real numbers, we define the equilibrium to be a source, and thus, unstable. If all of the real parts of the eigenvalues are negative real numbers, we define the equilibrium to be a sink, and thus, stable [7].

Theorem 8.(Routh-Hurwitz criterion)

Given the polynomial $P(x) = x^n + a_1x^{n-1} + ...a_{n-1}x + a_n$, where the coefficients a_i are

real constants, i=1,2,...,n, define the n^{th} Hurwitz matrix using the coefficients a_i of the characteristic polynomial:

$$H_n = \begin{bmatrix} a_1 & 1 & 0 & 0 & . & . & . & 0 \\ a_3 & a_2 & a_1 & 1 & . & . & . & 0 \\ a_5 & a_4 & a_3 & a_2 & . & . & . & 0 \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ . & . & . & . & . & . & . & . \\ 0 & 0 & 0 & o & . & . & . & a_n \end{bmatrix}$$

where $a_i = 0$, if $j > n$. All of the roots of the polynomial p(x) are negative or negative real part if and only if the determinants of all Hurwitz matrices are positive: $det(H_j) > 0$, j=1,2,...,n. Considering n=3 and n=4, the theorem simplifies and we are able to apply the theorem to the analysis of our system. For n=3 we must prove that: $a_1 > 0, a_3 > 0, a_1 a_2 > a_3$. For n=4 we must prove that: $a_1 > 0, a_3 > 0, a_4 > 0, a_1 a_2 a_3 > a_3^2 + a_1^2 a_4$. The Hartman-Grobman theorem is essential for showing how our analysis of the linearized system relates to the non-linear system[7].

Theorem 9. (The Hartman-Grobman)

Let E be an open subset of $\mathbb{R}^n$ containing the origin, let $f \in C^2(E)$ and let ϕ_t be the flow of the nonlinear system below. Suppose that f(0)=0 and that the Jacobian matrix J(0) has no eigenvalues with zero real part. Then there exists a homeomorphism H of an open set U containing the origin onto an open set V containing the origin such that for each $x_0 \in U$ there is an open interval $x_0 \subset \mathbb{R}$ and $t \in I_0$ [7]

$$H o \phi_t(x_0) = e^{At} H(x_0)$$

Theorem 10.(Castillo-Chavez and Song)

Consider the following general system of ordinary differential equations with a parameter ϕ,

$$\frac{dx}{dt} = f(x, \phi), f : \mathbb{R}^n X \mathbb{R} \to \mathbb{R}, and \quad f \in \mathbb{C}^2(\mathbb{R} X \mathbb{R}) \tag{5.0.1}$$

without loss of generality, it is assumed that 0 is an equilibrium for system (5.0.1) for all values of the parameter ϕ, (that if $f(0,\phi)=0$ for all ϕ). Assume

$(A_1): D_x f(0,0)=(\frac{\partial f}{\partial x_j},0,0)$ is the linearized matrix of system (5.0.1) around the equilibrium 0 with ϕ evaluated at 0: zero is a simple eigenvalue of A and all other eigenvalue of A have negative real parts;

(A_2): Matrix A has a non-negative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.

Let f_k be the k^{th} component of f and

$$a=\sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial f_k^2}{\partial x_i \partial x_j}(0,0)\ ,b=\sum_{k,j=1}^{n} v_k w_j \frac{\partial f_k^2}{\partial x_i \partial \phi}(0,0).$$

The local dynamics of system (5.0.1) around 0 are totally determined by a and b.

(i) In the case where $a>0, b>0$, we have that when $\phi<0$ with $|\phi|$ close to zero, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0<\phi\leq 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;

(ii) In the case where $a<0, b<0$, we have that when $|\phi|$ close to zero, 0 is unstable; when $0<\phi\leq 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;

(iii) In the case where $a>0, b<0$, we have that when $\phi<0$ with $|\phi|$ close to zero, 0 is unstable and there exists a locally asymptotically stable negative equilibrium; when $0<\phi\leq 1$, 0 is stable and a positive unstable equilibrium appears;

(iv) In the case where $a<0, b>0$, we have that when ϕ changes from - to +, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable. Particularly, if $a>0$ and $b>0$, then a backward bifurcation occurs at $\phi=0$[7].

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