A MATHEMATICAL STUDY OF TWO RETROVIRUSES, HIV AND HTLV-I

by

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ABSTRACT

In this thesis, we examine epidemiological models of two different retroviruses, which infect the human body. The two viruses under study are HIV or the human immunodefiency virus and HTLV-I, which is the human T lymphotropic virus type I. A retrovirus is a virus, which injects its RNA into the host, rather than it's DNA. We will study each of the different mathematical models for each of the viruses separately. Then we use MATLAB-SIMULINK to analyze the models by studying the reproductive numbers in each case and the disease progression by examining the graphs. In Chapter 1, we mention basic ideas associated with HIV and HTLV-I. In Chapter 2 some of the basic mathematical model of epidemiology is presented. Chapter 3 is devoted to a model describing the intra-host dynamics of HIV. Here, we take into account how HIV infects and replicates in the CD4+ T cells. The model studied in this thesis examines the difference between cells, which are susceptible to the virus, and cells, which are not susceptible. Through the graphs associated with this model, we are able to see how this difference affects disease progression. In Chapter 4, we examine the effect of HTLV-I virus on human body. The HTLV-I virus causes a chronic infection in humans and may eventually lead to other diseases. In particular, the development of Adult T-cell Leukemia or ATL is studied in this thesis. The T-cell dynamics and progression to ATL is described using a mathematical model with coupled differential equations. Using mathematical analysis and SIMULINK, we obtain results on stability, asymptotic stability and the manner of progression of the disease. In Chapter 5 and appendices, we mention our inference and the MATLAB-SIMULINK codes used in this thesis, so that a reader can verify the details of the work carried out in this thesis.

This thesis is dedicated to everyone who loved

and supported me through this entire process, especially my family.

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CHAPTER ONE - INTRODUCTION

1.1 Introduction

Disease has played an important part throughout the history of mankind. Diseases have influenced the growth or decline of a population and have impact on the economy. It causes more deaths than any other source, including war and natural disasters. The manner in which diseases infect and invade a population has perplexed doctors and scientist for many years. A branch of science called epidemiology was developed in order to help analyze and understand the spread of disease.

Aristotle and Hippocrates of Cos started studying the transmission of diseases during 300BC-400BC. Later, germ theory was first studied by Jacob Henle in 1840 and was later developed by Robert Koch, Joseph Lister, and Louis Pasteur. Modern mathematics was first used in the study of diseases in 1873 by P.D En'ko. Sir R. A. Ross, W. H. Hamer, A.G Mckendrick, and W. O Kermack laid the foundation of mathematics in epidemiology between 1900 and 1935. (See [15]) The study of epidemiology has grown tremendously since and most known communicable diseases have been modeled and analyzed.

Epidemiology not only helps us to understand disease transmission, but also to know how to control the spread of a particular disease. It is not a static science and is constantly changing. Infectious diseases are constantly evolving and changing, making them harder to control. New strains, which are immune to antibiotics, are found everyday. HIV and HTLV-I are two new viruses which were first discovered in the 1980's. These viruses have no known cure but doctors are working with epidemiologist, mathematicians, and scientist to find a cure and limit its

transmission. We will use mathematical models to help us understand the spread of these viruses in the human body and the progression of these viruses to disease.

1.2 Introduction to HIV

In 1981 the Center for Disease Control reported on an unusual collection of homosexual males that had Pneumocyctis carinii pneumonia and Kaposi's sarcoma. These men were previously healthy individuals. This was a new retroviral disease later to be named AIDS or Acquired Immunodeficiency Syndrome, a disease for which there is still no cure and is the fourth leading cause of death worldwide. The etiologic agent of this new epidemic is the human immunodeficiency virus or HIV, which will be studied in detail in this thesis. HIV is the retrovirus which causes AIDS. This virus slowly destroys the immune system over many years. Once the immune system is depleted, AIDS occurs.

AIDS was first discovered in the United States but now affects the entire world and is considered the new "plague". It has killed more than 25 million people worldwide and is considered the most destructive epidemic in recorded history. AIDS is now found in more than 163 countries with the most being in Africa and the Caribbean being the second. Sub-Saharan Africa is considered to be the global epicenter of the HIV epidemic. (See [5]) Ninety percent of the individuals infected with HIV are in developing countries and forty percent of those infected are females. Individuals in the 15-24 age group are the fastest growing segment who are being infected with HIV.

HIV can be transmitted in different ways. The virus is present in bodily fluids, specifically blood, therefore, any activity that results in the transfer of bodily fluid can potentially result in the transfer of HIV. Intimate sexual contact is one of the modes in which

fluid transfer occurs. Intravenous drug use is another mode in which HIV is transmitted between individuals because many drug users share needles. Two other modes which are not as common due to medical advances and new antiretroviral drugs are mother to child transmission and transmission through blood transfusion. Mother to child transmission can occur during the birthing process or through breast feeding. Although the rate of mother to child transmission has dropped in many developing countries, it is still very prevalent in the sub-Saharan regions of Africa. Transmission due to blood transfusions are rarely seen today due to examination of the blood from donors for presence of HIV prior to saving them in the blood bank for patient use. The U.S. blood supply is very safe due to the extensive questioning of blood donors and the extensive testing of donated blood.

HIV is characterized by immunosuppression, neurologic involvement and secondary tumors. HIV attacks the CD4+ T-cells, which are responsible for the immune system. The nature of this attack and how it occurs is modeled mathematically in Chapter Three in order to help us understand and predict the course of the disease. Many graphs developed from the mathematical model help demonstrate the progression to AIDS. The graphs were produced using Simulink and match those produced by Stilianakis and Schenzle in Fortran.

1.3 Introduction to HTLV-I

Human T-lymphotropic virus (HTLV-I) was the first retrovirus to be discovered. This virus was discovered in Japan in 1980. HTLV-I is a virus which lays latent for many years before causing other diseases to proliferate. This virus is the predominant cause of two diseases. The first one is Adult T Cell leukemia/lymphoma or ATL, which is a T cell non-Hodgkin's lymphoma with a leukemic phase of circulating CD4+T cells. The progression from HTLV-I to

ATL is mathematically modeled and studied in Chapter 4. The discovery of HTLV-I provided scientists with a clear proof of a relationship between viruses and cancer. The second disease that is cause by HTLV-I is myelopathy (HAM) which is also known as tropical spastic para paresis (TSP). Usually this virus does not produce disease until approximately twenty years after initial infection. HTLV-I can also cause autoimmune or chronic inflammatory disorders such as arthropathy, Sjogren's syndrome and facial nerve palsy. Identification of the HTLV-I virus facilitated the discovery and isolation of HIV.

HTLV-I infects ten to twenty million people world wide but only produces disease in approximately five percent of infected individuals. Women are twice as likely to contract HTLV-I as men. The HTLV-I infection is thought to occur in geographical clusters which are located in southern Japan, the Caribbean, parts of Africa, the Middle East, South America, Pacific Melanesian islands, and Papua New Guinea. The virus is also found in the southeastern United States in certain immigrant groups.

HTLV-I is transmitted in the same way as HIV, through bodily fluid transfer. Unlike HIV, the main transmission is through breast feeding. The HTLV-I antigen is found in the infected mother's milk and is transmitted most likely through lymphocytes in the milk. The prevalence of this vertical transmission through breast feeding has caused a clustering of cases in familial or geographically discrete groups. (See [14]) Other modes of are sexual transmission, infection from blood transfusion, and sharing needles among drug users.

Many people can be infected with HTLV-I and will never develop a disease from this virus. Chapter Four will feature a mathematical model of the HTLV-I infection of CD4+ T-cells and the eventual progression to ATL. The stability analysis will illustrate two different steady states. One steady state when the virus will not progress to ATL, and another steady state when

the virus will progress to ATL. A proposition for asymptotical stability is studied and a graph was produced using Simulink. Even after rigorous analysis, this graph does not match the graph presented by the authors and further work may be needed in order to explore the difference.

CHAPTER TWO – BACKGROUND STUDY

2.1 Introduction to mathematical models

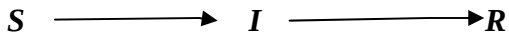
A mathematical model is a mathematical description of a real world system or event. (See [12]) Epidemiologists will use mathematical models in order to understand and predict the course of an infection or disease. A well-formulated model can help an epidemiologist determine where resources need to be allocated and how those resources can help control or eradication of the disease. In order to formulate a model for an infectious disease, an individual must first collect an abundance of empirical data through clinical testing. Once this data is collected and analyzed, the modelers develop a model using the following steps. Firstly, they note all the relevant assumptions, and then determine the relationship between the variables and parameters used in the model and finally, analyze any specific patterns that are found. Deciding which parameters and variables will be used in the model and how much importance should be given depend on the characteristics of the disease under study and the intention of the model. (See [2]) Once the model is formulated and analyzed, it will help the scientists to draw inferences form a set of hypotheses in order to determine the course of the disease in an individual or in a population.

Epidemiological models are usually formed using the general *MSEIR* model. This model places individuals from a constant population into certain groups within the model and describes the transition rate between each group. Each letter represents a different class or group. *M* represents the temporary immunity that a mother can pass on to her child through the placenta. The *S* describes the susceptibles, which are the members of the population who are at risk for contracting the disease. *E* stands for exposed and describes the individuals from the population

who are infected by the disease but are not infectious due to a latent period of a disease. The *I* group is the Infectious group or the individuals from the population who have the ability to pass the disease to other members of the population. *R* represents the group of individuals who have recovered from the disease, whether temporary or permanent, and also possess some type of immunity.

2.2 Basic SIR Model

The first model to consider is the basic *SIR* model. It is a simple epidemic model developed by Kermack and McKendrick in 1927 to predict the behavior of many historical epidemics such as cholera, influenza, and the Great Plague. This model is used by many epidemiologists because it can help predict the behavior and progress of different diseases. This model is also a building block for many of the other more complicated models. The *SIR* model considers a population that remains constant. The population is divided into three classes: first, the individuals who are susceptible, *S*, to the disease, second, the individuals being exposed and infected by the disease, *I*, and last the individuals who will recover, *R*, from the infection and gain immunity to the disease. This model does not consider any latent period of the disease. Once an individual is infected, he is automatically moved into the infectious classification. The progress of the individuals from class to class can be demonstrated by



Some models only consider the *S* and *I* classes. Other models consider a fourth class, *E*, which takes in account a latent period of the disease in which the virus is present in the host but has not

infected the host. When modeling a disease like AIDS, it is better to use a model which includes this class.

This model makes many assumptions. We must first assume the collection of individuals in each class is a differentiable function of time. This is reasonable as long as there are enough people in each class. Next, the model is deterministic. This means that the behavior of the model is determined by the past behavior of diseases. A stochastic model would be more effective if the model described classes with small populations. Third, this model does not include a latent phase of the disease, which means that once a susceptible becomes infected, the individual is automatically placed into the infected class. Fourth, the model assumes that an infected individual makes contact significant enough to transmit the disease at the contact rate, β. If $\beta N \frac{S}{N} I = \beta SI$, new cases will occur when N is the total number in the population, S is the number of susceptibles and I is the number of infecteds. The fifth assumption is that the model has a mass action principle, which means every individual within the population has an equal chance to have contact with every other individual in the population. This information implies that β, the contact rate, is the ratio of rate of contact to the population size. Another assumption is that the recovery rate is proportional to the number of infecteds, and is represented by aI, where a is the removal rate. The last assumption is that there is no entry or exit from the population except through death. This occurs when the progression to disease is so quick that birth and death rates can be ignored. This assumption can be changed in certain models.

Based on these assumptions, the classic Kermack and McKendrick model is:

$$\frac{dS}{dt} = -\beta SI \tag{2.1}$$

$$\frac{dI}{dt} = \beta SI - aI \tag{2.2}$$

$$\frac{dR}{dt} = aI \tag{2.3}$$

Note that only non-negative solutions for *S, I* and *R* are of interest. Also, remember the total population is constant and is embedded in the model. If we add equations (2.1)-(2.3), we will get:

$$\frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0 \tag{2.4}$$

Solving this differential equation will yield:

$$S(t) + I(t) + R(t) = N \tag{2.5}$$

where *N* is the population size. We also have the following initial conditions:

$$S(0) = S_0, I(0) = I_0, R(0) = R_0 \tag{2.6}$$

where $S_0 > 0$ and $I_0 > 0$.

The population is constant, therefore, *R* can be determined if *S* and *I* are known. For this reason, equation (2.3) can be dropped and the system can be reduced to only two equations. This system is not possible to solve analytically but the equations can be analyzed using a qualitative approach. Note that $S' < 0$ and $I' > 0$ if $S_0 > \frac{a}{\beta}$. Since *S* is decreasing, *I* will initially increase but then will decrease to zero. The possibility of *I* increasing is what indicates an epidemic because *I* represents the infected individuals. If $S_0 < \frac{a}{\beta}$, then *I* will go to zero and there is no epidemic. If $S_0 > \frac{a}{\beta}$, the number of infected individuals will first increase to $S = \frac{a}{\beta}$, and then decrease to zero. From this, we see a threshold parameter. The behavior of the disease will depend on the threshold quantity, $\frac{S_0\beta}{a}$. This number defines the reproduction number. The

reproduction number, R_0, of the system is defined as the number of secondary infections produced by one primary infection in the population of susceptibles. Therefore:

$$R_0 = \frac{S_0 \beta}{a} \tag{2.7}$$

This number measures how fast the infection will spread. If $R_0 < 1$, the infection will not continue and the disease will disappear. If $R_0 = 1$, the infection will remain stable in transmission. If $R_0 > 1$, an epidemic will occur. (See [3]) To find the trajectories in the phase plane, we first divide the two equations of the model and get:

$$\frac{dI}{dS} = \frac{(\beta S - a)I}{-\beta SI} = -1 + \frac{a}{\beta S} \tag{2.8}$$

Separation of variables and integration yields:

$$I = -S + \frac{a}{\beta} \log S + c \tag{2.9}$$

where *c* is an arbitrary constant of integration. Equation (2.9) can be defined as the following quantity:

$$J(S, I) = S + I - \frac{a}{\beta} \log S \tag{2.10}$$

where *J(S,I)=c*. Different constants will give different trajectories and this constant can be obtained by knowing the initial values of S, I, S_0 and I_0. We now have:

$$J(S_0, I_0) = S_0 + I_0 - \frac{a}{\beta} \log S_0 = c \tag{2.11}$$

If we assume a population of size *K* and introduce a small number of infecteds into the population so $S_0 \approx K$ and $I_0 \approx 0$, we can determine $R_0 = \frac{\beta K}{a}$ from equation (2.7). Taking the fact that $\lim_{t\to\infty} I(t) = 0$ and $\lim_{t\to\infty} S(t) = S_\infty$, we can find $J(S_0, I_0) = J(S_\infty, 0)$. This will yield:

$$K - \frac{a}{\beta}\log S_0 = S_\infty - \frac{a}{\beta}\log S_\infty \tag{2.12}$$

This helps to determine the reproduction number because it will give an expression for $\frac{\beta}{a}$ in parameters that can be determined:

$$K - S_\infty = \frac{a}{\beta}\log\frac{S_0}{S_\infty} \tag{2.13}$$

$$\frac{\beta}{a} = \frac{\log\frac{S_0}{S_\infty}}{K - S_\infty} \tag{2.14}$$

Note $S_0 > S_\infty$ because the initial number of susceptible will be greater than the number of susceptible who will become infected. This will occur because there are some who will not come into contact with the disease.

2.3 Basic SIS Model

The *SIS* model is another type of model to study infectious diseases. In this model, the infected will return to the susceptible class after recovery. This model is more effective to use when studying sexually transmitted diseases. The simplest model, which was also given by Kermack and McKendrick is:

$$\frac{dS}{dt} = -\beta SI + aI \tag{2.15}$$

$$\frac{dI}{dt} = \beta SI - aI \tag{2.16}$$

This model is different than the *SIR* model in that the recovered members will return to the susceptible class at a rate of *aI* instead of moving to a recovered class. Just as in the SIR model the total population is constant, since $(S+I)' = 0$. Again, let the constant population be represented by *K*. If $K = S + I$, we can replace *S* by *K-I* and reduce the model to a single differential equation. This equation is:

$$\begin{aligned} \frac{dI}{dt} &= \beta I(K - I) - aI \\ &= (\beta K - a)I - \beta I^2 \\ &= (\beta K - a)I(1 - \frac{I}{K - \frac{a}{\beta}}) \end{aligned} \tag{2.17}$$

This is a logistic equation with a growth rate of $\beta K - a$ and a carrying capacity of $K - \frac{a}{\beta}$. An analysis of this will show that if $\beta K - a < 0$ or $\frac{\beta K}{a} < 1$, then for any $I_0 > 0$, we see that $\lim_{t\to\infty} I(t) = 0$ and $\lim_{t\to\infty} S(t) = K$. If $\frac{\beta K}{a} > 1$, then for any $I_0 > 0$, we will see that $\lim_{t\to\infty} I(t) = K - \frac{a}{\beta}$ and $\lim_{t\to\infty} S(t) = \frac{a}{\beta}$. As seen here, there is a single limiting value for *I* and this limiting value is determined by the quantity, $\frac{\beta K}{a}$, regardless of the initial rate of infection. The infection will disappear or the number of infected will approach zero when $\frac{\beta K}{a} < 1$. Hence the equilibrium *I=0* and *S=K* is considered the disease free equilibrium. If $\frac{\beta K}{a} > 1$, the infection will continue.

The equilibrium, $I = K - \frac{\beta}{a}$, which corresponds to $S = \frac{a}{\beta}$, is defined as the endemic equilibrium.

The dimensionless quantity, $\frac{\beta K}{a}$, is the reproduction number for our system, noted as $R_0 = \frac{\beta K}{a}$. In Section (2.2), we discussed that the value of R_0 was the threshold parameter. We also defined R_0, as the number of secondary infections produced by one primary infection in the population of susceptible. The reproduction number helps determine the path which the disease will take. If $R_0 = \frac{\beta K}{a}$, where βK is the number of contacts made by an average infected per unit of time and $\frac{1}{a}$ is the mean infected period, we can clearly see if $R_0 < 1$, the infection will disappear and if $R_0 > 1$, the infection will persist.

CHAPTER THREE – INTRA-HOST DYNAMICS OF HIV

3.1 Introduction to intra-host dynamics of HIV

To understand how HIV destroys the immune system, we first must understand how the immune system works. When a foreign substance, or antigen, enters the body, the body will initiate an immune response. This immune response starts with macrophages and monocytes. These cells are the body's first defense against the antigen. They will seek out the antigen, surround it and overtake it. This process is known as phagocytosis. The macrophages will then analyze the content of the antigen and pass this information along to the CD4+ T lymphocytes, also called CD4+ T cells. The CD4+ T cells will call for the production of more CD4+T- cells or will call for the production of types of T-cells such as the CD+8-T cells. Another weapon used by the body's defense system is the B lymphocytes or B cells. These cell produce antibodies specifically engineered to destroy the pathogen detected by the macrophages. (See [7])

HIV is considered a lentivirus, meaning slow virus, which is a subclass of the retrovirus. In general, a virus will insert their own DNA into the host cell. When the host cell replicates their DNA, the virus' DNA is also replicated. A retrovirus, like HIV, will insert RNA rather than DNA into the host. Retroviruses have a unique enzyme , reverse transcriptase. (See [5]). This enzyme will prepare a DNA copy of the RNA genome into the host. This DNA copy is eventually inserted into the genome of the host cell where the virus will persist for years and is impossible to eradicate. (See [19]) The HIV DNA will get copied every time the host cell divides.

On the cellular level, the HIV particles target the CD4+ T lymphocyte. It attracts the CD4+T-lymphocyte through a glycoprotein called gp120. The protein enzyme, gp120, is located on the surface of the HIV particle and it is attracted to the CD4 protein on the surface of the T-c ells, macrophages, and monocytes. The CD4+ T cell attaches itself to the virus and is infected.

The HIV infection can typically be divided into three phases. The first phase is the primary infection. During this initial phase, the virus is present in the host and replicates in the manner describe previously. Three to six weeks after infection, 50-75% of patients develop an acute viral syndrome. (See [19]) There is also a significant reduction of CD4+ T cells. The second phase of HIV infection is the longest phase. It is the phase in which there is a long asymptomatic period and latency occurs. There are two major features of this phase. The first feature is the permanent viral replication in the lymphatic tissue and lymphoid organs. The second feature is the gradual decline of the CD4+ T cells. The final phase of the HIV infection shows a sharp decline of CD4+ T cells and the emergence of clinical immunodeficiency and progression to AIDS. The period of time from initial infection to the formation of AIDS can vary from person to person. The median estimate is eight to eleven years without treatment and even longer with treatment.

3.2 HIV Simple Model

Stilianakis and Schenzle developed this basic model to describe the long term dynamics of HIV progression through the body and the eventual development of AIDS. The basic biomedical assumption of this model is the genetic variation of HIV. It is assumed that the infection rate is the major source for the increase and selection of the HIV mutants.

Table 1: Variables used in the simple model

Variable	
X	Total number of susceptible CD4+ T cells
Y	Total number of productively infected CD4+ T cells
V	Total number of HIV particles
K	Factor that describes the increase of the CD4+ T cell infection rate

The model consists of the following non-linear differential equations:

$$\frac{dX}{dt} = \Lambda - \mu X - \kappa_0 KVX \tag{3.1}$$

$$\frac{dY}{dt} = \kappa_0 KVX - \delta Y \tag{3.2}$$

$$\frac{dV}{dt} = \beta Y - \gamma V \tag{3.3}$$

$$\frac{dK}{dt} = \omega_K V(K_{\max} - K) \tag{3.4}$$

The biological representation of each term in each equation will now be discussed in order to provide a better understanding of the system. In the first equation, equation (3.1), Λ represents the constant rate at which new CD4+ Tcells are produced. These newly produced CD4+ T cells are considered to be susceptible. The term μX is the rate at which susceptible cells die. The last term, $\kappa_0 KVX$, is considered a mass action term which describes the rate at which susceptible cells are infected by the HIV particles. This mass action term is also seen in the first term of equation (3.2). The second term in equation (3.2) is δY. This term describes the death rate of the infected CD4+ T cells.

The first term in equation (3.3) is βY. This term represents the rate in which infectious viral particles infect the CD4+ T cells. γV represents the rate at which virus particles are cleared.

In the last equation, equation (3.4), one term is seen. This equation represents how fast the virus can reproduce within the host and the maximum amount of virus particles that can be see within the host at any particular time within the evolutionary process.

The rate at which the virus reproduces is called the virus reproduction number. In this model it is a dynamic quantity and it changes over time. The virus reproduction number is:

$$R_0(t) = \frac{\beta\kappa_0 K(t) X_0}{\delta\gamma} \tag{3.5}$$

This reproduction number will increase monotonically toward:

$$R^*_0 = \frac{\beta\kappa_0 K_{\max} X_0}{\delta\gamma} \tag{3.6}$$

3.3 HIV Extended model

The following model is an extension of the original basic model. The extended model takes into account the total number of susceptible CD4+ T cells and how fast new CD4+ T cells become susceptible to the HIV infection.

Table 2: Variables used in the extended model

Variable		Initial Values
X	Total number of non-susceptible CD4+ T cells	$X(0) = X_0 = 0.7 \times 2.5 \times 10^{11}$
S	Total number of susceptible CD4+ T cells	$S(0) = S_0 = 0.3 \times 2.5 \times 10^{11}$
Y	Total number of productively infected CD4+ T cells	$Y(0) = Y_0 = 0$
V	Total number of HIV particles	$V(0) = V_0 = 1$
Z	Anti-HIV activity of the immune system	$Z(0) = Z_0 = 10^{-6}$
P	Fraction of new CD4+ T cells entering the pool of susceptible CD4+ T cells	$P(0) = P_0 = 0.3$
K	Factor that describes the increase of the CD4+ T cell infection rate	$K(0) = K_0 = 1.0$
N	Total number of uninfected CD4+ T cells	$N(0) = N_0 = X_0 + S_0 = 2.5 \times 10^{11}$

The model consists of the following non-linear differential equations:

$$\frac{dX}{dt} = \alpha(1-P) - \mu X \tag{3.5}$$

$$\frac{dS}{dt} = \alpha P - \mu S - \kappa_0 KV \frac{S}{(P+d)} \tag{3.6}$$

$$\frac{dY}{dt} = \kappa_0 KV \frac{S}{(P+d)} - (\mu_Y + \delta_Y Z)Y \tag{3.7}$$

$$\frac{dV}{dt} = \beta Y - (\mu_V + \delta_V Z)V \tag{3.8}$$

$$\frac{dZ}{dt} = \theta g(V) + \rho[f(S+X)Z_{\max} - Z] \tag{3.9}$$

$$\frac{dP}{dt} = \omega_P V(P_{\max} - P) \tag{3.10}$$

$$\frac{dK}{dt} = \omega_K V(K_{\max} - K) \tag{3.11}$$

where

$$f(N) = \frac{1+b^c}{1+(\frac{bN_0}{N})^c} \text{ and } g(V) = \frac{V}{a+V} \tag{3.12}$$

N can be divided into the number of non-susceptible T cells, *X*, and the number of susceptible T cells, *S*. Therefore, *N*=*X*+*S*.

To understand the system, an understanding of what each term biologically represents must first be presented. In equation (3.5), *P* is the fraction of new CD4+ T cells that enter the susceptible and *1-P* is the fraction of new CD4+ T cells that remain unsusceptible to the HIV virus. The first term in equation (3.5) is *α(1-P)* where α is the T cell production rate. This term represents the immigration rate of new non susceptible T cells. The second term is *μX* in which

μ is the natural death rate of the unsusceptible cells. Therefore, this term represents how many non susceptible CD4+ T cells die.

Equation (3.6) represents the dynamics of the susceptible cells in the system. The first term, αP, describes the immigration rate of the susceptible CD4+ T cells. The second term, μS, represents the natural death rate of the susceptible cells. The last term in equation (3.6) is $\kappa_0 KV \frac{S}{(P+d)}$. This is a mass action term which describes the infection process between cells and viruses. In particular, $\frac{S}{(P+d)}$ describes the dynamics changes in the susceptible cells. The variable, *P*, in this term is very important in helping determine the course of the infection and the progression of the disease. In fact, *P* shows that more cells can be attacked and infected by the virus than the immune system can combat.

Equation (3.7) has many terms and this equation determines how many productively infected cells are in the blood. The first term is the same mass action term that is seen in equation (3.6). The second term in equation (3.7) is $(\mu_Y + \delta_Y Z)Y$. μ_Y represents the death rate of productively infected cells and $\delta_Y Z$ represents how fast these dead cells are removed from the system. Equation (3.8) describes the number of HIV particles that are produced and destroyed. The first term in equation (3.8) is βY. In this term, β, describes the rate at which HIV particle cells are produced from infected cells. The second term, $(\mu_V + \delta_V Z)V$, describes the rate at which HIV particles are cleared and eliminated. μ_V is the rate in which virus particles are cleared and $\delta_V Z$ represents the anti-HIV activity and elimination.

Equation (3.9) is the most complicated equation within the model because not much is known about the dynamics of the HIV specific immune response, therefore, a general equation is

used to model this response. The equation shows the coupling of a time dependent decline of the CD4+ T cells and the intrinsic features of the immune response. The variable, ρ, in equation (3.9) represents the HIV specific immune response. This response occurs independently of the number of HIV particles that are present in the body. The function, g(V), models how the immune response is activated depending on the quantity of the virus. The term, $\rho[f(S+X)Z_{\max}]$, is the rate once primary infection occurs in which HIV will start producing specific antibodies and the cytotoxic cells will start multiplying. Once this occurs, the immune system will eventually become independent of the number of HIV particles and infected cells. In equation (3.9), the function *f(N)* describes how the activity of the immune system is related to the number of available uninfected cells. This function also takes account of the immune system's ability to combat HIV when the number of CD4+ T cells is not sufficiently high.

Equation (3.10) describes the increase in the rate of the fraction of new cells coming from the pool of susceptible cells and how they correspond to the generation and selection of HIV mutants. Equation (3.10) describes the rate at which the HIV infection increases due to the reproduction of each virus particle.

The virus reproduction number is also an important value to discuss. The reproduction number represents how quickly the virus is reproducing. The HIV reproduction number must be above one in order to show a persistent infection. The virus reproduction number for this model is:

$$\bar{R}_0 = \frac{\beta\kappa_0 \bar{K}\bar{S}}{(\mu_Y + \delta_Y \bar{Z})(\mu_V + \delta_V \bar{Z})(\bar{P} + d)} \tag{3.13}$$

If the values, *S*, *Z*, *K* could be held at fixed values, $\bar{S}, \bar{Z}, \bar{K}, \bar{P}$, the biological interpretation would be that one HIV particle will generate $\bar{R}_0$ secondary particles into the host. At initial HIV

infection with time, t, equal to 0, the virus reproduction number has a value of 10 and is represented by the following equation:

$$R_0 = \frac{\beta \kappa_0 S_0}{(\mu_Y \mu_V)(P_0 + d)} \tag{3.14}$$

This is the initial reproduction number with no anti-HIV activity. A reproduction number which represents the presence of a fully activated anti-HIV activity with a maximum number of susceptible cells can also be found. The reproduction number with maximum anti-HIV activity is represented by the following equation:

$$R' = \frac{\beta \kappa_0 S_0}{(\mu_Y + \delta_Y)(\mu_V + \delta_V)(P_0 + d)} \tag{3.15}$$

In this equation, Z and K are held at fixed values, $Z = Z_{\max} = 1$ and $K = 1$. If R' is greater than one, the infection will persist and cannot be cured. The calculated value of R' is 2.75. This value confirms that a patient with HIV will not be able to overcome the infection.

The HIV extended model is very complex and a full mathematical analysis is not possible. However, this model is also more realistic and applicable because it takes into account the difference between susceptible and non susceptible CD4+ T cells. Modeling with specific parameters will help explain the system better. Most of the parameters used were found through clinical and experimental data. (See [19]) The parameter values are described in Table 3:

Table 3: Parameter Values used in the extended model

Parameter		Values
α	CD4+ T cell production rate	5×10^{9} per day
μ	Natural death rate of uninfected cells	0.02 per day
κ_0	Initial rate at which a HIV particle transforms a susceptible CD4+ T cell to a productively infected cell	1.0×10^{-12} particles per day
μ_Y	Death rate of productively infected cells	0.6 per day
δ_Y	Maximum additional elimination rate of productively infected cell through anti-HIV activity	0.6 per day
β	HIV production rate from infected cells	150 particles per cell per day
μ_V	Clearance rate of infectious virus particles	6 per day
δ_V	Maximum additional elimination rate of virus particles through the anti-HIV activity	5 per day
θ	HIV dependent immune activation rate	10^{-6}
ρ	Autonomous immune activation rate	0.1 per day
ω_P	Rate of increase of the fraction of susceptible cells by generation and selection of HIV mutants	1.4×10^{-14} particles per day
ω_K	Rate of increase of reproduction per virus particle	1.1×10^{-15}
a	Constant	10^{3}
b	Constant	0.2
c	Constant	2.0
d	Constant	10^{-2}
$Z_{\max}$	Maximum ant-HIV activity	1.0
$P_{\max}$	Maximum fraction of susceptible cells	1.0
$K_{\max}$	Maximum infection rate of susceptible cells per infected cell	20

3.4 HIV Extended model Graphs and Biological Interpretation

The numerical results of the model using the parameter values from Section 3.3 were used to make the following graphs. Figure 1 represents the number of CD4+ T cells. Figure 2 represents the number of HIV particles. Figure 3 represents the anti-HIV activity. Each of the

graphs represents the initial phase of the HIV infection within the first six months and supports the model predictions.

During primary infection there are a large number of virus particles which enter the body and start infecting the CD4+ T cells. At the start of the infection, the number of HIV particles grows exponentially. The HIV viremia causes a temporary reduction of CD4+ T cells which then recover and remain at a lower level than before the infection. Notice in Figure 1 and Figure 2 the increase and decrease of HIV particles and CD4+ T cells occurs at the same time around 15 days. Right after the initial infection, the anti-HIV activity mounts an attack against the invading virus particles and we see a resurgence of CD4+ T cells. The anti-HIV activity increases rapidly and then reaches its max. The anti-HIV activity is not the only reason the viremia starts to break down. Note there are only a certain number of available CD4+ T cells to infect.

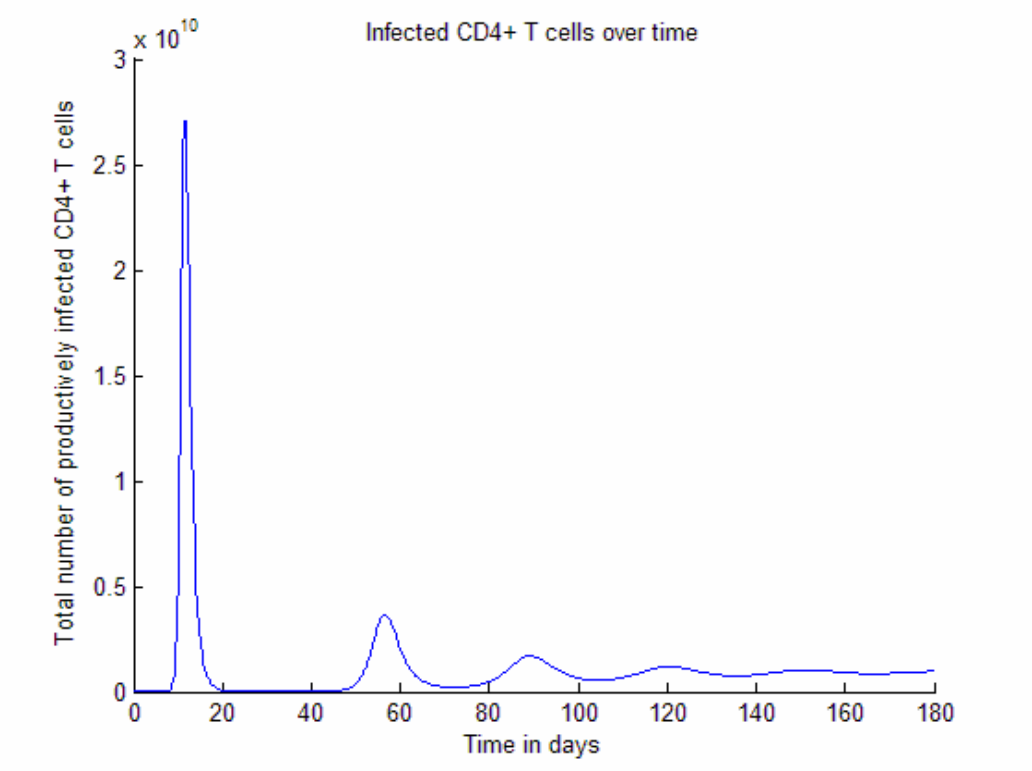


Figure 1: Decline of CD4+ T cells over first six months after initial infection.

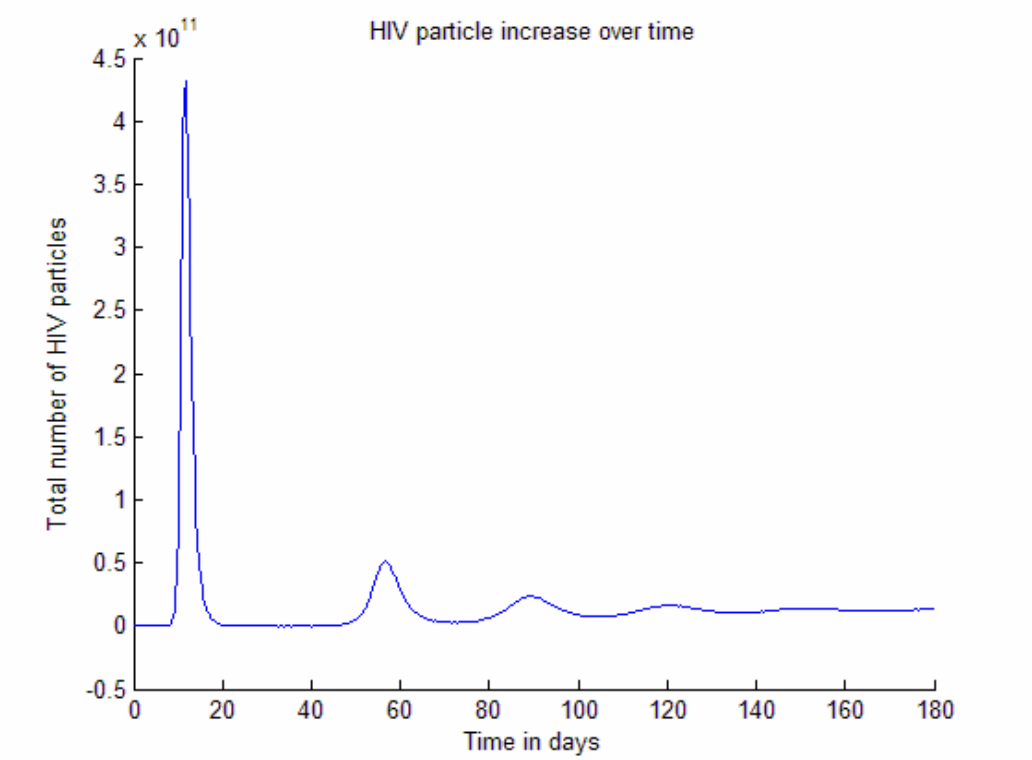


Figure 2: Increase in HIV particles within the first six months of infection.

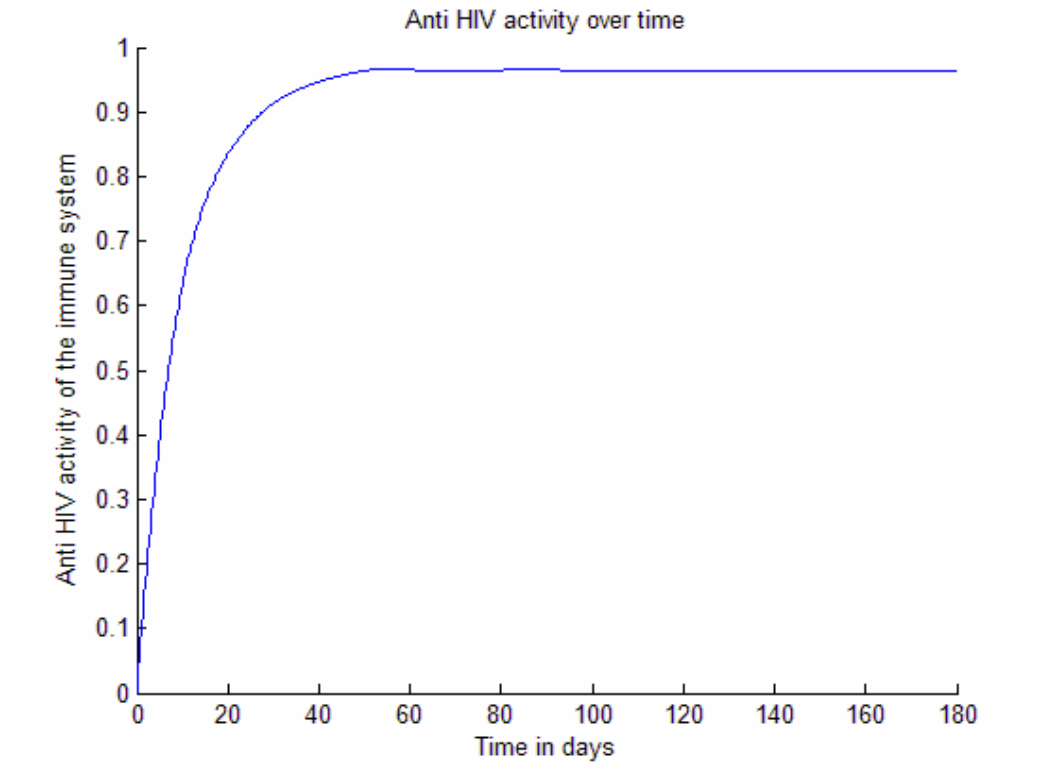


Figure 3: Decline of anti-HIV activity within the first six months of initial infection.

During the second phase of the infection for about ten years, the virus is slightly suppressed and increases slowly. This is the latent period of the infection. The model shows the immune system will hold to 50% of the normal value for about 10 years but will drop significantly during the two years following. After about twelve years, the CD4+ T cells will drop below 20% which is the definition of disease progression to AIDS. (See [19]). We see a decline of anti-HIV activity. The HIV virus particles replicate freely and reach a higher concentration than that of the primary infection. At this point, the immune system can't control other infections.

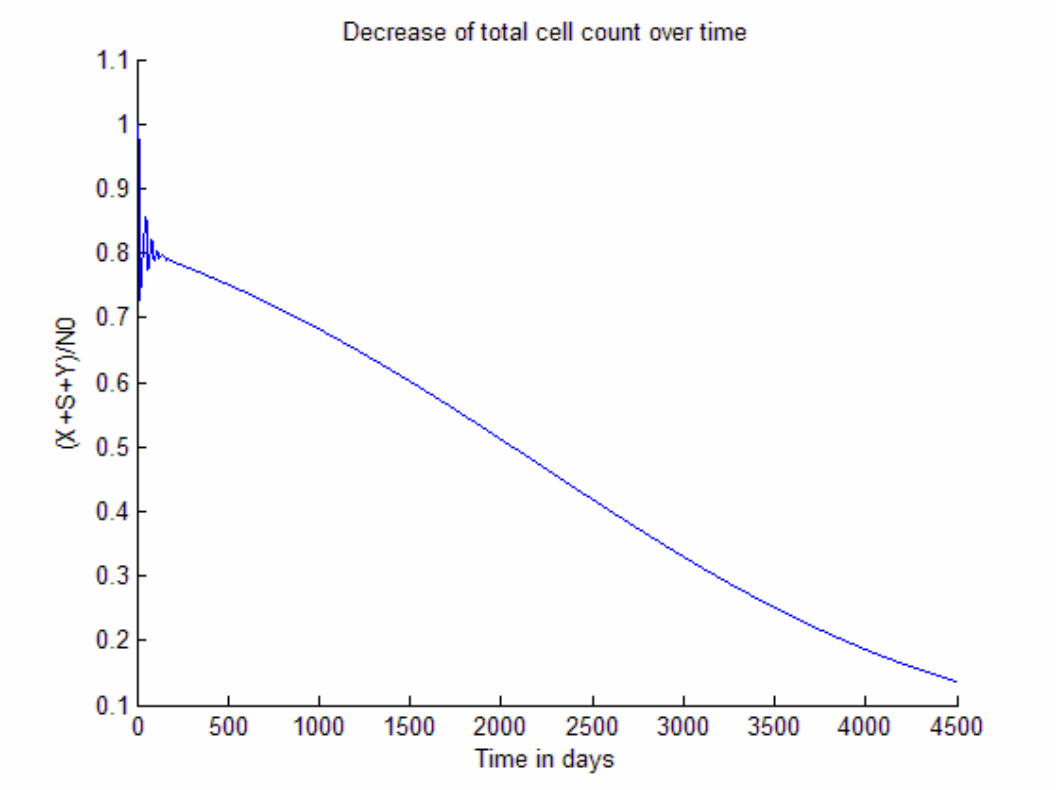


Figure 4: Total cell count after 12 years. Progression to AIDS occurs at y=0.2

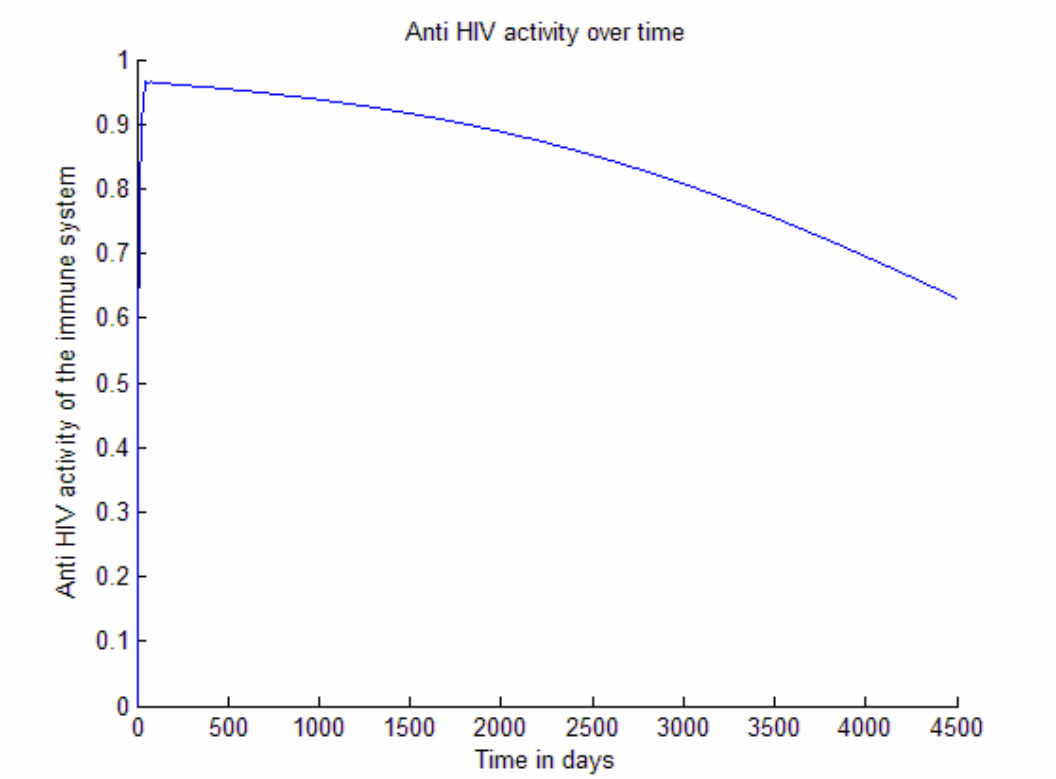


Figure 5: Anti-HIV activity after 12 years.

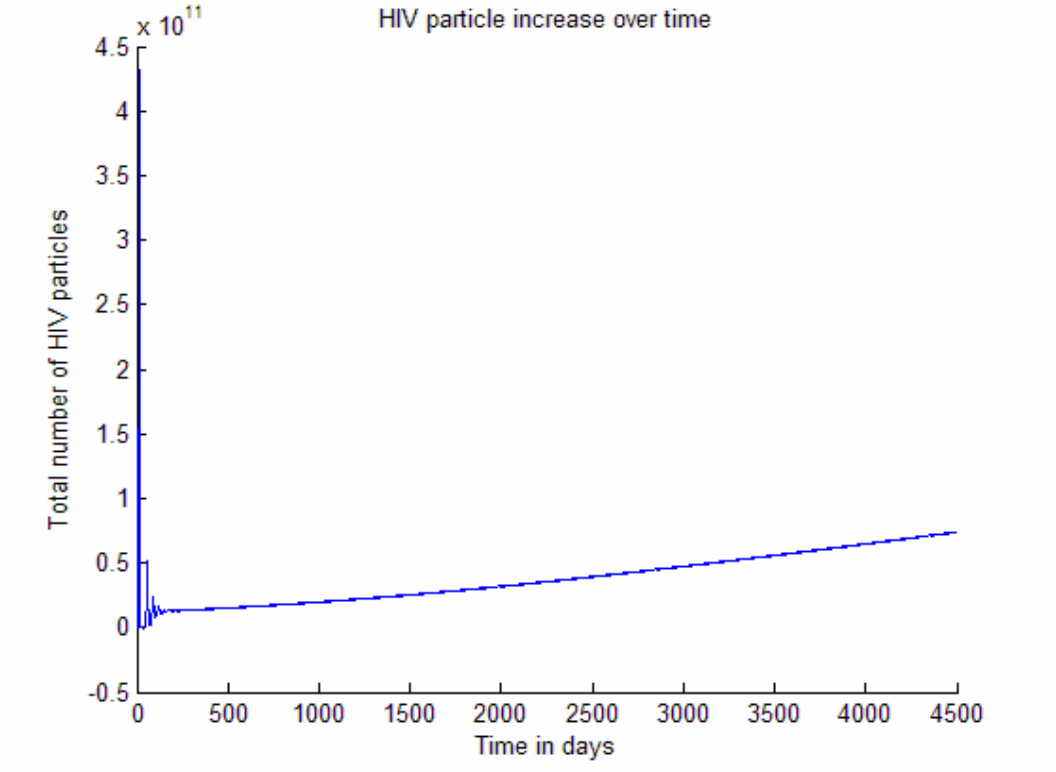


Figure 6: HIV particle increase over 12 years.

Surprisingly, the model predicts that the initial dose of HIV particles introduced into the host does not play an important role in progression to disease. A highly activated CD4+ T cell pool is one of the main determinants to infection and disease progression. If an individual is unhealthy, their CD4+ T cell pool would be larger than normal and would favor CD4+ T cell infection by the HIV virus. If an individual has an initial value of 1200 per mm^3 CD4+ T cells, then the progression to disease occurs much faster. If the initial value was 800 per mm^3 CD4+ T cells a much smoother progression occurs. The following graph shows the impact of initial cell count on the infection process.

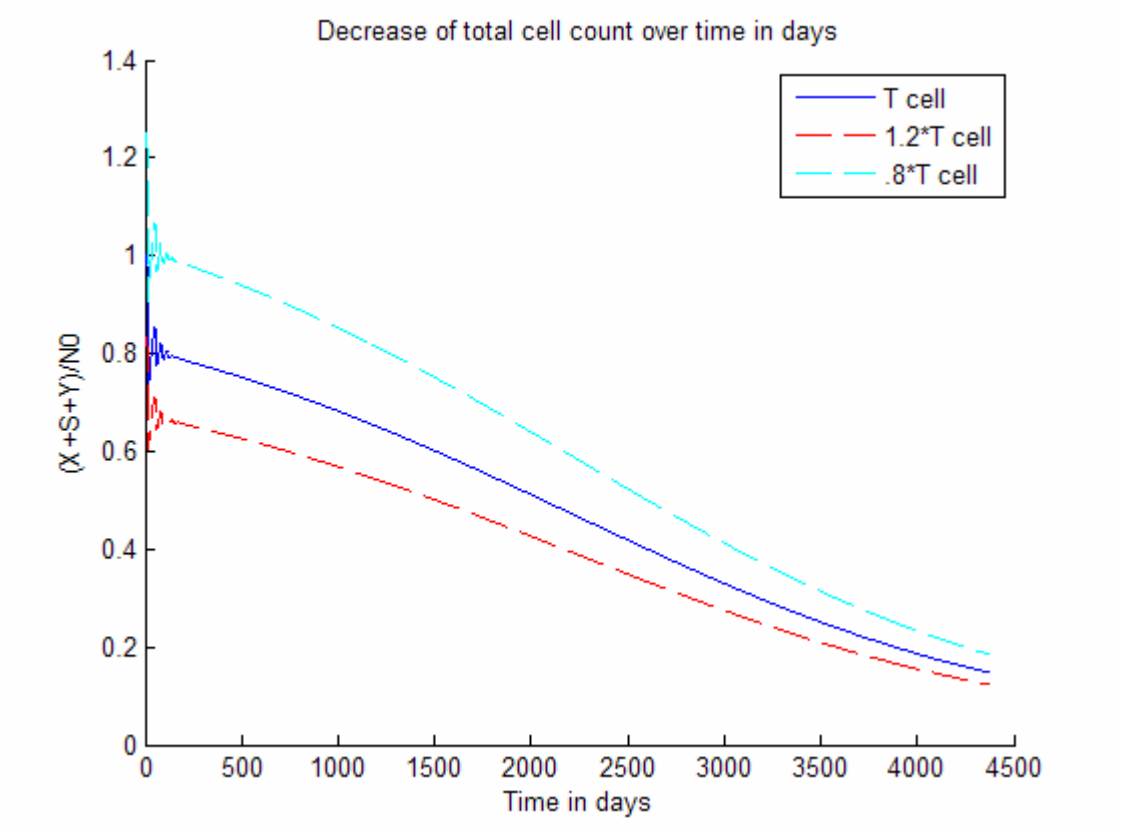


Figure 7: Total CD4+ T cell count after a 20% reduction of CD4+ T cell count (aqua), normal reduction (blue), and initial increase by 20% of CD4+ T cell count (red).

This model also looks at the dynamics of the susceptible and non-susceptible cells. The variable, P, in the model represents the proportion of new CD4+ T cells which are becoming

susceptible. The higher the amount of activated CD4+ T cells, the faster the virus progresses to disease. The initial value of P is important to the dynamics of this model. If the initial value of P is small, the immune system will hold at 50% for about twelve years. However, if P is a larger fraction, the progression to disease is much faster. This means through the generation and selection of HIV mutants, the HIV virus will increase the range of CD4+ T cells tropism over more and more CD4+ T cell clones, until after twelve years almost all of the clones are equally susceptible to be infected by the HIV virus. (See [19]) The variable, K, is the factor which represents the infection rate at which the CD4+ T cells increase by the generation and selection of HIV mutants.

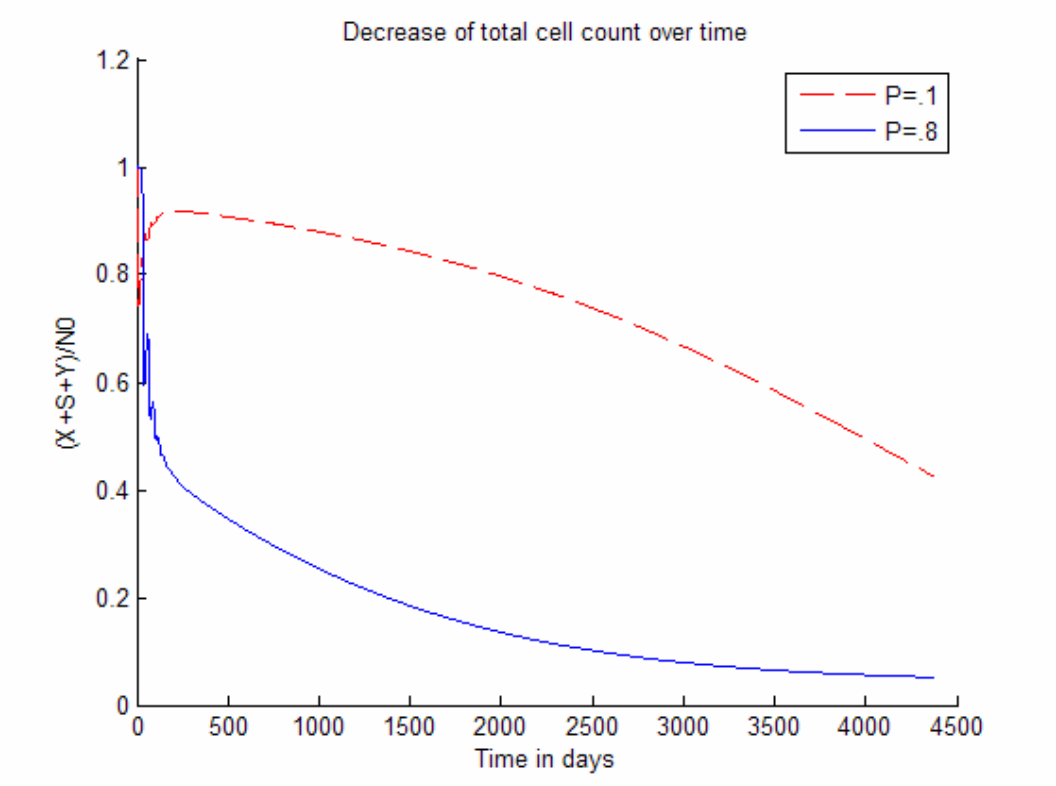


Figure 8: Changes in the P value and the impact on the total cell count.

The speed at which P and K change are measure by ω_P and ω_K. These values also play an important role in the model and the disease progression. If the value of ω_K were increased or

decreased by a factor of five, the reduction rate of the CD4+ T cells would look similar but the end result make be different. If ω_K was decreased by a factor of five, the model predicts the individual's life span would increase by two years. If ω_K was increased by a factor of five, the model predicts a faster progression to disease around eight years. There is a stark difference when the value of ω_P is changed by a factor of five. If ω_P is increased by the factor, progression to disease occurs after six years.

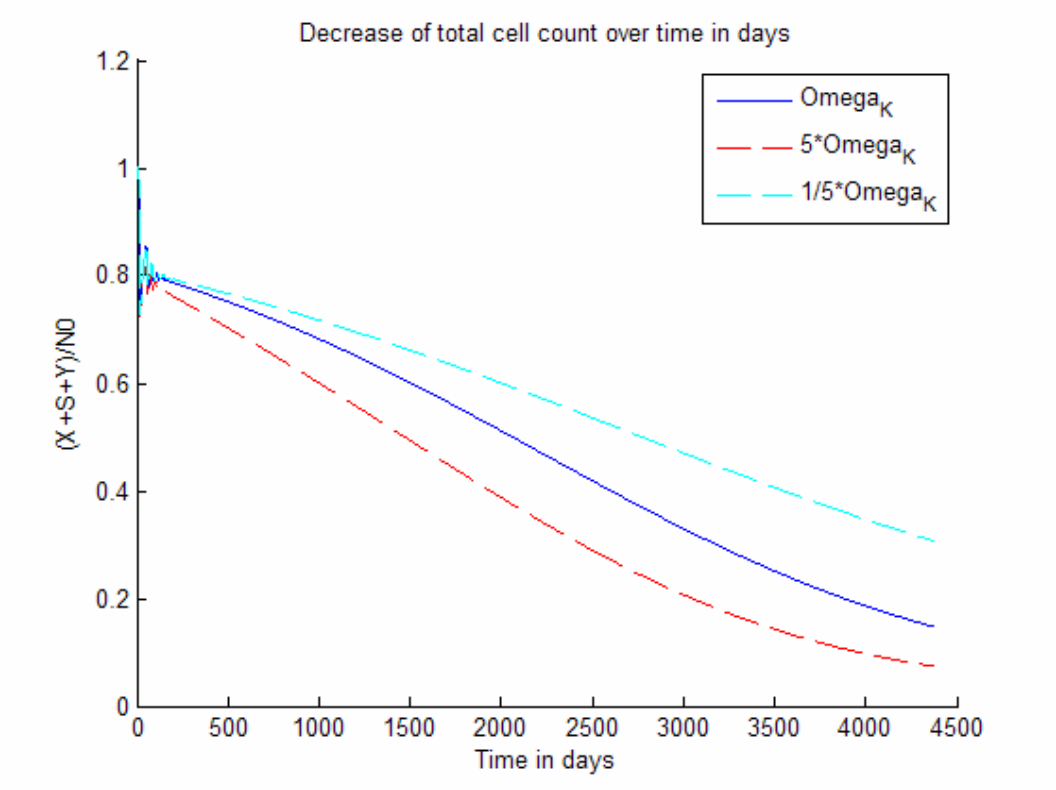


Figure 9: Impact on CD4+ T cells when the values of ω_K are varied.

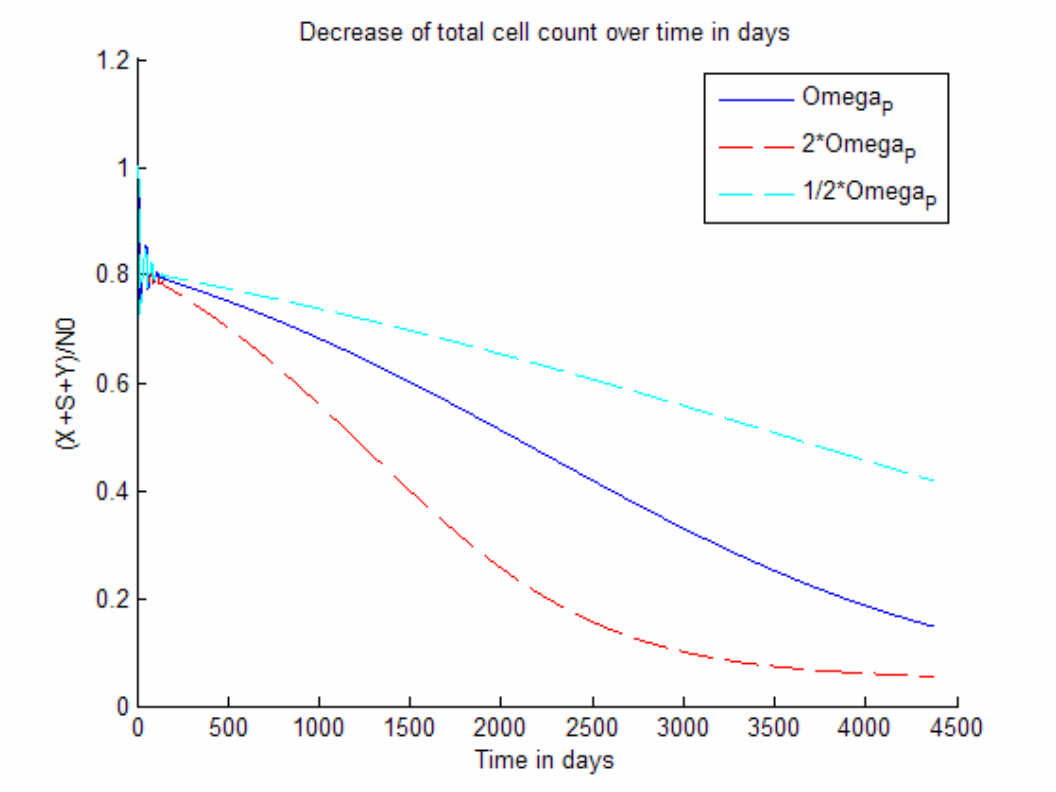


Figure 10: Impact on CD4+ T cells when the value of ω_P is varied.

As seen through the graphs, P,K, ω_P, and ω_K are very important to the intra-host dynamics of HIV. The effect of the rate of the fraction of susceptible cells by generation and selection of HIV mutants is very important in determining the progression to disease. (See [19])

HIV will affect many people in many different ways. This model helps to predict the course that HIV will take during the three stages of the disease. The model may loose applicability for the late part of the last stage of the disease because of the many other extreme pathological conditions. In the latter stage of the disease, the immune system is completely compromised and is no longer able to fight infection. When this happens, a simple cold could cause death. Understanding the course of this disease through the model presented can help doctors and scientist find a cure for this epidemic.

CHAPTER FOUR – HTLV-I VIRUS AND ADULT T-CELL LEUKEMIA

4.1 Introduction to the dynamics of HTLV-I

As we have seen in the previous chapter, the HIV infection takes place through cell to cell contact with infected CD4+ T-cells and eventually takes over the immune system. A virus that is similar and related to HIV is the first form of a human T-lymphotropic virus or HTLV. Just as HIV can lead to the AIDS virus, HTLV-I can lead to many diseases, including adult T-cell leukemia/lymphoma. Actively infected T-cells can infect other T-cells and can eventually convert to ATL cells. This process typically happens during the latent phase of the virus.

HTLV-I shares many similarities with HIV except in the range of diseases that it causes and how it causes these diseases. There are two major virologic differences between HIV and HTLV-I. One difference is that HTLV-I does not destroy the CD4+ T-cells but in fact, causes cell proliferation and transformation. The other is that HTLV-I has a low replication rate but a high fidelity of replication, which results in a low viral burden and high genetic stability. This reduces the possibility of immune escape. (See [14])

HTLV-I is an enveloped double stranded RNA retrovirus which attacks the CD4+ T-cells. Transmission of HTLV-I is mainly associated with the cells. The cells receive this virus through a glucose transporter called glut-1. Once received, the virus inserts a DNA copy into the host cell. The virus replicates with each mitotic cell division. As cells continue to divide, the virus spreads. HTLV-I will remain latent for many years before the virus causes Adult T-cell leukemia to manifest. The latently infected cells contain the virus but do not produce DNA, therefore, the cells are incapable of contagion. This chapter examines a math model which examines the process of how HTLV-I causes ATL.

Adult T-cell leukemia or lymphoma is a non-Hodgkins lymphoma. Adult T-cell leukemia occurs first, which is a cancer of the cells. Lymphona also occurs and is a cancer which attacks the B-lymphocytes and the lymphatic system. There are four distinct clinical forms of ATL. The disease can be classified as acute ATL, chronic ATL, lymphoma, and smoldering ATL. Once ATL develops, most individuals will survive for only a year or two. The median survival rate for the acute and lymphoma subtypes is less than one year. Individuals with acute or smoldering ATL may survive longer. (See [8]) Standard chemotherapy is not effective against ATL.

4.2 Mathematical Model of HTLV-I Infection to ATL

Stilianakis and Seydel produced a basic math model that describes the T-cell dynamics of the HTLV-I infection and the development of ATL.

Table 4: Variables used in the Stilianakis & Sydel model

Variable	
T	Number of susceptible CD4+ T cells
T_L	Number of latently infected CD4+ T cells
T_A	Number of actively infected CD4+ T cells
T_M	Number of leukemia T-cells
Λ	Constant rate at which new CD4+ Tcells are produced (assumed to be susceptible)
κ	Rate at which CD4+ T cells come into contact with actively infected cells.
α	Transmission rate in which latent cells become actively infected cells
ρ	Transmission rate in which actively infected cells convert to ATL cells
β	ATL proliferation rate of a classical logistic growth model
μ_T	Removal or death rate of susceptible CD4+T-cells
μ_L	Removal or death rate of latently infected CD4+ T cells
μ_A	Removal or death rate of actively infected CD4+ T cells

This model consists of the following non-linear differential equations:

$$T' = \Lambda - \mu_T T - \kappa T_A T \tag{4.1}$$

$$T_L' = \kappa T_A T - (\mu_L + \alpha) T_L \tag{4.2}$$

$$T_A' = \alpha T_L - (\mu_A + \rho) T_A \tag{4.3}$$

$$T_M' = \rho T_A + \beta T_M (1 - \frac{T_M}{T_{M_{\max}}}) - \mu_M T_M \tag{4.4}$$

The terms in this model each have a biological meaning. The first term in equation (4.1) is Λ. This term is the rate in which the new CD4+ T cells are produced. Each cell that is produced is assumed to be susceptible to the virus. The second term in equation (4.1) represents the rate at which all CD4+ T cells die. The last term in equation (4.1) is $\kappa T_A T$ and is considered the mass action term. This term represents the infection process of susceptible cells which come into contact with actively infected CD4+ T cells.

Equation (4.2) starts with the same mass action term that is seen in equation (4.1). The second term is $(\mu_L + \alpha)T_L$. Lets break this term up into two terms, $\mu_L T_L$ and αT_L and explain them separately. $\mu_L T_L$ describes how fast the latently infected cells are dying. αT_L describes how fast the latently infected cells become actively infected cells. In general, the whole term describes the dynamics of the latently infected cells.

The first term in equation (4.3) is αT_L. As seen in equation (4.2), this term represents how fast the latently infected cells become actively infected cells. The next term is $(\mu_A + \rho)T_A$. Again, lets break this up into two terms, $\mu_A T_A$, which describes the death rate of the actively infected cell, and ρT_A, which describes how fast the actively infected cells become ATL cells. The terms in equation (4.3) represent the dynamics of the actively infected cells and how they change to ATL cells.

Equation (4.4) is the equation which represents the growth of the leukemia cells, which follows the classical logistical growth function. This equation begins with ρT_A. This term was also seen in equation (4.3) and it describes the speed at which actively infected cells become ATL cells. The second term is $\beta T_M (1 - \frac{T_M}{T_{M_{\max}}})$. This term describes the growth of the ATL cells,

where β is the speed for which the saturation level for leukemia cells is reached and $T_{M_{\max}}$ is the maximum amount of ATL cells that can be attained. The last term, $\mu_M T_M$, describes the death rate of the ATL cells. This equation illustrates the dynamics of the ATL or leukemia cells in the body.

The virus reproduction number for this model is:

$$R_0 = \frac{\alpha\kappa T_0}{(\mu_L + \alpha)(\mu_A + \rho)} \tag{4.5}$$

This number helps to determine how fast the disease will spread throughout the body. R_0 represents the number of secondary infections caused by one primary infected cell introduced into the pool of susceptible CD4+ T cells during the infection period. (See [18]) If $R_0 > 1$, a chronic infection is seen. This is typical in most HTLV-I infections. If $R_0 \leq 1$, the virus cannot reproduce enough to sustain an infection. The reproduction number will be important to determining the stability of the system.

4.3 Stability of the system

To analyze the stability of this system, we must first find the equilibrium points. In order to find the equilibrium points, we set equations (4.1)-(4.4) equal to 0 and solve. The equation has two possible solutions or steady states. This system can have an uninfected steady state and a positively infected steady state. For the uninfected steady state, the T-cell population will have the following value:

$$T_0 = \frac{\Lambda}{\mu_T} \tag{4.5}$$

The initial conditions would then be $T(0) = T_0$, $T_L(0) = 0$, $T_A(0) = 0$, and $T_M(0) = 0$. Therefore the uninfected steady state would be $E_0 = (T_0, 0, 0, 0)$. The positive infected steady state would be $\bar{E} = (\bar{T}, \bar{T}_L, \bar{T}_A, \bar{T}_M)$ where:

$$\begin{aligned}
\bar{T} &= \frac{(\mu_L + \alpha)(\mu_A + \rho)}{\alpha\kappa} \\
\bar{T}_L &= \frac{\Lambda\alpha\kappa - \mu_T(\mu_L + \alpha)(\mu_A + \rho)}{\alpha\kappa(\mu_L + \alpha)} \\
\bar{T}_A &= \frac{\Lambda\alpha\kappa - \mu_T(\mu_L + \alpha)(\mu_A + \rho)}{\kappa(\mu_L + \alpha)(\mu_A + \rho)} \\
\bar{T}_M^2 &- \frac{(\beta - \mu_M)T_{M_{\max}}}{\beta}\bar{T}_M - \frac{\rho\bar{T}_A T_{M_{\max}}}{\beta} = 0
\end{aligned} \tag{4.6}$$

We are first going to examine the stability of the uninfected steady state. For this state, the values yield the following Jacobian matrix associated with equations (4.1)-(4.4):

$$J = \begin{pmatrix}
-\mu_T - \kappa T_A & 0 & -\kappa T & 0 \\
\kappa T_A & -\alpha - \mu_L & \kappa T & 0 \\
0 & \alpha & -\mu_A - \rho & 0 \\
0 & 0 & \rho & \beta\left(1 - 2\dfrac{T_M}{T_{M_{\max}}}\right) - \mu_M
\end{pmatrix} \tag{4.7}$$

In the uninfected steady state, the characteristic of the polynomial is found by taking the determinant of the Jacobian or $\det(J - \lambda I)$. The characteristic polynomial is:

$$p(\lambda) = (\beta - \mu_M - \lambda)(\mu_T - \lambda)(\lambda^2 + \lambda(\mu_L + \alpha + \mu_A + \rho) + (\mu_L + \alpha)(\mu_A + \rho) - \alpha\kappa \tag{4.9}$$

The eigenvalues of $p(\lambda) = 0$ are:

$$\lambda_1 = \beta - \mu_M$$
$$\lambda_2 = -\mu_T \tag{4.10}$$
$$\lambda_{3,4} = \frac{-(\mu_L + \alpha + \mu_A + \rho)}{2} \pm \frac{\sqrt{(\mu_L + \mu_A + \alpha + \rho)^2 - 4((\mu_L + \alpha)(\mu_A + \rho) - \alpha\kappa\frac{\Lambda}{\mu_T}}}{2}$$

The eigenvalues help determine the stability of the steady state. If $\lambda_1 = \beta - \mu_M > 0$, then the proliferation rate of the abnormal cells are greater than the death rate and the infection increases. If $\lambda_1 = \beta - \mu_M < 0$, then the death rate of the ATL cells is greater than the proliferation rate and the stability will actually depend on the other eigenvalues, λ_3, λ_4 . These eigenvalues are either real or complex conjugates. In both cases, the real parts are negative if and only if the reproduction number is less than or equal to one or:

$$R_0 = \frac{\alpha\kappa T_0}{(\mu_L + \alpha)(\mu_A + \rho)} \leq 1 \tag{4.11}$$

If we assume that the ATL cells grow at an uncontrollable rate, then $\lambda_1 > 0$ and the point, $E_0 = (T_0, 0, 0, 0)$, where $T_0 = \frac{\Lambda}{\mu_T}$, is an unstable saddle point. If $\lambda_1 < 0$, the reproduction number will determine the next steady state. If $R_0 \leq 1$ the uninfected steady state is the only state and it is stable. The system will move to the endemically infected steady state when $R_0 > 1$ and this represents a chronic infection. When this occurs, E_0 will become unstable and $\bar{E}$ will exist.

For the endemically infected steady state, the Jacobian and the determinant of equations (4.1)-(4.4) will give the following characteristic equation:

$$\lambda^3 + \lambda^2 A + \lambda B + C = 0 \tag{4.12}$$

Where:

$$
\begin{aligned}
A &= \mu_T + \mu_L + \mu_A + \rho + \alpha + \kappa\overline{T}_A \\
B &= \mu_T\mu_L + \alpha\mu_T + \mu_T\rho + \kappa\mu_L\overline{T}_A + \kappa\mu_A\overline{T}_A + \kappa\rho\overline{T}_A + \alpha\kappa\overline{T}_A \\
C &= \kappa\mu_L\mu_A\overline{T}_A + \kappa\alpha\mu_A\overline{T}_A + \kappa\rho\mu_L\overline{T}_A + \alpha\kappa\rho\overline{T}_A
\end{aligned}
\tag{4.13}
$$

We must use the Routh-Hurwitz condition in order to further determine the stability of the system. Note that $A > 0, B > 0$ and $C > 0$ By the Routh-Hurwitz criteria, the eigenvalues of equation (4.12) will have negative real parts if and only if $A > 0, C > 0$ and $AB - C > 0$. We have already noted that $A > 0$ and $C > 0$. We can also show $AB - C > 0$, therefore, we can determine that the eigenvalues are always negative. When the eigenvalues are negative, we can show that steady state is stable and the infection is chronic.

4.4 Katri and Ruan Model and the stability of the system

In 2004, Katri and Ruan developed a similar model which takes into account the difference between contact with the virus and infection by the virus. This is denoted using a κ_1 in certain equations. Remember that κ represents the rate at which uninfected cells are contacted by actively infected cells. In this model, κ_1 represents the rate of infection of the T-cells by the actively infected T-cells. The equations for the Katri and Ruan model are the same as the original model but in equation (4.2) κ is replace with κ_1 and the new model is:

$$T' = \Lambda - \mu_T T - \kappa T_A T \tag{4.14}$$

$$T_L' = \kappa_1 T_A T - (\mu_L + \alpha) T_L \tag{4.15}$$

$$T_A' = \alpha T_L - (\mu_A + \rho) T_A \tag{4.16}$$

$$T_M' = \rho T_A + \beta T_M (1 - \frac{T_M}{T_{M_{\max}}}) - \mu_M T_M \tag{4.17}$$

This small change in the model changes the reproduction number to be:

$$R_0 = \frac{\alpha\kappa_1 T_0}{(\mu_L + \alpha)(\mu_A + \rho)} \tag{4.18}$$

The uninfected steady state and stability analysis remains the same as the Stilianakis & Seydel model, however the new positive infected steady state would be $\bar{E} = (\bar{T}, \bar{T}_L, \bar{T}_A, \bar{T}_M)$ where:

$$\begin{aligned}
\bar{T} &= \frac{(\mu_L + \alpha)(\mu_A + \rho)}{\alpha\kappa_1} \\
\bar{T}_L &= \frac{\Lambda\alpha\kappa_1 - \mu_T(\mu_L + \alpha)(\mu_A + \rho)}{\alpha\kappa(\mu_L + \alpha)} \\
\bar{T}_A &= \frac{\Lambda\alpha\kappa_1 - \mu_T(\mu_L + \alpha)(\mu_A + \rho)}{\kappa(\mu_L + \alpha)(\mu_A + \rho)} \\
\bar{T}_M^2 &- \frac{(\beta - \mu_M)T_{M_{\max}}}{\beta}\bar{T}_M - \frac{\rho\bar{T}_A T_{M_{\max}}}{\beta} = 0
\end{aligned} \tag{4.19}$$

For this state, the values yield the following Jacobian matrix associated with equations (4.14)-(4.19):

$$J = \begin{pmatrix}
-\mu_T - \kappa\bar{T}_A & 0 & -\kappa\bar{T} & 0 \\
\kappa_1\bar{T}_A & -\alpha - \mu_L & \kappa_1\bar{T} & 0 \\
0 & \alpha & -\mu_A - \rho & 0 \\
0 & 0 & \rho & \beta\left(1 - 2\dfrac{\bar{T}_M}{T_{M_{\max}}}\right) - \mu_M
\end{pmatrix} \tag{4.20}$$

We will denote:

$$M' = \beta(1 - 2\frac{T_M}{T_{M_{\max}}}) - \mu_M \tag{4.21}$$

Then the eigenvalues of this Jacobian are M'. These eigenvalues will always be negative since $\bar{T}_M > T_{M_{\max}}$ when the infection is chronic. The Jacobian will yield the following characteristic equation:

$$\lambda^3 + \lambda^2 a_1 + \lambda(a_2 + a_4) + (a_3 + a_5) = 0 \tag{4.22}$$

Where:

$$\begin{aligned}
a_1 &= \kappa^2 \overline{T}_A + \kappa\mu_L + \kappa\rho + \kappa\mu_T + \alpha\kappa + \kappa\mu_A \\
a_2 &= \kappa^2 \overline{T}_A \mu_L + \kappa^2 \overline{T}_A \alpha + \mu_T \kappa\mu_L + \kappa^2 \overline{T}_A \mu_A + \kappa^2 \overline{T}_A \rho + \\
&\mu_A \kappa\mu_L + \mu_T \kappa\alpha + \mu_A \kappa\mu_T + \kappa\mu_L \rho + \kappa\alpha\mu_A + \kappa\alpha\rho + \mu_T \kappa\rho \\
a_3 &= \mu_T \kappa\alpha\rho + \kappa^2 \overline{T}_A \alpha\rho + \kappa^2 \overline{T}_A \mu_A \alpha + \mu_T \mu_A \kappa\mu_L \\
&+ \mu_T \kappa\mu_L \rho + \mu_T \kappa\alpha\mu_A + \kappa^2 \overline{T}_A (\mu_L \rho + \mu_L \mu_A) \\
a_4 &= -\kappa_1 \alpha\rho - \kappa_1 \mu_L \rho - \kappa_1 \alpha\mu_A - \kappa_1 \mu_L \mu_A \\
a_5 &= -(\mu_T \kappa_1 \alpha\rho + \mu_T \mu_A \kappa_1 \mu_L + \mu_T \kappa_1 \mu_L \rho + \mu_T \kappa_1 \alpha\mu_A)
\end{aligned} \tag{4.23}$$

Note: The coefficients were written in this manner for convenience and comparison in some later work by Katri & Ruan.

Again, we must use the Routh-Hurwitz condition in order to further determine the stability of the system. According to the Routh-Hurwitz condition, the eigenvalues of equation (4.23) will have negative real parts if and only if:

$$\begin{aligned}
&a_1 > 0, (a_3 + a_5) > 0 \\
&a_1(a_2 + a_4) - (a_3 + a_5) > 0
\end{aligned} \tag{4.24}$$

Proposition 1:.The infected steady state $\overline{E}$ is asympototically stable if $R_0 > 1$ and the inequalities in (4.24) are satisfied. This occurs if (a) $\kappa > \kappa_1$, or (b) $\kappa = \kappa_1$.(See [6])

.In order or check that this proposition is valid, we will use the following parameters and values estimated by Stilianakis & Seydel (See [18]).

Table 5: Variables and Parameter Values for contagion used in the model

Parameter		Values
T	Uninfected CD4+ T-cell population size	$1000 / mm^3$
T_L	Latently infected CD4+ T-cell density	$250 / mm^3$
T_A	Actively infected CD4+ T-cell density	$1.5 / mm^3$
T_M	Leukemic CD4+ T-cell density	0
μ_T	Natural death rate of CD4+ T-cells	$0.6 mm^3$ per day
μ_L	Blanket death rate of latently infected CD4+ T-cells	0.006 per day
μ_A	Blanket death rate of actively infected cells	0.05 per day
μ_M	Death rate of leukemic cells	0.0005 per day
κ_1	Rate uninfected CD4+ T-cells become latently infected	varies
κ	Rate infected cells are contacted	varies
β	Growth rate of leukemic CD4+ T-cell population	0.0003 per day
α	Rate latently infected cells become actively infected	0.0004 per day
ρ	Rate actively infected cells become leukemic	0.00004 per day
$T_{M_{\max}}$	Maximal population level of leukemic CD4+ T-cells	$2200 / mm^3$
λ	Source term for uninfected CD4+ T cells	6 per day
T_0	Derived quantity which represents the CD4+ T-cell population for HTLV-I negative persons	$1000 / mm^3$

We can use these parameter values and the estimated values of κ and κ_1, given by Stilianakis & Seydel on the basis of parameter values from the HIV infection process, to find that $R_0 = 1.25$ if $\kappa_1 = 0.1$. If we take $\kappa = \kappa_1 = 0.1$, we find that the inequalities in equation (4.24) are satisfied and part (b) of Proposition 1 is true. Furthermore, the steady state, $\bar{E} = (800, 187.5, 1.5, 1.3)$, would be asymptotically stable. If we take $\kappa = 0.5$ and $\kappa_1 = 0.1$, we will again find that the inequalities in equation (4.24) are satisfied and part (a) of Proposition 1 is also true. The steady state would be $\bar{E} = (800, 37.38, 0.3, 0.6)$, which is also asymptotically stable. The following graph was

created using the parameter values given in Table 5. The numerical simulation shows the number of healthy CD4+ T cells decreases dramatically while the latently infected cells increase, then remain steady.

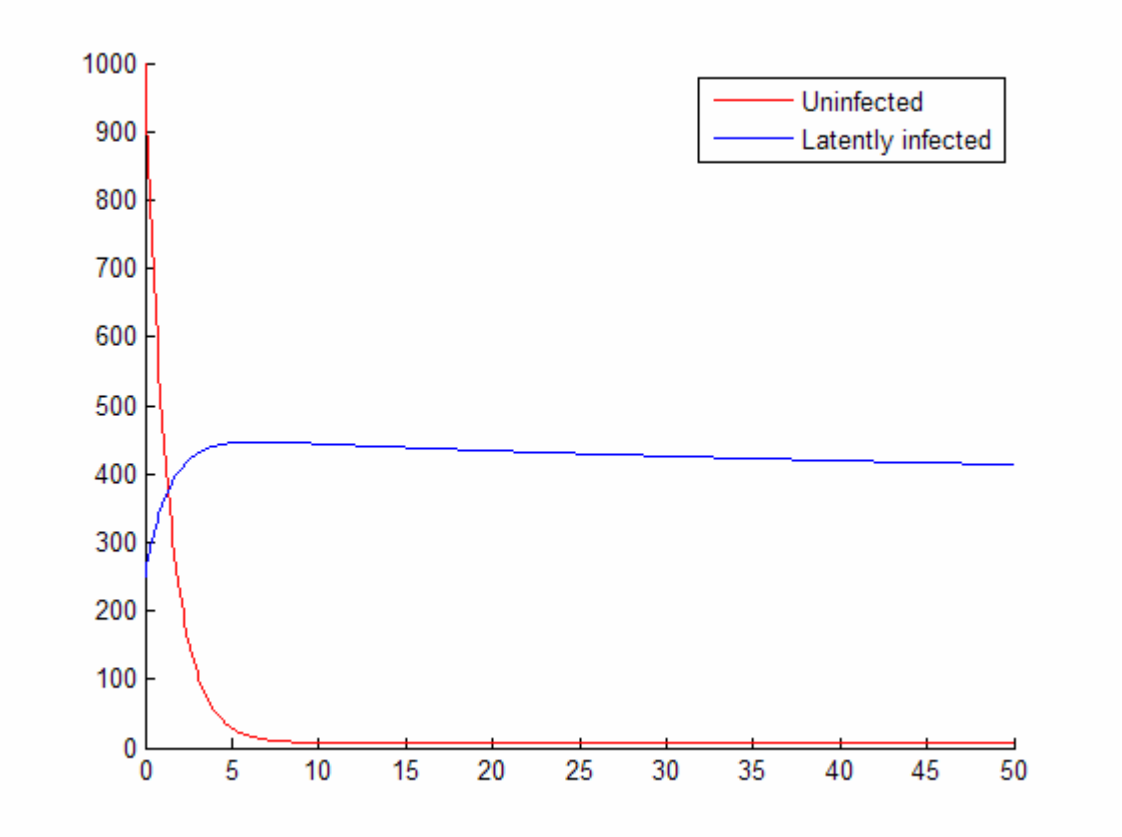


Figure 11: Latently infected CD4+ T cells vs. Uninfected CD4+ T cells

HTLV-I is a virus in which only 5% of infected individuals will ever develop any disease such as Adult T-cell Leukemia. We have shown through the stability analysis, we can predict when the infection will persist and become ATL.

CHAPTER FIVE - CONCLUSION

The interaction between HIV and the immune system is a dynamic process. Mathematical models are used to understand this process and explore which biological mechanisms cause disease progression. There is no cure or vaccine for HIV at the present time, but the treatment regimes used by doctors extend the lives of HIV patients. Doctors are also working to find a vaccine. Future work should be focused on finding the optimal treatment schedule in order to prolong the life of patients and hopefully, find a cure.

It is unclear why some HTLV-I carriers progress to disease while the majority of them do not do so. It is also not known why some infected individuals develop ATL and others develop HAM/TSP. (See [8]). Further studies should focus on finding the mechanism, which causes the virus to progress to disease and finding the genetic markers that will determine which disease the virus will trigger. HTLV-I also has no known cure or vaccine. However, a vaccine to prevent infection is currently being explored by scientists.

In this thesis we examined many mathematical models which are used to predict the course of a disease. Specifically, we examined two retroviruses, HIV and HTLV-I. A basic model and background study was given in Chapter Two. Chapter Three explored a model of the intra-host dynamics of HIV. Graphs which were obtained from each of the models help predict what factors are important for HIV to progress to AIDS. Chapter Four is concerned with two different models of HTLV-I progression to ATL. Using analytical techniques we study the stability and asymptotic stability and with the aid of SIMULINK, we obtain graphs associated with the models to obtain information on progression of the disease.

The mathematical models presented here are useful and can help predict the course of the infection. However, as more clinical data about the virus becomes available, the models can be refined further to reflect the new information.

APPENDIX A
SIMULINK OF STILIANAKIS AND SCHENZLE EQUATIONS

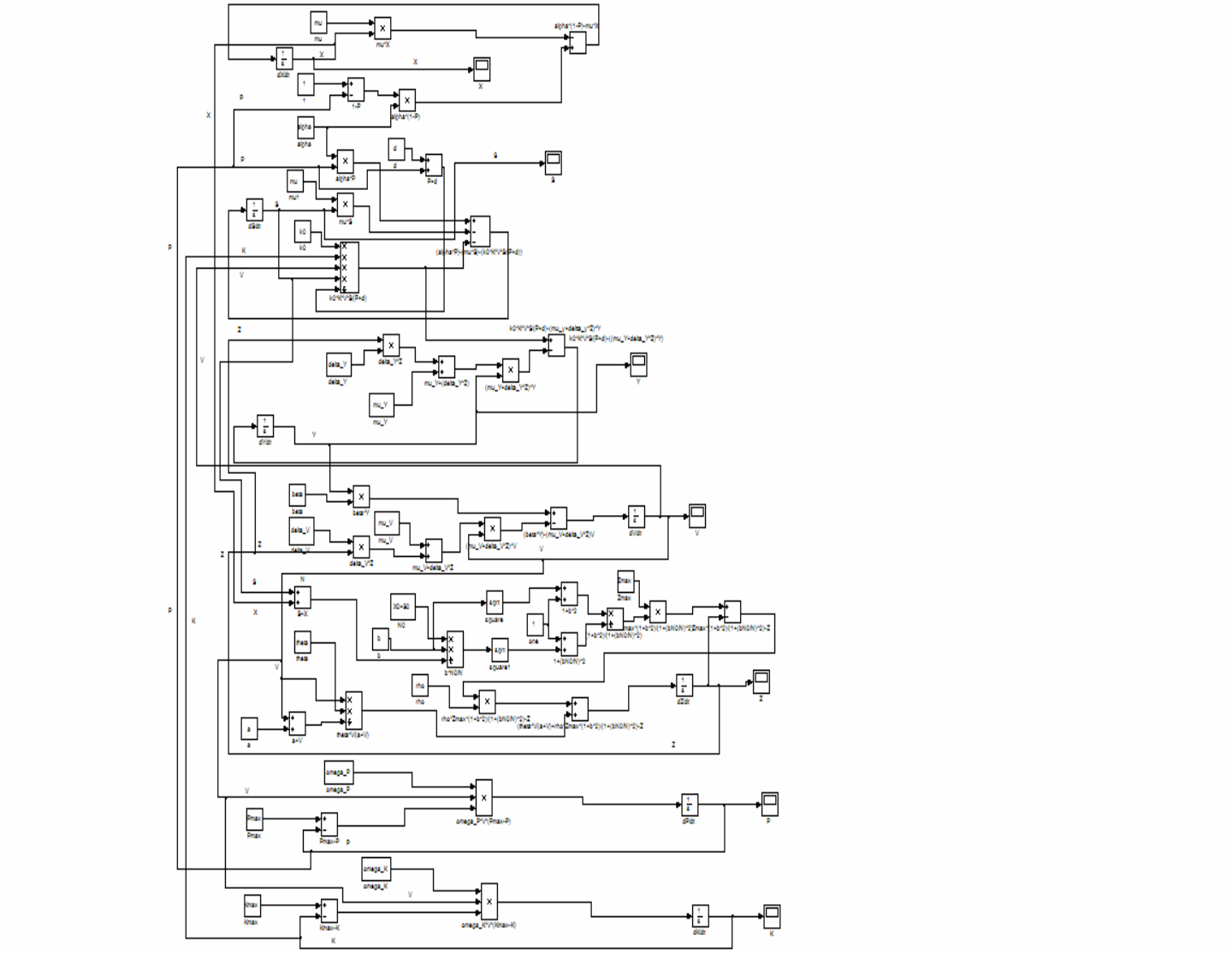


Figure 12: Simulink of Stilianakis and Schenzle equations

APPENDIX B
MATLAB OF STILIANAKIS AND SCHENZLE EQUATIONS

```
clear all
close all
clc
%first pass for plot of P=.1  in Figure 3
%days for simulation to run
days=4380;
% defining variables
alpha=5*10^9;
mu=.02;
k0=1*10^-12;
mu_Y=.6;
delta_Y=.6;
beta=150;
mu_V=6;
delta_V=5;
theta=10^-6;
rho=.1;
omega_P=1.4*10^-14;
omega_K=1.1*10^-15;
Zmax=1;
Pmax=1;
Kmax=20;
a=10^3;
b=.2;
c=2;
d=10^-2;
% initial values of intergration
N0=2.5*10^11;
X0=.7*2.5*10^11;
S0=.3*2.5*10^11;
Y0=0;
V0=1;
Z0=10^-6;
P0=.1;
K0=1;
% simulation
```

```
sim('untitled_P_01_08')
% plotting
t=X(:,1);
x1=X(:,2);
s1=S(:,2);
y1=Y(:,2);
v1=V(:,2);
z1=Z(:,2);
p1=P(:,2);
k1=K(:,2);
figure (8)
hold on
plot (t,(x1+s1+y1)/N0,'b')
ylabel('(X+S+Y)/N0')
xlabel('Time in days')
title('Decrease of total cell count over time')
%second pass for second plot on simulation with P=.8 from figure 3
%days for simulation to run
days=4380;
% defining variables
alpha=5*10^9;
mu=.02;
k0=1*10^-12;
mu_Y=.6;
delta_Y=.6;
beta=150;
mu_V=6;
delta_V=5;
theta=10^-6;
rho=.1;
omega_P=1.4*10^-14;
omega_K=1.1*10^-15;
Zmax=1;
Pmax=1;
Kmax=20;
a=10^3;
b=.2;
```

```
c=2;
d=10^-2;
% initial values of intergration
N0=2.5*10^11;
X0=.7*2.5*10^11;
S0=.3*2.5*10^11;
Y0=0;
V0=1;
Z0=10^-6;
P0=.8;
K0=1;
% simulation
sim('untitled_P_01_08')
% plotting
t=X(:,1);
x1=X(:,2);
s1=S(:,2);
y1=Y(:,2);
v1=V(:,2);
z1=Z(:,2);
p1=P(:,2);
k1=K(:,2);
plot (t,(x1+s1+y1)/N0,'g')
%first pass for plot of omega_k  in Figure 6
%days for simulation to run
days=4380;
% defining variables
alpha=5*10^9;
mu=.02;
k0=1*10^-12;
mu_Y=.6;
delta_Y=.6;
beta=150;
mu_V=6;
delta_V=5;
theta=10^-6;
rho=.1;
```

```
omega_P=1.4*10^-14;
omega_K=1.1*10^-15;
Zmax=1;
Pmax=1;
Kmax=20;
a=10^3;
b=.2;
c=2;
d=10^-2;
% initial values of intergration
N0=2.5*10^11;
X0=.7*2.5*10^11;
S0=.3*2.5*10^11;
Y0=0;
V0=1;
Z0=10^-6;
P0=.3;
K0=1;
% simulation
sim('untitled_P_01_08')
% plotting
t=X(:,1);
x1=X(:,2);
s1=S(:,2);
y1=Y(:,2);
v1=V(:,2);
z1=Z(:,2);
p1=P(:,2);
k1=K(:,2);
plot (t,(x1+s1+y1)/N0,'r')
%second pass for second plot on simulation with 5*omega_k from figure 6
%days for simulation to run
days=4380;
% defining variables
alpha=5*10^9;
mu=.02;
k0=1*10^-12;
```

```
mu_Y=.6;
delta_Y=.6;
beta=150;
mu_V=6;
delta_V=5;
theta=10^-6;
rho=.1;
omega_P=1.4*10^-14;
omega_K=5*1.1*10^-15;
Zmax=1;
Pmax=1;
Kmax=20;
a=10^3;
b=.2;
c=2;
d=10^-2;
% initial values of intergration
N0=2.5*10^11;
X0=.7*2.5*10^11;
S0=.3*2.5*10^11;
Y0=0;
V0=1;
Z0=10^-6;
P0=.3;
K0=1;
% simulation
sim('untitled_P_01_08')
% plotting
t=X(:,1);
x1=X(:,2);
s1=S(:,2);
y1=Y(:,2);
v1=V(:,2);
z1=Z(:,2);
p1=P(:,2);
k1=K(:,2);
```

```
plot (t,(x1+s1+y1)/N0,'c')
%third pass for second plot on simulation with 1/5*omega_k from figure 6
%days for simulation to run
days=4380;
% defining variables
alpha=5*10^9;
mu=.02;
k0=1*10^-12;
mu_Y=.6;
delta_Y=.6;
beta=150;
mu_V=6;
delta_V=5;
theta=10^-6;
rho=.1;
omega_P=1.4*10^-14;
omega_K=1/5*1.1*10^-15;
Zmax=1;
Pmax=1;
Kmax=20;
a=10^3;
b=.2;
c=2;
d=10^-2;
% initial values of intergration
N0=2.5*10^11;
X0=.7*2.5*10^11;
S0=.3*2.5*10^11;
Y0=0;
V0=1;
Z0=10^-6;
P0=.3;
K0=1;
% simulation
sim('untitled_P_01_08');
% plotting
t=X(:,1);
```

```
x1=X(:,2);
s1=S(:,2);
y1=Y(:,2);
v1=V(:,2);
z1=Z(:,2);
p1=P(:,2);
k1=K(:,2);
plot (t,(x1+s1+y1)/N0,'m')
% %first pass for plot of Omega_P in Figure 7
% %days for simulation to run
% days=4380;
%
% % defining variables
%
% alpha=5*10^9;
% mu=.02;
% k0=1*10^-12;
% mu_Y=.6;
% delta_Y=.6;
% beta=150;
% mu_V=6;
% delta_V=5;
% theta=10^-6;
% rho=.1;
% omega_P=1.4*10^-14;
% omega_K=1.1*10^-15;
% Zmax=1;
% Pmax=1;
% Kmax=20;
% a=10^3;
% b=.2;
% c=2;
% d=10^-2;
%
% % initial values of intergration
% N0=2.5*10^11;
% X0=.7*2.5*10^11;
```

```
% S0=.3*2.5*10^11;
% Y0=0;
% V0=1;
% Z0=10^-6;
% P0=.3;
% K0=1;
% % simulation
% sim('untitled_P_01_08')
% % plotting
% t=X(:,1);
% x1=X(:,2);
% s1=S(:,2);
% y1=Y(:,2);
% v1=V(:,2);
% z1=Z(:,2);
% p1=P(:,2);
% k1=K(:,2);
% plot (t,(x1+s1+y1)/N0,'k--')
%second pass for plot of 2*Omega_P in Figure 7
%days for simulation to run
days=4380;
% defining variables
alpha=5*10^9;
mu=.02;
k0=1*10^-12;
mu_Y=.6;
delta_Y=.6;
beta=150;
mu_V=6;
delta_V=5;
theta=10^-6;
rho=.1;
omega_P=2*1.4*10^-14;
omega_K=1.1*10^-15;
Zmax=1;
Pmax=1;
Kmax=20;
```

```
a=10^3;
b=.2;
c=2;
d=10^-2;
% initial values of intergration
N0=2.5*10^11;
X0=.7*2.5*10^11;
S0=.3*2.5*10^11;
Y0=0;
V0=1;
Z0=10^-6;
P0=.3;
K0=1;
% simulation
sim('untitled_P_01_08')
% plotting
t=X(:,1);
x1=X(:,2);
s1=S(:,2);
y1=Y(:,2);
v1=V(:,2);
z1=Z(:,2);
p1=P(:,2);
k1=K(:,2);
plot (t,(x1+s1+y1)/N0,'y')
%third pass for plot of 1/2*Omega_P in Figure 7
%days for simulation to run
days=4380;
% defining variables
alpha=5*10^9;
mu=.02;
k0=1*10^-12;
mu_Y=.6;
delta_Y=.6;
beta=150;
mu_V=6;
delta_V=5;
```

```
theta=10^-6;
rho=.1;
omega_P=.5*1.4*10^-14;
omega_K=1.1*10^-15;
Zmax=1;
Pmax=1;
Kmax=20;
a=10^3;
b=.2;
c=2;
d=10^-2;
% initial values of intergration
N0=2.5*10^11;
X0=.7*2.5*10^11;
S0=.3*2.5*10^11;
Y0=0;
V0=1;
Z0=10^-6;
P0=.3;
K0=1;
% simulation
sim('untitled_P_01_08')
% plotting
t=X(:,1);
x1=X(:,2);
s1=S(:,2);
y1=Y(:,2);
v1=V(:,2);
z1=Z(:,2);
p1=P(:,2);
k1=K(:,2);
plot (t,(x1+s1+y1)/N0,'k')
legend('P=.1','P=.8','Omega_K_&_P','5*Omega_K','1/5*Omega_K','2*Omega_P','.5*
Omega_P')
```

LIST OF REFERENCES

[1] Comerford, Amy, On Modeling HIV Infection Of CD4+ T cells, Masters Thesis, University of Central Florida, Orlando Fl, Spring Term 2006.

[2] Diekmann, O. & Heesterbeek, Mathematical Epidemiology of Infectious Diseases Model Building, Analysis, and Interpretation, New York Wiley (2002).

[3] Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J., On the Definition and Computation of the Basic Reproductive Ratio in Models for Infectious Diseases in Heterogeneous Population, J. Math Biol., 28 (1990), pp. 365-382.

[4] Freedman, Arnold S., Harris, Nancy Lee, Clinical and pathologic features of adult T cell lymphoma/leukemia, UpToDate, (2007), retrieved August 16, 2007 from http://www.utdol.com/utd/content/topic.do?topicKey=lymphoma/13762&view=print .

[5] Kartikeyan, S, Bharmal, R.N., Tiwari, R.P., Bisen, P.S., HIV and AIDS: Basic Elements and Priorities, The Netherlands Springer (2007).

[6] Katri, P., Ruan, S., Dynamics of human T-cell lymphotropic virus I (HTLV-I) infection of CD4+ T cells, C.R. Biologies, 327 (2004).

[7] Kirchner, Denise E., Using Mathematics to Understand HIV Immune Dynamics, Notices of the AMS, (February 1996), pp.191-202.

[8] Manns, Angela, Hisada, Michie, Grenade, Lois La, Human T-lymphotropic virus type I infection, The Lancet, 353, (1999).

[9] Pantaleo, Giuseppe, Graziosi, Cecilia, and Fauci, Anthony S., The Immunopathagenesis of Human Imunodeficiency Virus Infection, The New England Journal of Medicine, Volume 328 (1993), pp.327-335.

[10] Plemmons, Roderick, A Mathematical Study Of Malaria Models Of Ross And Ngwa , Masters Thesis, University of Central Florida, Orlando Fl, Fall Term 2006

[11] Pratt, Robert J, HIV & AIDS: A foundation for nursing and healthcare practice, London Arnold (2003)

[12] Rodin, E. Y., Murthy, D. N. P. and Page, N. W., Mathematical Modeling: A Tool for Problem Solving in Engineering, Physical, Biological and Social Sciences, Pergamon Press (1989).

[13] Scadden, David T, Freedman, Andrew R., Robertson, Paul, Human T-lymphotropic virus type I: Disease associations, diagnosis, and treatment, UpToDate, (2007), retrieved August 16, 2007 from http://www.utdol.com/utd/content/topic.do?topicKey=viral_in/25679&view=print .

[14] Scadden, David T, Freedman, Andrew R., Robertson, Paul, Human T-lymphotropic virus type I: Virology, Pathogenesis, and Epidemiology, UpToDate, (2007), retrieved October 30, 2007 from http://www.utdol.com/utd/store/index.do .

[15] Singh, Neeta, Epidemiological Models For Mutating Pathogen With Temporary Immunity, Doctoral Thesis, University of Central Florida, Orlando Fl, Spring Term 2006.

[16] Stevens, Christine Dorresteyn, Clinical Immunology and Serology, Philadelphia F.A. Davis Company (2003).

[17] Stilianakis, Nikolaos I., Dietz, Klaus, and Schenzle, Dieter, Analysis of a Model for the Pathogenesis of AIDS, Mathematical Biosciences, 145 (1997), pp. 27-46.

[18] Stilianakis, Nikolaos L, Seydel, Johannes, Modeling the T-cell Dynamics and Pathogenesis of HTLV-I Infection, Bulletin of Mathematical Biology, 61 (1999), pp.935-947.

[19] Stilianakis, Nikolaos I., Schenzle, Dieter, On the intra-host dynamics of HIV-1 infections, Mathematical Biosciences, 199 (2006), pp.1-25.

[20] Wang, Liancheng, Li, Michael Y., Kirschner, Denise, Mathematical analysis of the global dynamics of a model for HTLV-I infection and ATL progression, Mathematical Biosciences, 179 (2002), pp.207-217.

[21] Wessner, David, HIV and AIDS, San Francisco Pearson (2006).