DOKUZ EYLÜL UNIVERSITY
GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCE

THE NUMERICAL SOLUTIONS TO THE MODEL OF PRIMARY INFECTION BY HIV

by
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August, 2011
İZMİR

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M.Sc THESIS EXAMINATION RESULT FORM

We have read the thesis entitled **"THE NUMERICAL SOLUTIONS TO THE MODEL OF PRIMARY INFECTION BY HIV"** completed by **NAZİLE BUĞURCAN RÜZGAR** under supervision of **PROF. DR. ŞENNUR SOMALI** and we certify that in our opinion it is fully adequate, in scope and in quality, as a thesis for the degree of Master of Science.

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ABSTRACT

The local stability and the behaviors of the solution to the standard models of virus dynamics of primary HIV infection (Phillips, 1996) and the extended target-cell limited model which include infected cell depletion by immune effector cells (Stafford et al., 2000) are studied. If the basic reproduction number is smaller than 1, the virus is cleared and the disease dies out; if it is greater than 1, then the virus persists in the host, solutions approaches a chronic disease steady state. The results are supported by some experimental data which are given in Burg, D., et al., (2009).

Keywords: Human Immunodeficiency virus (HIV), Primary Infection, Viral Dynamics, Immune Control.

HIV'DEKİ TEMEL ENFEKSİYON MODELİNİN SAYISAL ÇÖZÜMLERİ

ÖZ

Virüs dinamiklerinin standart modellerinden temel HIV enfeksiyonu modeli (Phillips, 1996) ve enfeksiyonlu hücrelerin, bağışıklık efektör hücreleri tarafından azaltılmasını içeren, genişletilmiş sınırlı hedef hücre modelinin (Stafford et al., 2000) çözümlerinin davranışları ve bölgesel kararlılıkları çalışılmıştır. Eğer temel üretim sayısı 1'den büyük ise virüs temizlenir ve hastalık yok olur, eğer bu sayı 1'den küçük ise virüs konakçıda kalmaya devam eder ve çözümler kronik hastalık dengesine gelir. Sonuçlar, Burg, D. ve arkadaşlarının 2009 yılı yayınındaki bazı deneysel verilerle desteklenmektedir.

Anahtar Sözcükler: İnsan bağışıklık yetmezlik virüsü (HIV), Temel enfeksiyon, Virüs dinamikleri, Bağışıklık kontrolü.

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CHAPTER ONE
INTRODUCTION

1.1 Introduction

Primary human immunodeficiency virus (HIV) infection begins with exposure of the host to the virus and establishment of productive infection. Primary infection kinetics are characterized by the exponential increase in the number of virus particles in peripheral blood, reaching a peak followed by a spontaneous decline to the steady state level, which is often referred to as the viral setpoint (Kaufmann et al., 1998; Lindback et al., 2000). There is a corresponding decrease of the peripheral CD4+ T lymphocyte count from the initial steady state to a minimum which then increases to a new equilibrium that is lower than the preinfection value (Fauci, 1993). The subsequent chronic long-term stage is asymptomatic generally for a period of years. Immune system hyperactivation leads to its own destruction and culminates in acquired immunodeficiency syndrome (AIDS) (Mellors et al., 1996; Regoes et al., 2002) and immune activation (Deeks et al., 2004) at the setpoint have been shown to be predictors of disease evolution and progression to AIDS. Thus, it is clear that events during primary infection bear heavily on virus-host interactions, antiviral immune responses and pathogenesis (Centlivre et al., 2007).

HIV is able to lyse HIV-infected CD4+ T cells in vitro (Somasundaran and Robinson, 1987) and mathematical modeling of primary HIV kinetics has indicated that the control of infection may be attributed to viral-induced cytopathicity as well as to the availability of susceptible T cells (also known as the 'target-cell-limited' model) (Phillips, 1996). Stafford and his friends (2000) modified the target-cell-limited model by including a delayed immune response to predict viral kinetics beyond the transient viral peak.

Experimental studies have correlated the control of HIV during primary infection to the immune response (Koup et al., 1994). For example, CD8+ T cell depletion experiments in macaques abrogate the post-peak decline in viral load (Schmitz et al.,

1999). Also, high levels of HIV-specific CD8+ T cell frequencies were correlated with control of viral replication at early stages of infection in humans (Wilson et al., 2000).

In this thesis, we study the steady states and their local stability for the target-cell-limited model (Phillips, 1996)

$$\begin{aligned} \frac{dT}{dt} &= s - dT - \beta VT, \\ \frac{dI}{dt} &= \beta VT - \delta I, \\ \frac{dV}{dt} &= pI - cV, \end{aligned} \tag{1.1.1}$$

and the extended the target-cell-limited model (Burg et al., 2009) which is given by (1.1.2)-(1.1.5) by incorporating a term for the loss of infected cells that is dependent upon the infected cell frequency via a saturation function, which allows for the possible early control of the virus by cell-mediated immune response during the viral transient peak.

$$\frac{dT}{dt} = s - dT - \beta VT, \tag{1.1.2}$$

$$\frac{dI}{dt} = \beta VT - (\alpha d + k_0 E)I, \tag{1.1.3}$$

$$\frac{dV}{dt} = pI - cV, \tag{1.1.4}$$

$$\frac{dE}{dt} = a_E \frac{I}{\theta + I} - d_E E. \tag{1.1.5}$$

We show that the extended model can account for the varied HIV profiles during primary infection without the assumption of a delayed immune response against HIV infection after peak viremia.

This thesis is organized as follows: In Chapter 2, the structure of HIV and the connection between HIV and AIDS is given briefly. In Section 3.1, a mathematical model of the population dynamics of early HIV infection is formulated which ignores the immune response. In Section 3.2, we study the local stability of the

target-cell limited model by linearization technique and we also investigate the dynamical behaviors of the solution by reducing the model to a 2-D system. It is observed that the threshold value (or the basic reproduction number) governs whether the disease dies out or not. In Section 3.3, we discuss the behavior of solutions of the model by using the implicit trapezoid method by giving the numerical simulations for different values of loss rate constant of infected cells. In Section 4.1, the target-cell-limited model is extended to include immune response. In Section 4.2, the stability of steady states of the extended target-cell limited model is examined by reducing it to the 2-D system. The numerical simulations of the extended system for different threshold values are given in Section 4.3.

CHAPTER TWO
BIOLOGY OF HIV

2.1 Biology of HIV

Human Immunodeficiency Virus (HIV) infection, which ultimately leads to Acquired Immune Deficiency Syndrome (AIDS), is one of the most serious and widespread of human diseases. At the end of the twentieth century, it was estimated that 50 million people have been infected by HIV, 15 million had died from AIDS, and 35 million are currently infected (Nowak and May, 2000).

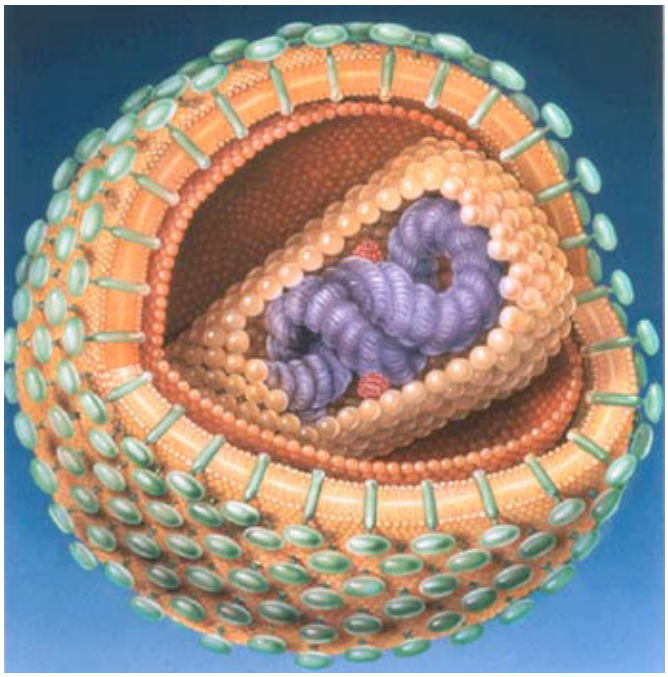

Figure 2.1 Structure of HIV (Sciencemuseum, 2011)

HIV infects cells in the immune system and the central nervous system. The main type of cell that HIV infects is the T helper lymphocyte. These cells play a crucial role in the immune system, by coordinating the actions of other immune system cells. A large reduction in the number of T helper cells seriously weakens the immune system. HIV infects the T helper cell because it has the protein CD4 on its surface, which HIV uses to attach itself to the cell before gaining entry. This is why the T

helper cell is sometimes referred to as a CD4+ lymphocyte. Once it has found its way into a cell, HIV produces new copies of itself, which can then go on to infect other cells. Over time, HIV infection leads to a severe reduction in the number of T helper cells available to help fight disease. The process usually takes several years.

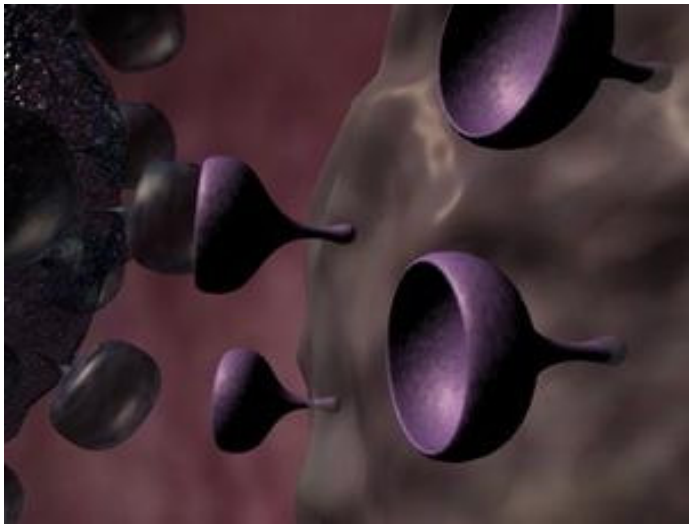

Figure 2.2 HIV and T lymphocyte with their receptors (Biyoloji dünyası, 2011)

The process of an HIV infection is as follows. Firstly, HIV enters the body, and cells with CD4 receptors become its targets, inside which it makes a DNA copy of its viral RNA in the presence of the enzyme reverse transcriptase (RT). After that, HIV falls into the class of so-called retroviruses. Retroviruses are RNA (ribonucleic acid) viruses, and to replicate (duplicate) they must make a DNA (deoxyribonucleic acid) copy of their RNA. It is the DNA genes that allow the virus to replicate. After infecting a cell, HIV uses an enzyme called reverse transcriptase to convert its RNA into DNA (deoxyribonucleic acid) and then proceeds to replicate itself using the cell's machinery. Then the viral DNA is inserted into the DNA of the T cell, following that the T cell produces viral particles to infect other infected T cells. Finally, the body will be susceptible to opportunistic infections due to the loss of humoral and cellular immune function. (Yang, Y., & Xiao, Y.)

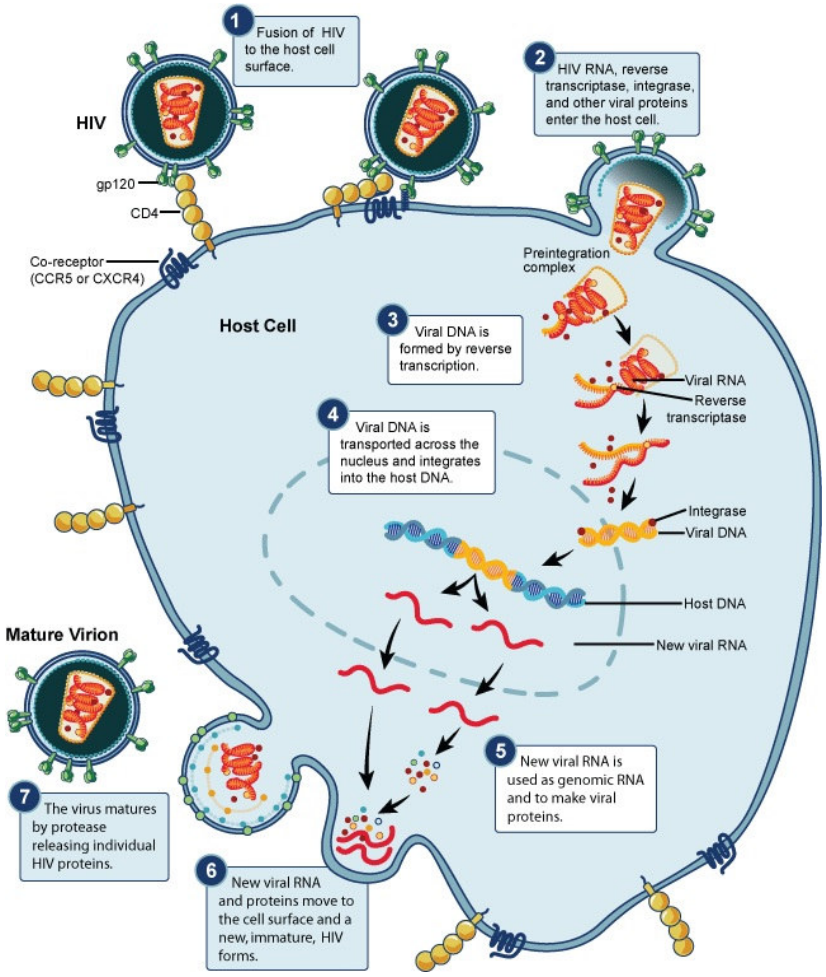

Figure 2.3 HIV replication cycle (National institute of allergy and infectious diseases, 2011)

Like all viruses, HIV can replicate only inside cells, commandeering the cell's machinery to reproduce. Only HIV and other retroviruses, however, once inside a cell, use an enzyme called reverse transcriptase to convert their RNA into DNA, which can be incorporated into the host cell's genes. Within the retrovirus family, HIV belongs to a subgroup known as lentiviruses, or "slow" viruses. Lentiviruses are known for having a long time period between initial infection and the beginning of serious symptoms. This is why there are many people who are unaware of their HIV infection, and unfortunately, can spread the virus to others.

2.1.1 The HIV-AIDS Connection

AIDS was first recognized in 1981 and has since become a major worldwide pandemic. Abundant evidence indicates that AIDS is caused by HIV, or the human immunodeficiency virus, which was discovered in 1983. By leading to the destruction and/or functional impairment of cells of the immune system, notably CD4+ T cells, HIV progressively destroys the body's ability to fight infections and certain cancers. AIDS is the final stage of HIV infection. A person infected with HIV is diagnosed with AIDS when he or she has one or more opportunistic infections, such as pneumonia or tuberculosis, and has a dangerously low number of CD4+ T cells (less than 200 cells per cubic millimeter of blood).

A healthy, uninfected person usually has 800 to 1.200 CD4+ T cells per cubic millimeter (mm^3) of blood. During untreated HIV infection, the number of these cells in a person's blood progressively declines. When the CD4+ T cell count falls below $200/mm^3$, a person becomes particularly vulnerable to the opportunistic infections and cancers that typify AIDS, the end stage of HIV disease. People with AIDS often suffer infections of the lungs, intestinal tract, brain, eyes, and other organs, as well as debilitating weight loss, diarrhea, neurologic conditions, and cancers such as Kaposi's sarcoma and certain types of lymphomas.

HIV infection can generally be broken down into four distinct stages: primary infection, clinically asymptomatic stage, symptomatic HIV infection, and progression from HIV to AIDS. But we only be interested in modeling the primary infection stage.

CHAPTER THREE
TARGET-CELL-LIMITED MODEL

3.1 Structure of the Target-Cell-Limited Model

Many mathematical models have been formulated on basic that govern the spread of a virus within an individual. These models have been used to determine the impact of the virus on the immune system and to test the responsiveness of the immune system function known as helper T cells (specifically, CD4+ T cells). The helper T cells are responsible for enhancing the production of antibodies by B cells. T cells and B cells are produced in the bone marrow (B=bone), but T cells migrate to the thymus (T=thymus), where they mature.

The basic model for T cell and virus dynamics is a system of three differential equations representing the interrelated changes over time in the concentration of target cells (T), infected cells (I) and serum viral (V) (Phillips, 1996). An important feature of this model is that it ignores the reaction of the immune system. This model also neglects virus mutations. In this model it is assumed that target cells (uninfected CD4+ T cells) are produced by the immune system at a constant rate s, and they become infected at a rate βVT after they have encountered free virus, so we obtain

$$\frac{dT}{dt} = s - dT - \beta VT , \tag{3.1.1}$$

where d is the per capita death rate of target cells T, and

$$\frac{dI}{dt} = \beta VT - \delta I , \tag{3.1.2}$$

where δ is the per capita death rate of infected cells I.

Each infected cell is taken over by the virus and the virus produces, on the average, N free virus particles, where $N \gg 1$. The rate of production of free viral particles from one infected cell is $p = N\delta$, and it leads

$$\frac{dV}{dt} = pI - cV, \tag{3.1.3}$$

where c is the per capita death rate of infected cells V.

By combining all of these we have the following system of differential equations which is called target-cell-limited model:

$$\begin{aligned} \frac{dT}{dt} &= s - dT - \beta VT, \\ \frac{dI}{dt} &= \beta VT - \delta I, \\ \frac{dV}{dt} &= pI - cV, \end{aligned} \tag{1.1.1}$$

where $T(0) = T_0$, $I(0) = I_0$ and $V(0) = V_0$ such that $T_0 > 0$, $I_0 = 0$ and $V_0 > 0$. All parameter values s, d, β, δ, p, c of the model are assumed non-negative.

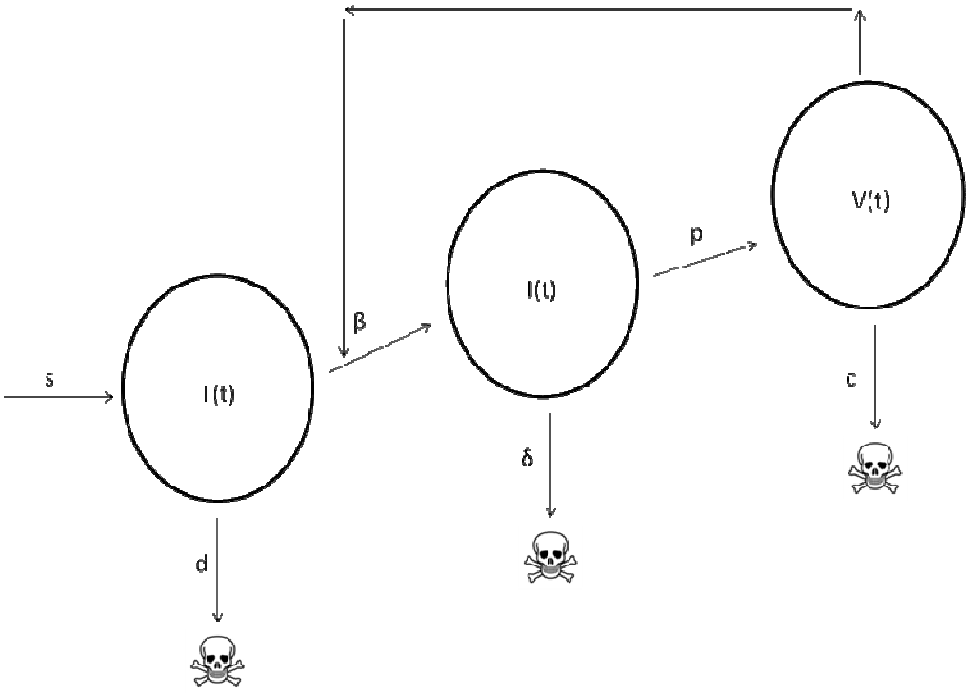

Figure 3.1 Diagram of the model

Table 3.1 The meaning of the parameters in the model (1.1.1)

Symbol	Interpretation
s	Constant influx rate of target cells
d	The target cell loss rate constant
β	The target cell infection rate constant
δ	Loss rate constant of infected cells
p	Viral production rate constant
c	Virus clearance rate constant

A healthy human adult has about 10^6 CD4+ T cells per milliliter of blood or 10^3 per microliter (mm^3) (Nowak and May, 2000). The units of T, I, V are number of cells or particles per milliliter of blood, and time is measured in days. For example, the units of s are the number of cells per milliliter produced per day, cells/mL/day. The units of β are mL/RNA/day, and the units of d and δ are mL/day. This model presents the primary phase of HIV which is seen in preliminary weeks, but progression to AIDS takes years.

3.2 Stability Analysis

We discuss a first-order autonomous system of differential equations of the form

$$\frac{dU}{dt} = F(U), \tag{3.2.1}$$

where

$$U = (u_1, ..., u_n)^T,$$

$$F(U) = (f_1(u_1, ..., u_n), ..., f_n(u_1, ..., u_n))^T,$$

and F does not depend explicitly on t.

Definition 3.2.1 An equilibrium solution (steady-state solution, fixed point, or critical point) of the differential system (3.2.1) is a constant solution U^* satisfying

$$F(U^*) = 0.$$

Theorem 3.2.1 Let U^* be an equilibrium point for the first order autonomous system (3.2.1). If all of the eigenvalues of the Jacobian matrix $F'(U^*)$ have negative real part, then U^* is asymptotically stable. If, on the other hand, $F'(U^*)$ has one or more eigenvalues with positive real part, then U^* is an unstable equilibrium.

Proof: Hoggatt, V.E., Jr., and Lind, D.A., (1969).

We now consider an 3×3 first-order autonomous system

$$\begin{aligned} \frac{du_1}{dt} &= f_1(u_1, u_2, u_3), \\ \frac{du_2}{dt} &= f_2(u_1, u_2, u_3), \\ \frac{du_3}{dt} &= f_3(u_1, u_2, u_3). \end{aligned} \tag{3.2.2}$$

In order to understand what happens to solutions of the system (3.2.2) near an equilibrium point (T_1, I_1, V_1) which satisfies

$$f_i(T_1, I_1, V_1) = 0 \quad \text{for} \quad i = 1, 2, 3, \tag{3.2.3}$$

we linearize the system near the equilibrium point. We introduce new variables

$$u_1 = T - T_1, \quad u_2 = I - I_1, \quad u_3 = V - V_1 \tag{3.2.4}$$

that move the equilibrium point to the origin. If T, I and V are close to the equilibrium point (T_1, I_1, V_1), then u_1, u_2 and u_3 are close to 0. Using (3.2.4), the system written in terms of u_1, u_2, u_3 is given as:

$$\begin{aligned} \frac{du_1}{dt} &= f_1(u_1 + T_1, u_2 + I_1, u_3 + V_1), \\ \frac{du_2}{dt} &= f_2(u_1 + T_1, u_2 + I_1, u_3 + V_1), \\ \frac{du_3}{dt} &= f_3(u_1 + T_1, u_2 + I_1, u_3 + V_1). \end{aligned}$$

We assume that $f_1,\ f_2,\ f_3$ are continuous and have continuous partial derivatives in some domain $D \subset \mathbb{R}^3$ containing the equilibrium point. By Taylor expansion about the point (T_1, I_1, V_1), we write $f_1,\ f_2,\ f_3$ in the form

$$f_1(u_1+T_1, u_2+I_1, u_3+V_1) = f_1(T_1, I_1, V_1) + \frac{\partial f_1}{\partial T}u_1 + \frac{\partial f_1}{\partial I}u_2 + \frac{\partial f_1}{\partial V}u_3 + \ldots$$
$$f_2(u_1+T_1, u_2+I_1, u_3+V_1) = f_2(T_1, I_1, V_1) + \frac{\partial f_2}{\partial T}u_1 + \frac{\partial f_2}{\partial I}u_2 + \frac{\partial f_2}{\partial V}u_3 + \ldots$$
$$f_3(u_1+T_1, u_2+I_1, u_3+V_1) = f_3(T_1, I_1, V_1) + \frac{\partial f_3}{\partial T}u_1 + \frac{\partial f_3}{\partial I}u_2 + \frac{\partial f_3}{\partial V}u_3 + \ldots,$$

where "…" are terms of higher order in $u_1,\ u_2,\ u_3$. If $u_1,\ u_2$ and u_3 are sufficiently small we would expect that we can ignore the higher order terms, and using (3.2.3) we write the linearized system at the equilibrium point (T_1, I_1, V_1) as:

$$\frac{dU}{dt} = JU\ ,$$

where

$$U = \left(u_1, u_2, u_3\right)^T$$

and J is the Jacobian matrix evaluated at (T_1, I_1, V_1)

$$J = \begin{pmatrix} \dfrac{\partial f_1(T_1,I_1,V_1)}{\partial T} & \dfrac{\partial f_1(T_1,I_1,V_1)}{\partial I} & \dfrac{\partial f_1(T_1,I_1,V_1)}{\partial V} \\ \dfrac{\partial f_2(T_1,I_1,V_1)}{\partial T} & \dfrac{\partial f_2(T_1,I_1,V_1)}{\partial I} & \dfrac{\partial f_2(T_1,I_1,V_1)}{\partial V} \\ \dfrac{\partial f_3(T_1,I_1,V_1)}{\partial T} & \dfrac{\partial f_3(T_1,I_1,V_1)}{\partial I} & \dfrac{\partial f_3(T_1,I_1,V_1)}{\partial V} \end{pmatrix}.$$

We use this linearized system to study the behavior of solutions of the nonlinear system near (T_1, I_1, V_1). As always, the derivative of a nonlinear function provides only a local approximation. Hence the solutions of the linearized system are close to solutions of the nonlinear system only near the equilibrium point. How close to the equilibrium point we must be for the linear approximation to be any good depends on the size of the nonlinear terms.

We can find the equilibrium points of the system (1.1.1) by setting the right-hand sides of the equations to zero and solving for T, I, V. The equilibrium points are

$$(T_1, I_1, V_1) = (\frac{c\delta}{\beta p}, \frac{s}{\delta} - \frac{cd}{\beta p}, \frac{ps}{c\delta} - \frac{d}{\beta}),$$

and

$$(T_2, I_2, V_2) = (s/d, 0, 0).$$

Of these, only the point

$$(\frac{c\delta}{\beta p}, \frac{s}{\delta} - \frac{cd}{\beta p}, \frac{ps}{c\delta} - \frac{d}{\beta}),$$

where

$$T_1 = \frac{c\delta}{\beta p}, \quad I_1 = \frac{s}{\delta} - \frac{cd}{\beta p}, \quad V_1 = \frac{ps}{c\delta} - \frac{d}{\beta}$$

has all three coordinates nonzero, so the target cells, infected cells and virus can coexist in equilibrium at these concentrations. The Jacobian matrix J for this system at (T_1, I_1, V_1) is

$$\begin{pmatrix} -\frac{\beta ps}{c\delta} & 0 & -\frac{c\delta}{p} \\ \frac{\beta ps}{c\delta - d} & -\delta & \frac{c\delta}{p} \\ 0 & p & -c \end{pmatrix}.$$

The characteristic polynomial of the matrix is

$$p(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 \ , \tag{3.2.5}$$

where

$$a_1 = c + \delta + \frac{p\beta s}{c\delta}, \quad a_2 = \frac{\beta ps}{c} + \frac{\beta ps}{\delta}, \quad a_3 = \beta ps - cd\delta.$$

For a system consisting of more than two differential equations, local asymptotic stability depends on the Routh-Hurwitz criteria described in Theorem 3.2.1 (Gantmacher, 1964). The stability criteria depend on the eigenvalues of the Jacobian matrix evaluated at (T_1, I_1, V_1). If all of the eigenvalues are negative or have negative real parts, then the equilibrium is locally asymptotically stable. The eigenvalues are determined by finding the roots of the characteristic equation, but characteristic

equation (3.2.5) of the target-cell-limited model is a cubic equation and it is difficult to derive the expression of eigenvalues from the equation, but the Routh-Hurwitz criteria can be applied to show local asymptotic stability.

Theorem 3.2.1 (Routh-Hurwitz Criteria)
Given the polynomial,

$$p(\lambda) = \lambda^n + a_1\lambda^{n-1} + ... + a_{n-1}\lambda + a_n \ ,$$

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

$$H_1 = (a_1), \quad H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, \quad H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix},$$

and

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & \dots & 0 \\ a_3 & a_2 & a_1 & 1 & \dots & 0 \\ a_5 & a_4 & a_3 & a_2 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \dots & \vdots \\ 0 & 0 & 0 & 0 & \dots & a_n \end{pmatrix},$$

where $a_j = 0$ if $j > n$. All of the roots of the polynomial $p(\lambda)$ are negative or have negative real parts iff the determinants of all Hurwitz matrices are positive:

$$\det H_j > 0, \ j = 1,...,n.$$

Proof: (Gantmacher, 1964).

When $n = 3$, the Routh-Hourwitz criteria simplify to

$$\det H_1 = a_1 > 0,$$

$$\det H_2 = a_1a_2 - a_3 > 0,$$

$$\det H_3 = a_1a_2a_3 - a_3^2 > 0$$

or

$$a_1 > 0, \ a_1a_2 > a_3, \ a_3 > 0 \ . \qquad (3.2.6)$$

For polynomial of degree 3, $p(\lambda)$ given in (3.2.5), we get

$$a_1 = c + \delta + \frac{\beta ps}{c\delta},$$

$$a_2 = \frac{\beta ps}{c} + \frac{\beta ps}{\delta},$$

$$a_3 = \beta ps - cd\delta.$$

They must satisfy the conditions (3.2.6) to have locally asymptotic stable equilibrium point (T_1, I_1, V_1). Since all parameters in system (1.1.1) are positive, the conditions $a_1 > 0$ and $a_1 a_2 > a_3$ are satisfied as follows:

$$c + \delta + \frac{\beta ps}{c\delta} > 0,$$

$$\beta ps\left(\frac{c}{\delta} + \frac{\delta}{c} + 1\right) + \frac{\beta ps^2}{c\delta}\left(\frac{1}{c} + \frac{1}{\delta}\right) > -cd\delta.$$

The last condition $a_3 > 0$ gives $\beta ps - cd\delta > 0$. Hence the polynomial (3.2.5) has roots which are all negative or have negative real parts for $R_0 = \frac{\beta ps}{cd\delta} > 1$, that is, the equilibrium point

$$\left(\frac{c\delta}{\beta p}, \frac{\beta ps - cd\delta}{\delta\beta p}, \frac{\beta ps - cd\delta}{\delta\beta c}\right)$$

is locally asymptotically stable. If $R_0 < 1$ then,

$$\beta ps - cd\delta < 0$$

which is not possible since the number of infected cells and viruses cannot be negative, hence there is no infected cells or virus in blood, that is, virus is cleared and disease dies out. If, however, $R_0 > 1$ then the virus persists in the host, solutions approaches a chronic disease steady state. Thus, R_0, is a threshold parameter for the model. The basic reproduction number, denoted R_0, is "the expected number of secondary cases produced, in a completely susceptible population, by a typical infective individual." If $R_0 < 1$, then on average an infected individual produces less than one new infected individual over the course of its infectious period, and the infection cannot grow. Conversely, if $R_0 > 1$, then each infected individual produces, on average, more than one new infection, and the disease can invade the population.

We said that the characteristic equation (3.2.5) of the target-cell limited model is a cubic equation and it is difficult to derive the expression of eigenvalues from the equation. So, in order to investigate the dynamical behaviors when the solution converges to a steady state, we first reduce the model to a 2-dimensional system.

Human immunodeficiency virus (HIV) is always working at maximal capacity (compared to the other cells), so it may approach a steady state very quickly. After this transitional period, its concentration V may be considered as constant, *i.e.,* $\frac{dV}{dt}=0$. Since this variable is still involved in the complex system, this state is considered as quasi-steady state. The condition (Nowak et al., 1997)

$$\frac{dV}{dt}=0 \quad \text{that is,} \quad V=\frac{pI}{c}$$

is called the quasi-steady-state assumption and allows one to replace the differential equation for the change of V by an algebraic equation describing how V depends on the other variables of the system. Hence the system (1.1.1) can be simplified to

$$\begin{aligned}\frac{dT}{dt}&=s-(d+\beta' I)T,\\ \frac{dI}{dt}&=(\beta' T-\delta)I,\end{aligned} \tag{3.2.7}$$

where $\beta'=\frac{\beta p}{c}$.

We can find the equilibrium points of the 2-D system by setting the right-hand sides of the equations to zero and solving for T and I. The equilibrium points are

$$(\tilde{T}_1,\tilde{I}_1)=(\frac{\delta}{\beta'},\frac{s}{\delta}-\frac{d}{\beta'}),$$

$$(\tilde{T}_2,\tilde{I}_2)=(\frac{s}{d},0).$$

The Jacobian matrix J at the equilibrium point $(\tilde{T}_1,\tilde{I}_1)$ is given as

$$J=\begin{pmatrix}-\frac{\beta ps}{\delta c} & -\delta\\ \frac{\beta ps}{c\delta}-d & 0\end{pmatrix}. \tag{3.2.8}$$

The characteristic polynomial of the Jacobian matrix is

$$p(\lambda) = \lambda^2 + \frac{\beta ps}{\delta c}\lambda + \frac{\beta ps - cd\delta}{c}.$$

Solving $p(\lambda) = 0$, we find the eigenvalues which are given by

$$\lambda_{1,2} = \frac{(-\beta ps / c\delta) \pm \sqrt{\Delta}}{2},$$

where

$$\Delta = (\frac{\beta ps}{c\delta})^2 - 4(\frac{\beta ps - cd\delta}{c})$$

and real part of $\lambda_{1,2}$ are negative when $\Delta < 0$. Hence linearized system of (1.1.1) has complex eigenvalues

$$\lambda = a \pm ib,$$

where

$$a = -\frac{\beta ps}{2c\delta},$$

$$b = \frac{1}{2}\sqrt{\left(\frac{\beta ps}{c\delta}\right)^2 - 4\left(\frac{\beta ps - cd\delta}{c}\right)}.$$

Since $a < 0,$ all of the eigenvalues of the Jacobian matrix (3.2.8) are complex numbers with negative real parts. In this case, origin is called spiral sink for the linear system, that is, the solutions spiral toward to origin as $t \to \infty$. The solution curves which are sketched in the phase plane are shown in Figure 3.2. For the nonlinear system, solutions that start near the equilibrium point $(T, I) = (\tilde{T}_1, \tilde{I}_1)$ approach it as $t \to \infty$. Hence we say that $(\tilde{T}_1, \tilde{I}_1)$ is a spiral sink.

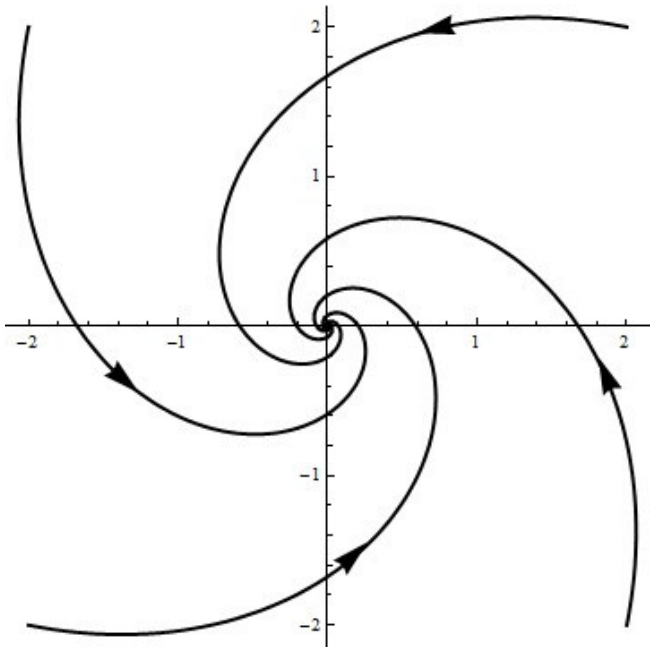

Figure 3.2 Example phase plane for spiral sink

We can write Δ in terms of $R_0 = \frac{s\beta'}{d\delta}$, that is,

$$\Delta = \left(\frac{\beta ps}{c\delta}\right)^2 - 4\left(\frac{\beta ps - cd\delta}{c}\right)$$
$$= d(dR_0^{\,2} - 4\delta R_0 + 4\delta).$$

If $\Delta < 0$ then

$$(dR_0^{\,2} - 4\delta R_0 + 4\delta) < 0$$

and

$$R_{0,1} = \frac{2}{d}\left(\delta + \sqrt{\delta(\delta - d)}\right),$$
$$R_{0,2} = \frac{2}{d}\left(\delta - \sqrt{\delta(\delta - d)}\right).$$

The sign of inside the square root is positive and making sign table we have;

$$\frac{2}{d}\left(\delta - \sqrt{\delta(\delta - d)}\right) < R_0 < \frac{2}{d}\left(\delta + \sqrt{\delta(\delta - d)}\right).$$

Since the death rate of target cells d is much smaller than δ, the left side of the above inequality can be approximated by $2(-f'(0))$, where $f(x)=\sqrt{\delta^2-\delta x}$. The right side can be approximated by $\frac{4\delta}{d}$, s.t.

$$\frac{2}{d}(\delta+\sqrt{\delta(\delta-d)}\approx\frac{4\delta}{d}.$$

Therefore, $\Delta<0$ is approximately equivalent to the inequality $1<R_0<\frac{4\delta}{d}$. The above inequality holds in the case of chronic infection, since d is relatively small compared with δ. Thus we claim that $\Delta<0$ in the target-cell-limited model.

3.3 The Application of Implicit Trapezoid Rule

In this section, we investigate the behavior of solutions of the target-cell-limited model by using the implicit trapezoid method which is A-stable. The advantage of an A-stable method is that the parasitic solutions will always decay, regardless of the step size. Hence they can be used to solve stiff systems.

The Implicit Trapezoid method is given by

$$Y_{i+1}=Y_i+\frac{h}{2}\left[F(Y_i)+F(Y_{i+1})\right],\quad i=0,1,2,...,n, \tag{3.3.1}$$

where

$$Y=\begin{pmatrix}T\\I\\V\end{pmatrix},\ F(Y)=\begin{pmatrix}s-dT-\beta VT\\ \beta VT-\delta I\\ pI-cV\end{pmatrix}$$

on the grid

$$\Omega=\{t_i:t_i=ih,\ \ i=0,1,...,n\ ,\ h=\frac{t_{\max}}{n}\}\ .$$

Thus we obtain $(n+1)$ algebraic non-linear equations for the $(n+1)$ unknowns. For this reason we next consider the application of Newton's method to (3.3.1). The recursion of Newton's method for the system $G(z)=0$ is defined by

$$z_{k+1} = z_k - \left[G'(z_k)\right]^{-1} G(z_k),$$

where $G'(z)$ is the Jacobian matrix. By using the above consideration, we obtain that

$$Y_{i+1} = Y_i + hJ^{-1}(Y_i)F(Y_i), \quad i = 0,1,2,...,n, \tag{3.3.2}$$

where

$$J(Y_i) = I - \frac{h}{2}F'(Y_i)$$

and I is 3×3 identity matrix.

The second order convergence property of Implicit Trapezoid method does not change. The observed orders $ord_i(h)$ are computed using the formulas

$$ord_1(h) = \log\left(\frac{T_h - T_{h/2}}{T_{h/2} - T_{h/4}}\right) / \log 2,$$

$$ord_2(h) = \log\left(\frac{I_h - I_{h/2}}{I_{h/2} - I_{h/4}}\right) / \log 2,$$

$$ord_3(h) = \log\left(\frac{V_h - V_{h/2}}{V_{h/2} - V_{h/4}}\right) / \log 2,$$

where $T_{h/4}$, $T_{h/2}$, T_h, $I_{h/4}$, $I_{h/2}$, I_h, $V_{h/4}$, $V_{h/2}$, V_h are approximate solutions that are computed by $h/4$, $h/2$ and h respectively. They are given in the Table 3.2.

Table 3.2 Order of the method for *T, I, V* .

$ord_1(h)$	$ord_2(h)$	$ord_3(h)$
2.01908	2.00104	2.01268

Solving (3.3.2) by using Mathematica, for different infected cell death rates

$$\delta = (0.1)k, \quad k = 0,1,2,...,10$$

and using parameter values $I_0 = 0$ cells/mL, $V_0 = 10^{-6}$ RNA copies/mL, $d = 10^{-2}$/day, $T_0 = 10^4$ cells/mL, $s = dT_0$ cells/mL/day, $c = 3$/day, $\beta = 1.3\times10^{-6}$ mL/RNA/day, $p = 10^3$ RNA copies/cell/day , we have the following simulations which show behavior of solutions T, I, V approximately.

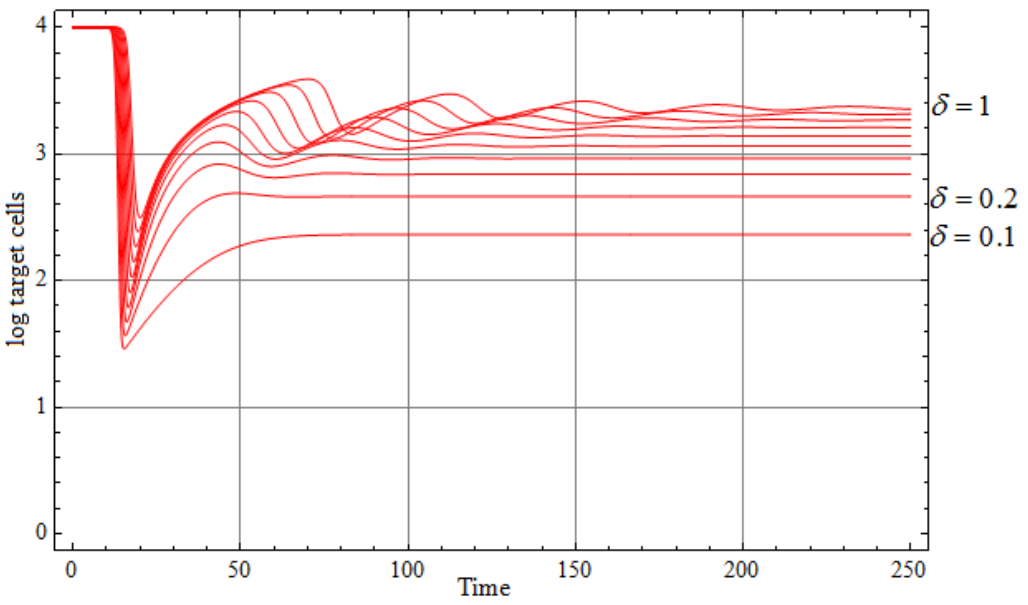

Figure 3.3 Logarithm of number of target cells T with base 10, in 250 days for different infected cell death rates $\delta = (0.1)k,\ \ k = 1,2,...,10$

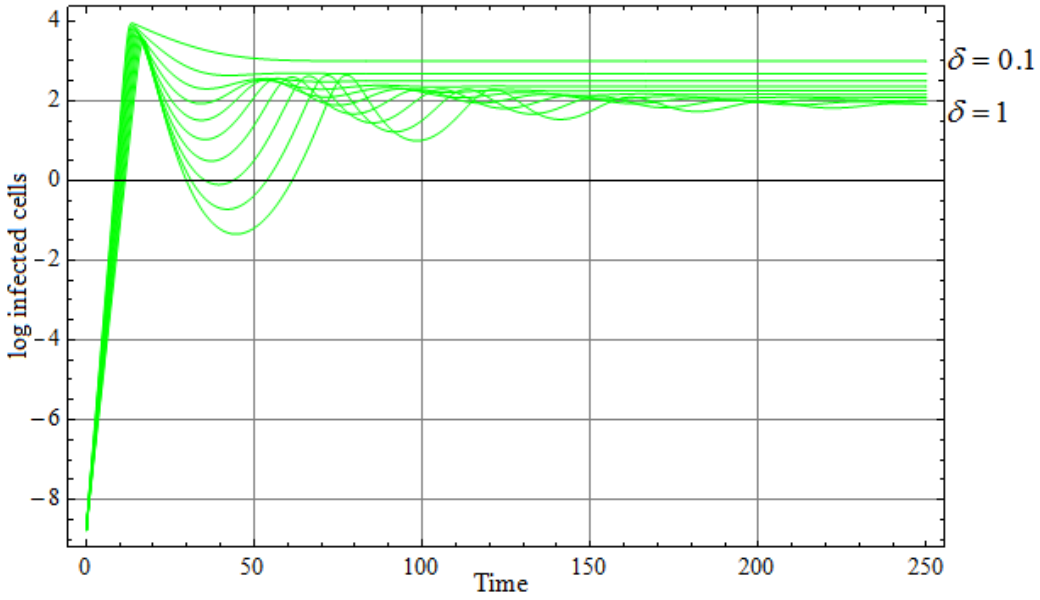

Figure 3.4 Logarithm of number of infected cells I with base 10, in 250 days for different infected cell death rates $\delta = (0.1)k,\ \ k = 1,2,...,10$

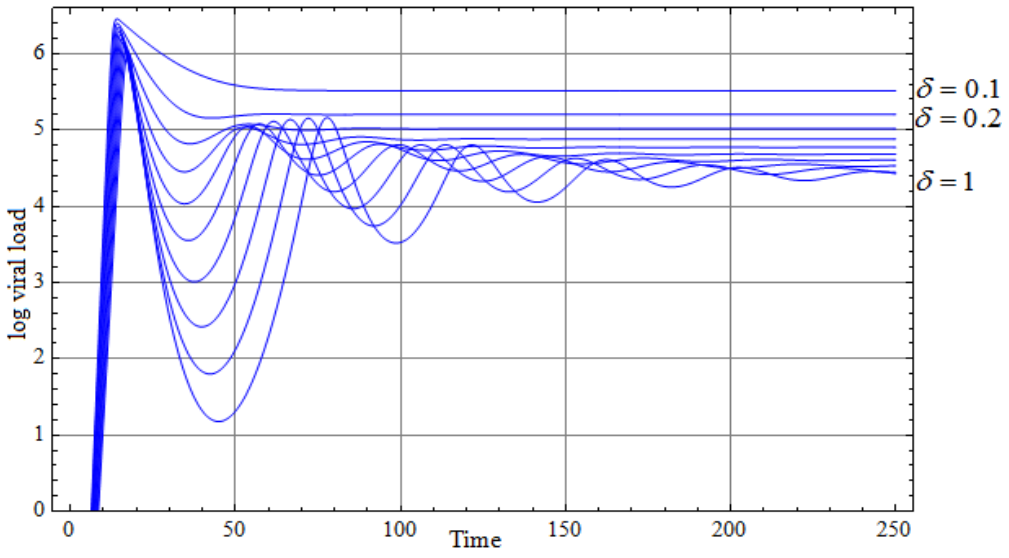

Figure 3.5 Logarithm of number of viruses V with base 10, in 250 days for different infected cell death rates $\delta = (0.1)k,\ \ k = 1, 2, ..., 10$

As it seems in last figure, for a large value of δ, the target-cell-limited model predicts that viral load reaches the steady state through damped oscillations. When δ decreases, oscillations become less apparent, but the viral load steady state is considerably increased.

CHAPTER FOUR
EXTENDED MODEL

4.1 Extended Model With Immune Control

We extend the target-cell-limited model (1.1.1) to include infected cell depletion by immune effector cells, $E(t)$, with a depletion rate $k_0 EI$. The extended model is then:

$$\frac{dT}{dt} = s - dT - \beta VT \tag{1.1.2}$$

$$\frac{dI}{dt} = \beta VT - (\alpha d + k_0 E)I \tag{1.1.3}$$

$$\frac{dV}{dt} = pI - cV \tag{1.1.4}$$

$$\frac{dE}{dt} = a_E \frac{I}{\theta + I} - d_E E \tag{1.1.5}$$

where E represents effector cells (e.g., CD8+ T cells) that are stimulated with a rate constant a_E, in a saturation dependent function of the level of infected cells I with a half-maximal stimulation threshold θ, and are lost with a rate constant d_E. The term αdI in equation (1.1.3) represents direct viral cytopathicity above normal target death rate d when $\alpha > 1$, or the absence of a viral cytopathic effect when $\alpha = 1$. However, since data on the number of effector cells is not available, there are a large number of parameters that cannot be currently estimated. Therefore, we simplify the model in equations (1.1.2)-(1.1.5) by using a quasi-steady state approximation over equation (1.1.5), assuming that the dynamics of effector cell stimulation is faster than the time course of acute HIV resolution (about 1 month). This derives a model similar to the target-cell-limited model, see equations (1.1.1):

$$\begin{aligned} \frac{dT}{dt} &= s - dT - \beta VT \\ \frac{dI}{dt} &= \beta VT - \left(\alpha d + k \frac{I}{I + \theta} \right) I \\ \frac{dV}{dt} &= pI - cV \end{aligned} \tag{4.1.1}$$

with only the difference being that the productively infected cell death rate is dependent on the infected cell concentration. The infected cell death rate constant in the target-cell-limited model, δ (eqn. (3.1.2)), is replaced with $\delta(I) = \alpha d + kI/(I+\theta)$ (Burg, 2006). The saturation function, $kI/(I+\theta)$ where $k = k_0 a_E / d_E$ (eqns. (1.1.3)-(1.1.5)) fluctuates between 0 (before infection) to a maximum value (k) of activity potential mimicking the loss of infected cells induced by an immune response stimulated by infected cells. Of note, the target-cell-limited model is a special case of the extended model where $k = 0$ or $\theta = 0$ and hence $\delta(I) = const.$ By using implicit trapezoid method, numerical simulations of the extended model with different values of θ are shown in Figures 4.1- 4.3.

4.2 Steady States And Stability Results

The dynamical behavior of the model (4.1.1) as the viral load approaches the steady state is determined by the eigenvalues of the system (λ), which are determined by the cubic equation $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0.$ Since the cubic system of equations is complex, it is difficult to derive the eigenvalues or display the phase-plane/nullclines analysis using the 3-D equations. Therefore, assuming a rapid time scale for the free virus dynamics, $V \approx pI/c$ (Spouge et al., 1996; Nowak et al., 1997), we simplify equations in (4.1.1) as follows:

$$\frac{dT}{dt} = s - (d + \beta' I)T,$$
$$\frac{dI}{dt} = (\beta' T - \alpha d - k\frac{I}{I+\theta})I,$$

where $\beta' = \beta p / c$. For the 2-D system there exists an uninfected steady state which is defined by ($T > 0,\ I = 0$):

$$(\overline{T}_1, \overline{I}_1) = (\frac{s}{d}, 0).$$

The infected steady state is determined by a quadratic equation

$$AI^2 + BI + C = 0,$$

where

$$A = \beta'(\alpha d + k),$$
$$B = \alpha d^2 - \beta' s + \alpha d\theta\beta' + kd,$$
$$C = (\alpha d^2 - \beta' s)\theta.$$

We define a new parameter, $\sigma = \beta' s / (\alpha d^2)$ which is the same as the basic reproductive ratio defined in the target-cell-limited model except that δ is replaced here with αd. When $\sigma < 1,$ we have $C > 0,$ thus, $B > 0.$ In this case, the infected steady state does not exist. When $\sigma > 1,$ we have $C < 0,$ thus, $B^2 - 4AC > 0.$ In this case, there exists a unique infected steady state $(\bar{I}_2)$ irrespective of the sign of B:

$$\bar{I}_2 = \frac{-B + \sqrt{B^2 - 4AC}}{2A}$$

and the corresponding target cell steady state is

$$\bar{T}_2 = \frac{s}{d + \beta'\bar{I}_2}.$$

The characteristic equation of the uninfected steady state is given by

$$\zeta^2 + (d + \alpha d - \frac{\beta' s}{d}) + \alpha d^2 - \beta' s = 0,$$

where ζ is the eigenvalue. There are two solutions for the eigenvalue:

$$\zeta_1 = -d,$$
$$\zeta_2 = \frac{\beta' s}{d} - \alpha d = (\sigma - 1)\alpha d.$$

Therefore, if $\sigma < 1$, then only the uninfected steady state exists and it is locally asymptotically stable. If $\sigma > 1,$ the infection-free steady state is not stable. For the infected steady state $(\bar{T}_2, \bar{I}_2) = (\frac{s}{d + \beta'\bar{I}_2}, \bar{I}_2)$, the corresponding characteristic equation is

$$\lambda^2 + \mu\lambda + \nu = 0,$$

where

$$\mu = d + \beta'\bar{I}_2 + k\theta\frac{\bar{I}_2}{(\bar{I}_2 + \theta)^2},$$
$$\nu = (d + \beta'\bar{I}_2)k\theta\frac{\bar{I}_2}{(\bar{I}_2 + \theta)^2} + (\beta')^2\bar{I}_2\bar{T}_2. \qquad (4.2.1)$$

It is clear that $\mu > 0$ and $\nu > 0$, thus, the infected steady state $(\bar{T}_2, \bar{I}_2)$ is locally asymptotically stable whenever it exists (i.e., when $\sigma > 1$).

4.3 Numerical Simulation

In this section, we investigate the behavior of solutions of the extended model by using the implicit trapezoid method which is A-stable. By using Mathematica with different values of $\theta = 3k$, $k = 0,1,2,...,10$ and using the same parameter values as in Figures 3.3-3.5 and $\alpha = 1$ and $k = 1$/day, we have the following simulations which shows behavior of solutions T, I, V approximately. $\theta = 0$ is a special case representing the target-cell-limited model.

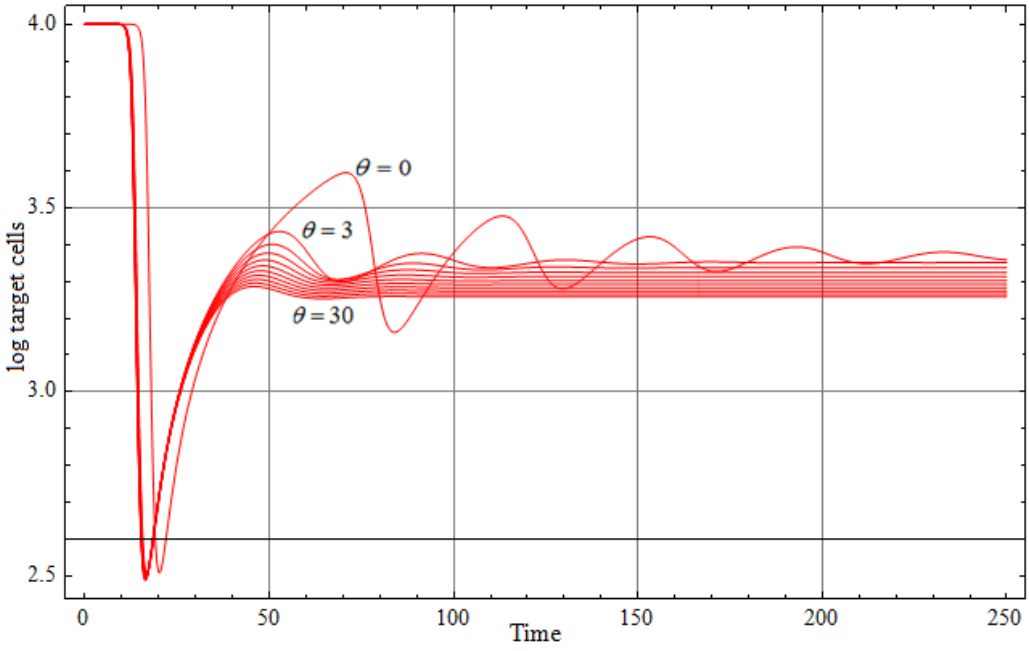

Figure 4.1 Logarithm of number of target cells T with base 10, in 250 days for different infected cell death rates $\theta = 3k$, $k = 0,1,...,10$.

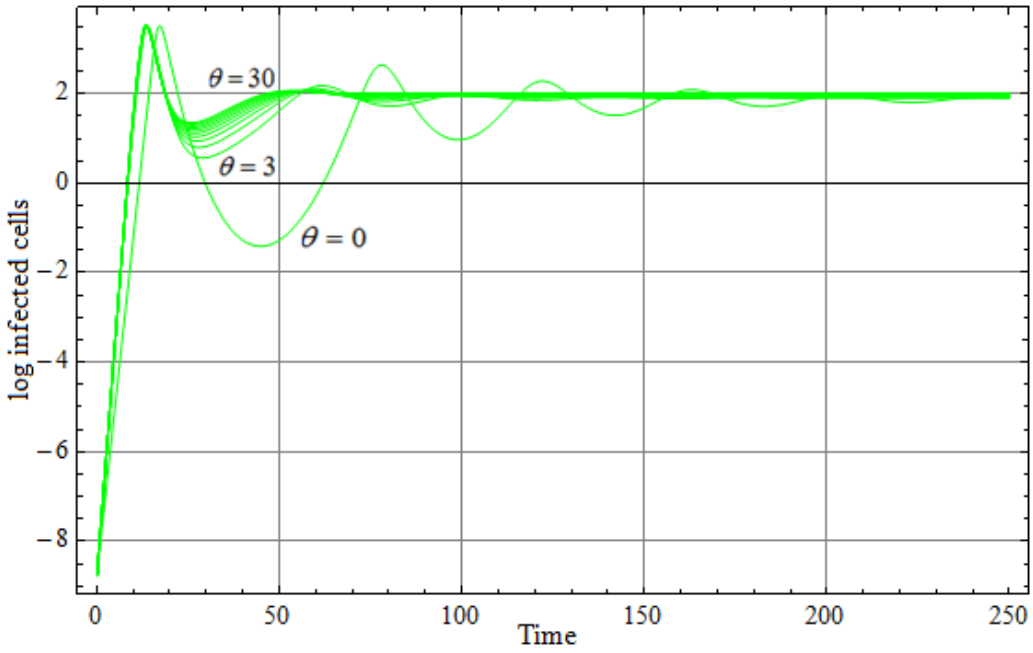

Figure 4.2 Logarithm of number of infected cells I with base 10, in 250 days for different infected cell death rates $\theta = 3k,\ k = 0,1,...,10$.

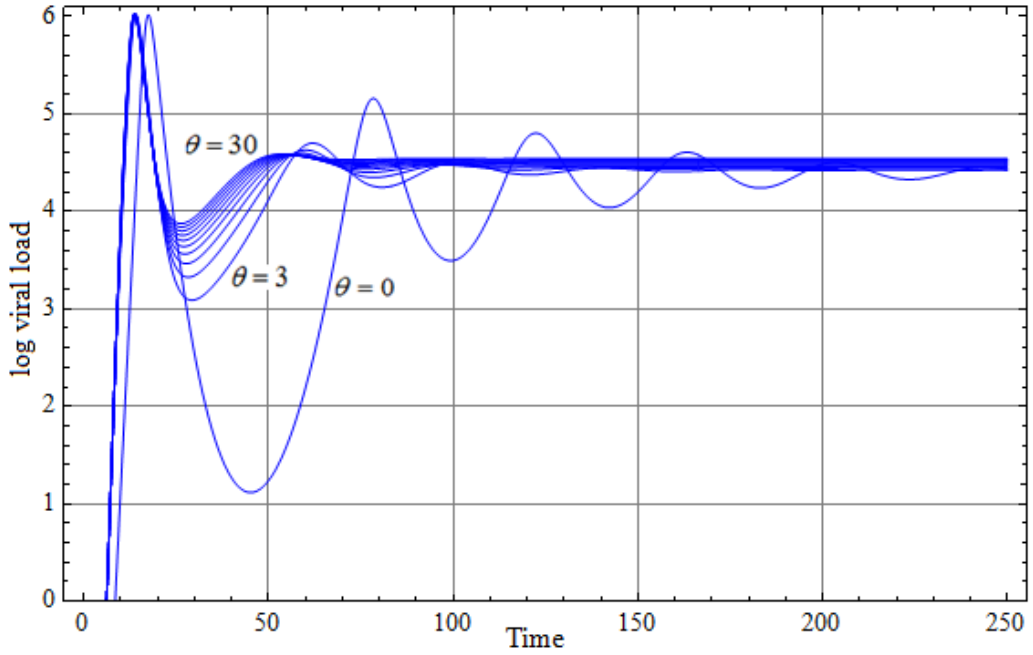

Figure 4.3 Logarithm of number of viruses V with base 10, in 250 days for different infected cell death rates $\theta = 3k,\ k = 0,1,...,10$. When θ is small, viral load reaches the steady state through frequent damped oscillations. When θ increases, the oscillations become less apparent, with only a slight increase of the predicted viral load.

In order to display fewer oscillations during the approach to the steady state one needs to obtain a higher value for μ. Increases in parameter θ can accomplish this without changing other parameters. Decreasing δ in the target-cell-limited model can also diminish the oscillations but it induces a considerably higher viral load steady state. Although we cannot compare the increases in the steady state viral load directly since not all parameters in the models are the same, we show that the steady state viral load in the target-cell-limited model is sensitive to changes in δ, whereas the steady state viral load in our model is not sensitive to changes in θ. This allows us to dampen the oscillation (increase θ) an simultaneously not to increase the steady state viral load level significantly.

CHAPTER FIVE
CONCLUSION

We have shown that a simple target-cell-limited model can be modified to include infected cell depletion by immune effector cells. Two models have been proposed here, and results agree with observed data and evidence in the literature. Though much research must be done to determine the complete dynamic of AIDS, simple models such as these may help to further the understanding of the pathogenesis of HIV.

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