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# On Modeling HIV Infection Of Cd4+ T Cells

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# ON MODELING HIV INFECTION OF CD4+ T CELLS

by

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# ABSTRACT

We examine an early model for the interaction of HIV with CD4+ T cells in vivo and define possible parameters and effects of said parameters on the model. We then examine a newer, more simplified model for the interaction of HIV with CD4+ T cells that also considers four populations: uninfected T cells, latently infected T cells, actively infected T cells, and free virus. The stability of both the disease free steady state and the endemically infected steady state are examined utilizing standard methods and the Routh-Hurwitz criteria. We show that if $N$, the number of infectious virions produced per actively infected T cell, is less than a critical value, $N_{crit}$, then the uninfected state is the only steady state in the non negative orthant, and this state is stable. We establish an expression for $N_{crit}$. If $N > N_{crit}$, then the uninfected steady state is unstable, and the endemically infected state can be stable or unstable, depending on the value of the parameters utilized.

This thesis is dedicated to Dr. Wendy Bush without whom
“we” would never have made it through grad school.

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# CHAPTER 1: INTRODUCTION

Epidemiology is the study of mathematical models that explain and predict the spread of infectious diseases. These models are important in predicting the effectiveness of possible preventions or cures to a disease such as immunization, vaccination, quarantine, and education. Since the early times of the Greek and Roman cultures, scientists and mathematicians have sought to understand and control the ways that diseases are transmitted. Initially, individuals sought to model specific diseases that plagued mankind. For example, Daniel Bernoulli formulated a smallpox model in 1760, a time when smallpox was killing thousands. W.H. Hamer, in an attempt to explain recurring measles epidemics, formulated a discrete time model for the disease in 1906. Sir R.A. Ross created a differential equation model for malaria in 1911. These individuals laid the ground work for mathematical models that divide the population into compartments or epidemiological classes based on whether individuals were not sick, sick and not infectious, or sick and infectious, immune to sickness, etc. (Brauer & Castillo-Chavez, 2001). These compartments will be examined in this paper.

A. G. McKendrick and W.O. Kermack were the first to incorporate the idea of an epidemic threshold in their papers which were published beginning in 1926. An epidemic is a disease that suddenly and sometimes explosively affects a significant proportion of a population (though not necessarily the entire population) as opposed to an endemic disease which is constantly present to some extent within the population. For example, an outbreak of cholera or smallpox would be considered an epidemic while influenza would be considered an endemic. McKendrick and Kermack stated that the spread of a disease is directly related to the number of individuals that someone infected

with that disease could infect in a specified time (Kermack & McKendrick, 1927). This threshold number, also called the basic reproduction number, will be discussed later in this thesis. The study of epidemiology has grown exponentially since the publication of Kermack and McKendrick's contributions, with virtually every known communicable disease being modeled and analyzed.

Epidemiology is not a static science. The evolution of industrialized countries such as the United States, England, Canada, France, etc. led to the decline of the spread of infectious diseases. The decline occurred in the countries that could afford to implement programs that cured or vaccinated against infectious diseases by taking appropriate steps and allocating resources. However, because infectious diseases constantly evolve and adapt, new strains of diseases that were thought to be eradicated have emerged. These new strains can be antibiotic resistant. In addition, new infections such as HIV, which emerged in 1981, demonstrate behavior not typical of previously modeled diseases. Global warming and increased pollution have both changed existing ecosystems and created new ones. Individuals are now able to freely travel the globe in a matter of hours. Due to these and other factors, current epidemiological models must be adapted and transformed to accommodate the latest data available and to keep up with new and evolving diseases (Hethcote, 2000).

One goal of mathematical epidemiology is to formulate models that validate the dynamics of disease causing agents such as viruses, bacteria, or vectors (vectors usually being insects such as mosquitoes). A second goal is to outline procedures to control the spread of disease or to eradicate it entirely. Mathematicians who formulate the models for a specific infectious disease must strike a balance in the model between overly simple

and exceedingly complicated models. A simple model is more easily analyzed and highlights general trends in data at the expense of omitted details and possibly unrealistic assumptions. A complicated model may be more accurate in its assumptions and may contain crucial details, but it may be so complex that it is impossible to analyze and therefore provides no conclusion for the disease (Diekmann & Heesterbeek, 2000).

This thesis examines the behavior of HIV in the bloodstream of an infected individual. Since the early 1980's, mathematicians have worked to model HIV, the virus which eventually leads to AIDS (Acquired Immune Deficiency Syndrome). The tactics utilized to model HIV either focus on the spread of the disease from one individual to another or on the effect of HIV on an infected individual's bloodstream. This thesis will focus on the latter. To this end, an introduction to HIV immunology is required and is presented later in this thesis (see section 3.1).

A mathematical analysis of HIV dynamics in vivo (in the bloodstream) closely emulates the behavior of epidemic and endemic compartmental models. The compartmentalization of T4 cells into uninfected T4 cells, latently infected T4 cells (cells that are infected but do not produce other infected T4 cells), and actively infected T4 cells (cell that are infected and produce other infected T4 cells) mirrors the process of dividing a population into Susceptibles, Exposeds, and Infecteds in classic epidemiological models. HIV immune dynamics will be described in this thesis and each of these compartments, or categories, will be examined and defined.

In Chapter 2 of this thesis, we will discuss two basic SIR models. In Section 2.1, we examine an epidemic model in which no demographic effects are taken into account i.e. the disease occurs rapidly enough that the number of births and deaths that change the

number of individuals in the population are negligible. Section 2.2 contains an endemic SIR model that includes demographic effects i.e. the disease occurs slowly enough so that birth and death rates significantly change the number of individuals in the population.

Chapter 3 is an introductory examination if HIV dynamics in vivo. Section 3.1 will contain an introduction to the basics of HIV immunology and interactions in the bloodstream. Section 3.2 will contain one of the first proposed models for the depletion of T4 cells in the bloodstream. This model is extremely complex and does not lend itself to realistic analysis due to the fact that, at the time of the model's creation, scientists were still discovering the values of the parameters as well as attempting to plot the course of HIV.

Chapter 4 examines a more recent model for HIV dynamics. We analyze this model in a similar fashion to the classic epidemiological models in Chapter 2. The chapter begins with an assessment of the T cells of an uninfected individual. This is then compared to the T cells of an individual infected with HIV. The first model in the chapter assumes that the influx of new, healthy T cells is constant. This assumption is discarded in Section 4.4 when it is assumed that infection with HIV causes a decrease in new, healthy T cells.

Thus, this thesis is intended to discuss two basic SIR models, examine an early model of T cell depletion in an HIV infected individual, and explore and analyze a more recent, simpler model of T cell depletion. The mathematical analysis of the latter model will find an expression for what is equivalent to a basic reproduction number in an SIR model.

# CHAPTER 2: BACKGROUND STUDY

This chapter provides an overview of deterministic modeling as applied to the dynamics of infectious diseases in populations. These complex systems in which the relationships between cause and effect have multifaceted interdependence evolve and adapt constantly over time. In Section 2.1 we describe a basic epidemic SIR model and discuss the assumptions and conclusions involved in that model. In Section 2.2, we will examine a basic endemic SIR model including deaths due to the disease in question. As a reminder, an epidemic model contains no movement in or out of the population i.e. no terms for births or deaths whereas an endemic model accounts for these terms.

To formulate a mathematical model for an infectious disease, an individual should state all relevant assumptions, determine the relationships between the variables and parameters utilized within the model, and analyze any significant patterns that emerge. The admission or exclusion of certain parameters and variables depends on the characteristics of the disease being studied and the intention of the model (Diekmann & Heesterbeek, 2000).

Epidemiological models generally utilize the generalized MSEIR model which places individuals into compartments within the model as well as describe the transition rates between each subgroup. Each letter of this model (M, S, E, I, and R) represents a specific class (or compartment) of individuals. These classes are defined as follows. Susceptibles describes the members of the population at risk of contracting the disease in question. Exposeds are the members of the population that are infected, but are not yet infectious during a latent period of the disease. The compartment (or classification) for those who have the ability to pass the disease to another member of the population is the

Infectious subgroup. Those who have recovered and possess some kind of immunity to the disease, whether permanent or temporary, fall into the Recovered compartment. This compartment also contains those removed from the possibility of becoming infected again by either isolation or death from the disease. The class M represents infants with passive immunity that was passed to them through the placenta of their infected mother (Trottier & Philippe, 2001).

Although mathematical models can contain all five subgroups, not all models will necessarily include all compartments. The choice of which subgroups to include in a model of infectious disease depends on the characteristics of that disease. For example, a disease with a relatively short or non-existent latent period could omit the E subgroup. Alternatively, if an infected mother does not pass immunity to her newborn the M group would not be necessary. Acronyms for various models describe the compartments included in each model. For example, a SEIR model eliminates the immunity passed on from mother to newborn and the model begins with a fully susceptible population. The susceptibles pass to the latent exposed category followed by the infectious subgroup and finally pass to the recovered compartment with permanent immunity. Alternatively, a SEIRS model proceeds in a similar manner with the modification being that immunity is not permanent. Thus those who pass through the R group return to the S category after temporary immunity ended. Other possible acronyms include, but are not limited to, SIR, SIRS, MSIR, SIS, SI, etc. Each model is based on the flow of individuals through the compartments (Trottier & Philippe, 2001). Table 2.1 summarizes the notation found within this chapter.

**Table 1:Notation**

| | |
|---|---|
| S | Susceptibles |
| E | Exposed individuals (latent period) |
| I | Infecteds (contagious) |
| R | Recovereds (immune) |
| $\beta$ | Contact rate |
| $1/\delta$ | Average period of passive immunity |
| $1/\varepsilon$ | Average latent period |
| $1/\gamma$ | Average infectious period |
| $R_o$ | Basic reproduction number |
| $\sigma$ | Contact number |
| $R$ | Replacement number |
| $\mu$ | Birth/Death rate |
| N | Number of individuals in the population |

This notation will be utilized for both the epidemic and endemic SIR models discussed in Sections 2.1 and 2.2.

## Section 2.1: SIR Epidemic Model

In this section, we will begin by examining a basic SIR epidemic model originally formulated by McKendrick and Kermack. When this model was first introduced in 1927, it predicted the behavior of numerous historical epidemics such as cholera, influenza, and the Great Plague.

This model makes multiple assumptions. First, the number of individuals within each compartment is assumed to be a differentiable function of time. This is reasonable as long as there are sufficient members in each compartment. If this assumption is not reasonable, i.e. the population is small then a stochastic model would be appropriate as it takes into account random variations that are nullified by a large population. Second, the

model is deterministic meaning that the behavior of the model is determined by past behavior of diseases. Third, an SIR model assumes no latent phase of the disease, meaning that a susceptible that is infected with the disease is immediately put into the infected subgroup. Fourth, the model assumes that an average infective makes contact sufficient to transmit the disease to susceptible individuals at a rate of β, called the contact rate, so that $\beta N \frac{S}{N} I = \beta SI$ new cases occur when $N$ is the total number in the population, *S* is the number of susceptibles, and *I* is the number of infecteds. Fifth, every individual is assumed to have an equal opportunity to contact every other individual within the population. Generally, this is referred to as the mass action principle. This implies that the rate of contacts is proportional to the population size and that this ratio is the contact rate $\beta$. This assumption depends on the type of disease being modeled and social and behavioral factors. Sixth, this model contains no entry or exit to the population except possibly through death from the disease (this assumption will be discarded in a later section). This assumption holds when the progression of a disease occurs so quickly that the demographics of birth and death may be ignored, as in an epidemic. The last assumption to be discussed is that recovery rate is proportional to the number of infecteds. The argument for this assumption comes from the examination of individuals still infected at time *s*. Let $u(s)$ denote the number of these members. If a fraction γ of these leave per unit time, then $u' = -\gamma u$. Hence $u(s) = u(0)e^{-\gamma s}$ and the length of the infective period is distributed exponentially with the mean $\int_0^\infty e^{-\gamma s} ds = \frac{1}{\gamma}$.

For the basic SIR epidemic model, $S(t)$ represents the number of individuals in the population that are susceptible to a disease at time t. Similarly, $I(t)$ represents the

number of individuals that are infected with the disease and are capable of infecting susceptibles with the disease at time *t*. $R(t)$ denotes the number of individuals recovered from the disease with permanent immunity or removed from the population entirely due to isolation or death at time *t*. The model is given by the following three equations (Kermack & McKendrick, 1927):

$$\frac{dS}{dt} = S' = -\beta SI \qquad S(0) = S_0 > 0 \tag{2.1}$$

$$\frac{dI}{dt} = I' = \beta SI - \gamma I = (\beta S - \gamma)I \qquad I(0) = I_0 > 0 \tag{2.2}$$

$$\frac{dR}{dt} = R' = \gamma I \qquad R(0) = 0 \tag{2.3}$$

In this model, *R* is determined once *S* and *I* are known, since N = *S* + *I* +*R*. Therefore we can drop equation (2.3) from the model leaving only the first two equations. Note that $S' < 0$ and that

$$I' > 0 \Leftrightarrow \beta S - \gamma > 0 \Rightarrow S > \frac{\gamma}{\beta}. \tag{2.4}$$

Since *S* is constantly decreasing, *I* must eventually decrease to 0. However, *I* increases as long as $S > \frac{\gamma}{\beta}$. So if initially $S < \frac{\gamma}{\beta}$, then no epidemic occurs. On the other hand, if initially $S > \frac{\gamma}{\beta}$, then the number of infecteds first increases to $S = \frac{\gamma}{\beta}$ and then decreases to approach zero. It is at this point we can discuss a threshold. The rate of infection of a population is determined by the basic reproduction number, $R_0$, which is defined as the average number of secondary infections produced by an infectious case during the individual's entire infectious period when he or she enters a host population in which everyone is susceptible. Mathematically this translates to

$$R_0 = \frac{\beta S(0)}{\gamma} \tag{2.5}$$

This number measures the force of the infection. $R_0$ is dependent on the risk of transmission per contact, the ratio of potentially infectious contacts to unit time, and the duration of time in which the disease is contagious. The rate limiting step in the force of an infection is $R_0$ . In general, if $R_0$ falls below 1 i.e. an infectious will not necessarily pass the disease on to one other per during his contagious period, the disease will disappear from the population. If $R_0$ is equal to 1, the disease remains relatively stable in its transmission. Hence the disease remains in the population, but neither greatly dissipates nor greatly escalates. Finally, if $R_0$ is greater than 1, then an epidemic builds up.

For our basic SIR model, note that

$$\frac{I'}{S'} = \frac{dI}{dS} = \frac{(\beta S - \gamma)I}{-\beta SI} = -1 + \frac{\gamma}{\beta S} \tag{2.6}$$

Separation of variables and integration of both sides yields

$$I = -S + \frac{\gamma}{\beta}\log S + const. \tag{2.7}$$

In other words,

$$J(S, I) = S + I - \frac{\gamma}{\beta}\log S \tag{2.8}$$

so that each orbit in the *SI* phase plane is given by *J(S,I) = const*. Different constants will yield different trajectories in the phase plane. The constant is determined by the initial values of *S, I, $S_0$,* and *$I_0$* since

$$J(S_0, I_0) = S_0 + I_0 - \frac{\gamma}{\beta}\log S_0 = const. \tag{2.9}$$

If a small number of infecteds is introduced to a population of size *N*, note that $N \approx S_0$ (the initial number of susceptibles is approximately the entire population) and $I_0 \approx 0$ (the number of infecteds in the population is approximately 0). This determines $R_0 = \frac{\beta N}{\gamma}$ from (2.5). If we utilized the fact that $\lim_{t\to\infty} I(t) = 0$ and let $\lim_{t\to\infty} S(t) = S_\infty$ we determine

$$J(S_0, I_o) = J(S_\infty, 0) \Rightarrow N - \frac{\gamma}{\beta}\log S_0 = S_\infty - \frac{\gamma}{\beta}\log S_\infty \tag{2.10}$$

This assists in a determination of the basic reproduction number, $R_0$, because it gives an expression for $\frac{\beta}{\gamma}$ in terms of parameters that can be determined:

$$\frac{\beta}{\gamma} = \frac{\log\frac{S_0}{S_\infty}}{N - S_\infty} \tag{2.11}$$

Note that $S_0 > S_\infty$. This is due to the fact that the initial number of susceptibles will be greater than the number of susceptibles that actually become infected i.e. some individuals will not contact the disease.

## Section 2.2: SIR Endemic Model

In this section, we will examine an SIR model with demographic effects for a disease that may be fatal to some infecteds. This model makes multiple assumptions,

many of which are identical to the assumptions for the SIR epidemic model in section 2.1. For thoroughness, the list of assumptions for this endemic model are enumerated below:

First, the number of individuals within each compartment is assumed to be a differentiable function of time. This is reasonable as long as there are sufficient members within each compartment. If this assumption is not reasonable, i.e. the population is small, a stochastic model would be appropriate as it takes into account random variations that are nullified by a large population. Second, the model is deterministic, meaning that the behavior of the model is determined by past behavior of diseases. Third, an SIR model assumes no latent phase of the disease, meaning that a Susceptible that is infected with the disease is immediately put into the Infected subgroup. Fourth, the subgroup of Recovereds in this model should contain only members who have recovered from the disease, not individuals who have been removed by death from the disease. Therefore, the population size cannot be assumed to remain constant. Fifth, the model also assumes that an average Infected makes contact sufficient to transmit the disease to susceptible individuals at a rate of $\beta$, called the contact rate. Sixth, every individual is assumed to have an equal opportunity to contact every other individual within the population. Generally, this is referred to as the mass action principle. This implies that the rate of contacts is proportional to the population size and that this ratio is the contact rate, $\beta$. This assumption depends on the type of disease being modeled, as well as social and behavioral factors. Seventh, the birth rate of the population is assumed to be constant with $\mu K$ new births into the susceptible class per unit time. Eighth, each subgroup also includes a death rate proportional to the number of individuals in the subgroup. This is

called an endemic model since the evolution of the disease occurs over a long enough period that birth rates and death rates affect the progress of the model. Finally, the birth rate and death rate are assumed to be equal.

In the SIR endemic model, *S(t)* represents the number of individuals in the population that are susceptible to a disease at time t. Similarly, *I(t)* represents the number of individuals that are infected with the disease and are capable of infecting susceptibles with the disease at time t. *R(t)* denotes the number of individuals recovered from the disease with permanent immunity or removed from the population entirely due to isolation or death at time t. The model is given by (Hethcote, 2000):

$$\frac{dS}{dt} = S' = \mu K - \mu S - \beta IS = -\beta IS + \mu(K - S) \qquad S(0) = S_0 \geq 0 \qquad (2.12)$$

$$\frac{dI}{dt} = I' = \beta IS - \gamma I - \mu I - \alpha I \qquad I(0) = I_0 \geq 0 \qquad (2.13)$$

$$\frac{dR}{dt} = R' = \gamma I - \mu R \qquad R(0) = R_{0i} \geq 0 \qquad (2.14)$$

In the first equation, $\mu K$ represents the influx of births into the Susceptible class, $-\mu S$ represents the deaths out of the Susceptibles, and $-\beta IS$ is the movement of Susceptibles into the Infecteds subgroup. For the second equation, $\beta IS$ is the influx to the Infecteds from the Susceptibles, $-\mu I$ is the term that represents deaths out of the Infecteds (not due to disease), $-\alpha I$ is the deaths out of the Infecteds due specifically to the disease, and $-\gamma I$ is the movement from the Infecteds to the Recovereds. Finally, in the third equation $\gamma I$ is the influx from the Infecteds to the Recovereds and $-\mu R$ is the term that represents deaths out of the Recovereds.

We can make the following observations about this model. If $\alpha > 0$, i.e. the disease is fatal to some individuals, then the population size is not constant. Therefore *K* does not represent a constant population size, but rather a maximum possible population size also known as a carrying capacity. Due to the fact that the first two equations do not contain any terms with *R*, we may drop the third equation. This is because the first two equations determine *S* and *I* and the third equation will determine *R* once *S* and *I* are known.

In order to analyze the model, we will first determine the equilibrium points.

$$-\beta IS + \mu(K - S) = 0 \tag{2.15}$$

$$I(\beta S - \gamma - \mu - \alpha) = 0 \tag{2.16}$$

The first equilibrium occurs when $I = 0$ and therefore $S = K$. This is a disease free equilibrium as there are no Infecteds in the model. The second equilibrium occurs when

$$\beta S = \gamma + \mu + \alpha \tag{2.17}$$

and therefore

$$I = \frac{\mu K}{\mu + \gamma + \alpha} - \frac{\mu}{\beta} \tag{2.18}$$

This is the endemic equilibrium. We linearize the model and find that

$$A = \begin{pmatrix} -\beta I - \mu & -\beta S \\ \beta I & \beta S - \mu - \alpha - \gamma \end{pmatrix} \tag{2.19}$$

At the disease-free equilibrium,

$$A = \begin{pmatrix} -\mu & -\beta K \\ 0 & \beta K - \mu - \gamma - \alpha \end{pmatrix} \tag{2.20}$$

The eigenvalues are $\lambda_1 = -\mu$ and $\lambda_2 = \beta K - \mu - \gamma - \alpha$. Therefore, this equilibrium point is asymptotically stable when $\beta K < \mu + \gamma + \alpha$ and unstable when $\beta K > \mu + \gamma + \alpha$. At the endemic equilibrium,

$$A = \begin{pmatrix} -\beta I - \mu & -\beta S \\ \beta I & 0 \end{pmatrix} \tag{2.21}$$

Note that this matrix has a positive determinant and a negative trace. Therefore this equilibrium point is always asymptotically stable. It is at this point we can discuss a threshold. The rate of infection of a population is determined by the basic reproduction number, $R_0$, which is defined as the average number of secondary infections produced by an infectious case during the individual's entire infectious period when he or she enters a host population in which everyone is susceptible. Mathematically this translates to

$$R_0 = \frac{\beta S(0)}{\gamma} \tag{2.22}$$

This number measures the force of the infection. $R_0$ is dependent upon the risk of transmission per contact, the ratio of potentially infectious contacts to unit time, and the duration of time in which the disease is contagious. The rate limiting step in the force of an infection is $R_0$. In general, if $R_0$ falls below 1, i.e. an infected will not necessarily pass the disease on to one other person during his contagious period then the disease will disappear from the population. If $R_0$ is equal to 1, the disease remains relatively stable in its transmission. Hence the disease remains in the population, but neither greatly dissipates nor greatly escalates. Finally, if $R_0$ is greater than 1, an epidemic builds up. For this model,

$$R_0 = \frac{\beta K}{\mu + \gamma + \alpha} \tag{2.23}$$

which is the basic reproduction number in (2.22) adjusted for birth/death rates not due to the disease and for deaths due to the disease itself.

Another observation that can be made regarding the model comes from an examination of the reduction of the population size. Note that adding the equations from (2.12) through (2.14) yields

$$N' = S' + I' + R' = \mu K - \mu(S + I + R) - \alpha I = \mu K - \mu N - \alpha I \tag{2.24}$$

At the endemic equilibrium

$$N = K - \frac{\alpha}{\mu} I \tag{2.25}$$

Therefore, the reduction to the population size from the carrying capacity is expressed by

$$K - N = \frac{\alpha}{\mu} I = \frac{\alpha K}{\mu + \gamma + \alpha} - \frac{\alpha}{\beta} \tag{2.26}$$

which comes from (2.18). Notice that if $\alpha$ is large, then it is not likely that $R_o > 1$, from (2.22), and the disease will die out. Also, note that if $\alpha$ is small, then the total population size at the endemic equilibrium is close to the carrying capacity $K$ of the population since if there are few deaths from the disease the population remains nearly constant. In other words, the maximum decrease to the population comes from diseases with intermediate ability to kill those infected.

This analysis of the SIR endemic model will mirror some of the analysis done on the model for T cell dynamics in an HIV infected individual in Chapter 4. Of especial consideration is the basic reproduction number which serves as a critical value that determines whether or not a disease will spread. The model in Chapter 4 will have a

similar value that determines whether or not the T cells of a person with HIV will be depleted. However, before we can examine this model, an introduction to immunology is required. This introduction in Chapter 3 will discuss behavior of HIV in vivo (in the bloodstream) and explain the terminology utilized when presenting models involving HIV.

# CHAPTER 3: PRELIMINARY T CELL MODEL

## Section 3.1: Introduction to HIV Immunology

This section will serve as an introduction to HIV immune dynamics. When a foreign substance, also known as an antigen, enters the body, the body initiates an immune response to eliminate the antigen. The first lines of defense to the antigen are macrophages and monocytes. These are cells that seek out the antigen, surround and engulf it (also known as phagocytosis), analyze its contents, and then pass this information to CD4+ T lymphocytes, also known as CD4 T cells or just T4 cells. These T4 cells serve as the general in the army of the immune system. T4 cells can either call upon the production of other T4 cells to assist in the fight against the antigen or can activate other types of T cells, such as CD8+ T cells, which then destroy cells infected with the antigen. Another weapon the T4 cells can call upon is B lymphocytes (B cells) which produce antibodies specifically engineered to destroy the pathogen detected by the macrophages (Kirschner, 1996).

HIV is a virus and as such cannot reproduce itself without a host. In general, viruses insert their own DNA into the host cell which is then replicated whenever the host's DNA is replicated. What distinguishes HIV from other viruses is the method by which it reproduces when it comes into contact with a host. While other viruses carry copies of their DNA to inject into the host cell's DNA, HIV carries RNA which is a precursor to DNA. This RNA must first be transcribed to DNA before it can be copied along with the DNA of the host. Modern medicine has exploited this extra step in the reproductive process by creating drugs that prevent the virus from converting its RNA to

DNA. If this step is not prevented then the viral DNA, also known as the provirus, gets copied along with the DNA of the cell every time the cell divides. This provirus can either immediately produce new virus particles or remain latent and undetected for months. This accounts for the lengthy latent period between an individual's infection and severe depletion of T cells. Antigen stimulation of T4 cells is required on order to change a latently infected cell to an actively infected cell (Kirschner, 1996).

When HIV infects an individual, its target for host cells are the T4 cells responsible for the eradication of the virus, as well as macrophages and monocytes. A protein that is on the surface of HIV, gp120, is attracted to the CD4 protein on the surface of the T cells, macrophages, and monocytes. Typically, the swift reproduction of the provirus occurs in infected T4 cells and the gradual reproduction occurs in macrophages and monocytes

After the DNA of the virus has been duplicated by the host cell, new virus particles bud (pinch themselves off of the new cell). Budding can either leave the original cell intact or cause lysis in which the original cell's is membrane is perforated causing the cell to burst. These new buds are called virions.

While the actual progression of HIV infection is not clear cut, what can be agreed upon is that there are four main stages through which an infected individual passes. The first stage is initial infection when the virus is first introduced into the body. This is followed by a short period in which both the T cell population and the virus population experience large fluctuations. The third stage is characterized by large numbers of both T cells and virus which undergo incredible dynamics (Kirschner, 1996). This is the stage in which latency occurs and in which a disease steady state appears. Finally, the last stage

of HIV is distinguished by a drastic and dangerous drop in T cells and unlimited growth in the virus which leads to death. The last stage is what is referred to as AIDS (Kirschner, 1996).

## Section 3.2: T cell Model

This section will examine one of the first rudimentary models of HIV in vivo (in the blood stream). The model is extremely general and contains multiple unknown parameters and functions of unknown form. However, it could potentially account for the many consequences of HIV on the immune system (Perelson, 1989).

This model contains multiple assumptions and parameters. Cells in the bloodstream are considered either uninfected, latently infected (contain the virus but do not reproduce it), or actively infected (contain the virus and reproduce it). Spatial dependence is ignored. Since the interactions occur within the bloodstream, this is a reasonable assumption. As a result, the model contains ordinary differential equations. The model is assumed to be deterministic i.e. behavior is determined by past behavior.

Let T denote the total concentration of uninfected T4 cells. Let $T_k$ denote the concentration of uninfected T4 cells specific for some antigen *k*. Note that $T = \sum T_k$ . Let $a_k$ be the concentration of antigen *k*. HIV is itself one type of antigen and any subpopulation of T4 cells can be infected by HIV regardless of its antigen specificity. Let $T_k^*$ and $T_k^{**}$ denote the concentrations of T4 cells specific for antigen *k* that are latently infected and actively infected respectively. Also, $m$ and $m^*$ denote the

uninfected and actively infected monocytes/macrophage populations respectively. Note that these do not have a latent phase and this population shall be referred to as the monocyte population with the understanding that the macrophages may be part of this population. The following equations, (3.1) through (3.10), model HIV in vivo (Perelson, 1989). They include T cells equations, a syncytia equation, an equation for free virus, monocyte/macrophage equations, and an antigen equation.

T cell equations:

$$\begin{aligned}\frac{dT_k}{dt} &= s(v) - \mu_T T_k + rT_k(1-\frac{T_k}{T_{\max}})e^{-\eta T_{tot}} f_s(a_k,...) - k_1 v T_k \\ &\quad - k'_s T_k(T^{**}+m^*) - k' T_k S - \mu_{ai} T_k g_{ai}(gp120,...)\end{aligned} \tag{3.1}$$

$$\frac{dT_k^*}{dt} = -\mu_T T_k^* + k_1 v T_k - k_2 f_s(a_k) T_k^* - k_s T_k^*(T^{**}+m^*) - k'_s T_k^* S \tag{3.2}$$

$$\begin{aligned}\frac{dT_k^{**}}{dt} &= k_2 f_s(a_k) T_k^* - \mu_b T_k^{**} - k_s T_k^{**}(T_{tot}+m_{tot}) - k''_s T_k^{**} S \\ &\quad - \mu_{is} T_k^{**} g_{is}(CTL,...) - k'_{phag}\, m T_k^{**} g_{opson}(A_v)\end{aligned} \tag{3.3}$$

where the total T4 population, $T_{tot}$, is composed of

$$T = \sum_k T_k, \qquad T^* = \sum_k T_k^*, \qquad T^{**} = \sum_k T_k^{**} \tag{3.4a}$$

and

$$T_{tot} = T + T^* + T^{**} \tag{3.4b}$$

Syncytia equation (actively infected cells fused with uninfected or latently infected cells) (Perelson, 1989):

$$\frac{dS}{dt} = k_s T^{**}(T_{tot} + m_{tot}) + k_s m^{*}(T + T^{*} + m_{tot}) - \mu_s S \tag{3.5}$$

Equation for free virus:

$$\frac{dv}{dt} = N\mu_b \sum_k T_k^{**} + k_{vm} m^{*} + N_s \mu_s S - k_1 v T_{tot} - k_m v m_{tot} - \mu_v v - k_n v h(A_v) \tag{3.6}$$

Monocyte/macrophage equations:

$$\begin{aligned} \frac{dm}{dt} &= s_m - \mu_m m - k_m v m - k_s m(T^{**} + m^{*}) - k'_s\, mS \\ &\quad - k_{phag} m v h(A_v) + k'_{phag}\, m T^{**} g_{opson}(A_v) \end{aligned} \tag{3.7}$$

$$\begin{aligned} \frac{dm^{*}}{dt} &= k_m v m - k_s m^{*}(T_{tot} + m_{tot}) - k'_s\, m^{*} S + k_{phag} m v h(A_v) \\ &\quad + k'_{phag}\, m T^{**} g_{opson}(A_v) \end{aligned} \tag{3.8}$$

where

$$m_{tot} = m + m^{*} \tag{3.9}$$

Antigen equation:

$$\frac{da_k}{dt} = s_a(t) + r_a a_k (1 - \frac{a_k}{a_{\max}}) - \mu_a a_k - \mu_{ir} a_k g_{ir}(T_k, ...) \tag{3.10}$$

For equation (3.1), $s(v)$ represents an influx of new, uninfected T4 cells. Since HIV can infect the precursor cells that produce the new T4 cells, their supply may be

hampered. Therefore $s(v)$ may be either a constant or a decreasing function of $v$ (free virus). The second term, $-\mu_k T_k$, accounts for the decrease in T4 cells due to the natural extinction at the end of their lifespan. The third term of equation (3.1) shows a logistic growth rate governed by the logistic growth rate law with the maximum specific growth rate denoted by $r$. This is based on the presumption that cell growth approaches a threshold maximum denoted $T_{\max}$, so as to avoid exponential growth. Also presented in the third term is an assumption that a fraction, $f_s$, of $T_k$ cells are stimulated to grow in the presence of the antigen $k$. The expression $f_s$ is a function of antigen concentration and other unspecified variables such as antigen presentation by macrophages. For the fourth term in the equation, $-k_1 v T_k$, $k_1$ is a rate of infection in this mass action term that models the possibility that a free virus, $v$, infects a T4 cell. This T cell then becomes a latently infected cell and is therefore moved to the second subgroup. The fifth term, $-k_s' T_k (T^{**} + m^*)$, symbolizes loss to the uninfected subgroup due to syncytia formation of an uninfected T cell with an actively infected T cell or monocyte. Syncytia form when either an uninfected or latently infected T cell fuses with an infected T cell or an infected monocyte. The term controlling syncytia formed from latent T cells appears later (in the second equation). Note that this fifth term assumes equal likelihood that infected T cells and infected monocytes are equally likely to form syncytia. The sixth term in the first equation, $-k' T_k S$, arises from the fact that syncytia, once formed, have the ability to fuse with T4 cells as well. However, since the size of syncytia is significantly different from the size of a single cell, an alternative fusion rate, $k'_s$, has been utilized. $S$ represents the concentration of syncytia so that, overall, this term represents the loss of uninfected cells

to syncytia formation. Finally, the last term in equation (3.1), $-\mu_{ai} T_k g_{ai}(gp120,...)$, accounts for the effect of autoimmune mechanisms on the number of uninfected T4 cells. The function $g_{ai}$ determines which immune system influences are important to the autoimmune response. For example, one factor that has a decreasing effect on uninfected T4 cells is $gp120$ which was discussed in section 3.1. The protein $gp120$ is shed at varying rates by the virus and binds to CD4 molecules on uninfected cells (the number of available molecules differs from cell to cell) with varying results. The function $g_{ai}$ would have to account for these characteristics of $gp120$ as well as other immune system influences.

In equation (3.2), the first term, $-\mu_T T_k^*$, accounts for the decrease in latently infected T4 cells due to the natural extinction at the end of their lifespan. Note that the lifespan of latently infected T4 cells is exactly the same as the uninfected T4 cells. The second term, $k_1 v T_k$, represents the movement from the first group to the second group (see previous paragraph). Movement from the latently infected T4 cells compartment to the actively infected T4 cells compartment is represented by the third term in this equation, $-k_2 f_s(a_k) T_k^*$. The fourth term, $-k_s T_k^* (T^{**} + m^*)$, symbolizes the loss of latently infected T cells to syncytia as explained in the previous paragraph. Finally, the last term, $-k_s' T_k^* S$, represents the loss of latently infected T4 cells to syncytia formation with already present syncytia (similar to the sixth term of the previous equation).

For equation (3.3), the first term, $k_2 f_s(a_k) T_k^*$, is the influx to the actively infected subgroup from the latently infected subgroup. The second term, $-\mu_b T_k^{**}$, accounts for the decrease in actively infected T4 cell due to the natural extinction at the end of their

lifespan. Note that the lifespan of actively infected T4 cells is not equal to the life span of uninfected and latently infected cells. It is expected that the lifespan of an actively infected T4 cell is shorter than the other subgroups. The third term of this equation, $-k_s T_k^{**}(T_{tot} + m_{tot})$, represents the loss of actively infected T4 cells to syncytia formation. This term contains $T_{tot}$ and $m_{tot}$ because the actively infected cells fuse with uninfected cells, latently infected cells, uninfected monocytes, actively infected monocytes, as well as other actively infected cells. Like the fourth term from the first equation and the fifth term from the second equation, the fourth term of equation (3.3), $-k''_s T_k^{**} S$, accounts for the fusion of syncytia with actively infected T4 cells. Again note that the rate of fusion is not assumed to be the same for either uninfected or latently infected T4 cells. The fifth term of equation (3.3), $-\mu_{is} T_k^{**} g_{is}(CTL,...)$, depends on the ability of the immune system to recognize viral proteins on the surface of actively infected cells (represented by the function $g_{is}$). It represents the loss of actively infected cells due to an immune system attack. CTL is one type of immune system effector that determines if a cell is resistant to an immune system attack and hence is one of the factors measured by $g_{is}$. Finally, the last term of equation (3.3), $-k'_{phag}\, mT_k^{**} g_{opson}(A_v)$, accounts for the loss of actively infected T4 cells to phagocytosis. This is the process of a cell, called a phagocyte, fully encompassing the T4 cell and in a sense "ingesting" it. The level of antibody coating determines the efficiency of opsonization (antigens are attached to phagocytes to increase the efficiency of phagocytosis) and is included in the function $g_{opson}(A_v)$.

Equation (3.5) models the population dynamics of syncytia. Note that these terms contain the entire T cell population, regardless of antigen specificity. It is assumed that when an already existing syncyium fuses with a T4 cell, it does not change the current number of syncytia. Syncytia have a finite life span, denoted by $\mu_s$. Thus a term is included to account for the loss of syncytia due to termination at the end of their life span.

The equation in (3.6) models the population dynamics for free virus. The first term, $N\mu_b \sum_k T_k^{**}$, includes the number of free virus, *N*, produced when any T4 cell, regardless of antigen specificity, is exposed to an adequate degree of its specific antigen, *k*. The second and third terms, $k_{vm} m^*$ and $N_s \mu_s S$, show production of free virus by infected monocytes at rate $k_{vm}$ and syncytia at rate $N_s \mu_s$ respectively (Lifson et al, 1986). The fourth and fifth terms, $-k_1 v T_{tot}$ and $-k_m v m_{tot}$, account for the loss of free virus to binding with T4 cells and monocytes respectively. The term $-\mu_v v$ represents the loss of free virus due to natural life span. Finally, the last term, $-k_n v h(A_v)$, represents the loss of free virus to antibody neutralization where $k_n$ is the rate of virus neutralization and $A_v$ is the concentration of viral specific antibody. The function $h(A_v)$ determines the amount of antibody bound to HIV (Brendel & Perelson, 1987).

Equation (3.7) models the uninfected monocytes and is similar to the equation for uninfected T4 cells. It has a source term, $s_m$, and a term that removes monocytes due to the natural life span, $-\mu_m m$. The third term, $-k_m v m$, models the infection of monocytes by free virus at the rate $k_m$. This term denotes the movement from the uninfected subgroup to the infected subgroup. Note that $k_m$ does not necessarily equal $k_1$, the rate of

infection for T4 cells (Gartner et al, 1986). Syncytia formation between uninfected monocytes and infected T4 cells is accounted for in the fourth term of the equation, $-k_s m(T^{**} + m^*)$ with a rate of $k_s$. The term $-k'_s\, mS$ accounts for the loss of uninfected monocytes by fusion with syncytia. A similar term was present in the T cell equations. The sixth term, $-k_{phag} mvh(A_v)$, models the infection of monocytes through phagocytosis of free virus. Note that this term is added to the equation for infected monocytes. Monocytes can also phagocyte actively infected T cells, and thereby become infected. Hence the seventh term, $k'_{phag}\, mT^{**} g_{opson}(A_v)$, is removed from both equation (3.7) and (3.3) and reappears in the actively infected monocyte equation (3.8).

The terms of equation (3.8) are similar to those in (3.7). The first term, $k_m vm$, is the influx of newly infected cells from the uninfected category. The second term, $-k_s m(T_{tot} + m_{tot})$, is the loss of infected monocytes due to syncytia formation between infected monocytes and infected T4 cells. The third term, $-k'_s\, m^* S$, accounts for the loss of infected monocytes by fusion with syncytia. The fourth and fifth terms, $k_{phag} mvh(A_v)$ and $k'_{phag}\, mT^{**} g_{opson}(A_v)$, model the increase in infected monocytes due to uninfected monocyte phagocytosis with free virus and actively infected T4 cells respectively.

Finally, the antigen equation (3.10) models the change in antigen concentration in the bloodstream. It is assumed that an antigen can be produced at a rate of $s_a(t)$ for the first term. The source term is dependent on time because of the variability of introduction of antigen to the body. For example, a vaccine would introduce a one-time increase of antigen whereas $gp120$ naturally and gradually produces antigen in the body.

Antigen is sustained and grown logistically with a growth rate $r_a$, as shown in the second term, $r_a a_k (1 - \frac{a_k}{a_{\max}})$. The third term, $-\mu_a a_k$, represents the loss of the antigen through natural elimination processes at a rate of $\mu_a$. The term $\mu_{ir} a_k g_{ir}$ represents the loss of antigen due to an immune response, which is dependent on the population level of T4 helpers specific for the antigen. This dependency is accounted for in the function $g_{ir}$.

This model, while comprehensive and detailed, is extremely complicated and does not lend itself for easy analysis. In order to obtain useful information from this model, certain assumptions will have to be made in order to simplify it. However, the model does provide a comprehensive archetype and ideal starting place for a simpler model that can be analyzed. In the next chapter, we will examine a simplified version of this model in order to obtain manageable results.

# CHAPTER 4: HIV DYNAMICS IN VIVO

This chapter will examine a newer model of the dynamics of HIV. Unlike the model in the previous chapter, this model does not deal with the immune response to HIV. The immune response is certainly present and an argument could be made that immune responses could influence the parameters in this model. In addition, both certain mechanisms for cell death, such as syncytia formation, and antigen specific viral strains are also eliminated in this model. However, this model attempts to determine if HIV infection alone can account for the T cell depletion in infected individuals. This will focus the model on the effects of HIV on T cell dynamics. The model aims to explain the long latency between initial infection and the final stage of infection when a person suffers from AIDS, as well as the low concentration of free virus in vivo (in the bloodstream).

In order to understand the dynamics of T4 cells in an HIV infected individual, we first consider the dynamics of T cells in an uninfected person. The number of T4 cells in a healthy individual is relatively constant, since T cells are replenished by the bone marrow. Therefore, the number of T cells in the bloodstream can be modeled by the differential equation (Perelson et al, 1993)

$$\frac{dT}{dt} = s + rT(1 - \frac{T}{T_{\max}}) - \mu_T T \qquad (4.1)$$

In this equation, $s$ is a constant source term that represents the replenishment of T4 cells. The second term governs the growth of T cells with a logistic equation where $r$ depends on the average degree of antigen stimulation of T cell production. The last term signifies the depletion of T4 cells due to the natural life span. Here $\mu_T$ represents the

average per capita death rate of T cells, since no distinction has been made between different types of T cells and the life span of each type of T cell varies. We will first find the equilibrium point by setting the left hand side of (4.1) equal to zero.

$$f(T) = s + rT(1 - \frac{T}{T_{\max}}) - \mu_T T = 0 \tag{4.2}$$

Simplifying (4.2) we have

$$f(T) = \frac{-r}{T_{\max}} T^2 + (r - \mu_T)T + s = 0 \tag{4.3}$$

so that $T_0$, the steady state equilibrium point, is given by

$$T_0 = \frac{T_{\max}}{2r}\{r - \mu_T + [(r - \mu_T)^2 + \frac{4sr}{T_{\max}}]^{1/2}\} \tag{4.4}$$

Only one solution is relevant since the other one, being negative, is not biologically applicable.

In order to ensure that the entire model represents biologically relevant information, certain restrictions must be imposed upon the parameters. The thymus, where T cells are produced, never halts the manufacturing of T4 cells (Eisen, 1980). Therefore we assume $s > 0$. The number of T cells demonstrated by $T_0$ should be less than $T_{\max}$ so that, if an infection of some kind occurs, the number of T cells can increase to fight the infection. Also, once the population of T cells achieves the maximum, it should decrease. Therefore,

$$\mu_T T_{\max} > s \tag{4.5}$$

so that the death rate at $T_{\max}$ is greater than the supply rate. Otherwise the number of T cells could exceed $T_{\max}$. Now note that $f(0) = s > 0$ and $f(T_{\max}) = s - \mu_T T_{\max} < 0$.

Therefore, $T_0 < T_{\max}$, as we expect. All solutions to the model (equation (4.1)) that begin with an initial number of T4 cells, T(0), in $I = [0, T_{\max}]$ will remain bounded and stay in the open interval, $0 < T(t) < T_{\max}$, for all t. $T_0$ is the only equilibrium point in the interval I and therefore $T_o$ is stable and globally attracting in I.

In order to model the T4 cell dynamics of an individual infected with HIV, we consider the uninfected T cells, the latently infected T cells, the actively infected T cells, and the free virus particles, defined as in the model in Chapter 3 (see pp. 21-22). Again, spatial dependence is ignored and we will utilize similar notation as in Chapter 3. The dynamics of the populations are given by (Perelson et al, 1993)

$$\frac{dT}{dt} = s - \mu_T T + rT\left(1 - \frac{T_{tot}}{T_{\max}}\right) - k_1 VT \qquad (4.6(a))$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^* \qquad (4.6(b))$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**} \qquad (4.6(c))$$

$$\frac{dV}{dt} = N\mu_b T^{**} - k_1 VT - \mu_V V \qquad (4.6(d))$$

where $T_{tot} = T + T^* + T^{**}$. Definitions of the parameters can be found in Table 4.1.

**Table 2: Variables and Parameters**

| Variable/Parameter/ Constant/Derived Quantity | Description | Initial/Default Values |
|---|---|---|
| T | Uninfected T4 cell population size | $1000 mm^{-3}$ |
| $T^*$ | Latently infected T4 cell population size | 0 |
| $T^{**}$ | Actively infected T4 cell population size | 0 |
| V | Free virus (HIV) population size | $10^{-3} mm^{-3}$ |
| s | Rate of supply of T4 cells | $10\ day^{-1} mm^{-3}$ |
| r | Rate of growth for T4 cell population | $0.03\ day^{-1}$ |
| $T_{\max}$ | Maximum number of T4 cells | $1500 mm^{-3}$ |
| $\mu_T$ | Death rate for uninfected/latently infected T4 cells | $0.02\ day^{-1}$ |
| $\mu_b$ | Death rate for actively infected T4 cells | $0.24\ day^{-1}$ |
| $\mu_V$ | Death rate for free virus | $2.4\ day^{-1}$ |
| $k_1$ | Rate constant for T4 cells becoming infected by free virus | $2.4\times10^{-5} mm^{-3} day^{-1}$ |
| $k_2$ | Rate latently infected T4 cells convert to actively infected T4 cells | $3\times10^{-3} day^{-1}$ |
| N | Number of free virus produced by lysing a T4 cell | Varies |
| $\theta$ | Viral concentration required to half the source term | $1 mm^{-3}$ |
| $T_0$ | Steady state level of T4 cells in an uninfected individual | $1000 mm^{-3}$ |
| $N_{crit}$ | Critical number of viral progeny needed for endemic infection | 774 |
| $k_3$ | $k_2 + \mu_T$ | $0.023\ day^{-1}$ |
| $k_4$ | $k_1 T_0 + \mu_V$ | $2.424\ day^{-1}$ |
| $\hat{k}_4$ | $k_1 \overline{T} + \mu_V$ | |
| $\gamma$ | $r / T_{\max}$ | $2\times10^{-5} day^{-1}$ |
| p | $r - \mu_T$ | $0.01\ day^{-1}$ |

In (4.6(a)), *s* is again a source term for T cells. In this model it is assumed to be constant. We will discard this assumption in a later examination in section 4.4. The uninfected T cells are assumed to have a finite life span and die at a rate of $\mu_T$. Note that this is the same death rate as in both uninfected T cells (equation (4.1)) and latently infected T cells (equation (4.6(b)).

As stated earlier in the chapter, *r* depends in the average degree of antigen stimulation of T cell production. This is due to the fact that *r* represents the rate of growth of the T4 cell population and this rate depends on the presence of a T cell specific antigen presence in the bloodstream. In this model, it is assumed that a constant fraction, $f_s$, of T cells are stimulated to grow. Recall that in Chapter 3, which contained a more elaborate model (see pp. 21-22), $f_s$ was left as a function of antigen concentration and other unspecified variables. The *r* in equation (4.6(a)) is given by $r = \hat{r} f_s$ where $\hat{r}$ is the average antigen-induced per capita T cell growth rate in the absence of population density limitation.

The remaining terms of equations (4.6(a)-4.6(d)) function in similar fashion to those described in Chapter 3. To avoid redundancy, we will discuss only the parameter and variable values and not the movement of terms from group to group in the model. Note that actively infected cells are assumed to be generated from latently infected cells with a rate constant of $k_2$. This constant involves the antigen specific stimulation of T4 cells. Therefore, $k_2$ should be a function of antigen concentration and the fraction of cells stimulated by the antigen as well as the probability that stimulation leads to viral reproduction. In (4.6(d)), *N* denotes the total number of infectious particles produced by one infected cell. In this model, *N* is treated as a constant. However, *N* can vary with

different strains of HIV and therefore another model could treat *N* as a variable rather than a constant.

Due to the fact that, in an uninfected individual, the T cell population has a steady state value of $T_0$, the following are considered reasonable initial conditions for infection by free virus for the proposed model (Perelson et al, 1993): $T(0) = T_0$, $T^*(0) = 0$, $T^{**}(0) = 0$, and $V(0) = V_0$.

In order to determine the biological relevance of the model, note that

$$\left.\frac{dT}{dt}\right|_{T=0} = s \geq 0, \left.\frac{dT^*}{dt}\right|_{T^*=0} = k_1 VT \geq 0, \left.\frac{dT^{**}}{dt}\right|_{T^{**}=0} = k_2 T^* \geq 0, \text{ and } \left.\frac{dV}{dt}\right|_{V=0} = N\mu_T T^{**} \geq 0.$$

On each hyperplane bounding the nonnegative orthant, the vector field points into ${R_+}^4 := \{x \in R^4 | x \geq 0\}$, i.e. ${R_+}^4$ is positively invariant, so that no population either grows without bound or becomes negative.

It is worth mentioning that if $T(0) < T_{\max}$, then $T(t) < T_{\max} \forall t$ due to the influence of the logistic equation from equation (4.1). Since the presence of HIV only decreases the T cell population, this property should also remain true for $T_{tot}$. From (4.6(a) – 4.6(c)) notice that

$$\frac{dT_{tot}}{dt} = s - \mu_T T + rT(1 - \frac{T_{tot}}{T_{\max}}) - \mu_T T^* - \mu_b T^{**}. \tag{4.7}$$

Since $\mu_b > \mu_T$ (see Table 4.1), we have

$$\frac{dT_{tot}}{dt} < s - \mu_T T_{tot} + rT(1 - \frac{T_{tot}}{T_{\max}}). \tag{4.8}$$

Hence at $T_{tot} = T_{\max}$,

$$\left.\frac{dT_{tot}}{dt}\right|_{T_{tot}=T_{\max}} < s - \mu_T T_{\max} < 0. \tag{4.9}$$

The negativity of $s - \mu_T T_{\max}$ follows from equation (4.5). Since $\left.\frac{dT_{tot}}{dt}\right|_{T_{tot}=T_{\max}} < 0$, the total T cell population is bounded by $T_{\max}$. For the remainder of this chapter we will analyze this model.

## Section 4.1: Determination of Equilibrium Points

The equilibrium points of the model are found by setting (4.6(b)) and (4.6(c)) equal to zero:

$$k_1 VT - \mu_T T^* - k_2 T^* = 0, \tag{4.10}$$

so that we have

$$T^* = \frac{k_1 VT}{k_2 + \mu_T}, \tag{4.11}$$

and

$$k_2 T^* - \mu_b T^{**} = 0, \tag{4.12}$$

so that by solving for $T^{**}$ and substituting from (4.11) we have

$$T^{**} = \frac{k_2 T^*}{\mu_b} = \frac{k_2 k_1 VT}{\mu_b (k_2 + \mu_T)}. \tag{4.13}$$

Substituting (4.11) and (4.13) into (4.6(d)) yields

$$\frac{dV}{dt} = V\left[\left(\frac{Nk_2}{k_2 + \mu_T} - 1\right)k_1 T - \mu_V\right] \tag{4.14}$$

The equation $\frac{dV}{dt} = 0$ has two possible solutions, $V = 0$ and $T = \frac{\mu_V}{\alpha}$ where

$$\alpha = k_1\left(\frac{Nk_2}{k_2 + \mu_T} - 1\right). \tag{4.15}$$

If $V = 0$, i.e. there is no virus and the individual is uninfected, then, biologically, there should be no latently infected or actively infected T4 cells. This is confirmed mathematically in equations (4.11) and (4.13) by looking at the value of $T^*$ and $T^{**}$ when $V = 0$.

$$T^* = \frac{k_1(0)T}{k_2 + \mu_T} = 0. \tag{4.16}$$

Also, with $V = 0$, the only steady state that occurs is the one given by $T_0$ in the uninfected individual. The uninfected state for this model will be denoted by

$$T_0 = \overline{T} = \frac{p + (p^2 + 4s\gamma)^{1/2}}{2\gamma},\ \overline{T}^* = \overline{T}^{**} = \overline{V} = 0 \tag{4.17}$$

where an overbar denotes a steady state value and $\overline{T}$ is equation (4.4) with parameters

$$p = r - \mu_T \tag{4.18}$$

and

$$\gamma = \frac{r}{T_{\max}}. \tag{4.19}$$

Utilizing the second solution, $T = \frac{\mu_V}{\alpha}$, and equations (4.11), (4.13), and (4.6(a)), we arrive at the endemically steady state of:

$$\overline{T} = \frac{\mu_V}{\alpha} = \frac{\mu_V k_3}{k_1(Nk_2 - k_3)}, \tag{4.20}$$

$$\overline{T}^* = \frac{k_1 \mu_V \overline{V}}{\alpha k_3} = \frac{\mu_V \overline{V}}{Nk_2 - k_3}, \tag{4.21}$$

$$\overline{T}^{**} = \frac{k_2 k_1 \mu_V \overline{V}}{\mu_b \alpha k_3} = \frac{k_2 \mu_V \overline{V}}{\mu_b (Nk_2 - k_3)}, \tag{4.22}$$

$$\overline{V} = \frac{s\alpha^2 + p\alpha\mu_V - \gamma\mu_V^{\ 2}}{k_1 \mu_V (\alpha + \beta\mu_V)}, \tag{4.23}$$

where

$$k_3 = k_2 + \mu_T \text{ and } \beta = \frac{\gamma}{k_3}\left(1 + \frac{k_2}{\mu_b}\right). \tag{4.24}$$

Note that the product of number of free virus produced and the rate of conversion from latently infected cells to actively infected cells must be greater than the sum of the rate of conversion from latently infected cells to actively infected cells and the death rate for uninfected/latently infected cells in order for $\overline{T}^{**}$ to remain positive. We will now examine the stability of each of the equilibrium points.

## Section 4.2: Stability of the Disease-Free Steady State

For the disease free equilibrium to be asymptotically stable, it must attract nearby solutions i.e. following the introduction of a small amount of virus, $\frac{dV}{dt} < 0$. By setting $T = T_0$ in equation (4.14), we discover that this inequality occurs if and only if $N < N_{crit}$ where

$$N_{crit} = \frac{k_3(\mu_V + k_1 T_0)}{k_2 k_1 T_0} \tag{4.25}$$

Therefore the uninfected steady state is stable if and only if $N < N_{crit}$. To prove this, we must linearize the model by first finding the Jacobian for the system of equations 4.6(a) through 4.6(d).

$$A = \begin{pmatrix} p - \gamma\left(2T + T^* + T^{**}\right) - k_1 V & -\gamma T & -\gamma T & -k_1 T \\ k_1 V & -k_3 & 0 & k_1 T \\ 0 & k_2 & -\mu_b & 0 \\ -k_1 V & 0 & N\mu_b & -k_1 T - \mu_V \end{pmatrix} \tag{4.26}$$

By evaluating at the disease free equilibrium values from (4.17) and using the notation

$$k_4 = k_1 T_0 + \mu_V, \; a = -p + 2T_0\gamma, \tag{4.27}$$

we can rewrite A as

$$A = \begin{pmatrix} -a & -\gamma T_0 & -\gamma T_0 & -k_1 T_0 \\ 0 & -k_3 & 0 & k_1 T_0 \\ 0 & k_2 & -\mu_b & 0 \\ 0 & 0 & N\mu_b & -k_4 \end{pmatrix}. \tag{4.28}$$

The characteristic equation for A is now given by

$$(\lambda + a)[(\lambda + \mu_b)(\lambda + k_3)(\lambda + k_4) - k_1 k_2 T_0 N \mu_b] = 0 \tag{4.29}$$

One eigenvalue for this equation is $\lambda = -a < 0$, since from (4.26) $a = (p^2 + 4s\gamma)^{1/2} > 0$.

Hence we are left with the reduced equation

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0 \tag{4.30}$$

where

$$a_1 = \mu_b + k_3 + k_4 > 0; \tag{4.31}$$

$$a_2 = k_3 k_4 + \mu_b(k_3 + k_4) > 0; \tag{4.32}$$

$$a_3 = \mu_b(k_3k_4 - k_1k_2T_0N). \tag{4.33}$$

Using (4.25), $a_3$ can be rewritten as

$$a_3 = \mu_b k_1k_2T_0(N_{crit} - N). \tag{4.34}$$

By the Routh-Hurwitz criteria (Willems, 1970), the three eigenvalues of (4.30) will have negative real parts if and only if $a_1, a_3 > 0$ and $a_1a_2 - a_3 > 0$. Since $a_1$ and $a_2$ are both sums of positive terms, they are both positive. Under the condition $N < N_{crit}$, $a_3 > 0$ and

$$a_1a_2 - a_3 = \mu_b{}^2(k_3 + k_4) + \mu_b(k_3{}^2 + k_4{}^2 + 2k_3k_4 + k_1k_2T_0N) + k_3k_4(k_3 + k_4) > 0 \tag{4.35}$$

Therefore, if $N < N_{crit}$, the uninfected equilibrium is asymptotically stable.

If $N = N_{crit}$, then $a_3 = 0$ and the characteristic equation reduces to

$$\lambda(\lambda^2 + a_1\lambda + a_2) = 0 \tag{4.36}$$

The three eigenvalues for this equation are $\lambda_1 = 0$, $\lambda_{2,3} = \dfrac{-a_1 \pm (a_1{}^2 - 4a_2)^{1/2}}{2}$. Since one eigenvalue is 0 and the others have a negative real part, if $N = N_{crit}$ we conclude that the uninfected equilibrium is neutrally stable which means it is Liapunov stable, but not attracting.

If $N > N_{crit}$ then $a_3 < 0$. Hence there is exactly one sign change in (4.30) and by Descartes' rule of signs we can conclude that there is exactly one positive eigenvalue (Murray, 1989). Therefore, the uninfected equilibrium is unstable if $N > N_{crit}$.

So overall, for the steady state, the equilibrium point is asymptotically stable if $N < N_{crit}$, it is neutrally stable if $N = N_{crit}$, and it is unstable if $N > N_{crit}$.

## Section 4.3: Stability of the Endemic Equilibrium

Evaluating the Jacobian in (4.26) at the endemically infected steady state values given by (4.20) through (4.23) gives us

$$A = \begin{pmatrix} -\hat{a} & -\gamma\overline{T} & -\gamma\overline{T} & -k_1\overline{T} \\ k_1\overline{V} & -k_3 & 0 & k_1\overline{T} \\ 0 & k_2 & -\mu_b & 0 \\ -k_1\overline{V} & 0 & N\mu_b & -\hat{k}_4 \end{pmatrix} \tag{4.37}$$

where

$$k_3 = k_2 + \mu_T\,, \tag{4.38}$$

$$\hat{k}_4 = k_1\overline{T} + \mu_V\,, \tag{4.39}$$

$$\hat{a} = -p + \gamma(2\overline{T} + \overline{T}^{*} + \overline{T}^{**}) + k_1\overline{V}\,. \tag{4.40}$$

To examine the sign of $\hat{a}$, note that from the steady state of (4.6(a)) we have

$$0 = s + p\overline{T} - \gamma\overline{T}(\overline{T} + \overline{T}^{*} + \overline{T}^{**}) - k_1\overline{V}\overline{T} \tag{4.41}$$

so that $\hat{a}\overline{T} = s + \gamma\overline{T}^{2}$ and therefore

$$\hat{a} = \gamma\overline{T} + \frac{s}{\overline{T}} > 0\,. \tag{4.42}$$

The characteristic equation for (4.37) is as follows:

$$\lambda^4 + b\lambda^3 + c\lambda^2 + d\lambda + e \tag{4.43}$$

where

$$b = \hat{a} + k_3 + \hat{k}_4 + \mu_b > 0\,, \tag{4.44}$$

$$c = \hat{a}(k_3 + \hat{k}_4 + \mu_b) + \mu_b(k_3 + \hat{k}_4) + k_3\hat{k}_4 + k_1\overline{T}\overline{V}(\gamma - k_1), \tag{4.45}$$

$$\begin{aligned} d = {} & \hat{a}[k_3\hat{k}_4 + \mu_b(k_3 + \hat{k}_4)] + k_1\overline{VT}[\gamma(\mu_v + k_2 + \mu_b) - k_1(k_3 + \mu_b)] \\ & + \mathrm{k_3\mu_b\hat{k}_4 - k_1k_2\mu_bN\overline{T}} \end{aligned}, \tag{4.46}$$

$$e = k_1\overline{VT}[k_1\mu_b(Nk_2 - k_3) + \gamma\mu_V(k_2 + \mu_b)] + \hat{a}k_3\hat{k}_4\mu_b - \hat{a}k_1k_2N\mu_b\overline{T}\,. \tag{4.47}$$

To simplify *d* and *e*, we examine the last two terms of each equation and use the definitions of $\hat{k}_4$ from (4.39) and $\overline{T}$ from (4.20). With this we see that

$$\frac{k_1k_3^{\,2}\mu_b\mu_V}{k_1(Nk_2 - k_3)} + k_3\mu_b\mu_V - \frac{k_1k_2k_3\mu_b\mu_V}{k_1(Nk_2 - k_3)} = 0, \tag{4.48}$$

so that

$$d = \hat{a}[k_3\hat{k}_4 + \mu_b(k_3 + \hat{k}_4)] + k_1\overline{VT}[\gamma(\mu_v + k_2 + \mu_b) - k_1(k_3 + \mu_b)], \tag{4.49}$$

and

$$\frac{\hat{a}k_1k_3^{\,2}\mu_b\mu_V}{k_1(Nk_2 - k_3)} + k_3\mu_b\mu_V\hat{a} - \frac{\hat{a}k_1k_2k_3N\mu_b\mu_V}{k_1(Nk_2 - k_3)} = 0, \tag{4.50}$$

so that

$$e = k_1\overline{VT}[k_1\mu_b(Nk_2 - k_3) + \gamma\mu_V(k_2 + \mu_b)]. \tag{4.51}$$

To examine the stability, we again apply the Routh-Hurwitz criteria. For the parameters given in Table 4.1, b, c, and d are all positive. However, e is only positive when $N > N_{crit}$. To see this, note that if $N > N_{crit}$, from (4.25) we have

$$Nk_2 > N_{crit}k_2 = \frac{k_3(\mu_V + k_1T_0)k_2}{k_2k_1T_0} > k_3. \tag{4.52}$$

However, if the inequality from (4.52) is reversed, *e* is no longer positive. To satisfy the Routh-Hurwitz criteria, we must also note that, for the parameters given in Table 4.1,

$$\frac{(bc-d)b^2}{d} > e\,. \tag{4.53}$$

Therefore, this solution is stable when $N > N_{crit}$.

When $N = N_{crit}$, the uninfected steady state and the endemic steady state concur. To see this, substitute $N = N_{crit} = \frac{k_3(\mu_V + k_1 T_0)}{k_2 k_1 T_0}$ from (4.25) into (4.15) and use the definition of $k_3$ so that

$$\alpha = k_1\left[\frac{\frac{k_2 k_3(\mu_V + k_1 T_0)}{k_1 k_2 T_0}}{k_2 + \mu_T} - 1\right] = \frac{k_3(\mu_V + k_1 T_0)}{T_o(k_2 + \mu_T)} - k_1 = \frac{\mu_V}{T_0} \tag{4.54}$$

which mirrors the disease free equilibrium. Also, $\overline{V} = 0$ since, when $N = N_{crit}$, we mirror the disease free steady state. Hence at $N = N_{crit}$ there is a transcritical bifurcation and the endemically infected state emerges for $N > N_{crit}$ as a new steady state in $R_+^4$.

For $N < N_{crit}$, the infected steady state does not lie in $R_+^4$, because $\overline{V}, \overline{T}^*, \overline{T}^{**} < 0$, and hence it is not biologically relevant. Therefore, the only stability of concern is the previously examined condition of $N > N_{crit}$.

## Section 4.4: Source Term as a Decreasing Function

HIV may be able to infect cells in the thymus and bone marrow which provide the influx of new, healthy T4 cells in an uninfected individual. The infection can decrease

the production of these new T cells. In the previous model (p. 31), we assumed that the source term was constant. In some studies on mice, it has been shown that HIV infection decreases the number of T cells produced by the thymus and bone marrow (Wu et al, 1991). Now let us examine the consequences of assuming that the source, *s*, is equation (4.6(a)) is a decreasing function of the viral load. If we assume, as Perelson did in (Perelson, 1989), that $s(v) = se^{-\theta v}$ where θ is a constant, our model will involve transcendental equations. To avoid this, we shall assume that

$$s(v) = \frac{\theta s}{\theta + v}. \tag{4.55}$$

If $v = 0$, then *s* is a constant as in equation (4.1). However, if the viral load increases to the point that $v = \theta$, then *s* is decreased to half of its normal value.

Replacing *s* by $s(v)$ in (4.6(a) and (4.6(b)) still yields two equilibrium points. One is a disease free equilibrium and the other is an endemic equilibrium. For the endemic steady state, equations (4.20), (4.21), and (4.22) still hold for the values of $\overline{T}, \overline{T}^*$, and $\overline{T}^{**}$ respectively due to the fact that *s* did not affect their values. However, in order to determine $\overline{V}$, we made substitutions into (4.6(a)) which contained the source term which we are altering. Therefore, $\overline{V}$ is now given by the one positive solution of

$$V^2[k_1\mu_V(\alpha + \beta\mu_V)] + V[\theta k_1\mu_V(\alpha + \beta\mu_V) - p\alpha\mu_V + \gamma\mu_V{}^2 = 0 \tag{4.56}$$

which is a result of replacing *s* by $\frac{\theta s}{\theta + v}$ in equation (4.23). To see that there is only one positive solution, note that in the limit of large θ we can ignore the terms not proportional to θ in (4.56). Therefore,

$$\overline{V} = \frac{s\alpha^2 + p\alpha\mu_V - \gamma\mu_V{}^2}{k_1\mu_V(\alpha + \beta\mu_V)} \tag{4.57}$$

This is the same result as when $s$ was taken to be a constant. Also note that (4.56) has only one positive root due to Descarte's rule of signs, as it has only one sign change. Thus the effect of replacing $s$ by a decreasing function, $s(v)$, is quantitative, not qualitative.

## Section 4.5: Discussion

We have examined the dynamics of T cell populations in both healthy and HIV infected individuals. Although this model is relatively simple compared to the model in Chapter 3, in that it does not examine immune response to HIV infection, mechanisms for cell death other than direct HIV-mediated killing (such as syncytia formation), or multiple viral strains, it does demonstrate that HIV by itself can cause partial T4 cells depletion. The analysis shows that, on the NT phase plane, the uninfected equilibrium is a transcritical bifurcation point. From the parameters in Table 4.1, we see that for $N < N_{crit} = 774$, the uninfected steady state with $T = 1000$ is stable. At $N = N_{crit}$ this state loses its stability and the endemically infected state, with T as a decreasing function of N, becomes stable.

We also examined two forms of the model given by (4.6(a) – (4.6(d)). The first assumed the rate of T cell production in an HIV infected individual was constant. The second modified the model so that the rate of T cell production decreased with time. We found that this alteration would produce a quantitative difference, but did not otherwise profoundly alter the model.

The model from Chapter 4 predicts that N, the number of infectious viral particles produced per actively infected T cell, needs to be above some critical level, $N_{crit}$, for successful HIV infection. If $N < N_{crit}$, then the level of free virus will monotonically decrease and ultimately be eliminated. This is equivalent to the reproductive number, $R_0$, discussed in Chapter 2. In fact, the entire model is similar to a classical epidemiological model. Note the presence of two equilibrium points, one a "disease free" or "virus free" steady state and the other an endemic equilibrium point in which the "disease" or virus is stably maintained.

Experimental evidence supports the prediction of a critical value for $N$ (Fenyo et al, 1988). In this study, it was discovered that some viruses could not be grown into activated peripheral blood mononuclear cells of normal donors. The lack of successful transmission was not dependent on the amount of virus introduced into the culture. This independence from $V_0$ is exactly what this model predicts when $N < N_{crit}$.

In conclusion, from this model we predict that HIV cytopathicity is a major factor in producing many of the features of HIV infection. However, infection and direct T cell depletion due to a single strain of the virus is probably not the only factor involved. Other factors such as increases in $N$, increase in $k_1$ (an increase in the rate uninfected T cells become latently infected T cells), a decrease in $\mu_V$ (viral particles live longer), or mutation of HIV may also contribute to the observed characteristics of HIV. However, these results show that these factors do not need to play a major role in explaining the observed characteristics of HIV.

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