Combination Therapy of HIV Infection: an Analysis in Optimal Control

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SENIOR THESIS

1 Introduction

1.1 The continuing problem of HIV infection

Back in 1984, when AIDS was first shown to be caused by the human immunodeficiency virus (HIV), the world was skeptical that any successful treatment would ever be found. Since then, much has been discovered about preventing and slowing the infection process, and we now have at our disposal more weapons than were ever thought possible. However, a cure still eludes all research efforts made in the past 13 years.

AIDS is fast becoming an epidemic in many parts of the world, with an estimated 30.6 million people infected globally - 20 million of whom reside in sub-Saharan Africa. Still, the large amount of infected individuals is miniscule in comparison to the high percentage of these people who don't even know that they are infected [1]. Just this past year, the U.N. Program on HIV/AIDS estimated that nine out of ten HIV infected people in Africa are unknowingly harboring the virus and are ignorantly contributing to the spread of AIDS. Clearly, HIV infection is still one of the major health concerns of our time and will remain a problem until a readily available vaccine is developed.

Though the present situation of HIV infection looks grim for less industrialized countries such as those in Africa, the other side of the globe is experiencing new hope. Due to concentrated research and public awareness efforts, the United States has actually experienced a drop in the HIV infected population. The difference here lies in the availability of medical care, heightened awareness and educational programs, and access to quick and accurate HIV-positive testing. The sooner these measures can be adopted by underdeveloped countries, the closer we may be to totally eradicating this harmful virus.

Thanks to research efforts made by scientists in 1996, many new anti-HIV drugs have been developed, and some are now available by prescription. These chemotherapies, although not a cure, help delay the onset of the many symptoms of AIDS and prolong the life of many HIV infected patients. One must be cautious in the scheduling of this treatment though, since a large variety of side effects exist for each chemotherapy. These side effects have caused physicians and medical scientists to be locked in a tug-of-war be-

tween treating a patient with maximal chemotherapy and administering a mediocre treatment schedule to lessen the detrimental effects of the drugs.

1.2 Infection Background

HIV belongs to the well known retroviral family, *Retroviridae*, which consists of viruses having an unique form of RNA replication. This replication begins with reverse transcription of virion RNA into a single strand of cDNA and is catalyzed by the enzyme reverse transcriptase. Synthesis of cDNA involves the concurrent digestion of the viral RNA with the RNAse portion of the reverse transcriptase. After the linear double stranded DNA is complete, it is subsequently circularized, integrated into the host chromosomal DNA, and then used for transcription of the mRNA (for viral protein translation) and the full-length genomic RNA (for the newly formed virions) [5].

The host cells which HIV infects are human lymphocytes known as helper T cells. The helper T cell plays an integral role in immune response, and without them the human body is severely handicapped in fighting disease. Many opportunistic conditions can result if the helper T cell count is low enough, including fungal infections, bacterial infections, and rare forms of cancer. The first step of infection involves the binding of a virion to a receptor molecule on the host cell surface. The receptor for HIV, CD4, is a transmembrane protein which normally plays an important role in signaling between the helper T cells and the antigen presenting cells which provide antibody mediated immunity. Even when a portion of the CD4 receptor is bound to other cell surface molecules, it retains the HIV receptor activity and the virus can enter the cell by recognizing the receptor with its own 'key' molecule, gp120 or surface protein (SU) [5]. Also, the presence of a specific 'fusion receptor' for HIV is being invoked to explain the lack of infection of mouse hybrids expressing the human CD4 protein. Clearly, there must be some other factor which allows viral entry. This second essential receptor is known as a chemokine receptor, an example of which is CXCR4 [13].

In brief, the replication cycle followed by HIV consists of the following steps [5]:

1) Attachment of the virion to the specific receptor on the host cell surface.
2) Penetration of the virion core into the cell.
3) Reverse transcription to copy viral genome RNA into DNA which can be inserted into the host.
4) Transportation of the DNA to the nucleus.
5) Integration of the viral DNA into random sites in cell DNA to form the provirus.
6) Synthesis of viral RNA by cellular RNA polymerase II using the integrated provirus as the template.
7) Post-transcriptional processing of RNA to form genome and mRNAs.
8) Virion protein synthesis (translation of viral mRNAs).
9) Assembly and budding of new virions.
10) Proteolytic processing of capsid proteins via the viral protease enzyme.

Since the HIV life cycle is quite different from any other cell in the human body, many antiretroviral treatments are available which take advantage of its uniqueness. AZT, for example, is a drug which inhibits the viral enzyme reverse transcriptase. AZT and other types of retroviral chemotherapy are collectively referred to as anti-HIV therapies. This designation includes any treatment which specifically stops HIV from reproducing or infecting its primary target, the helper T cells. It is conceivable that any of the above steps may be inhibited by a certain treatment, but as of now there are three main catagories of drugs available.

The three basic types of anti-HIV chemotherapy currently available by prescription or through experimental trials are nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors. All of these agents limit HIV infection for some amount of time, but since the virus is highly mutagenic it eventually develops resistance, and the treatment soon becomes useless. Many experts believe that using combination or 'cocktail' chemotherapy - two or more drugs administered simultaneously - may help slow the development of resistance by HIV and also act more efficiently in inhibiting viral reproduction.

1.3 An optimal control of HIV infection

The main thrust of this investigation is to suggest an optimal method of treating HIV infection given the known facts about the infection process. Many mathematical models already exist describing HIV infection, and we propose using one of these models to monitor the progression of HIV infection in a patient. Of the many chemotherapies available, an experimental chemokine derivative was first chosen to prevent the virus from entering a T cell [13]. Recently, combination therapy has been applied to our study with an additional viral protease inhibitor.

While anti-HIV chemotherapy has been used for some time, an optimal treatment schedule has been at best a rough approximation. Until a cure is found, the primary problem faced by physicians today is one of balance. Their objective is to inhibit the virus as much as possible while simultaneously holding the side effects of treatment to a minimum. This must be done by an 'optimal' chemotherapy schedule - one which both maximizes patient's uninfected T cells, and minimizes any harmful effects that the chemotherapy might incur. Through mathematical modeling and optimal control theory, we propose an optimal treatment strategy to strike a balance between the two effects.

Our analysis begins with a description of the mathematical model used and then compares this model with others adopted by medical researchers today. Optimal control theory will then be applied to the model, and methods for solving our problem will be explained. Once our problem is set up, numerical methods will then be used to generate the resultant optimal treatment schedule for an HIV infected patient. A discussion of the results and potential future applications will follow thereafter.

2 Mathematically Modeling HIV Infection

In the recent past, many mathematical models for the treatment of HIV infection have been developed [9], [11], [14], and [15]. An overwhelmingly similar aspect of these models is their use of first order ordinary differential equations (ODE's) describing the interaction between the viral particles and the T cells. In each model, the T cells are assumed to express the CD4 and CXCR4 protein receptors on their surface and any others found in the future to be central to HIV entry [13]. This just means that for the modeled helper T cells, all of the requirements for HIV entry are met, and each helper T cell has an equal probability of being infected. Also notice that any other cell expressing the receptor can also be infected by HIV. This is how HIV 'hides out' in areas of the brain protected from chemotherapies by the blood-brain barrier [18]. In the model which was used, we assumed that these secondary infection sites play such a small role in the infection process that they may be neglected. However, some models take these other sites into account, and we will go over an example of this later in the section. For now, the model which was used in our analysis will be presented and explained.

2.1 Our Model

In order to begin the optimal control procedure, it is necessary to obtain a model which describes the basic interaction between HIV and the immune system's T cells. In [14] and [16], a model is given which simulates the infected scenario. We utilize this model and recommend that the reader see these papers for a complete derivation and verification. A brief discussion is presented below.

The model consists of four states, three of which are T cell categories and another represents the HIV virus. We let $T(t)$ represent the concentration (number of T cells per mm^3) of uninfected T cells at time t, and $T^*(t)$ and $T^{**}(t)$ are used to denote the concentrations of latently infected and actively infected T cells, respectively at time t. Latently infected T^* cells are those in which HIV has inserted its genetic material, but as of yet no virus is being produced from the host cell. Actively infected T^{**} cells, as the name implies, actively produce HIV virions since, unlike T^* cells, the viral genetic information has been 'turned on.' The concentration of *free* infectious virus at time t will be denoted by $V(t)$ (viral particles which

are able to infect and have not already entered a cell). Time t is measured in days in all equations in the following analysis.

Each of the four states is a function of time and represents a solution to a first order differential equation describing infection kinetics. The left hand side of each equation is the first derivative of the state with respect to time. Hence, this derivative term represents the rate of growth of each state (in concentration per time) or equivalently, the slope of the state function at each time point. Therefore, the units on the right hand side of the equation must agree with the concentration per unit time dimensions, so each major term separated must also have these units. For example, in equation (1) the second term $-\mu_T T$ is actually $-\mu_T(\text{days})^{-1}T(\text{concentration of T cells})$. Notice that the combination of units yields the desired result of concentration per unit time. The system of equations describing HIV infection consists of the following first order ODE's:

$$(1) \qquad \frac{dT}{dt} = \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T+T^*+T^{**}}{T_{max}}\right) - k_1 VT,$$

$$(2) \qquad \frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^*,$$

$$(3) \qquad \frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**},$$

$$(4) \qquad \frac{dV}{dt} = N\mu_b T^{**} - k_1 VT - \mu_v V.$$

- In (1), $\frac{s}{1+V}$ is positive and represents the production of new T cells inversely affected by the amount of virus [3, 10]. The second term, $-\mu_T T$, models the exponential decay of the T cell population, with a death rate of $-\mu_T T$. Our third term is the logistic growth of the T cell population with saturation occuring at T_{max}. In order to see this, notice that when the *total* T cell population reaches its maximum, i.e. when $T+T^*+T^{**} = T_{max}$, the entire term $rT\left(1 - \frac{T+T^*+T^{**}}{T_{max}}\right)$ becomes zero and will therefore not contribute to the growth of T cells.

  The fourth and final term in equation (1), $-k_1 VT$, deals with the interaction between the viral particles. This term is analogous to a second order rate law in enzyme kinetics in that

it assumes that both the concentration of T cells, T, and the virion concentration, V, contribute to the formation of infected T cells by combining with a rate constant of k_1. Once a T cell is invaded by the virus, it then becomes a latently infected T^* cell. $-k_1VT$ is thus a loss term for healthy T cells in equation (1), and k_1VT is a gain term for T^* in equation (2).

- In the ODE (2), the first term k_1VT is a growth term for the population of latently infected cells. Also, these cells have two separate removal rates. The first, $-\mu_T$, is as before a natural death rate constant for those T cells not producing virus. The second death rate constant, $-k_2$, actually represents a transfer rate for this population into the next state T^{**} described by equation (3).

- The ODE (3) models the actively infected T cell population. As stated before, latently infected cells become actively infected with a rate constant of k_2. The second term $-\mu_b T^{**}$ in (3) is a death rate for the actively infected T cells due to the production of virus.

- The free virus population is described by our final ODE of the system, equation (4). We assume that each actively infected cell produces N viral particles before it dies. Also, whenever a virion infects a healthy T cell, the virion itself enters the cell and is removed from the *free* virus population. Thus, the term $-k_1VT$ is a loss term for the free viral population, V. Any interaction of the virus with previously infected T cells is neglected since these cells soon lose their CD4 protein after initial infection due to down regulation of transcription by viral gene products [5]. The last term, $-\mu_v V$, lumps together viral loss of infectivity and removal from the body into a common death rate for the virus.

Analysis of the stability is given in [9] and [16]. This system was shown to have two steady states, an uninfected steady state and an endemically infected steady state. The uninfected steady state occurs when no virus is present, i.e $T = T_0$, $T^* = 0$, $T^{**} = 0$, and $V = 0$. The second, *endemically infected steady state*, occurs with

each of the cell populations at positive values. This second type is analogous to a remission period during the infection process. During this period, symptoms seemingly disappear from the patient and the T cell population appears to remain constant. However, the body is constantly producing T cells, but at this stage there exists a balance between the body's efforts and the rate of infection by the virus. Remission is a very delicate stage in any type of infection, and any perturbance could wildly shift the equilibrium toward problematic infection.

In fact, Perelson *et al.* [16] showed that if the parameter N was below a critical value, N_{crit}, the uninfected steady state is stable and the infected steady state is unstable. At $N = N_{crit}$, The stability is exchanged through a bifurcation and the infected state becomes locally stable. For $N > N_{crit}$, other bifurcations in the eigenvalues can occur, and therefore global stability could not be shown. As an example, it was shown that stability can be lost for the infected steady state giving rise to stable limit cycles. This behavior is believed to occur only for parameter values lying outside of the possible ranges of biological feasibility.

Notice that these equations are coupled and nonlinear. In order to solve the first ODE, $\frac{dT}{dt}$, we must also have information about V, T^*, and T^{**} at each time t. Since these other equations are described by ODE's, we must solve the entire system at each time step until we can proceed to the next.

2.2 Other Models

Many other models describing HIV infection exist, and without a brief summary of the modeling progress we would leave the reader believing that everything about the modeling of HIV infection has been said and done. This is hardly the case. The disease course is far too complicated a process for an easy analysis to be performed. With the available data and hypothesized mechanisms gaining more and more support, the interaction between the virus and humans has been approached in a variety of different ways. Among many modelers, there is some controversy over which model is the best. We will discuss a few of these attempts to give the reader a better flavor of the model development process. Our starting point is a general model of two ordinary differential equations, and an expansion on

this primary model will lead us to an inclusion of variable parameters and non-lymphatic infection sites.

In [17], the dynamics of cell infection and virion production are represented by

$$\frac{dT^*}{dt} = k\bar{T}V - \delta T^*, \tag{5}$$

$$\frac{dV}{dt} = N\delta T^* - cV, \tag{6}$$

where $T^* \equiv T^*(t)$ and $V \equiv V(t)$ are the populations of infected target cells and roaming virus, respectively at time t. The rate of decay of infected cells is $-\delta T^*$, and the infection rate is given by $k\bar{T}V$ where $\bar{T}$ is the total population of uninfected T cells and is assumed constant in the time of treatment, i.e., it does not depend on time. This is the main difference between this model and our four-ODE model which accounts for longer intervals of treatment by assuming $\bar{T} \equiv T(t)$.

In the second ODE, (6), N is the average number of virions escaping the infected cell before complete cell lysis and is measured per infected cell per day and per lifetime of an infected cell. In a short period of time, the system is assumed to be in a steady state with $T^*(t) = \bar{T}^*$ and $V(t) = \bar{V}$ as constant values. This model, (5) and (6) is then perturbed by a protease inhibitor which interrupts viral production by inhibiting correct viral protein processing. The effect of this treatment is that only noninfectious viral particles escape from the host cell. The differential equations for the perturbed system are

$$\frac{dT^*}{dt} = k\bar{T}V_I - \delta T^*, \tag{7}$$

$$\frac{dV_I}{dt} = -cV_I, \tag{8}$$

$$\frac{dV_{NI}}{dt} = N\delta T^* - cV_{NI}, \tag{9}$$

where $V_I(t)$ and $V_{NI}(t)$ are the concentrations of infectious and noninfectious virions, respectively, at the time after chemotherapy begins. Although this model describes the general flow of the disease progression during a shortened time period, it does not take into account a change in the daily turnover rates of virus and T cell

populations with time. Another model which attempts to do so is being developed presently by Kirschner and Webb [11].

Kirschner and Webb's version of a predator-prey (Lotka-Volterra type) model consists of a two differential equations in the general form of the equations

$$\frac{dT^*}{dt} = k(t)TV - \delta(t)T^*, \tag{10}$$

$$\frac{dV}{dt} = \hat{\delta}(t)T^* - c(t)V, \tag{11}$$

where the constant rate parameters have been replaced by disease-course, time-dependent parameters. The equations (10) and (11) are identical to equations (5) and (6) except for this assumption of time dependence, and because of this, equations (10) and (11) more effectively model the nonlinearities of disease dynamics. Over the long frame of time that is used to model the effects of treatment on T cell and viral population, this variable coefficient model should be a better model. However, the previous model, (5) and (6), may be needed when modeling faster processes occuring in short period treatment intervals.

As a final case of HIV infection models, an example using secondary sources of infection is now presented. These secondary infection sites may be neurons of the central nervous system or possibly other immune system cells such as macrophages. This model, by Perelson et al. [15], includes macrophage cells, $M(t)$, in addition to T cells, $T(t)$. Both uninfected cell types serve as hosts to the virus, $V(t)$. Also, actively infected T cells are represented by $T^*(t)$ while latently infected T cells are represented by $L(t)$. Notice that this contrasts our designation of the two infected states (see pages 5 and 6), but one can easily see that the two states are essentially the same as $(T^*) \equiv L$ and $(T^**) \equiv T^*$ with our model's state values represented in parentheses. Perelson's new kinetic model is proposed as follows:

$$\frac{dT^*}{dt} = kVT + aL - \delta T^*, \tag{12}$$

$$\frac{dL}{dt} = fkVT - \mu_L L, \tag{13}$$

$$\frac{dM^*}{dt} = k_M VM - \mu_M M^*, \tag{14}$$

$$(15) \qquad \frac{dV}{dt} = N\delta T^* + pM^* - cV.$$

In this model, all variables T, T^*, M^*, L, and V are functions of time. The immune system's cytotoxic T cells or macrophages, M, become infected at a rate constant k_M and enter the long-lived infected cell state, M^*. These cells continuously produce virus at an average rate per cell, pM^*, and are lost at a death rate of $-\mu_M M^*$.

Another assumption in this model is that when T cells are infected, actively infected T^* cells are generated with a rate constant k, and latently infected T cells harboring viral information in their genome (total DNA) are generated with a rate constant fk, smaller by a factor of f. The growth of the latently infected T cells is modeled by equation (13), and they have a death rate of $-\delta_L L$ and a rate $-aL$ of transformation into actively infected T^* cells. The combination of the two rates of removal corresponds to a combination removal rate constant of $-\mu_L = -a - \delta_L$. In equation (12), T^* are lost with a removal rate of $-\delta$ and produce a total of N viral particles in the course of their infected lifetime. In the last ODE (15), virions, V, are cleared at a rate $-cV$.

This model, like ours, was used to obtain an optimal combination of chemotherapies. The cocktail treatment included a protease inhibitor and two reverse transcriptase inhibitors [15].

Clearly, there is not only one correct way to model the HIV infection process. Our model may account for longer treatment periods and different infective states of the T cells, but it does not model the activity of the virus in other regions of the body. In some cases, such as when the patient exhibits AIDS related dementia, a more flexible model should be used, eg., one that models neuronal infection in the brain. Due to different initial assumptions, each model may be justifiable in different situations. Our treatment situation may neglect the presence of other compartments in the body susceptible to HIV infection, but it does take into account the latent and active states of T cell infection and more thoroughly describes the interaction between virus and healthy T cell.

Having a more complicated model does not necessarily mean having a better model. It is entirely up to the medical researcher to decide which variables he or she wishes to neglect in an optimal treatment schedule for a patient. Our model, equations (1)-(4), will

soon be modified with chemotherapy terms and will be used as structural support for the objective function we seek to maximize. One should keep in mind that the following procedures may be initiated for the other models stated above. Before commenting on the modifications made in our model to include dual chemotherapies, the theory behind optimal control will briefly be explained. For more information on the existence and application optimal control, please refer to [7] and [12].

3 Optimal Control

3.1 Introduction to Optimal Control Theory

Optimal control theory is a method used to solve for an extremum value of an objective functional involving dynamic variables. This maximizing or minimizing process is accomplished by adjusting the control variable, u, until the maximum or minimum is achieved. The control which yields the extreme value is denoted by u^* and is called an optimal control. This control variable, which in our case is a function of time, can be used in many modeling situations and could be a function of any controlable variable, i.e. if one could directly manipulate the number of viruses, the u could be V.

If the mathematical model consists of PDE's (partial differential equations), the control will exhibit its action on infinite dimensional systems. In our case however, we use a deterministic control of a finite dimensional system in time, and the states of infection are described by ODE's. The variables are divided into two classes: state variables and control variables, both of which are functions of time in our model. The movement of state variables of infection is governed by first order ODE's, and the control affects the behavior of the ODE's in some way. The maximum principle developed by L.S. Pontryagin in the late 1950's gives a method to find the optimal control [7].

3.2 Our Objective

Our control, $u(t)$, represents an effective chemotherapy dosage bounded between 0.0% and 100.0%, or $u(t) \in [0, 1]$ where u ranges from no chemotherapy (0.0) to a maximum dosage (1.0). In this problem, the primary goal is to maximize the healthy T cell count of an HIV infected patient, and the secondary aim is to minimize any side effects caused by the chemotherapy control. Thus, the problem is to find the optimal chemotherapy percentage, $u(t)$, throughout the length of treatment $t_0 \leq t \leq t_f$. This optimal control should maximize our objective, i.e., it should maximize both the healthy T cell concentration, $T(t)$, and the *negative* value representing side effects, which is denoted by $-\frac{1}{2}Bu^2(t)$. In the side effects term, the $\frac{1}{2}B$ represents a balancing (B) constant which relates the percentage of chemotherapy in a meaningful way to the healthy T cell concentra-

tion. Both the T cell concentration and side effects of chemotherapy are included in the objective functional, $J(u)$. By definition [12], a functional maps functions into numbers. In our case, the functional $J(u)$ is an integral over the treatment time. Therefore, a control $u(t)$ is sought to maximize the objective functional $J(u)$ in equation (16):

(16)
$$max \quad J(u) = \int_{t_0}^{t_f} \left[T(t) - \frac{1}{2} B u^2(t) \right] dt.$$

If we apply two different control chemotherapies $u_1(t)$ and $u_2(t)$, the problem is very similar except that the functional $J(u_1, u_2)$ will be maximized with respect to both controls. The new objective functional is stated in equation (17), and takes into account the side effects of combination chemotherapy:

(17)
$$max \quad J(u_1, u_2) = \int_{t_0}^{t_f} \left[T(t) - \frac{1}{2} B_1 u_1^2(t) - \frac{1}{2} B_2 u_2^2(t) \right] dt.$$

One can easily imagine implementing many more controls by simply tacking on each one's side effects to our objective functional. In both equations (16) and (17), chemotherapy benefits a patient by increasing the healthy T cell population, $T(t)$, which is described by ODE (1) in our system. There also exists a certain 'cost' on the patient for administering a chemotherapy, and this cost represents the potential for harmful side effects from each drug. These side effects are taken into account by the balancing constants B_i for the control chemotherapy u_i. Each balancing term balances the systemic cost of its respective chemotherapy to the benefit measured in healthy T cell concentration.

Although a consensus on the apparent costliness of chemotherapy does not yet exist, the solution of the maximum of J was pursued with an adjustable value for each B. Practicing physicians using this study should weigh the apparent side effects of each drug administered to the patient and proceed according to the optimal treatment

schedule generated by the following analysis. The solutions and effects of two optimal chemotherapies will now be implemented in our model.

3.3 The Modified Model

The optimal control used in this problem represents the percentage of the *effect* a chemotherapy has on inhibiting the virus. As stated before, each control $u_i(t)$ is bounded on the interval $[0, 1]$ where $u = 0$ implies no chemotherapy and $u = 1$ indicates maximum chemotherapy. Our control class consists of measurable functions defined on a limited window of treatment time $[t_0, t_f]$. This treatment period is limited in order to lessen the effects of resistance or side effects on the immediate state of the model. Since HIV has an extremely high rate of mutation, a portion of the viral population may develop resistance to a chemotherapy treatment after some finite amount of time. This necessitates a finite interval of treatment since the ineffective drug can still exhibit side effects.

Previous work has already been done with controls which decreased viral load by multiplying the parameter N in equation (4) by the chemotherapy control representing a reverse transcriptase inhibitor [9, 16]. In our model, a similar type of control was used as well as another which inhibited the interaction between virus and T cell. The objective function used was essentially equation (17). The first control $u_1(t)$ represents an inhibitory drug used to block viral binding to the T cell. This control is analogous to a chemokine-like substance which competitively or irreversibly inhibits a secondary receptor on a T cell required for HIV entry, for example the chemokine receptor CXCR4 [13]. Since $u_1(t)$ blocks binding, it is attached to the term k_1VT in both equations (1) and (2), but not equation (4). By applying the control in the manner of $(1-u_1(t))k_1VT$, the virus to T cell interaction is multiplied by zero if our control is at its maximum dosage of $u_1(t) = 1$. If however, the chemotherapy is absent (i.e. $u_1(t) = 0$), complete interaction at a rate k_1 will resume in the system.

The second control used in the model is denoted by $u_2(t)$. This control represents a viral protease inhibitor or any other chemical (such as AZT, ddC, etc) which decreases viral production from an actively infected host cell. As in the case of our first control, this

chemotherapy will be applied as $(1 - u_2(t))$. Instead of inhibiting virus to T cell interaction, u_2 affects the amount (N) of correctly processed virus budding from a T^{**} cell. This control is applied in equation (4) in our system of equations.

After applying both controls to our model, the system of equations is altered as follows, with the control terms in **bold** type:

$$\frac{dT}{dt} = \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T+T^*+T^{**}}{T_{max}}\right) - (\mathbf{1} - \mathbf{u_1(t)})k_1 VT, \tag{18}$$

$$\frac{dT^*}{dt} = (\mathbf{1} - \mathbf{u_1(t)})k_1 VT - \mu_T T^* - k_2 T^*, \tag{19}$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**}, \tag{20}$$

$$\frac{dV}{dt} = (\mathbf{1} - \mathbf{u_2(t)})N\mu_b T^{**} - k_1 VT - \mu_v V. \tag{21}$$

Now that the model has been modified to include two different controls, the optimization process can begin. Our goal, as stated previously, is to characterize the optimal controls $u_1^*(t)$ and $u_2^*(t)$ satisfying the maximum of the objective functional (17). The existence of an optimal control may be found in Fleming and Rishel [6]. In this problem, the necessary concavity of $J(u_1^*, u_2^*)$ holds, and therefore the required conditions of Pontryagin's Maximum Principle have been met.

4 Solving the Optimal Control Problem

4.1 Setting up the Maximum Problem

In order to set up this maximization problem, the system of ODE's (equations (18-21)) must first be attached to the objective functional (equation (17)). This is accomplished by using the Lagrangian function, equation (22), with penalty terms attached for the bounds on the controls. For our problem, the Lagrangian is the integrand of the objective functional $J(u_1, u_2)$, equation (17), coupled with the state ODE's by means of functions known as *adjoints*, each of which is denoted by $\lambda_i(t)$ corresponding to the *ith* state. The penalty terms are denoted by $\omega_i(t)$ with $\omega_i(t) \geq 0$ for $i = 1, 2, 3, 4$, and $\frac{dS_i}{dt}$ denotes the right hand side of each ODE in our system, for states $S_i = T, T^*, T^{**}, V$ from equations (18-21). The Lagrangian, L, is:

$$
\begin{aligned}
(22) \qquad L = & \left\{ T(t) - \tfrac{1}{2} B_1 u_1^2(t) - \tfrac{1}{2} B_2 u_2^2(t) \right\} \\
& + \lambda_1 \frac{dT}{dt} + \lambda_2 \frac{dT^*}{dt} + \lambda_3 \frac{dT^{**}}{dt} + \lambda_4 \frac{dV}{dt} \\
& + \omega_1(u_1(t)) + \omega_2(1 - u_1(t)) + \omega_3(u_2(t)) + \omega_4(1 - u_2(t)).
\end{aligned}
$$

Since our problem contains bounded controls $0 \leq u_1, u_2 \leq 1$, we made use of penalty multipliers, ω_i, representing functions of time. These ω_i's are used to attach our control constraints. The penalty multipliers satisfy $\omega_1(u_1(t)) = 0$, $\omega_2(1 - u_1(t)) = 0$, $\omega_3(u_2(t)) = 0$, and $\omega_4(1 - u_2(t)) = 0$ on $u_1, u_2 \in (0, 1)$, with the additional constraint $\omega_i \geq 0$ for all i. The penalty terms act to keep each control bounded in the interval $[0, 1]$. By Pontryagin's Maximum Principle, the Lagrangian is maximized with respect to u_1, u_2 at u_1^*, u_2^* when the Lagrangian is evaluated at the optimal states and adjoints.

Since we will now be maximizing the Lagrangian function with respect to each u, we must choose controls which are bounded on $[0, 1]$. In order to see this, consider what would happen to the penalty terms if either $u < 0$. This choice of a control would cause the terms $\omega_1(u_1(t))$ and $\omega_3(u_2(t))$ to become negative and *pull* the Lagrangian function down and way from the maximum. Therefore negative values of u would not be chosen as controls for a maximum

L value. The same idea holds whenever our control escapes its upper bound of 1, again causing the Lagrangian to decrease and not attain its absolute maximum. Clearly, the only values which can maximize L are those between 0 and 1. The penalty terms will soon be implemented in order to put bounds on the optimal solution in section **4.3**.

4.2 Adjoint Conditions

In order to attach the system of ODE's onto the objective function, adjoint functions were used. Pontryagin's maximum principle gives the necessary conditions that the adjoint functions must satisfy. The differential equation satisfied by the *ith* adjoint function, derived in reference [7], is the following:

$$\frac{d\lambda_i}{dt} = -\frac{dL}{dS_i}$$

where $i = 1, 2, 3, 4$ and $S_i = T, T^*, T^{**}, V$.

The adjoints have the following boundary conditions at the final time of treatment, t_f:

$$\lambda_i(t_f) = 0, \qquad i = 1, 2, 3, 4.$$

As one can easily see, there are as many adjoints as there are state equations, and the adjoint λ_i corresponds to the *ith* state variable. Now, another difficulty has been introduced into the problem. Not only must four more first order ODE's be solved, but these adjoint ODE's have final conditions as opposed to the initial conditions of the state ODE's. This creates a problem in the iterative solving program which will be explained later in the following paragraphs. The ODE's describing the rate of change of each adjoint with respect to time will now be presented. Differentiating the Lagrangian (22) with respect to each state variable by the *ith* generating condition above gives the following equations:

$$(23) \qquad \frac{d\lambda_1}{dt} = -1 + \lambda_1(\mu_T - r + r\left(\frac{2T + T^* + T^{**}}{T_{max}}\right) + (1-u_1)k_1V)$$

$$-\lambda_2(1-u_1)k_1V + \lambda_4 k_1 V,$$

$$(24) \qquad \frac{d\lambda_2}{dt} = \lambda_1\left(\frac{rT}{T_{max}}\right) + \lambda_2(\mu_T + k_2) - \lambda_3 k_2,$$

$$(25) \qquad \frac{d\lambda_3}{dt} = \lambda_1\left(\frac{rT}{T_{max}}\right) + \lambda_3\mu_b - \lambda_4(N\mu_b(1-u_2)),$$

$$(26) \qquad \frac{d\lambda_4}{dt} = \lambda_1(1-u_1)k_1T - \lambda_2(1-u_1)k_1T + \lambda_4(k_1T + \mu_v).$$

For the untreated case (no controls), these adjoints are not needed and the iterative algorithm Runge-Kutta [2] may be used to solve the system of four state equations forward in time. Once formulas were obtained for the optimal controls (see next section), the solving program was implemented to find the solution values during the treatment of an HIV infected patient. In order to solve for our optimal controls, a method commonly used in Calculus (differentiation with respect to each control) was generalized for finding the maximum value of the Lagrangian's curve where the first derivative equals zero.

Each of the adjoint ODE's has a boundary condition of zero at the final time of treatment, t_f. This creates a problem in developing an iterative solver. Not only must the first four coupled ODE's (18-21) be solved forward in time from initial conditions, but also the second system of adjoint ODE's (23-26) must be solved backward in time from their final conditions. The program would be a lot easier to implement if the ODE's were uncoupled, i.e., if they did not depend on one another, because then a simple Runge-Kutta program could solve the state ODE's forward in time, and a separate loop could walk the adjoint ODE's backward in time. However, these two systems of four ODE's present a unique problem in that they *are* coupled to each other, and therefore the two systems must be solved simultaneously.

A unique program was developed specifically for this need, and it iteratively solves the ODE systems by first guessing values

for the adjoints at all time $t \in [t_0, t_f]$. These guesses were then used to solve the state ODE system which, in turn, yielded values for each state T, T^*, T^{**}, and V at time t. These state values were then plugged into the adjoint system which was subsequently solved using the Runge-Kutta method of order four backward in time from t_f.

After each run through the algorithm, the convergence was tested by comparing the absolute error between each state value at run k and the previous state value at run $k-1$. If the difference between the two values was greater than a specified tolerance, ϵ, the newly generated adjoints from run k were cycled through the initial loop in place of the adjoint guesses. If however, the error was less than the specified tolerance, the iterative solve was terminated and the state data at $t \in [t_0, t_f]$ was collected and placed in a matrix. This matrix was subsequently exported to MATLAB4.2c, and graphs of the various states and controls versus time were obtained.

4.3 The Optimality Condition

The Lagrangian is maximized with respect to both u_1 and u_2 separately in order to obtain the optimal value of u_1^* and u_2^*. At both of these control values, the maximum Lagrangian is obtained. The derivative of the Lagrangian with respect to both u_1^* and u_2^* is thus zero, since at the absolute maximum the slope of a function is zero. First, partially differentiating our L with respect to u_1 yields:

$$\frac{\partial L}{\partial u_1} = -B_1 u_1 + \lambda_1 k_1 VT - \lambda_2 k_1 VT + \omega_1 - \omega_2 = 0 \text{ at } u_1^*,$$

which can then be solved for our optimal u_1^*, giving us:

$$u_1^* = \frac{(\lambda_1 - \lambda_2) k_1 VT + \omega_1 - \omega_2}{B_1}.$$

Thus, from the conditions on our penalty multipliers, $\omega_i \geq 0$, the following expression may be obtained:

$$(27) \qquad u_1^* = Min\Big(Max(\star_1, 0), 1\Big),$$

$$\text{where } \star_1 = \frac{(\lambda_1 - \lambda_2) k_1 VT}{B_1}.$$

In order to obtain an expression for our second optimal control, u_2^*, the same method will be followed. This second analysis will proceed step-by-step. As before, the derivative of L with respect to u_2 is set equal to zero, giving us:

$$\frac{\partial L}{\partial u_2} = -B_2 u_2 - \lambda_4 N \mu_b T^{**} + \omega_3 - \omega_4 = 0 \text{ at } u_2^*,$$

which can then be solved for u_2^* as follows:

$$u_2^* = \frac{-\lambda_4 N \mu_b T^{**} + \omega_3 - \omega_4}{B_2}.$$

In order to eliminate the unknown penalty functions, consider 3 disjoint and exhaustive cases on the optimal control:

- Case (i) On the set $\{t \mid 0 < u_2^*(t) < 1\}$, we may set $\omega_3(t) = \omega_4(t) = 0$, hence generating the optimal control,

$$u_2^*(t) = \frac{-\lambda_4 N \mu_b T^{**}}{B_2}.$$

- Case (ii) On the set $\{t \mid u_2^*(t) = 1\}$, $\omega_3(t) = 0$ and $\omega_4(t) \geq 0$, therefore giving us:

$$u_2^*(t) = 1 = \frac{-\lambda_4 N \mu_b T^{**} - \omega_4}{B_2} \leq \frac{-\lambda_4 N \mu_b T^{**}}{B_2},$$

which implies

$$\frac{-\lambda_4 N \mu_b T^{**}}{B_2} \geq 1 = u_2^*(t).$$

- Case (iii) On the set $\{t \mid u_2^*(t) = 0\}$, $\omega 3(t) \geq 0$ and $\omega_4(t) = 0$, which gives us the relation:

$$u_2^*(t) = 0 = \frac{-\lambda_4 N \mu_b T^{**} + \omega_3}{B_2} \geq \frac{-\lambda_4 N \mu_b T^{**}}{B_2}.$$

From this expression, our solution for the third case is obtained:

$$\frac{-\lambda_4 N \mu_b T^{**}}{B_2} \leq 0 = u_2^*(t).$$

Now the reader can more easily see how the condition for u_2^* in equation (28) is generated:

$$(28) \qquad u_2^* = Min\Big(Max(\star_2, 0), 1\Big),$$

where $\star_2 = \frac{-\lambda_4 N \mu_b T^{**}}{B_2}$.

5 Discussion of Results and Conclusions

5.1 The Results

The analysis is now complete. The equations for each optimal control have been obtained and have been implemented into a program which iteratively solves both systems of equations. Equations describing the HIV infected scenario have been implemented with dual chemotherapy - one, a chemokine-like derivative that inhibits binding (u_1^*) and the other being that of a viral protease inhibitor that inhibits correct protein processing of new virions (u_2^*). Both of these optimal controls represent solution curves for an optimal treatment schedule. Through a computational algorithm including both forward and backward Runge-Kutta, we were able to numerically solve the two systems of ODE's, the state system and the adjoint system.

The figures on the following pages are presented for perception of the process of infection, the optimal treatment schedule, and the effects that the optimal controls have on an HIV positive patient. Although the model without controls has been verified, the effect of this optimal combination treatment has not yet been shown to mimic our data. However, the methods which were used to attain the optimal chemotherapy schedule has been verified previously [2, 6, 7], and research suggests that these optimal treatment schedules are the true solution for this problem.

The following is a description of each of the figures, all of which were produced using MATLAB:

- **FIGURE 1: The optimal treatment schedule of $u_1^*(t)$, $B_1 = 50$, interval 100 days:**

  Figure 1 represents the optimal 100 day treatment schedule for the first chemotherapy, u_1^* - a chemokine-like binding inhibitor with $B_1 = 50$. % chemotherapy is plotted on the y-axis, and the number of days is on the x-axis.

- **FIGURE 2: The optimal treatment schedule of $u_2^*(t)$, $B_2 = 400$, interval 100 days:**

  Figure 2 represents the optimal 100 day treatment schedule for the second chemotherapy, $u2^*$ - a protease inhibitor with $B_2 = 400$.

- **FIGURE 3: The optimal treatment schedule of both $u_1^*(t)$ and $u_2^*(t)$, with $B_1 = 50$ and $B_2 = 400$, 350, 250, and 150:**

  Figure 3 consists of four separate graphs, each containing solution curves of u_1 in a solid line and u_2 in a dashed line. As we decrease the cost of u_2 from 400 to 150, the length of time of maximal u_2 treatment increases from about 27 days to 67 days, while the u_1 treatment decreases proportionally.

- **FIGURE 4: T cell behavior, with and without optimal combination treatment for two sequential intervals of 100 days:**

  The solid line represents healthy T cell behavior during HIV infection, while the dashed line represents what would happen to the T cell population given optimal combination chemotherapy for two successive 100 day intervals starting at day 900.

- **FIGURE 5: HIV behavior, with and without optimal combination treatment for two sequential intervals of 100 days:**

  The solid line represents viral behavior during infection, while the dashed line indicates viral population changes under optimal combination treatment for two successive 100 day intervals beginning at day 900.

- **PRINTOUT:**

  This printout contains the Fortran program used to solve our optimal control problem. The data generated from the program was plotted using MATLAB.

5.2 Future Analysis

Although anti-HIV treatment does slow the progression of the disease in HIV infected patients, much uncertainty exists about how to best administer the drug during the treatment period. Through this analysis, an optimal treatment schedule is put forward, to maximize a patient's healthy T cell count while also keeping track of potential side effects of each chemotherapy. When a new drug has

passed FDA guidelines and has been tested through clinical trials, the maximum percentage dosage can be obtained and side effects will be recorded. After relating the side effects to the balancing constant in the objective equation, $J(u_1, u_2, ...)$, one can then solve for an optimal treatment schedule which can serve as a guideline for HIV infected patients to follow.

The unique numerical algorithm developed to solve this problem will serve as a template for future applications in the medicinal treatment of HIV infection. With new combinations of chemotherapies being developed, one can imagine the usefulness of such a computer program. Mathematical modeling of HIV infection and solutions of optimal control may serve as a stepping stone between clinical medical research trials and actual implementation of the drug regiment throughout the HIV infected population. Truly, mathematics does have a place in the medical field today.

Other interesting studies would make use of modifications to the structure of our model. For example, one could check the reliability of the parameters by setting each as a function of time and performing a sensitivity analysis on them. Most seem to have one or two significant digits, and therefore they could vary significantly, i.e. .02 could vary from .015 to .024. Checking the sensitivity by perturbing each parameter would be useful in verifying the stability of this model.

Special thanks to Dr. Suzanne Lenhart, Dr. Renee Fister, Dr. Charles Collins, Dr. Raj Pal Soni, and Rick Moran, without whom none of this would have been possible.

FIGURE 1: optimal control 1

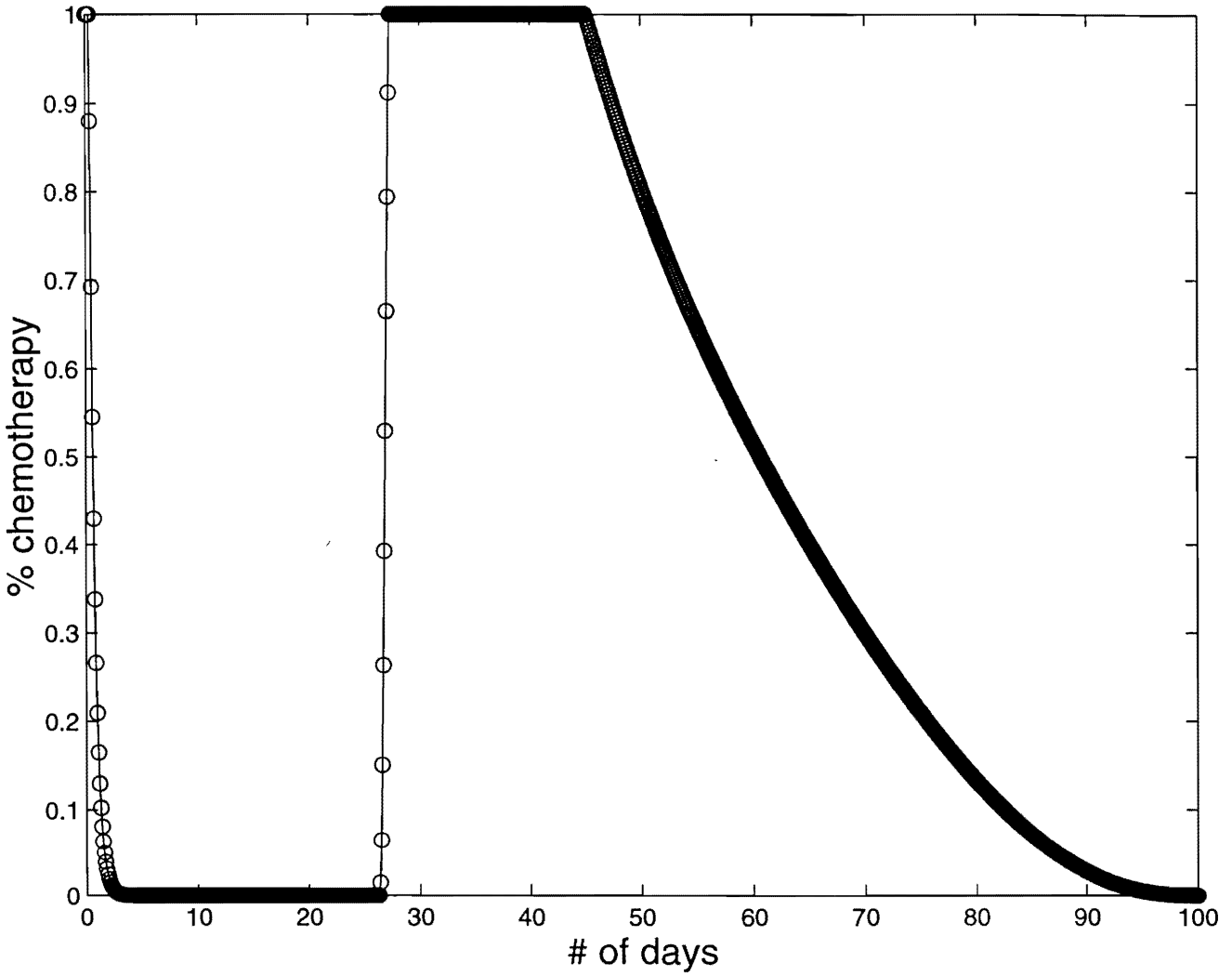


FIGURE 2: optimal control 2

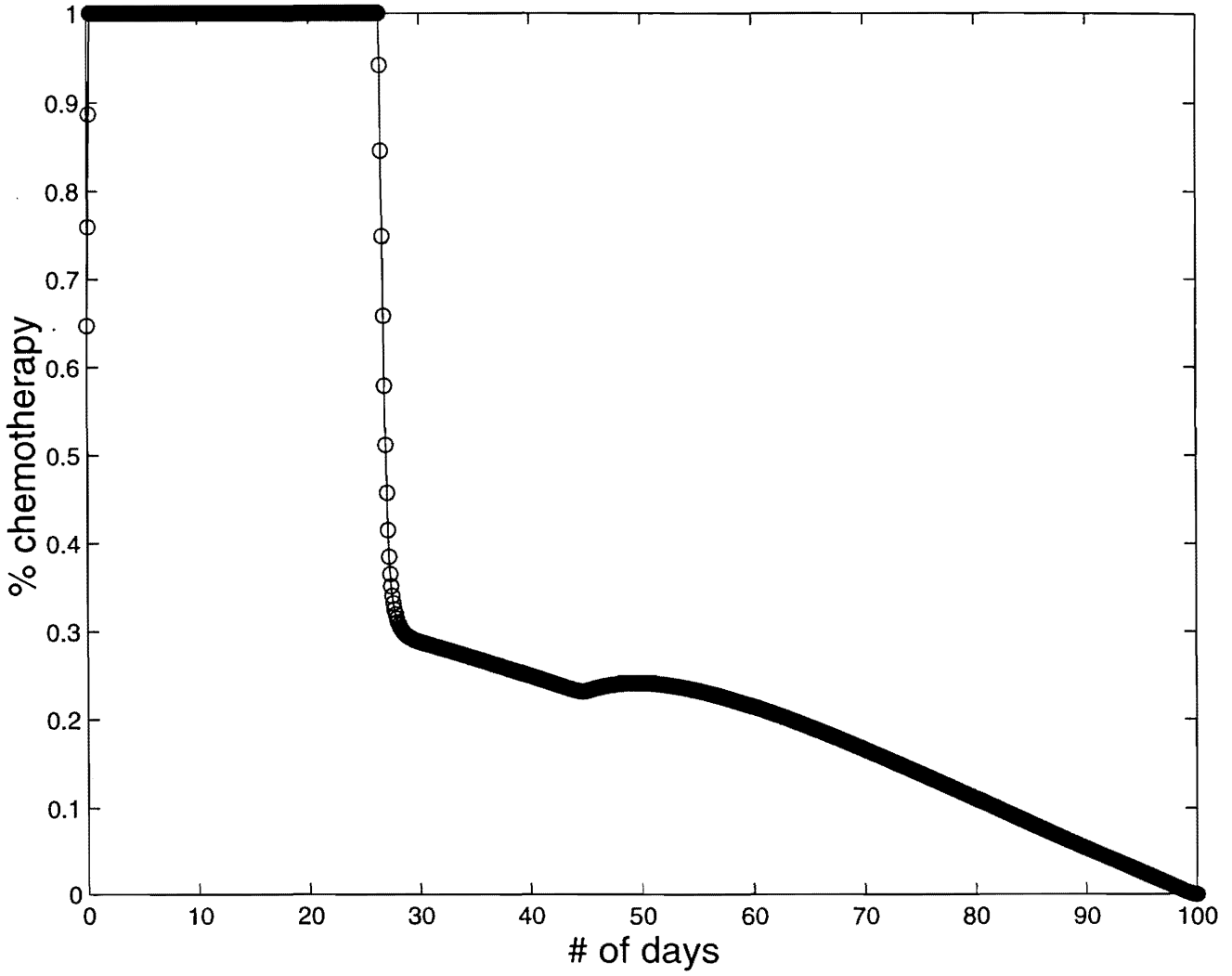


FIGURE 3: B1=50, B2=400, u1 solid, u2 dashed

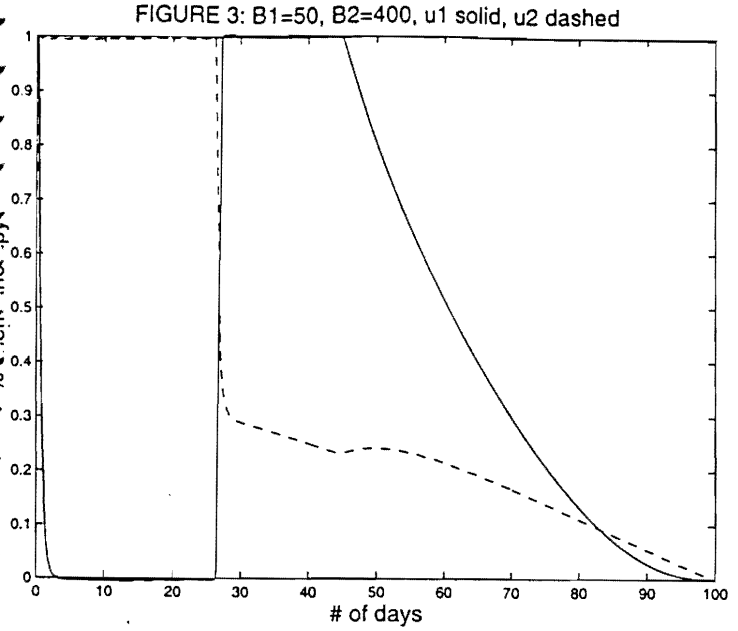


FIGURE 3: B1=50, B2=250, u1 solid, u2 dashed

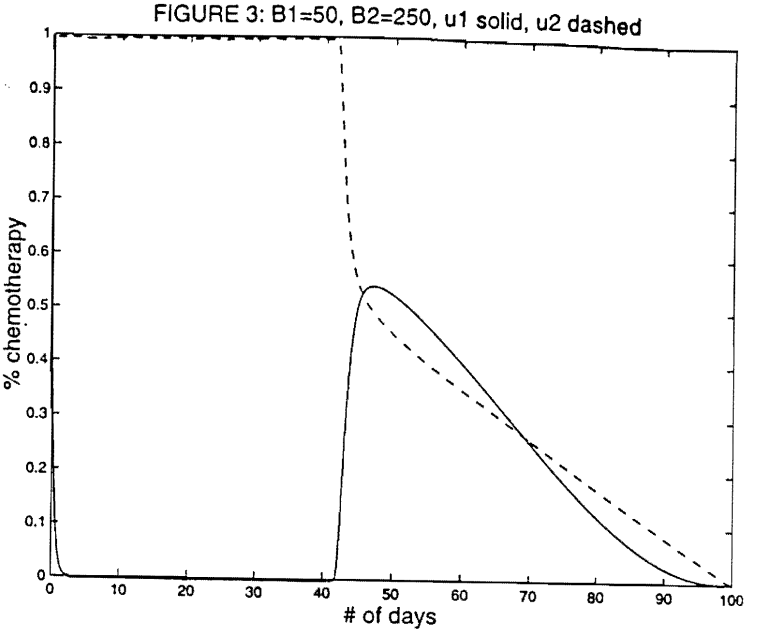


FIGURE 3: B1=50, B2=150, u1 solid, u2 dashed

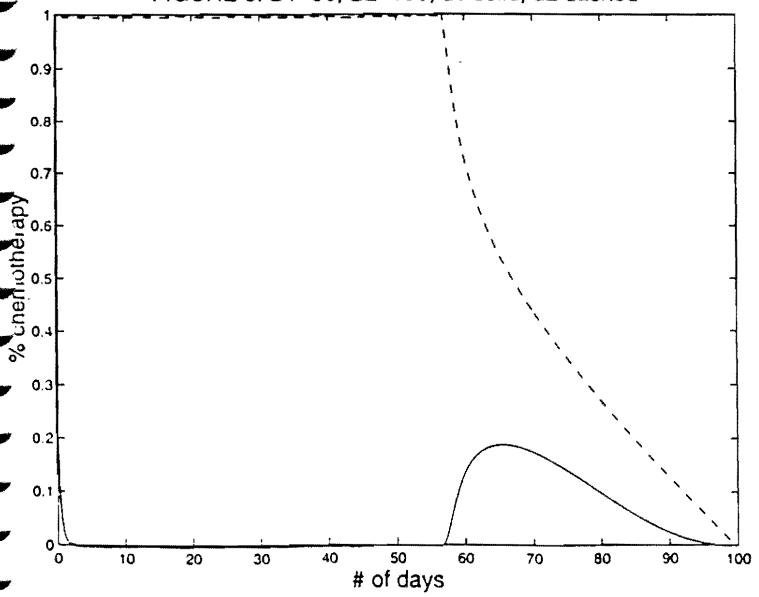


FIGURE 3: B1=50, B2=100, u1 solid, u2 dashed

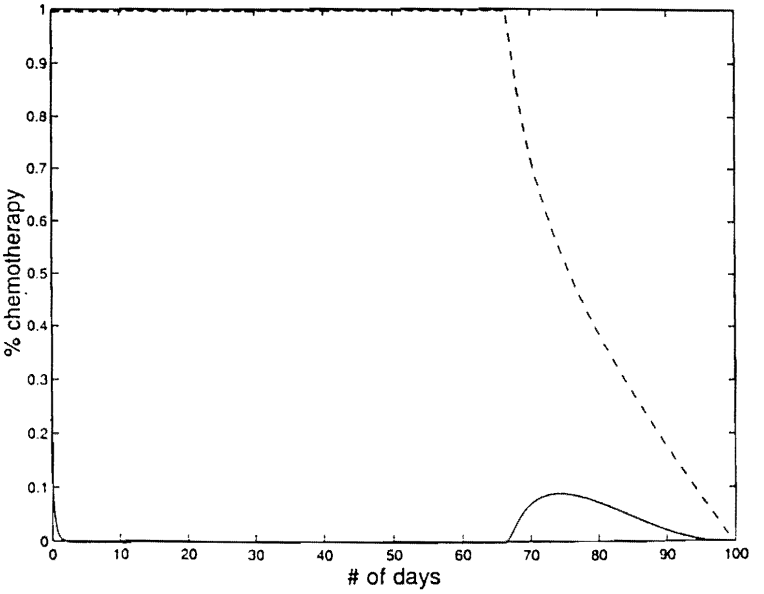


FIGURE 4: Healthy T Cell Behavior

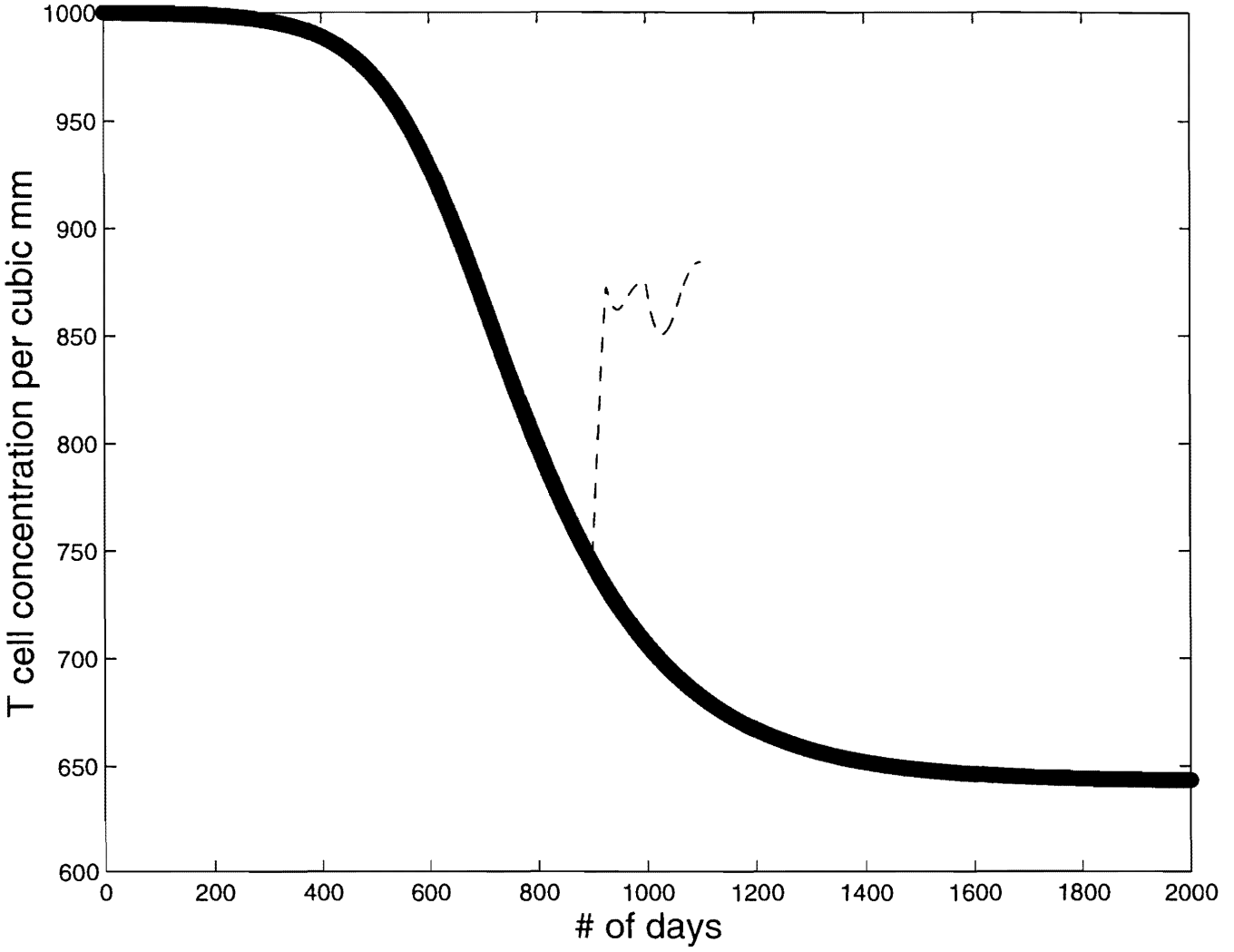
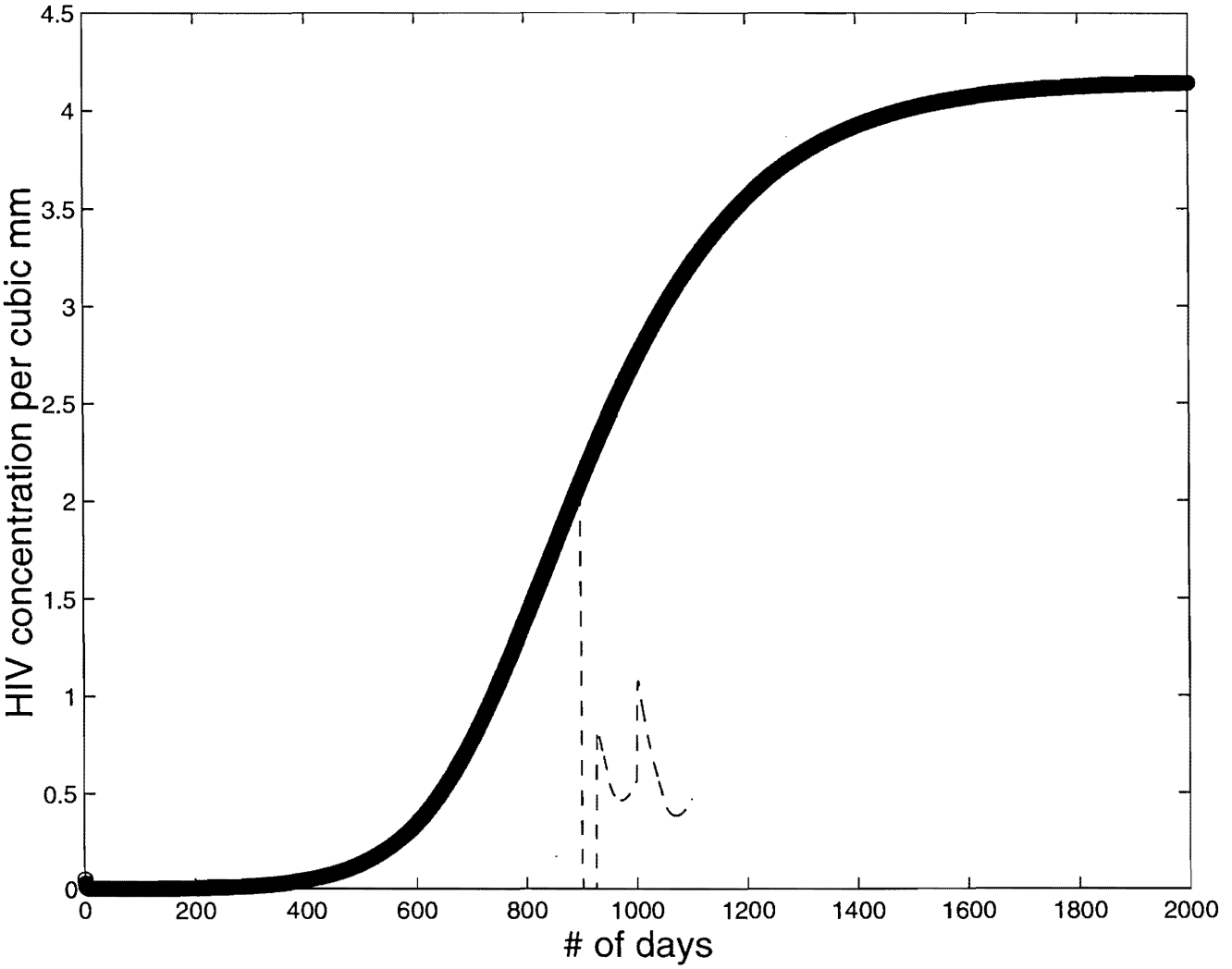


FIGURE 5: HIV behavior



```
      IMPLICIT NONE
      REAL B,B2,H,ICX(4),FCY,KX(4,4),KY(4,4),X(4,1001)
      REAL XN(4,1001),Y(4,1001),YN(4,1001),T,T1,T2,V,Y1,Y2,Y3,Y4
      REAL U1(1001),U2(1001),EPSI,SUM,TI,TF,X1,X2,X3,X4,Z1,Z2,Z3,Z4
      INTEGER I,N,M,K,P,COUNTER,Z
      X1(T,T1,T2,V,U1)=
     !10/(1+V)-.02*T+.03*T*(1-(T+T1+T2)/1500)-2.4E-5*(1-U1)*V*T
      X2(T,T1,V,U1)=2.4E-5*(1-U1)*V*T-(.02+.003)*T1
      X3(T1,T2)=.003*T1-.24*T2
      X4(T,T2,V,U2)=(1-U2)*1200*.24*T2-2.4E-5*V*T-2.4*V

C Watch out for the 2.4's above and below, some should be 2.4*10^-5 etc...!

      Z1(Y1,Y2,Y4,T,T1,T2,V,U1)=
     !-1+Y1*(.02-.03+.03*(2*T+T1+T2)/1500+
     !2.4E-5*(1-U1)*V)-2.4E-5*V*(Y2*(1-U1)-Y4)
      Z2(Y1,Y2,Y3,T)=(Y1*.03*T)/1500+.023*Y2-.003*Y3
      Z3(Y1,Y3,Y4,U2)=Y1*(.03*T)/1500+.24*(Y3-(1-U2)*1200*Y4)
      Z4(Y1,Y2,Y4,T,V,U1)=
     !Y1*(10/((1+V)**2)+2.4E-5*T*(1-U1))-Y2*2.4E-5*(1-U1)*T+
     !Y4*(2.4E-5*T+2.4)

      COUNTER=0
      TI=0.0
      TF=100.0
      N=1000
      M=1001
      H=(TF-TI)/N
      FCY=0.0
      EPSI=.01
      Z=2
      B=.50E2
      B2=4.0E2
      ICX(1)=874.022
      ICX(3)=1.51225E-02
      ICX(2)=1.10754
      ICX(4)=.566098

      XN(1,1)=ICX(1)
      XN(2,1)=ICX(2)
      XN(3,1)=ICX(3)
      XN(4,1)=ICX(4)

C This is the initial guess for the 4 adjoint eqns
      DO P=1,4
        DO I=1,M
        Y(P,I)=1.0
        END DO
      END DO

C The next step is the start of the MAjor loop!!
C MAybe use a GO TO statement at the end of the loops to the line directly below
C Y(1) is the initial condition, all the way to Y(101) which is Y at time = 2
C The next loop is to find ICU (U(1))and all other U values


57    DO I=1,M
        IF (2.4E-5*XN(4,I)*XN(1,I)*(Y(1,I)-Y(2,I))/B.GT.0.AND.
     !2.4E-5*XN(4,I)*XN(1,I)*(Y(1,I)-Y(2,I))/B.LT.1) THEN
          U1(I)=2.4E-5*XN(4,I)*XN(1,I)*(Y(1,I)-Y(2,I))/B
        ELSE
            IF(2.4E-5*XN(4,I)*XN(1,I)*(Y(1,I)-Y(2,I))/B.LE.0) THEN
              U1(I)=0.0
            ELSE
                U1(I)=1.0
            END IF
```

```
          END IF

          IF (-Y(4,I)*1200*.24*XN(3,I)/B2.GT.0.AND.
     !-Y(4,I)*1200*.24*XN(3,I)/B2.LT.1) THEN
            U2(I)=-Y(4,I)*1200*.24*XN(3,I)/B2
          ELSE
              IF(-Y(4,I)*1200*.24*XN(3,I)/B2.LE.0) THEN
                U2(I)=0.0
              ELSE
                  U2(I)=1.0
              END IF
          END IF

        IF (I.EQ.M) THEN
          GO TO 123
        ELSE
          END IF

        KX(1,1)=H*X1(XN(1,I),XN(2,I),XN(3,I),XN(4,I),U1(I))
        KX(2,1)=H*X2(XN(1,I),XN(2,I),XN(4,I),U1(I))
        KX(3,1)=H*X3(XN(2,I),XN(3,I))
        KX(4,1)=H*X4(XN(1,I),XN(3,I),XN(4,I),U2(I))

        KX(1,2)=H*X1(XN(1,I)+KX(1,1)/2,XN(2,I)+KX(2,1)/2,XN(3,I)+
     !KX(3,1)/2,XN(4,I)+KX(4,1)/2,(U1(I+1)+U1(I))/2)
        KX(2,2)=H*X2(XN(1,I)+KX(1,1)/2,XN(2,I)+KX(2,1)/2,XN(4,I)+
     !KX(4,1)/2,(U1(I+1)+U1(I))/2)
        KX(3,2)=H*X3(XN(2,I)+KX(2,1)/2,XN(3,I)+KX(3,1)/2)
        KX(4,2)=H*X4(XN(1,I)+KX(1,1)/2,XN(3,I)+KX(3,1)/2,XN(4,I)+
     !KX(4,1)/2,(U2(I+1)+U2(I))/2)

        KX(1,3)=H*X1(XN(1,I)+KX(1,2)/2,XN(2,I)+KX(2,2)/2,XN(3,I)+
     !KX(3,2)/2,XN(4,I)+KX(4,2)/2,(U1(I+1)+U1(I))/2)
        KX(2,3)=H*X2(XN(1,I)+KX(1,2)/2,XN(2,I)+KX(2,2)/2,XN(4,I)+
     !KX(4,2)/2,(U1(I+1)+U1(I))/2)
        KX(3,3)=H*X3(XN(2,I)+KX(2,2)/2,XN(3,I)+KX(3,2)/2)
        KX(4,3)=H*X4(XN(1,I)+KX(1,2)/2,XN(3,I)+KX(3,2)/2,XN(4,I)+
     !KX(4,2)/2,(U2(I+1)+U2(I))/2)

        KX(1,4)=H*X1(XN(1,I)+KX(1,3),XN(2,I)+KX(2,3),XN(3,I)+
     !KX(3,3),XN(4,I)+KX(4,3),U1(I+1))
        KX(2,4)=H*X2(XN(1,I)+KX(1,3),XN(2,I)+KX(2,3),XN(4,I)+
     !KX(4,3),U1(I+1))
        KX(3,4)=H*X3(XN(2,I)+KX(2,3),XN(3,I)+KX(3,3))
        KX(4,4)=H*X4(XN(1,I)+KX(1,3),XN(3,I)+KX(3,3),XN(4,I)+
     !KX(4,3),U2(I+1))


C Walk the T,T*,T**, and the V eqns here!!!

        XN(1,I+1)=XN(1,I)+(KX(1,1)+2*KX(1,2)+2*KX(1,3)+KX(1,4))/6.
        XN(2,I+1)=XN(2,I)+(KX(2,1)+2*KX(2,2)+2*KX(2,3)+KX(2,4))/6.
        XN(3,I+1)=XN(3,I)+(KX(3,1)+2*KX(3,2)+2*KX(3,3)+KX(3,4))/6.
        XN(4,I+1)=XN(4,I)+(KX(4,1)+2*KX(4,2)+2*KX(4,3)+KX(4,4))/6.

123     END DO

C Now work from final time to initial time!
C Given the guess on Y's, we got the X's,
C now we have to work
C backwards to see if it's correct! The next small loop is to initialize
C the X() values for the first time through only

        IF (Z.EQ.2) THEN
         DO P=1,4
```

```
            DO I=1,M
              X(P,I)=XN(P,I)
            END DO
           END DO
            Z=0
          ELSE
          END IF

C Next work backwards..

          DO P=1,4
            YN(P,M)=FCY
          END DO

C NOW we must walk the 4 adjoints ! (JUST the Y eqns!)

          DO I=1,N

           K=2+N-I

            KY(1,1)=H*Z1(YN(1,K),YN(2,K),YN(4,K),XN(1,K),XN(2,K),XN(3,K),
     !XN(4,K),U1(K))
            KY(2,1)=H*Z2(YN(1,K),YN(2,K),YN(3,K),XN(1,K))
            KY(3,1)=H*Z3(YN(1,K),YN(3,K),YN(4,K),U2(K))
            KY(4,1)=H*Z4(YN(1,K),YN(2,K),YN(4,K),XN(1,K),XN(4,K),U1(K))

            KY(1,2)=H*Z1(YN(1,K)-KY(1,1)/2,YN(2,K)-KY(2,1)/2,YN(4,K)-
     !KY(4,1)/2,(XN(1,K-1)+XN(1,K))/2,(XN(2,K-1)+XN(2,K))/2,(XN(3,K-1)+
     !XN(3,K))/2,(XN(4,K-1)+XN(4,K))/2,(U1(K-1)+U1(K))/2)
            KY(2,2)=H*Z2(YN(1,K)-KY(1,1)/2,YN(2,K)-KY(2,1)/2,YN(3,K)-
     !KY(3,1)/2,(XN(1,K-1)+XN(1,K))/2)
            KY(3,2)=H*Z3(YN(1,K)-KY(1,1)/2,YN(3,K)-KY(3,1)/2,YN(4,K)-
     !KY(4,1)/2,(U2(K-1)+U2(K))/2)
            KY(4,2)=H*Z4(YN(1,K)-KY(1,1)/2,YN(2,K)-KY(2,1)/2,YN(4,K)-
     !KY(4,1)/2,(XN(1,K-1)+XN(1,K))/2,(XN(4,K-1)+XN(4,K))/2,(U1(K-1)+
     !U1(K))/2)


            KY(1,3)=H*Z1(YN(1,K)-KY(1,2)/2,YN(2,K)-KY(2,2)/2,YN(4,K)-
     !KY(4,2)/2,(XN(1,K-1)+XN(1,K))/2,(XN(2,K-1)+XN(2,K))/2,(XN(3,K-1)+
     !XN(3,K))/2,(XN(4,K-1)+XN(4,K))/2,(U1(K-1)+U1(K))/2)
            KY(2,3)=H*Z2(YN(1,K)-KY(1,2)/2,YN(2,K)-KY(2,2)/2,YN(3,K)-
175  !KY(3,2)/2,(XN(1,K-1)+XN(1,K))/2)
            KY(3,3)=H*Z3(YN(1,K)-KY(1,2)/2,YN(3,K)-KY(3,2)/2,YN(4,K)-
     !KY(4,2)/2,(U2(K-1)+U2(K))/2)
            KY(4,3)=H*Z4(YN(1,K)-KY(1,2)/2,YN(2,K)-KY(2,2)/2,YN(4,K)-
     !KY(4,2)/2,(XN(1,K-1)+XN(1,K))/2,(XN(4,K-1)+XN(4,K))/2,(U1(K-1)+
     !U1(K))/2)


            KY(1,4)=H*Z1(YN(1,K)-KY(1,3),YN(2,K)-KY(2,3),YN(4,K)-
     !KY(4,3),XN(1,K-1),XN(2,K-1),XN(3,K-1),XN(4,K-1),U1(K-1))
            KY(2,4)=H*Z2(YN(1,K)-KY(1,3),YN(2,K)-KY(2,3),YN(3,K)-
     !KY(3,3),XN(1,K-1))
            KY(3,4)=H*Z3(YN(1,K)-KY(1,3),YN(3,K)-KY(3,3),YN(4,K)-
     !KY(4,3),U2(K-1))
            KY(4,4)=H*Z4(YN(1,K)-KY(1,3),YN(2,K)-KY(2,3),YN(4,K)-
     !KY(4,3),XN(1,K-1),XN(4,K-1),U1(K-1))


           YN(1,K-1)=YN(1,K)-(KY(1,1)+2*KY(1,2)+2*KY(1,3)+KY(1,4))/6.
           YN(2,K-1)=YN(2,K)-(KY(2,1)+2*KY(2,2)+2*KY(2,3)+KY(2,4))/6.
           YN(3,K-1)=YN(3,K)-(KY(3,1)+2*KY(3,2)+2*KY(3,3)+KY(3,4))/6.
           YN(4,K-1)=YN(4,K)-(KY(4,1)+2*KY(4,2)+2*KY(4,3)+KY(4,4))/6.
```

```
        END DO

C Now the test for convergence...

        SUM =0.0
        DO P=1,4
          DO I=1,M
            SUM=SUM+ABS(YN(P,I)-Y(P,I))+ABS(XN(P,I)-X(P,I))
          END DO
        END DO


        IF (SUM.GT.EPSI) THEN
         DO P=1,4
          DO I=1,M
            Y(P,I)=YN(P,I)
            X(P,I)=XN(P,I)
          END DO
         END DO
          COUNTER=COUNTER+1
          IF(COUNTER.GE.1000) THEN
            PRINT*, 'NO convergence!!'
            STOP
          ELSE
          GO TO 57
          END IF
        ELSE
        END IF

        DO I=1,M
          PRINT*, H*(I-1),XN(1,I),XN(4,I),U1(I),U2(I)
        END DO
          PRINT*, XN(2,101),XN(3,101)
        END
```

6 Table of Parameters

$B_1 = 50 \quad mm^{-3}$, $B_2 = 400 \quad mm^{-3}$ balancing constants

$s = 10 \quad days^{-1}mm^{-3}$, a linear growth rate constant

$\mu_T = .02 \quad days^{-1}$, a death rate constant for both healthy and latently infected T cells

$r = .03 \quad days^{-1}$, a logistic growth rate constant

$T_{max} = 1500 \quad mm^{-3}$, the maximum number of T cells (healthy and infected) per mm^3

$k_1 = 2.4 \times 10^{-5} \quad mm^3 days^{-1}$, a rate constant for the infective interaction of viral particles and T cells

$k_2 = .003 \quad days^{-1}$, a rate constant describing the transfer of T cells from the latently infected state T^* to an actively infected state T^{**}

$\mu_b = .24 \quad days^{-1}$, a death rate constant for actively infected T cells, or equivalently a birthing rate for the HIV virus

$N = 1200$, the number of viral particles produced per dying T cell

$\mu_v = 2.4 \quad days^{-1}$, a death rate constant for the HIV virus

References

[1] Associated Press: UN AIDS Report. Daily Beacon. Monday, December 8(1997).

[2] Burden, R.L., and Faires, J.D.: Numerical Analysis. ed. 3. Prindle, Weber, and Schmidt, Boston, 220-269.

[3] Conner, R.I. *et al.*: Increased viral burden and cytopathicity correlate temporarily with CD4+ T lymphocyte decline and clinical progression in HIV-1 infected individuals. J. Virology **67**, 1772-1777 (1993).

[4] Dewitt, P.E.: "Turning the Tide." Time, Dec. 30, 1996-Jan.6, 54-68 (1997).

[5] Fields, Bernard N., Howley, Peter M., and Knipe, David M.: Fundamental Virology. ed. 3. Lippincott-Raven, Philadelphia, 40-41, 763-826, 845-897 (1998).

[6] Fleming, W. and Rishel, R.: Deterministic and Stochastic Optimal Controls. Ch. 3, Thm. 4.1, p. 68. Springer-Verlag, New York (1975).

[7] Kamian, M.I. and Schwartz, N.L.: Dynamic Optimization: The calculus of variations and optimal control in Economics and Management. ed. 2, vol. 31, 185-194.

[8] Keshet, L.E.: Mathematical Models in biology. Random House, New York, 210-254.

[9] Kirschner, D.E., Lenhart, S., Serbin, S.: Optimal Control of the Chemotherapy of HIV.

[10] Kirschner, D.E., Mehr, R., and Perelson, A.: The Role of the Thymus in HIV Infection. (to appear in J. AIDS Hum. Retrovirol.)

[11] Kirschner, D.E. and Webb, G.F.: Immunotherapy of HIV-1 Infection. Preprint(1997).

[12] Mesterton - Gibbons, M.: A Concrete Approach to Mathematical Modeling. Wiley, New York (1995).

[13] News and editorial staffs of Science: New Hope in HIV Disease. Science, vol. 274, December 20, 1988-1989 (1996).

[14] Perelson, A.S.: Modeling the interaction of the immune system with HIV, In C. Castillo-Chavez; Mathematical and Statistical Approaches to AIDS Epidemiology, (Lect. Notes in Biomath., vol. 83, pp. 350-370) Springer-Verlag, New York (1989).

[15] Perelson, A.S., Essunger, P., Cao, Y., Vesanen, M., Hurley, A., Saksela, K., Markowitz, M., and Ho, D.: Decay characteristics of HIV-1 infected compartments during combination therapy. Nature, vol 387, May 8 (1997).

[16] Perelson, A.S., Kirschner, D., Deboer, R.: The dynamics of HIV infection of CD4+ T cells. Math. Biosciences 114, 81-125 (1993).

[17] Perelson, A.S., Neumann, A.U., Markowitz, M., Leonard, John M., and Ho, David D.: HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life Span, and Viral Generation Time. Science, vol. 271, Mar. 15 (1996).

[18] Redfield, R., Burke, D., Weber, J., Weiss, R., Yarchoan, R., Mitsuya, H., and Broder, S.: HIV Infection and AIDS Therapies. Scientific American, October, 70-97 (1988).