OPTIMAL CONTROL OF CHEMOTHERAPY
AFFECTING THE INFECTIVITY OF HIV

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ABSTRACT:Using an ordinary differential equation model which describes the interaction of the immune system with the human immunodeficiency virus (HIV) we solve for an optimal chemotherapy strategy. The control represents the percentage of effect the chemotherapy has on the viral infectivity (this would simulate a drug such as AZT). Using an objective function based on a combination of maximizing benefit based on T cell counts and minimizing the systemic cost of chemotherapy, we solve for the optimal control in the optimality system composed of three ordinary differential equations and three adjoint ordinary differential equations. This optimal control corresponds to a dynamical chemotherapy regime.

Key Words. Chemotherapy, HIV, optimal control, ordinary differential equation system.

1. INTRODUCTION.

Different chemotherapies for treating patients with the human immunodeficiency virus (HIV) are being tested to find an optimal methodology for administering the treatment. We present an ordinary differential equation model which describes the interaction of the immune system with HIV. We investigate chemotherapy through the use of an optimal control, assuming the chemotherapy control effects the "infectivity" of the virus. In [Kirschner et al.(1996)], a similar problem was studied whereby the chemotherapy reduced viral production rather than viral infectivity; however, it was more applicable to drugs such as protease inhibitors rather than AZT, which is a reverse transcription inhibitor. During the life cycle of HIV within a host cell, each of these enzyme inhibitors interrupts key stages of the infection process. There is much support in the clinical literature for the use of reverse transcriptase inhibitors [Cox et al.(1990), Fischl et al.(1990), Hamilton et al.(1992), Hirsch(1990), McLeod et al.(1992)]. We explore in this paper the chemotherapy of a reverse transcriptase inhibitor such as AZT.

This paper deals specifically with the question of optimizing treatment scheduling; i.e., when and how treatment should be initiated assuming that treatment can only be continued for a finite interval, the average time until drug resistance develops [Nara et al.(1990)]. We base the 'benefit' of treatment solely on an increase or retention of the CD4$^+$ T cell count [Conner et al.(1993)]. To this end, we introduce a model which describes the interaction of HIV with the immune system. We then present the optimal control problem in which the coefficient of the viral production term is the control, resulting from chemotherapy. We seek to maximize the objective function, which is the benefit based on T cell counts less the systemic cost of chemotherapy. The optimal control is characterized using Pontryagin's Maximum Principle. We utilize the representation of the optimal control and solve numerically the optimality system – which is defined as the original state system coupled with the adjoint system. In conclusion, we discuss the results of the numerical simulations as treatment initiation is varied.

The Model. A number of works have been done using mathematical models for modeling drug treatment in different settings: [Agur(1989), Beretta and Solimano(1993), Kirschner et al.(1996),Kirschner and Webb(1996), McLean and Nowak(1992), Perelson et al.(1993)]. Let T denote the concentration of uninfected $CD4^+$ T cells, and let T^i denote the concentration of infected $CD4^+$ T cells. The concentration of free infectious virus particles is V. Here, concentration refers to the population number per unit volume, mm^{-3}. Definitions and numerical information for the parameters can be found in Table 1. We

assume that the dynamics of the various populations are:

$$(1) \qquad \frac{dT}{dt} = \frac{s}{1+V} - \mu_1 T + rT\left(1 - \frac{(T+T^i)}{T_{\max}}\right) - k_1 VT$$

$$(2) \qquad \frac{dT^i}{dt} = k_1 VT - \mu_2 T^i$$

$$(3) \qquad \frac{dV}{dt} = N\mu_2 T^i - \mu_3 VT$$

with initial conditions $T(0) = T_0, T^i(0) = T_0^i, V(0) = V_0$.

In (1), $\frac{s}{1+V}$ is a source term from the thymus and represents the rate of generation of new $CD4^+T$ cells [Kirschner, Mehr and Perelson(1996)]. The T cells are also assumed to have a finite life-span and die with rate μ_1 per cell. In (2), infected T cells have the natural death-rate, μ_2, although other factors can augment the natural death-rate. In (1), r represents the growth rate of T cells (per day), which is presented as a logistic-type term, so the T cells never grow larger than $T_{\max}$.

The other terms in (1) and (2) deal with the effects of HIV. The term $k_1 VT$ models the rate that free virus V infects $CD4^+T$ cells. Once a T cell has been infected, it becomes an infected T cell, thus this term is subtracted from (1) and added to (2).

Equation (3) models the free virus population. We assume that when an infected $CD4^+$ T cell becomes stimulated through exposure to antigen, replication of the virus is initiated and an average of N viruses are produced before the host cell dies. The term, $-\mu_3 V$, accounts for viral loss through death and/or immune clearance. Similar models of HIV infection can be found in [Kirschner and Perelson(1994), Kirschner and Webb(1996), Perelson(1989)].

Since drugs such as AZT reduce viral infectivity, we multiply the $k_1 VT$ term in equations (4) and (5) by a chemotherapy function, $u(t)$, to achieve this affect mathematically.

2. Optimally Controlling Chemotherapy.

Our control represents the percentage of effect the chemotherapy has on the interaction of T cells with the virus. The control for the chemotherapy, $u(t)$, multiplies the parameter k_1 in equations (1) and (2). Therefore, we choose as our control class, measurable functions defined on $[t_{start}, t_{final}]$, with the restriction $0 \le u(t) \le 1$. The finite interval of treatment is necessary since we assume the chemotherapy only has a window of allowable treatment. This is due to the fact that HIV has the ability to mutate and develop resistance to

the chemotherapy treatment after some finite time frame [Nara et al.(1990)]. Also, the treatment has potentially harmful side effects, and these side effects increase with duration of treatment. Therefore, for $t_{start} \leq t \leq t_{final}$ (where for most of the HIV chemotherapy drugs, $t_{final} - t_{start} < 2$ years), the state system would be:

$$\text{(4)} \qquad \frac{dT}{dt} = \frac{s}{1+V} - \mu_1 T + rT\left(1 - \frac{(T+T^i)}{T_{\max}}\right) - u(t)k_1 VT$$

$$\text{(5)} \qquad \frac{dT^i}{dt} = u(t)k_1 VT - \mu_2 T^i$$

$$\text{(6)} \qquad \frac{dV}{dt} = N\mu_2 T^i - \mu_3 TV$$

with given initial values for T, T^i, and V at *tstart*.

Define the objective function

$$\text{(7)} \qquad J(u) = \int\limits_{t_{start}}^{t_{final}} \left[T(t) - \frac{1}{2}B(1 - u(t))^2\right] dt.$$

In words, we are maximizing the benefit based on the T cell count, and minimizing the systemic 'cost' of chemotherapy to the body based on the percentage effect of the chemotherapy given (i.e. $(1 - u)$); hence, we are maximizing the difference. If the control $u(t) = 0$ corresponds to maximal use of chemotherapy, then the maximal cost is represented as $(1 - u(t))^2$. We assume that the relationship between the benefit to cost functionals is not linear, and hence, we choose a simple non-linear control in the cost term. The parameter $B \geq 0$ represents the desired 'weight' on the benefit and cost. The goal, therefore is to characterize the optimal control u^* satisfying $\max\limits_{0 \leq u \leq 1} J(u) = J(u^*)$.

Define the Lagrangian (which is the Hamiltonian augmented with penalty terms for the constraints) to be:

(8)
$$L\left(T(t), T^i(t), V(t), u(t), \lambda_1(t), \lambda_2(t), \lambda_3(t)\right)$$
$$= T(t) - \tfrac{1}{2}B(1 - u(t))^2$$
$$+ \lambda_1\left(\tfrac{s}{1+V} - \mu_1 T + rT\left(1 - \tfrac{(T+T^i)}{T_{\max}}\right) - u(t)k_1 VT\right)$$
$$+ \lambda_2(u(t)k_1 VT - \mu_2 T^i) + \lambda_3(N\mu_2 T^i - \mu_3 V) + w_1(t)u(t) + w_2(t)(1 - u(t)),$$

where $w_1(t) \geq 0, w_2(t) \geq 0$, are the penalty multipliers satisfying $w_1(t)u(t) = 0$, and $w_2(t)(1 - u(t)) = 0$. Thus, the Maximum Principle [Kamien and

Schwartz(1991)] gives the existence of adjoint variables satisfying:

(9)
$$\frac{d\lambda_1}{dt} = -\frac{\partial L}{\partial T} = -\left[1 + \lambda_1\left(-\mu_1 + r\left(1 - \frac{(2T + T^i)}{T_{\max}}\right) - u(t)k_1V\right) + \lambda_2 u(t)k_1V\right],$$

(10)
$$\frac{d\lambda_2}{dt} = -\frac{\partial L}{\partial T^i} = \frac{\lambda_1 rT}{T_{\max}} + \lambda_2\mu_2 - \lambda_3 N\mu_2,$$

(11)
$$\frac{d\lambda_3}{dt} = -\frac{\partial L}{\partial V} = \lambda_1\left(\frac{s}{(1 + V)^2} + u(t)k_1T\right) - \lambda_2 u(t)k_1T + \lambda_3 u_3,$$

where $\lambda_i(t_{final}) = 0$ for $i = 1, 2, 3$ are the transversality conditions. Since,

$$L = \left(-\frac{1}{2}B(1 - u(t))^2\right) + \lambda_1(-u(t)k_1VT) + \lambda_2(u(t)k_1VT) + w_1(t)u(t)$$
$$+ w_2(t)(1 - u(t)) + \text{terms without } u,$$

differentiating this expression for L with respect to u gives:

$$\frac{\partial L}{\partial u} = k_1VT(\lambda_2 - \lambda_1) + B(1 - u) + w_1(t) - w_2(t) = 0.$$

Solving for the optimal control yields

$$u^*(t) = \frac{(\lambda_2 - \lambda_1)k_1VT + w_1(t) - w_2(t) + B}{B}.$$

Consider 3 cases in examining the expression for u^*:

(i) On the set $\{t|0 < u^*(t) < 1\}$: $w_1(t) = w_2(t) = 0$, hence the optimal control is:

$$u^*(t) = \frac{(\lambda_2 - \lambda_1)k_1VT + B}{B}$$

(ii) On the set $\{t|u^*(t) = 1\}$: $w_1(t) = 0, w_2(t) \geq 0$, hence $u^*(t) = 1 = \frac{(\lambda_2 - \lambda_1)k_1VT - w_2(t)}{B} + 1$, which implies $0 \leq w_2(t) = (\lambda_2 - \lambda_1)k_1VT$, and $1 \leq \frac{(\lambda_2 - \lambda_1)k_1VT + B}{B}$.

(iii) On the set $\{t|u^*(t) = 0\}$: $w_2(t) = 0, w_1(t) \geq 0$. Hence, the optimal control is:

$$u^*(t) = \frac{(\lambda_2 - \lambda_1)k_1VT + w_1(t) + B}{B} = 0.$$

Therefore, $w_1(t) \geq 0$ implies that $\dfrac{(\lambda_2 - \lambda_1)kVT + B}{B} \leq 0$, which implies

$$u^*(t) = \left(\frac{(\lambda_2 - \lambda_1)k_1VT + B}{B}\right)^+ = 0.$$

Combining these 3 cases, the optimal control is characterized as

(12) $$u^* = \min\left(\left(\frac{(\lambda_2 - \lambda_1)k_1VT + B}{B}\right)^+, 1\right)$$

where

$$\left(\frac{(\lambda_2-\lambda_1)k_1VT+B}{B}\right)^+ = \left\{ \begin{array}{cl} \frac{(\lambda_2-\lambda_1)k_1VT}{B}+1 & \text{if } (\lambda_2 - \lambda_1)k_1VT + B > 0 \\ 0 & \text{if } (\lambda_2 - \lambda_1)k_1VT + B \leq 0 \end{array} \right\}.$$

If $(\lambda_2 - \lambda_1) < 0$, for some t, then $u^*(t) \neq 1$. Hence $0 \leq u^*(t) < 1$ for those t, which implies treatment should be administered. Notice the control depends on the adjoints λ_1 and λ_2, since those adjoints correspond to the state variables T and T^i; and the first two state equations contain the control terms. The optimality system is formed by the state system (4)–(6) coupled with the adjoint system (9)–(11) with corresponding initial/final time conditions and by substituting in the expression (12) for u^* in equations (4), (5), (9), and (11). Solving the optimality system with (12) for u^*, characterizes the dynamic optimal control. Note that the existence and uniqueness of the optimal control can be obtained by standard results [Flemming and Rishel(1975)]. We obtain the explicit characterization for u^* in (12).

3. Numerical Results.

In order to solve the optimality system, we need initial values for the T cells, infected T cells, and the virus. We solve the model (1)–(3) without chemotherapy treatment to get these initial values. The numerical results of the model (1)–(3) were created using MATLAB, and were used to find starting values for different treatment initial conditions. Using a collocation code COLNEW (obtained via NETLIB), the optimality system was solved. The optimality system, is a two-point boundary value problem due to the state system initial data and adjoint system final time data. Included are graphs that represent the solution to the optimality system (4)–(6) coupled with (9)–(11) at different treatment initiations (i.e. different initial data for (4)–(6)) (See Figures 1-4, Section 6). The parameters used in solving (1)–(3), (4)–(6), and (9)–(11) were obtained from [Kirschner et al.(1996)], and are summarized in (Table 1, Section 6).

(Table 2, Section 6) summarizes the numerical results of solving the optimality system for different simulations. The J values are presented for the

benefit functional (7) for each simulation. Treatment was simulated for 100 days in each case. Information for Figures 1-4 is presented, and we also give information about other simulations (runs 5-11), without figures, for brevity. We vary initial conditions and values of B to gain insight into the optimality system.

4. DISCUSSION.

We have used an optimal control theory paradigm to model HIV chemotherapy. Our approach uses an existing model for the interaction of HIV with the immune system and then includes a chemotherapy control as a way to suppress viral infectivity, k_1. We use methods of optimal control to determine the optimal dynamic control analytically, then use numerical methods to simulate different outcomes.

Numerical results indicate that the optimal chemotherapy is a dynamic one, in which treatment is adjusted over the long course of administration whereby one begins with a strong dosing scheme, followed by a lessening of treatment (either by drug dosing or strength).

We can also draw from the control problem that the dynamic optimal chemotherapy does not correspond to a regime where treatment is 100% effective, 100% of the time. Rather, if treatment is strong at the outset, and then gradually lessens in strength over time (whether because of a change in dosage or other effects), it is still effective in balancing the benefit to T cells and systemic costs. This is seen, in particular, with drug treatments such as AZT and DDT [Volberding et al.(1990)].

Exploring initiation of treatment, Table 2 compares the values of the objective function, J at the optimal control u^*. There is not a significant difference between the presented scenarios; however the greatest effect of treatment does occur when treatment is initiated earliest – i.e. when T cell counts are highest, after the onset of infection. The recovery of T cells to larger values makes the biggest difference late in infection after the T cells have begun to decline significantly; but balanced with the effects of drug cost, the earlier initiated treatment is optimal. Also, a lower value of B implies the systemic cost is lower, and the optimal u^* results on a higher value of J^*, the objective functional evaluated at the optimal control.

The results presented here do not depend on the treatment duration. When comparing different treatment intervals, the results are the same; namely, that the earlier treatment is better no matter what the length of the treatment interval in this early scenario.

The model studied here is a simple one, and further studies need to be done to incorporate a more accurate model of the immune system and such

things as direct pharmacology for combined drug treatments together with the resistance effects. This model and the analysis presented here provide a simple framework for the testing and development of such models which can lead to new and improved chemotherapy strategies.

Finally, it is worrisome that early treatment of HIV infection with drug chemotherapy may, and usually has, led to drug resistance. This, of course, will reduce the time period over which therapy can be administered. New research suggests combination drug treatments are preferred since there is a reduced chance of the virus mutating simultaneously to be resistant to all of the drugs present in the 'cocktail'[Hirsch(1990); McLeod et al.(1992), Nara et al.(1990), Volberding at al.(1990)]. We are presently exploring these phenomenon through a revised model.

5. Figures and Tables.

Table 1

Dependent variable Initial Values

T	= Uninfected $CD4^+T$ cell population	$1000\ mm^{-3}$
T^i	= Infected $CD4^+T$ cell population	0.0
V	= Infectious HIV population	$1.0\ mm^{-3}$

Parameters and Constants

μ_1	= death rate of uninfected $CD4^+T$ cell population	$0.02\ d^{-1}$
μ_2	= death rate of infected $CD4^+T$ cell population	$0.5\ d^{-1}$
μ_3	= death rate of free virus	$4.4\ d^{-1}$
k_1	= rate $CD4^+T$ cells become infected by free virus	$2.4 \times 10^{-5}mm^3d^{-1}$
r	= rate of growth for the $CD4^+T$ cell population	$0.03\ d^{-1}$
N	= number of free virus produced by T^i cells	300
T_{max}	= maximum $CD4^+T$ cell population level	$1.5 \times 10^3 mm^{-3}$
s	= source term for uninfected $CD4^+T$ cells	$10\ d^{-1}mm^{-3}$

Table 2

Output	Day	B	T_0	T_0^i	V_0	J^*
Figure 1	21	10	806.4	0.04	1.5	93,561
Figure 2	26	10	766.5	0.1	1.5	93,296
Figure 3	37	10	684.0	0.14	2.9	88,088
Figure 4	74	0.005	494.3	0.04	1.6	80,566
Run 5	54	5	580.0	0.17	2.9	83,535
Run 6	54	10	580.0	0.17	2.9	83,477
Run 7	45	10	630.8	0.18	3.4	85,671
Run 8	74	1	494.3	0.04	1.6	80,554
Run 9	76	1	488.3	0.03	1.4	80,412
Run 10	86	1	463.5	0.01	0.8	79,607
Run 11	74	0.05	494.3	0.04	1.6	80,566

Day: Number of days since the onset of infection

B: weight ratio of benefit to cost of objective function J.

T_0, T_0^i, V_0: Initial conditions at Day of treatment initiation

J: Objective function value , $J^* = J(u^*)$, evaluated at the optimal control (see eqn. (7)).
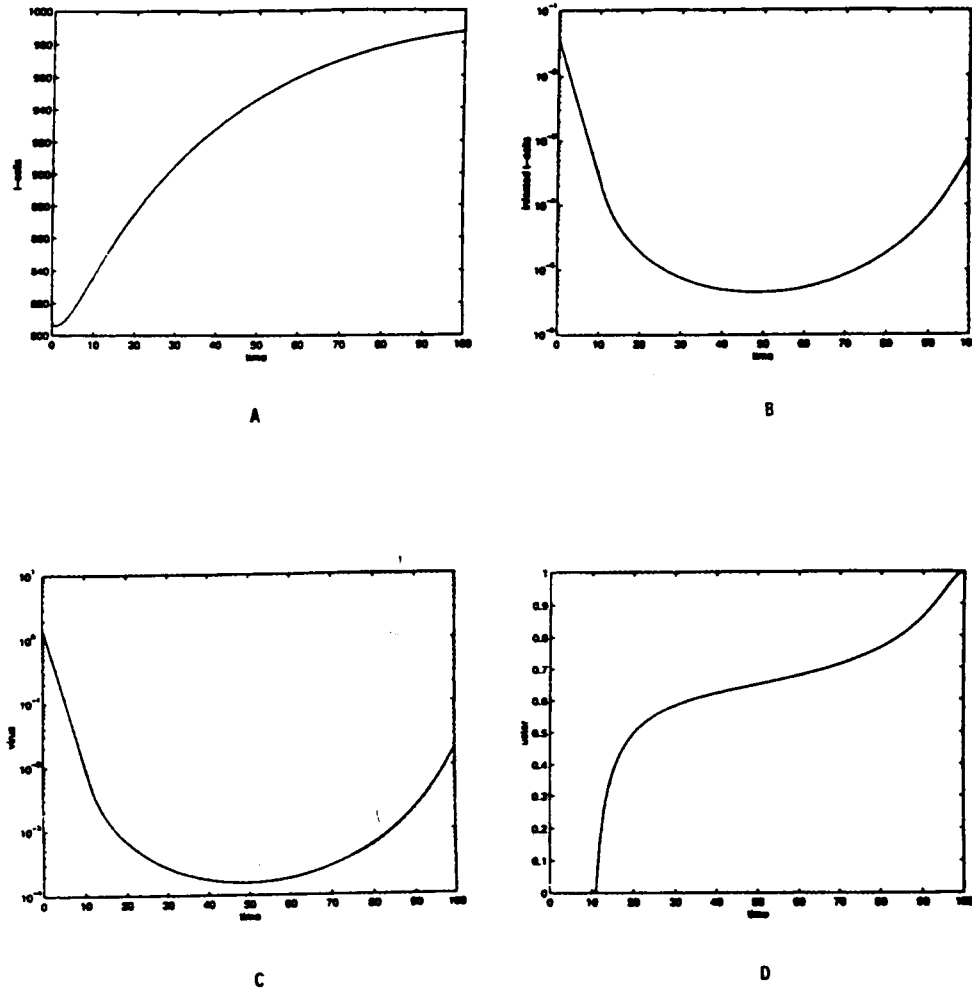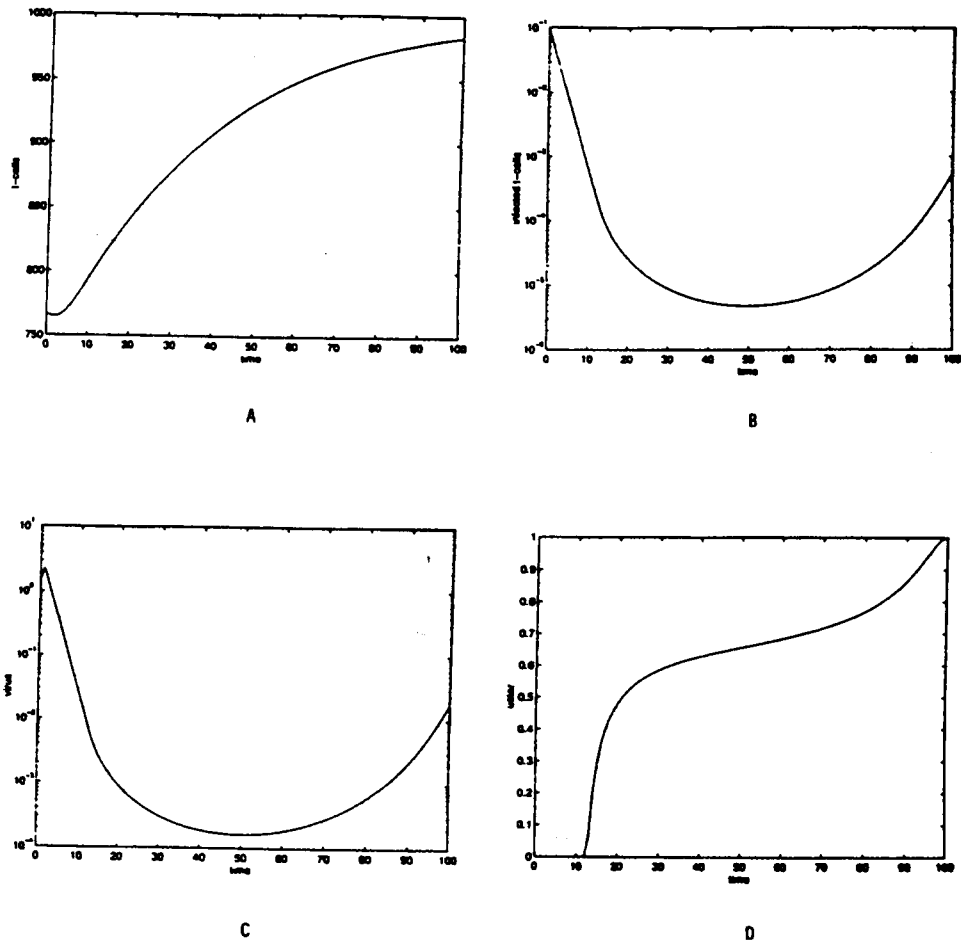
Figure 1: Graph of the solution to the optimality system (4-6) coupled with (9-11). The control, u^* is defined in (2). Here we initiate treatment when the T cell count was 806 per mm^3 for a treatment period of 100 days. Figure shows the following 4 graphs: **Panel A**: Uninfected T cells during treatment; **Panel B**: Infected T cells during treatment; **Panel C**: Virus population during treatment; and **Panel D**: The optimal chemotherapy, u^*.
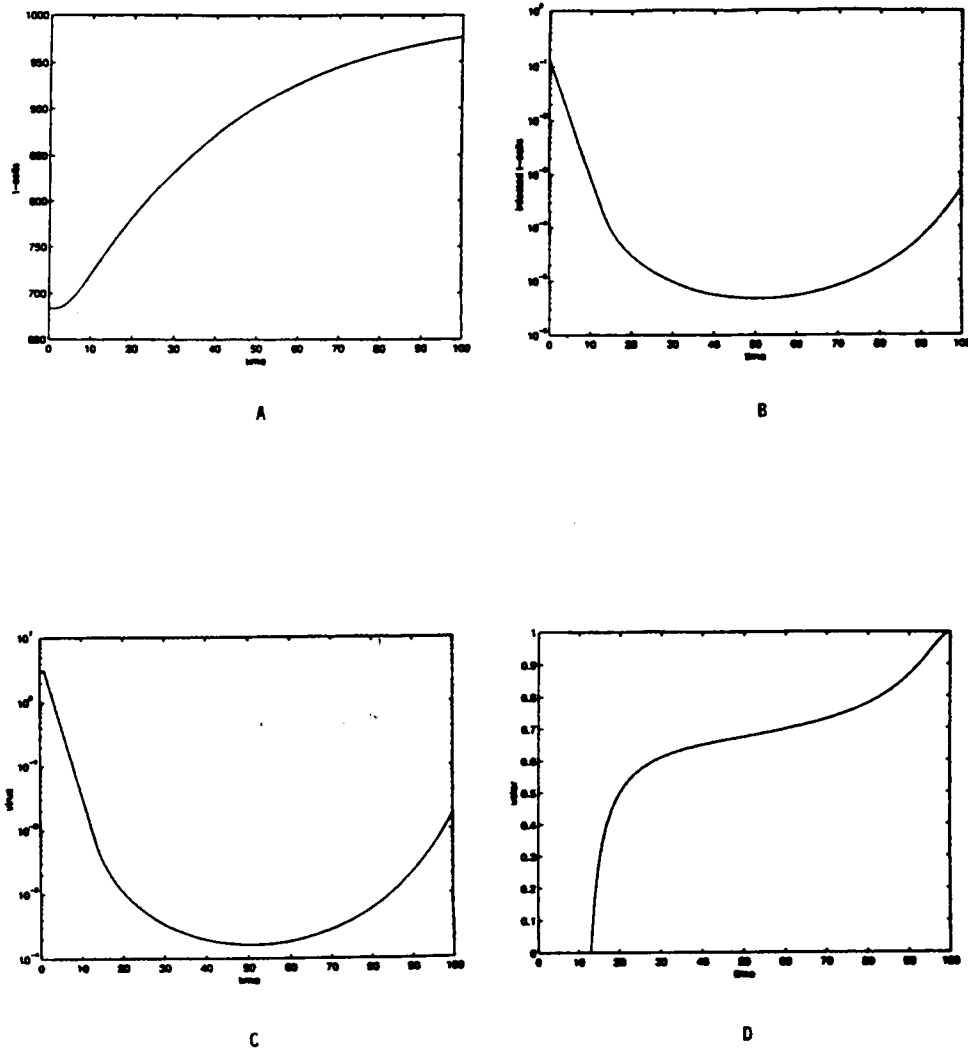
Figure 2: Graph of the solution to the optimality system (4-6) coupled with (9-11). The control, u^* is defined in (2). Here we initiate treatment when the T cell count was 766 per mm^3 for a treatment period of 100 days. Figure shows the following 4 graphs: **Panel A**: Uninfected T cells during treatment; **Panel B**: Infected T cells during treatment; **Panel C**: Virus population during treatment; and **Panel D**: The optimal chemotherapy, u^*.

Figure 3: Graph of the solution to the optimality system (4-6) coupled with (9-11). The control, u^* is defined in (2). Here we initiate treatment when the T cell count was 684 per mm^3 for a treatment period of 100 days. Figure shows the following 4 graphs: **Panel A**: Uninfected T cells during treatment; **Panel B**: Infected T cells during treatment; **Panel C**: Virus population during treatment; and **Panel D**: The optimal chemotherapy, u^*.
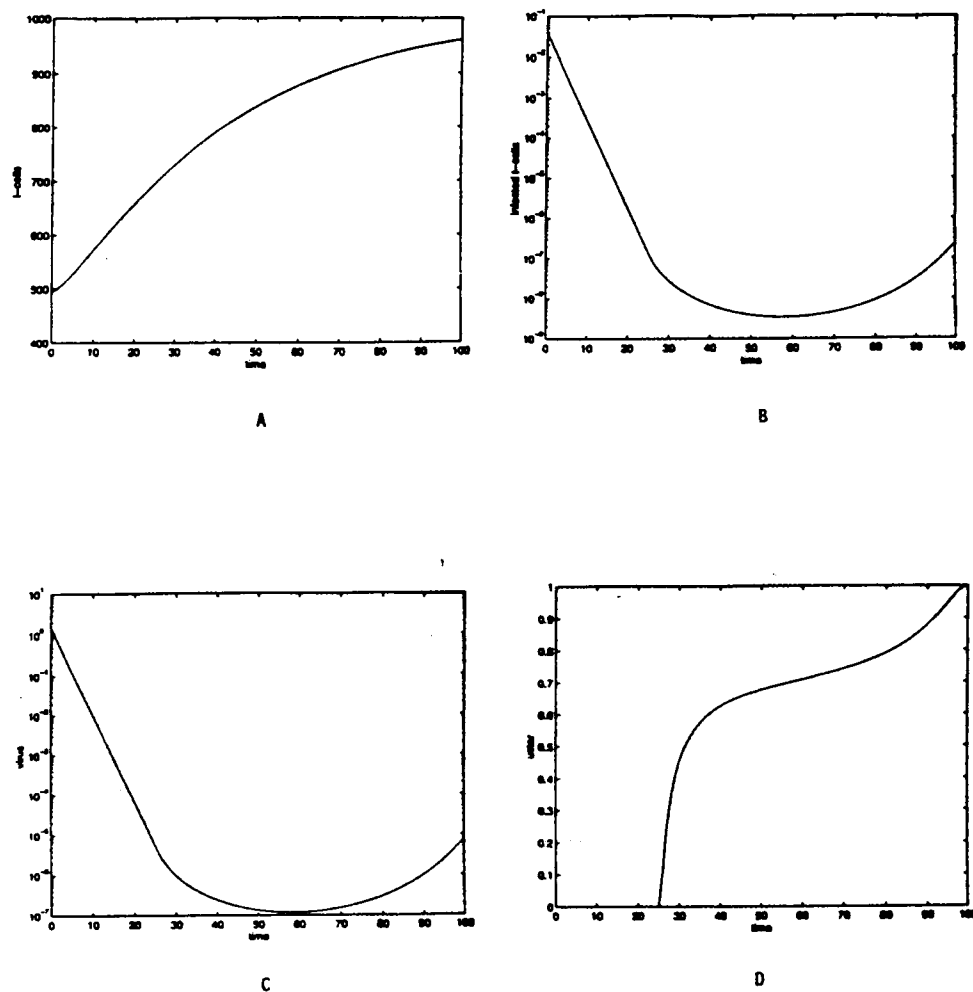
Figure 4: Graph of the solution to the optimality system (4-6) coupled with (9-11). The control, u^* is defined in (2). Here we initiate treatment when the T cell count was 494 per mm^3 for a treatment period of 100 days. Figure shows the following 4 graphs: **Panel A**: Uninfected T cells during treatment; **Panel B**: Infected T cells during treatment; **Panel C**: Virus population during treatment; and **Panel D**: The optimal chemotherapy, u^*.