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Optimal control of the chemotherapy of HIV

Denise Kirschner[1], **Suzanne Lenhart**[2], **Steve Serbin**[2]

[1] Department of Mathematics, Texas A and M University, College Station, TX 77843, USA
e-mail: dek@math.tamu.edu
[2] Department of Mathematics, University of Tennessee at Knoxville, Knoxville, TN 37996, USA
e-mails: lenhart@math.utk.edu; serbin@sugarbowl.math.utk.edu

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Abstract. Using an existing ordinary differential equation model which describes the interaction of the immune system with the human immunodeficiency virus (HIV), we introduce chemotherapy in an early treatment setting through a dynamic treatment and then solve for an optimal chemotherapy strategy. The control represents the percentage of effect the chemotherapy has on the viral production. Using an objective function based on a combination of maximizing benefit based on T cell counts and minimizing the systemic cost of chemotherapy (based on high drug dose/strength), we solve for the optimal control in the optimality system composed of four ordinary differential equations and four adjoint ordinary differential equations.

Key words: Chemotherapy – HIV – Optimal control – Ordinary differential equation system

1 Introduction

Of great concern today is the treatment of patients infected with the human immunodeficiency virus (HIV). Different chemotherapies are continually being tested and, even once FDA approved, these are under intense study to find the optimal methodology for administering the treatment.

Presently, the most widely used drugs for chemotherapy of HIV infection are AZT, DDI, DDC and D4T. These drugs all work as inhibitors of reverse transcriptase which is an enzyme. HIV is an RNA virus. When HIV infects a human immune cell (the ones we are concerned with here are the $CD4^+$ T cells), its RNA is transcribed into DNA (a unique feature of a retrovirus) using the enzyme reverse transcriptase. Reverse transcriptase inhibitors interfere with this process by halting the cellular infection and the growth of virus.

There are many data available on the treatment of HIV infection (cf., [25, 18]) and many laboratories and clinics are keeping close accounts of

patient treatment courses with respect to effectiveness and results. Of interest here is the fact that there are conflicting results as to whether treatment is better at the early stage of disease (when the $CD4^+$ T cell count is between $200/mm^3$ and $500/mm^3$ of blood), (see [13, 15]) or at the later stage (when the count is below $200/mm^3$) [16, 11]. The recent Concorde study was devoted entirely to this issue [8].

There are a few models which study the effects of chemotherapy on an immune system infected with HIV. For example, McLean and Nowak [26] have presented a model which addresses the complications arising from the appearance of AZT-resistant strains of HIV during treatment. Agur [2] and Cojocaru and Agur [7] have examined the effects of chemotherapy on normal, uninfected cells through cell cycle drug protocols. Kirschner and Webb [21] developed a model which incorporates the application of chemotherapy in the periodic manner in which it is presently administered, thus affecting only those cells which are in the early stages of infection. This is done by marking the age of cellular infection.

Kirschner and Perelson, [20], introduce to their model the effect of a drug that reduces viral replication by multiplying the terms responsible for viral load by a scalar step function,

$$z(t) = \begin{Bmatrix} 1 & \text{outside the treatment period} \\ P & \text{during the time of AZT treatment} \end{Bmatrix}.$$

Since most chemotherapies reduce viral production in a dose-dependent manner, P is chosen to be proportional to the dose of the drug. (Another interpretation for the proportion P is that efficacy of the drug may differ from patient to patient; therefore, P could also represent the varying effectiveness of the drug in halting viral reproduction.) The results in [20] indicate that introducing treatment at the beginning of the T cell depletion, when T cell counts are still relatively high, seems to be the most beneficial in restoring and mantaining T cell counts. When given in the early stages of the disease, the drug increases the time to profound T cell depletion, which suggests an increase in the time to the onset of opportunistic infections.

A problem arising from the use of most chemotherapies is the multiple and sometimes harmful side effects, as well as the ineffectiveness of treatment after a certain time due to the capability of the virus to mutate and become resistant to the treatment. Although we do not intend to model effects of resistance or side effects, we impose a condition called a *limited treatment window*, that monitors the global effects of these phenomena: The treatment lasts for a given period from time *tstart* to *tfinal*, say. The results, however, are not interval-dependent.

This paper deals specifically with the question of optimizing treatment scheduling; i.e., when and how treatment should be initiated. This study focuses on patients who are in the early stages of infection where T cell counts are high. Health and civil workers, for example, know the moment of infection and may want to treat under asymptomatic conditions. We base the 'benefit'

of treatment solely on an increase or retention of the $CD4^+$ T cell count. To this end, in Sect. 2, we introduce an existing model that describes the interaction of HIV with the immune system. Section 3 presents 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 by use of Pontryagin's Maximum Principle. In Sect. 4, utilizing the representation of the optimal control, we solve numerically the optimality system, which is defined as the original state system coupled with the adjoint system. We conclude by discussing the results of the numerical simulations as treatment initiation is varied.

2 Presentation of a working model

To begin the control procedure, it is necessary to have a model which describes the infected scenario. In [29, 30], a simple model is given which simulates the interaction of the immune system with HIV. We use this model and recommend that the reader see those papers for a more complete background and analysis of the model. We present a brief discussion below.

Let T denote the concentration of uninfected $CD4^+$ T cells, and let T^* and T^{**} denote the concentrations of latently infected and actively infected $CD4^+$ T cells. The concentration of free infectious virus particles is V. Definitions and numerical information for the parameters can be found in Table 1. We assume that the dynamics of the various populations are:

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

$$\frac{dT^*}{dt} = k_1 V T - \mu_T T^* - k_2 T^*, \tag{2}$$

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

$$\frac{dV}{dt} = N\mu_b T^{**} - k_1 V T - \mu_V V\,. \tag{4}$$

In (1), $s/(1+V)$ is a source term and represents the rate of generation of new $CD4^+$ T cells.[1] T cells have a finite life-span and die at a rate of μ_T per cell. In (2), latently infected T cells are also assumed to have the same natural death-rate, μ_T, although other factors can augment the natural death rate.

[1] We obtained the best results as compared to the clinical data (e.g., [9]), when we allowed the source of $CD4^+$ T cells to be a monotonically decreasing function depending on the viral concentration, V. This viral dependent source models the infection of T cell precursors by virus, hence which reduces the uninfected viral source. This is explored more fully in [22].

Table 1

Parameters and constants	Values
μ_T = death rate of uninfected CD4$^+$ T cell population	0.02 d^{-1}
μ_{T^*} = death rate of latently infected CD4$^+$ T cell population	0.02 d^{-1}
μ_b = death rate of actively infected CD4$^+$ T cell population	0.24 d^{-1}
μ_V = death rate of free virus	2.4 d^{-1}
k_1 = rate CD4$^+$ T cells becomes infected by free virus	2.4×10^{-5} mm^3 d^{-1}
k_2 = rate T^* cells convert to actively infected	3×10^{-3} d^{-1}
r = rate of growth for the CD4$^+$ T cell population	0.03 d^{-1}
N = number of free virus produced by T^{**} cells	1200
$T_{\max}$ = maximum CD4$^+$ T cell population level	1.5×10^3 mm^{-3}
s = source term for uninfected CD4$^+$ T cells	10 d^{-1} mm^{-3}
where s is the parameter in the term	$s/(1 + V)$

That is, we assume that although the cell is a host to virion, it is unaffected by their presence. In (1), r represents the growth rate of T cells, which is presented as a logistic-type term, so that the T cells never grow larger than a value, $T_{\max}$.

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

Equation (3) models the actively infected CD4$^+$ T population. Latently infected cells become actively infected at the rate $k_2 T^*$. Actively infected cells produce virus and die at per capita rate μ_b. Equation (4) models the free virus population. We assume that when an actively infected CD4$^+$ T cell becomes stimulated through exposure to antigen, replication of the virus is initiated and N viruses are produced before the host cell dies. Free virus is lost by binding to uninfected CD4$^+$ T cells at rate $k_1 VT$. Infected cells tend to lose their CD4, and hence their binding to infected cells is ignored. The next term, $-\mu_V V$, accounts for viral loss of infectivity and/or removal from the body.

In the absence of virus, the T cell population has the steady state value

$$T_0 = \frac{T_{\max}}{2}\left[1 - \frac{\mu_T}{r} + \sqrt{\left(1 - \frac{\mu_T}{r}\right)^2 + \frac{4s}{rT_{\max}}}\right]. \tag{5}$$

Thus reasonable initial conditions for the system of equations (1)–(4) are $T(0) = T_0$, $T^*(0) = 0$, $T^{**}(0) = 0$, and $V(0) = V_0$ for infection by free virus, or $T(0) = T_0$, $T^*(0) = T_0^*$, $T^{**}(0) = T_0^{**}$, $V(0) = V_0$ for infection by both infected cells and virus.

There are certain parameter restrictions that we impose to ensure that this model gives realistic population dynamics. See [30] for the analysis leading to parameter restrictions and stability results. Even after the thymus involutes (a normal process is adulthood by where the thymus retrogresses), the thymus still remains functional. Thus, we assume $s > 0$. The steady state population size, T_0 should be less than $T_{\max}$, so that the T cell population will expand

when stimulated as occurs during infection with HIV. Further, after the population reaches $T_{\max}$, it should decrease. Therefore, for the death rate at $T_{\max}$ to be greater than the supply rate, we choose

$$\mu_T T_{\max} > s \,. \tag{6}$$

If this were not the case, then the population could increase past $T_{\max}$. Equations (5) and (6), together with the condition $s > 0$, imply that $T(t) < T_{\max}$ as desired. Thus, all solutions that begin with an initial number of T cells, $T(0)$ in the interval $(0, T_{\max})$ remain bounded and in that corresponding interval for all t.

The system (1)–(4) has two steady states. The first, when no virus is present (the *uninfected steady state*), occurs when $T = T_0$, $T^* = 0$, $T^{**} = 0$ and $V = 0$. The second, the *endemically infected steady state*, has each of the cell populations at positive values. Perelson et al. [30] 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 $N = N_{\text{crit}}$, the stability is exchanged through a transcritical bifurcation and the infected steady state becomes locally stable. For $N > N_{\text{crit}}$, global stability could not be shown because other bifurcations may occur. For example, stability can be lost for the infected steady state, giving rise to stable limit cycles. Perelson et al. [30] believe that this occurs for parameter values that lie outside of the biologically possible ranges.

In Perelson et al. [30] and Kirschner and Perelson [20] chemotherapy was studied with this simple model and a related one. Treatment was simulated by a drug which reduces viral production. The models showed that if the number of virion product per $CD4^+$ T cell is forced below N_{crit} through treatment, then the immune system can recover to state where the uninfected state is stable. Otherwise, infection continues.

3 Optimally controlling chemotherapy

Our control represents the percentage of effect the chemotherapy has on the viral production. As in the previous work done with chemotherapy and HIV ([30, 20]), we assume that the chemotherapy reduces the viral load, so in equations (1)–(4), the control $u(t)$ multiplies the parameter N in equation (4). Therefore, we choose as our control class, measurable functions defined on $[tstart, tfinal]$, with the restriction $0 \leqq u(t) \leqq 1$. Although we do not intend to model effects of resistance or side effects, we can impose a condition that monitors the global effects of these phenomena: a limited treatment window. Thus, a finite interval of treatment is necessary since we assume HIV has the ability to mutate at such a fast pace that it is able to build up resistance to the chemotherapy treatment after a finite time. The treatment period is finite in any treatment scenario. Also, the treatment has potentially harmful side effects. Therefore, for $tstart \leqq t \leqq tfinal$ where, for most of the present HIV

chemotherapy drugs, $tfinal - tstart < 2$ years, the state system would be:

$$\frac{dT}{dt} = \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T + T^* + T^{**}}{T_{\max}}\right) - k_1 VT \,, \tag{7}$$

$$\frac{dT^*}{dt} = k_1 VT - \mu_T T^* - k_2 T^* \,, \tag{8}$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_b T^{**} \,, \tag{9}$$

$$\frac{dV}{dt} = \boldsymbol{u(t)} N\mu_b T^{**} - k_1 VT - \mu_V V \,, \tag{10}$$

with given initial values for T, T^*, T^{**}, and V at *tstart*. For our purposes, we use $N > N_{\text{crit}}$ so we are not in the region of stability for the uninfected state.

Define the objective function

$$J(u) = \int_{tstart}^{tfinal} [\,T(t) - \tfrac{1}{2} B(1 - u(t))^2]\, dt \,. \tag{11}$$

In words, we are maximizing the *benefit* based on the T cell count, and minimizing the systemic *cost* based on the percentage effect of the chemotherapy given (i.e. $(1 - u)$), since large drug concentrations can be harmful; hence, we are maximizing the difference. We have reason to believe that the cost function is a nonlinear function of u^*; we choose a quadratic cost here. This is based on the fact that there is not a linear relationship between the effects of treatment on T cells or virus. If the control $u(t) = 0$ corresponds to maximal use of chemotherapy, then the maximal cost is represented as $(1 - u(t))^2$. The parameter $B \geqq 0$ represents the desired 'weight' on the benefit and cost. The goal, therefore is to characterize the optimal control u^* satisfying, $\max_{0 \leqq u \leqq 1} J(u) = J(u^*)$.

We note that the existence of an optimal control can be found in Fleming and Rishel ([14], chapter III). In this maximization problem, the necessary concavity of the objective functional in u holds. The right hand sides of the state equations are linearly bounded, due to *a priori* bounds on the T variable, which implies the needed *a priori* bounds on the other state variables. These bounds insure the compactness needed for the existence of the optimal control. At this point we can proceed with the Pontryagin Maximum Principle.

If $\boldsymbol{u}^*$ is an optimal control, then we apply Pontryagin's Maximum Principle to the constrained control problem [19]. The Lagrangian for our problem is the integrand of the objective functional, coupled with the right hand sides of the state equations through the adjoint variables $\lambda_1(t), \lambda_2(t), \lambda_3(t)$. Penalty multipliers $\omega_1(t)$, $\omega_2(t)$ attach the control con-

straints. Define the Lagrangian to be:

$$L(T, T^*, T^{**}, V, u, \lambda_1, \lambda_2, \lambda_3, \lambda_4) = T(t) - \tfrac{1}{2}B(1-u(t))^2$$
$$+ \lambda_1\left(\frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T+T^*+T^{**}}{T_{\max}}\right) - k_1 V T\right)$$
$$+ \lambda_2(k_1 V T - \mu_T T^* - k_2 T^*) + \lambda_3(k_2 T^* - \mu_b T^{**})$$
$$+ \lambda_4(\boldsymbol{u(t)} N\mu_b T^{**} - k_1 V T - \mu_V V) + \omega_1(t)u(t) + \omega_2(t)(1-u(t)), \quad (12)$$

where $\omega_1(t) \geqq 0, \omega_2(t) \geqq 0$, are the penalty multipliers satisfying $\omega_1(t)u(t) = 0$, and $\omega_2(t)(1-u(t)) = 0$. Thus, the Maximum Principle gives the existence of adjoint variables satisfying:

$$\lambda_1' = \frac{-\partial L}{\partial T} = -\left[1 + \lambda_1\left(-\mu_T + r\left(1 - \frac{T+T^*+T^{**}}{T_{\max}}\right) - \frac{rT}{T_{\max}} - k_1 V\right)\right.$$
$$\left. + \lambda_2 k_1 V - \lambda_4 k_1 V\right], \quad (13)$$

$$\lambda_2' = \frac{-\partial L}{\partial T^*} = -\left(\frac{-\lambda_1 rT}{T_{\max}} - \lambda_2(\mu_T + k_2) + \lambda_3 k_2\right), \quad (14)$$

$$\lambda_3' = \frac{-\partial L}{\partial T^{**}} = -\left(\frac{-\lambda_1 rT}{T_{\max}} - \lambda_3\mu_b + \lambda_4 \boldsymbol{u(t)} N\mu_b\right), \quad (15)$$

$$\lambda_4' = \frac{-\partial L}{\partial V} = -\left[-\frac{\lambda_1 s}{(1+V)^2} - \lambda_1 k_1 T + \lambda_2 k_1 T + \lambda_4(-k_1 T - \mu_V)\right], \quad (16)$$

where $\lambda_i(tfinal) = 0$ for $i = 1, 2, 3, 4$ are the transversality conditions. The Lagrangian is maximized with respect to u at the optimal u^*, so the derivative of the Lagrangian with respect to u at u^* is zero. Since

$$L = (u(t)\lambda_4 N\mu_b T^{**} + \omega_1 u(t) + \omega_2(1-u(t))$$
$$- \tfrac{1}{2}B(1-u(t))^2) + \text{terms without } u\,,$$

differentiating this expression for L with respect to u gives:

$$\frac{\partial L}{\partial u} = \lambda_4 N\mu_b T^{**} + \omega_1 - \omega_2 + B(1-u) = 0 \text{ at } u^*\,.$$

Solving for the optimal control yields

$$u^*(t) = \frac{\lambda_4 N\mu_b T^{**} + \omega_1(t) - \omega_2(t) + B}{B}\,.$$

Consider 3 cases:

(i) For $\{t \mid 0 < u^*(t) < 1\}$, we have $\omega_1(t) = \omega_2(t) = 0$, hence the optimal control is:

$$u^*(t) = \frac{\lambda_4 N \mu_b T^{**} + B}{B};$$

(ii) For $\{t \mid u^*(t) = 1\}$, we have $\omega_1(t) = 0$ hence, $u^*(t) = 1 = \lambda_4 N \mu_b T^{**} - \omega_2(t)/B + 1$, which implies $0 \leqq \omega_2(t) = \lambda_4 N \mu_b T^{**}$, and $1 \leqq (\lambda_4 N \mu_b T^{**} + B)/B$;

(iii) For $\{t \mid u^*(t) = 0\}$, we have $\omega_2(t) = 0$, $\omega_1(t) \geqq 0$. Hence, the optimal control is:

$$0 = u^*(t) = \frac{\lambda_4 N \mu_b T^{**} + \omega_1 + B}{B}.$$

Therefore, $\omega_1(t) \geqq 0$ implies that $(\lambda_4 N \mu_b T^{**} + B)/B \leqq 0$, hence

$$\left(\frac{\lambda_4 N \mu_b T^{**} + B}{B}\right)^+ = 0 = u^*(t).$$

Combining these 3 cases, the optimal control is characterized as

$$u^* = \min\left(\left(\frac{\lambda_4 N \mu_b T^{**} + B}{B}\right)^+, 1\right), \tag{17}$$

where

$$\left(\frac{\lambda_4 N \mu_b T^{**} + B}{B}\right)^+ = \begin{cases} \dfrac{\lambda_4 N \mu_b T^{**}}{B} + 1 & \text{if } \lambda_4 N \mu_b T^{**} + B > 0 \\ 0 & \text{if } \lambda_4 N \mu_b T^{**} + B \leqq 0 \end{cases}.$$

If $\lambda_4(t) < 0$ for some t, then $u^*(t) \neq 1$. Hence, $0 \leqq u^*(t) < 1$ for those t, which implies treatment should be administered.

Theorem *An optimal control* $\boldsymbol{u^*}$ *for system* (7)–(10) *which maximizes the objective function* (11) *is characterized by* (17), *where the notation* $a^+ = \max\{a, 0\}$.

The uniqueness of solutions to the optimality system, (7)–(10) coupled with (13)–(16) together with u^* characterization (17), can be obtained by standard results. Thus the unique optimal control is represented in terms of the unique solution of the optimality system. Note that we could have easily treated the case $\varepsilon \leqq u \leqq 1$, $\varepsilon > 0$, which would say that the chemotherapy never completely stopped viral reproduction.

4 Numerical results

The numerical results of the untreated model (1)–(4) were created using **Mathematica** [33], and are presented in Fig. 1. We present these results for comparison purposes. Numerical results for the optimality system of eight

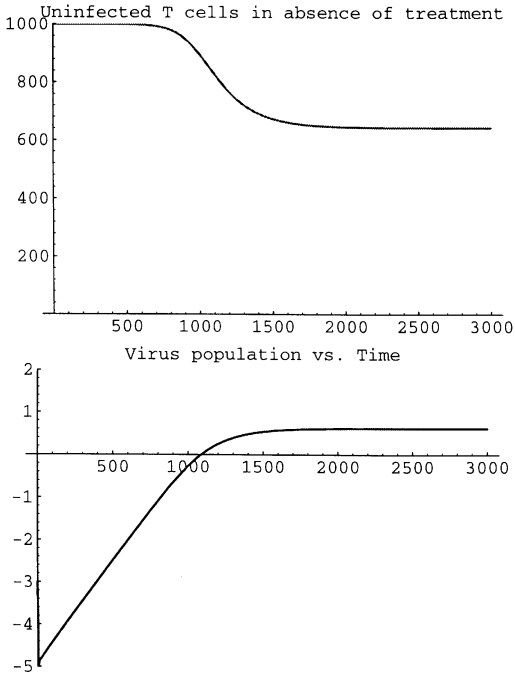


Fig. 1a, b. Graph of the solution to the system of Eqs. (1)–(4) representing the untreated system. **a** The uninfected T cell population, **b** the virus population. The parameter values and initial conditions are given in Table 1

equations are also presented. We point out that for the state variables, T, T^*, T^{**}, V, we have given *a priori* initial conditions. However, for the adjoint variables, λ_i, $i = 1, 2, 3, 4$, we have only the ending values $\lambda_i(t_{final}) = 0$, $i = 1, 2, 3, 4$. The problem is thus a two-point boundary value problem. Using a collocation code COLNEW [1, 4] (obtained via NETLIB), the optimality system was solved. Figures 2–4 represent the graphs of the solution to the optimality system (7–10) coupled with (12–16) at three different early treatment initiations. We vary initiation of treatment beginning with T cell counts: at 950/mm^3, 800 days after the onset of infection (Fig. 2); at 890/mm^3, 1000 days after the onset of infection (Fig. 3); at 760/mm^3, 1200 days after onset of infection (Fig. 4). We ran simulations with different values of B, the control parameter which adjusts the balance between benefit of treatment and systemic cost of chemotherapy, but present only the case $B = 100$ for brevity. This is because the magnitude of T cell concentration is much larger than the magnitude of the chemotherapy cost in the objective function in (11). Therefore, this difference in magnitudes is best balanced by choosing B on the order of a hundred to represent this magnitude difference. We also examined different treatment periods (in number of days) but found that there was not much variation in the results so we only show the case of 500 days of treatment.

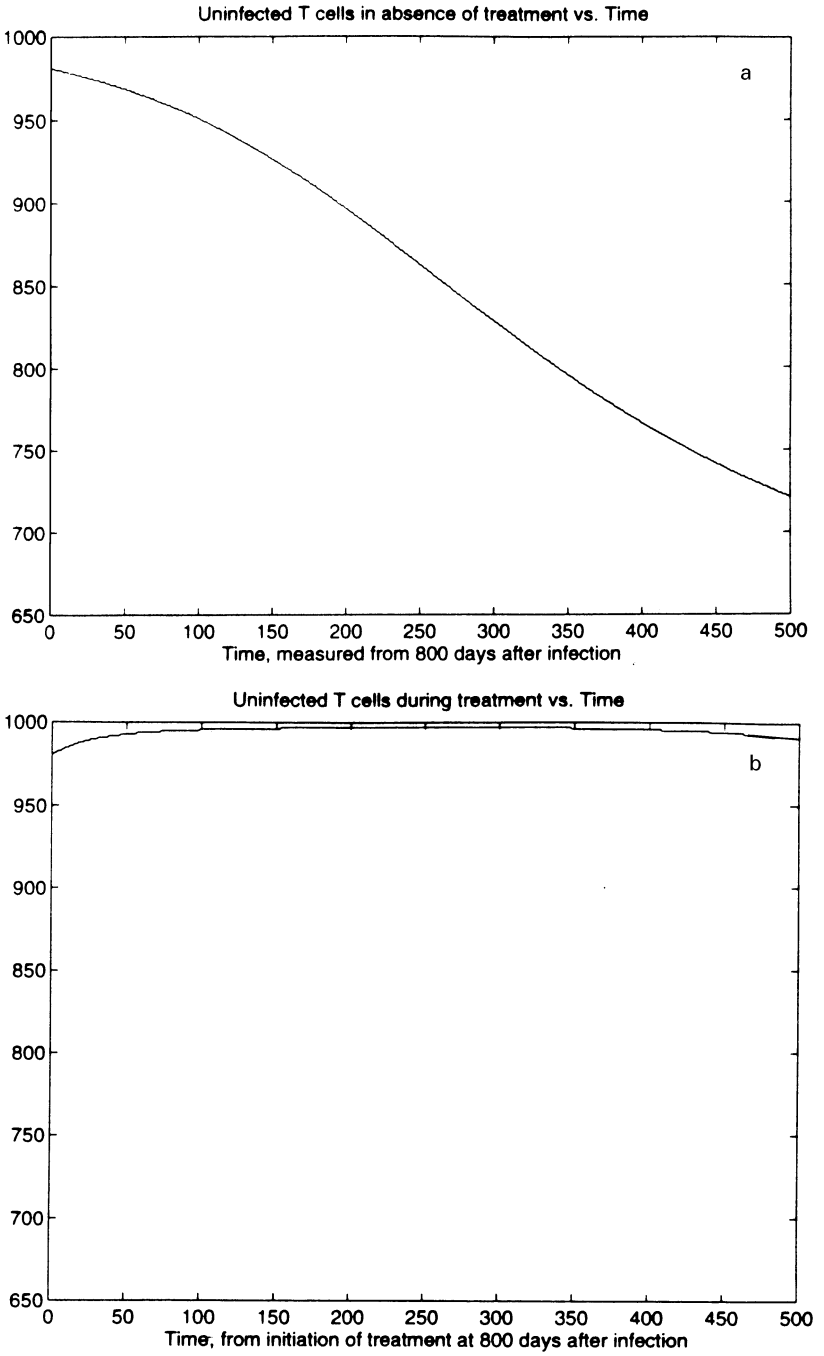
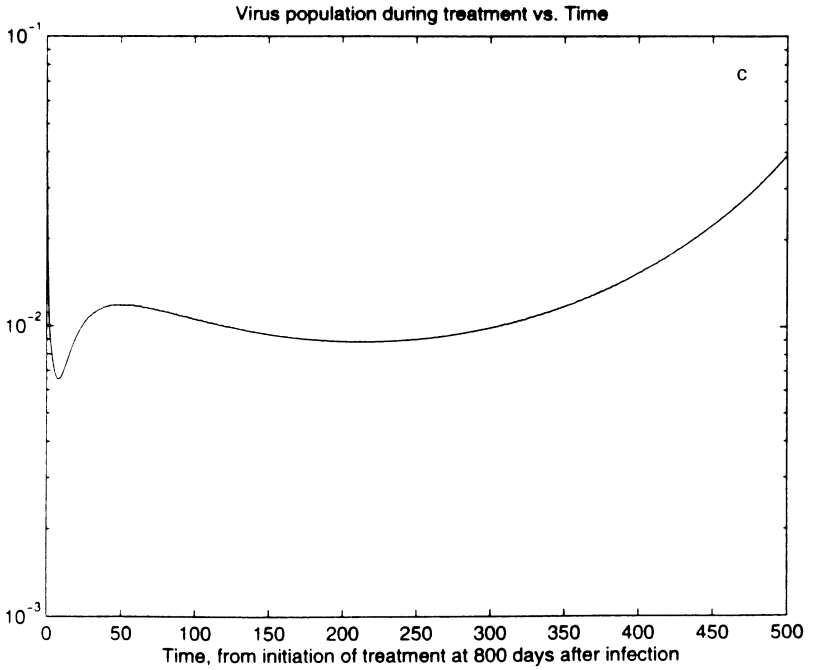


Fig. 2a–d. Graph of the solution to the optimality system (7–10) coupled with (12–16). The control, u^* is defined in (17). Here we initiate treatment after 800 days (T cell count is 975) for a treatment period of 500 days. Figure shows the following 4 graphs: **a** Uninfected T cells in the absence of treatment; **b** Uninfected T cells during treatment; **c** Virus population during treatment; and **d** The optimal chemotherapy, given as $(1 - u^*)$ for ease of interpretation



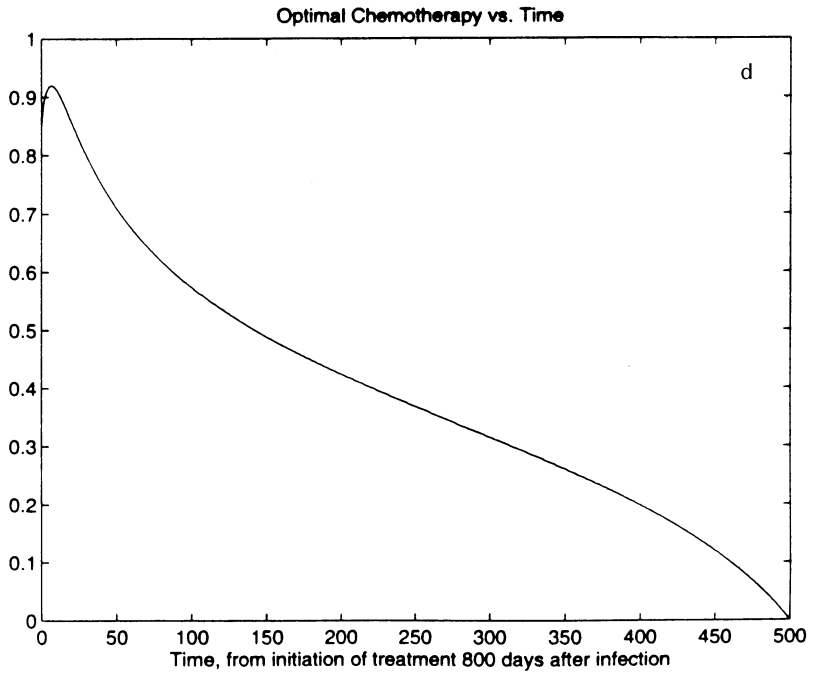


Fig. 2. Continued

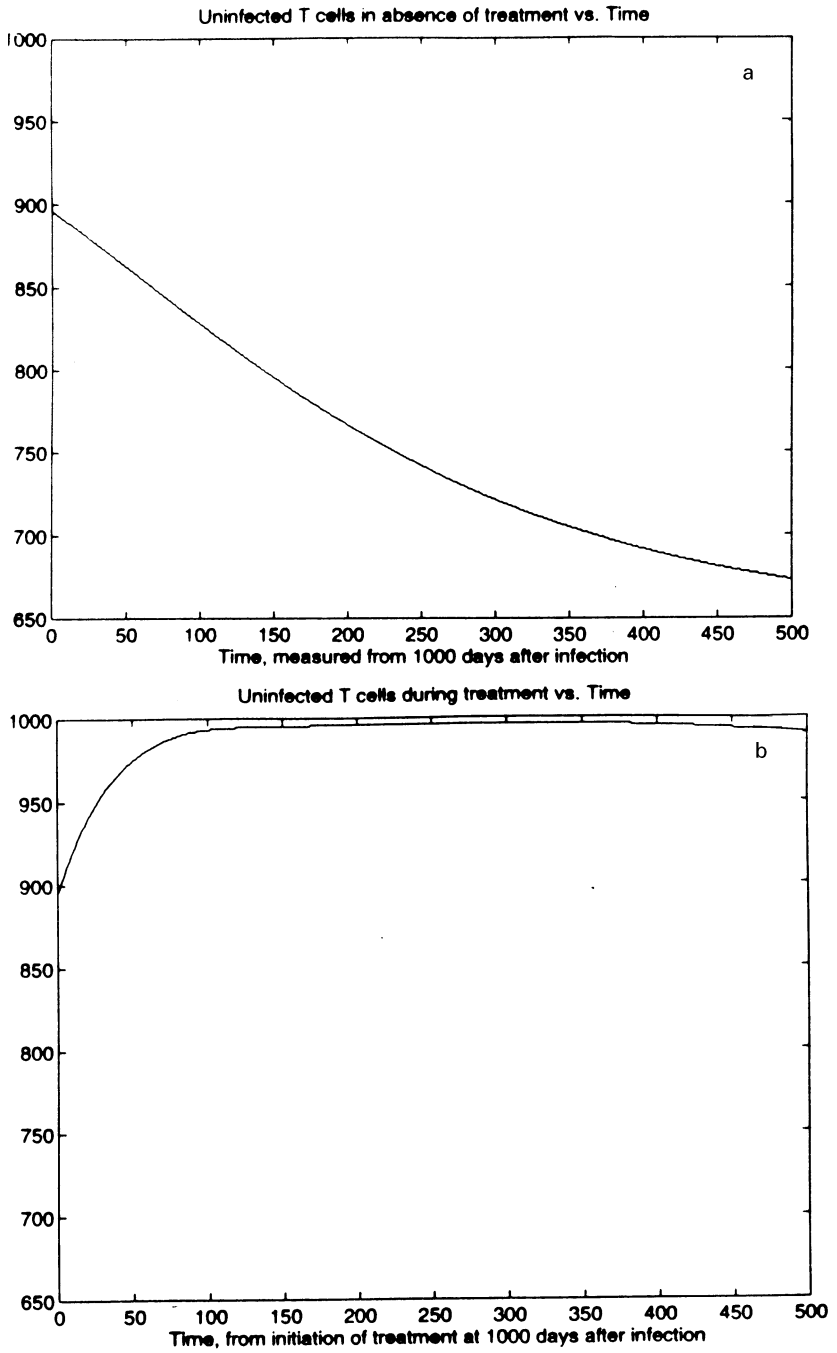
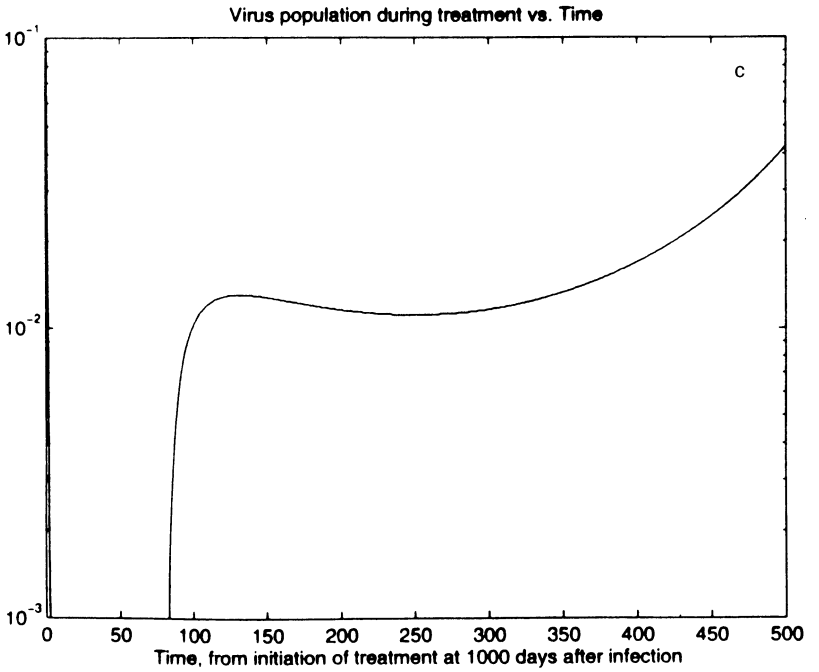


Fig. 3a–d. Graph of the solution to the optimality system (7–10) coupled with (12–16). The control, u^* is defined in (17). Here we initiate treatment after 1000 days (T cell count is 900) for a treatment period of 500 days. Figure shows the following 4 graphs: **a** Uninfected T cells in the absence of treatment; **b** Uninfected T cells during treatment; **c** Virus population during treatment; and **d** The optimal chemotherapy, given as $(1 - u^*)$ for ease of interpretation



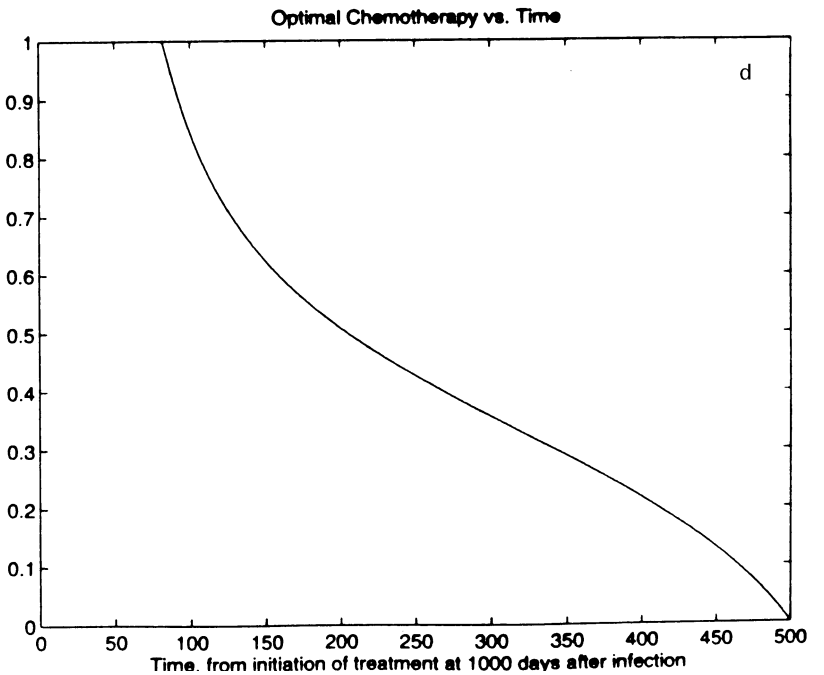
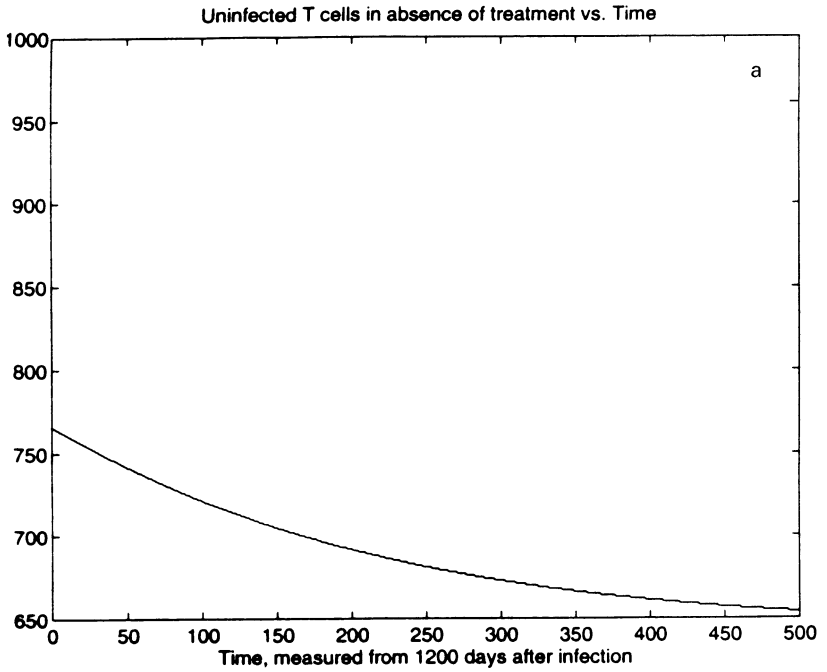


Fig. 3. Continued



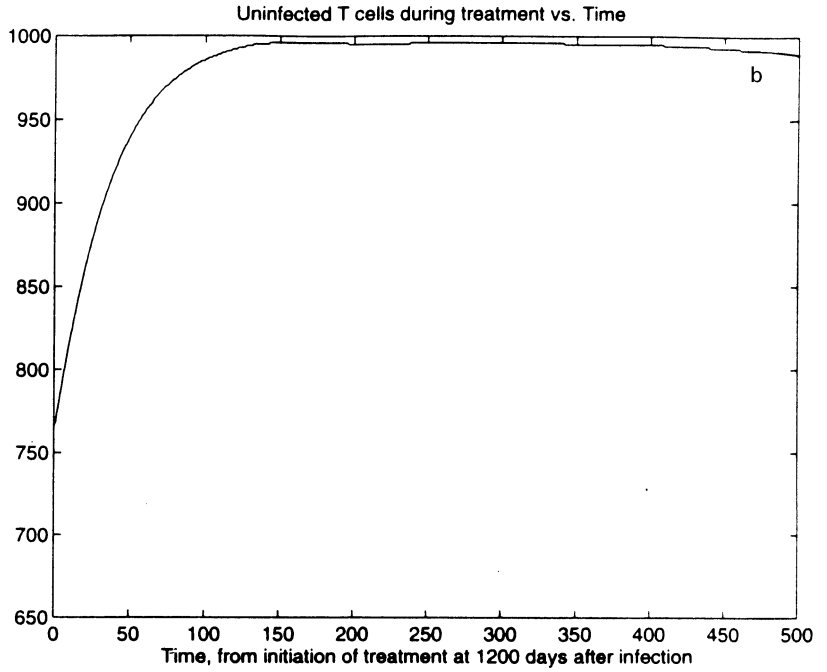
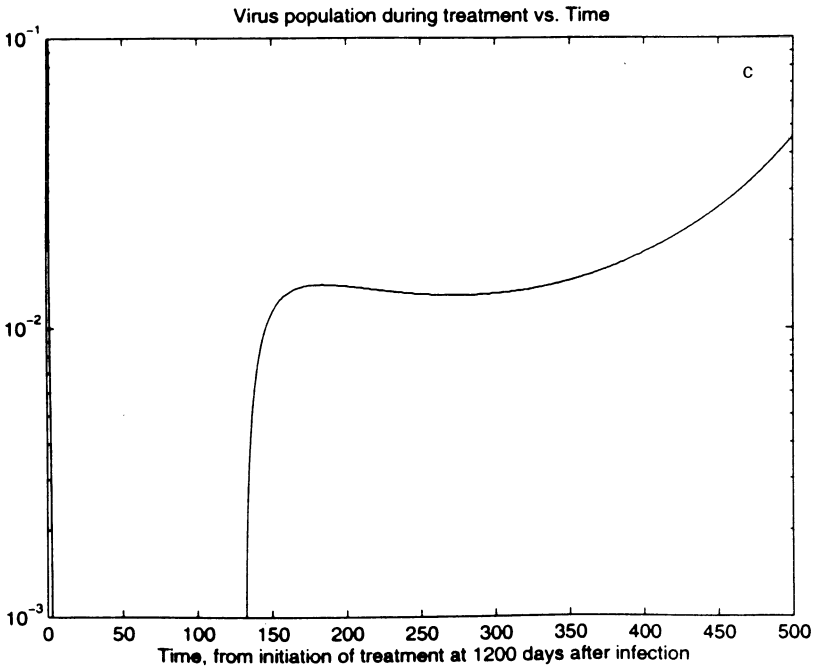


Fig. 4a–d. Graph of the solution to the optimality system (7–10) coupled with (12–16). The control, u^* is defined in (17). Here we initiate treatment after 1200 days (T cell count is 775) for a treatment period of 500 days. Figure shows the following 4 graphs: **a** Uninfected T cells in the absence of treatment; **b** Uninfected T cells during treatment; **c** Virus population during treatment; and **d** The optimal chemotherapy, given as $(1 - u^*)$ for ease of interpretation



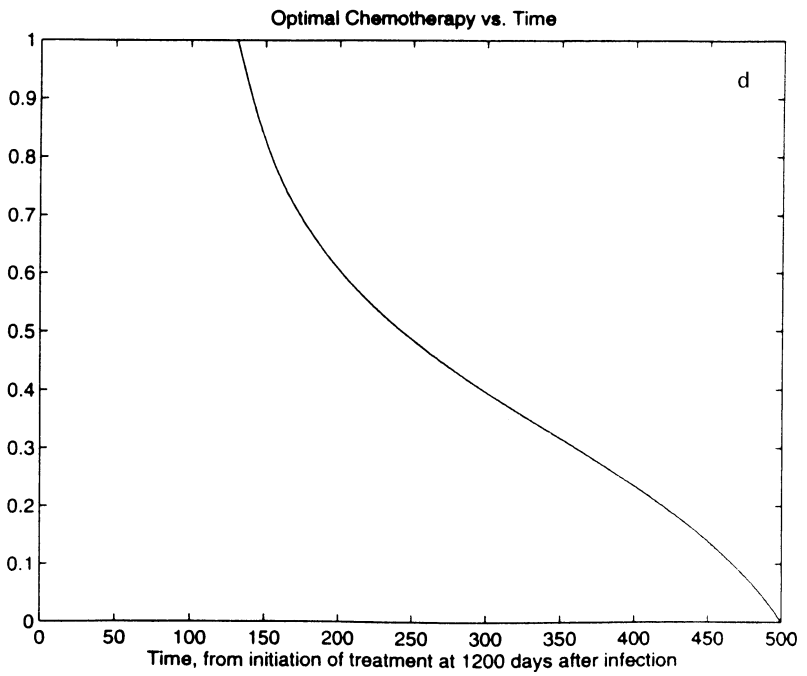


Fig. 4 Continued

Table 2

Initiation time	T cell counts (at initiation)	Objective function value, J
800 days after onset of infection	T cell count 950/mm^3	493,450
1000 days after onset of infection	T cell count 890/mm^3	487,060
1200 days after onset of infection	T cell count 760/mm^3	480,020

Table 2 is a summary of these results. These simulations reveal that earliest treatment, with a moderate treatment schedule, is optimal. Notice that, in the last panel with treatment initiated at 760 T cells/mm^3, the treatment must be given at the highest possible dose for almost 100 days to achieve basically the same effect at the first case, where treatment is never administered at 100% strength.

5 Conclusions

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 production, N. 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 with AZT and DDT [25].

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 three 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.

The results presented here do not depend on the treatment duration. When one is 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.

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 provides 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 that combination drug treatments is preferable since there is a reduced chance of the virus mutating simultaneously to strains resistant to all of the drugs present in the 'cocktail' [6, 27]. We are presently exploring these phenomena through a revised model.

References

1. Ascher, U., Matteij, R. and Russell, R.: Numerical Solution of Boundary Value Problems, Prentice-Hall, Engelwood, NJ, 1988 pp. 526–533
2. Agur, Z.: A new method for reducing cytotoxicity of the anti-AIDS drug AZT. In: D. S. Levine, J. C. Baltzer: AG, Biomedical Modeling and Simulation, 1989 (IMACS), pp. 59–61, Scientific Publishing Co
3. Anderson, D. J., et al.: Effects of disease stage and AZT therapy on the detection of HIV-1 in semen. Journal of the American Medical Association **267(20)**, 2769–2774 (1992)
4. Bader, G. and Ascher, U., "A new basis implementation for a mixed order boundary value ode solver," SIAM J. Sci. Stat. Comp. **8** (1987) 483–500
5. Beretta, E. and Solimano, F.: An Optimal Time Control Problem for the Administration of 2′,3′-Dideoxycytidine by using Red Blood Cells as Bioreactors. **55(4)**, 715–730 (1993)
6. Chow, Y. K. and Hirsch, M. S., et al.: Use of evolutionary limitations of HIV-1 multidrug resistance to optimize therapy. Nature **361**, 650–655 (1993)
7. Cojocaru, L. and Agur, Z.: New mathematical methods for evaluating toxicity of anti-cancer drugs and AZT. Preprint. (1993)
8. Concorde Coordinating Committee: MRC/ANRS randomized double-blind controlled trial of immediate and deferred AZT in symptom-free HIV infection. The Lancet **343**, 871–881 (1994)
9. Conner, R. I., et al.: Increased viral burden and cytopathicity correlate temporally with $CD4^+$ T-Lymphocyte decline and clinical progression in HIV-1 infected individuals. J. Virology **67**, 1772–1777 (1993)
10. Cooper, D. A., et al.: The efficacy and safety of AZT with or without acyclovir in the treatment of patients with AIDS related complex. AIDS **5**, 933–943 (1991)
11. Cox, H. P., et al.: Outcomes of treatment with AZT of patients with AIDS and symptomatic HIV infection. Nurse Practitioner **15**, 36–43 (1990)
12. Fenyo, E. M., et al.: Distinct replicative and cytopathic characteristics of HIV isolates. J. Virology **62**, 4414–4419 (1988)
13. Fischl, M. A., et al.: The safety and efficacy of AZT in the treatment of subjects with mildly symptomatic HIV type 1. Annals of Internal Medicine **112**, 727–737 (1990)

14. Fleming, W. and Rishel, R.: Deterministic and Stochastic Optimal Controls (Chapter 3, Theorem 4.1, p. 68) Springer-Verlag, NY (1975)
15. Graham, M. H., et al.: The effects on survival of early treatment of HIV infection. New England Journal of Medicine **326**, 1037–1042 (1992)
16. Hamilton, J. D., et al.: A controlled trial of early vs. late treatment with AZT in symptomatic HIV infection, New England Journal of Medicine **326**, 437–443 (1992)
17. Heinricher, A., Lenhart, S., Solomon, A.: The Application of Optimal Control to Bioremediation Processes. (1993)
18. Hirsch, M. S.: Chemotherapy of HIV infections: Current practice and future prospects. Journal of Infectious Diseases **161**, 845–857 (1990)
19. Kamien, M. and Schwartz, N. L.: Dynamic Optimization, 2nd Edition, North-Holland, NY (1991)
20. Kirschner, D. and Perelson, A.: Model for the Immune System Response to HIV: AZT Treatment Studies. O. Arino, D. Axelrod and M. Kimmel: (Mathematical Population Dynamics III-Theory of Epidemics, 1) Wuerz Publishing, Winnipeg, Manitoba (1994), 295–310
21. Kirschner, D. and Webb, G. F.: A Model for Treatment Strategy in the Chemotherapy of AIDS. Bulletin of Mathematical Biology **58**(2), 367–390 (1996)
22. Kirschner, D., Mehr, R. and Perelson, A.: The Role of the Thymus in HIV infection. In preparation (1996)
23. Lenhart, S. and Bhat, M. G.: Applications of Distributed Parameter Control Model in Wildlife Damage Management, Preprint (1993)
24. Ho, D. D., Pomerantz, R. J., and Kaplan, J. C.: Pathogenesis of infection with human immunodeficiency virus. N. Engl. J. Med. **317**, 278 (1987)
25. McLeod, G. X., et al.: Zidovudine: 5 years later. Annals of Internal Medicine **117**, 487–501 (1992)
26. McLean, A., Nowak, M.: Competition between AZT sensitive and AZT resistant strains of HIV. AIDS **6**, 71–79 (1992)
27. Meng, T. C., et al.: Combination Therapy with AZT and DDC in patients with advanced HIV infection, Annals of Internal Medicine, **116**, 13–19 (1992)
28. Nara, P. L., et al.: Emergence of viruses resistant to neutralization by V3-specific antibodies in experimental HIV type 1 IIIB infection of chimpanzees. J. Virology **64**, 3779–3791 (1990)
29. 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)
30. Perelson, A., Kirschner, D., DeBoer, R.: The dynamics of HIV infection of $CD4^+$ T cells. Math. Biosciences **114**, 81–125 (1993)
31. Swan, G. W.: Applications of Optimal Control Theory in Biomedicine, Dekker, Inc., NY (1984)
32. Volberding, P. A., et al.: AZT in asymptomatic HIV infection. New England Journal of Medicine **322**, 940–949 (1990)
33. Wolfram, S. A.: MATHEMATICA, A system for doing Mathematics by computer, Addison-Wesley (1988)

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