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OPTIMIZING CHEMOTHERAPY IN AN HIV MODEL

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Abstract. We examine an ordinary differential system modeling the interaction of the HIV virus and the immune system of the human body. The optimal control represents a percentage effect the chemotherapy has on the interaction of the $CD4^+T$ cells with the virus. We maximize the benefit based on the T cell count and minimize the systemic cost based on the percentage of chemotherapy given. Existence of an optimal control is proven, and the optimal control is uniquely characterized in terms of the solution of the optimality system, which is the state system coupled with the adjoint system. In addition, numerical examples are given for illustration.

1. Introduction

Various chemotherapies for patients with human immunodeficiency virus (HIV) are being examined to determine the optimal scheme for treatment. The questions of when and how treatment should be initiated given that treatment can only be continued for a finite interval are analyzed. An ordinary differential equation model which describes the interaction of HIV in the immune system is utilized, and optimal control of this ordinary differential equation model is explored. Also, the concept that the treatment control affects the ability of the virus to further infect the patient is assumed.

The challenge of this disease is that the $CD4^+T$ cells (CD4 positive T lymphocytes, a type of white blood cells) that HIV infects are the very ones that are necessary to ward off the invasion. The $CD4$ represents a protein marker on the surface of the $CD4^+T$ cell. The T in the $CD4^+T$ cell describes the connection to the thymus gland. After the initial $CD4^+T$ cells flow from the bone marrow where they are produced, they arrive in the thymus gland where they mature. On their surfaces, they possess proteins that can bind to foreign substances, such as HIV. At these connectors, the HIV is fused into the host $CD4^+T$ cell. Since HIV is a retrovirus, the RNA of the virus is converted into DNA inside the $CD4^+T$ cell. Thus, the DNA of the virus is duplicated and the new virus particles bud from the $CD4^+T$ cell. This process can proceed slowly and allow the $CD4^+T$ cell to survive, or it can cause the host cell to erupt and die. The hallmark of the onset of AIDS (Acquired Immune Deficiency Syndrome) is the depletion of the $CD4^+T$ cell population, which lowers the effectiveness of the immune system. The $CD4^+T$ cells serve as command centers for the immune system and elicit responses from the

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$CD8^+$T cells and the B cells that can lead to the destruction of the virus. See the discussion in reference [10] and the survey paper by Kirschner [7] for background and references in HIV models.

Let T represent the concentration of the uninfected $CD4^+$T cells, and let T^*, T^{**} denote the concentrations of latently infected and actively infected $CD4^+$T cells. Let V denote the concentration of free infectious virus particles. Definitions and numerical data for the parameters can be found before the references. Using the model from [9], the assumption is made that the populations evolve as follows:

$$\frac{dT}{dt} = \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T+T^*+T^{**}}{T_{\max}}\right) - K_1 VT \tag{1.1}$$

$$\frac{dT^*}{dt} = K_1 VT - \mu_T T^* - K_2 T^* \tag{1.2}$$

$$\frac{dT^{**}}{dt} = K_2 T^* - \mu_b T^{**} \tag{1.3}$$

$$\frac{dV}{dt} = N\mu_b T^{**} - K_1 VT - \mu_v V \tag{1.4}$$

with initial conditions $T(0) = T_0$, $T^*(0) = T_0^*$, $T^{**}(0) = T_0^{**}$, and $V(0) = V_0$ for infection by both infected cells and virus.

In (1.1), $s/(1+V)$ is a source term from the thymus and represents the rate of generation of new $CD4^+$T cells. The T cells have a finite life span with a death rate μ_T per cell. In (1.2), latently infected T cells are assumed to have a natural death rate, μ_T, even though other factors can change the natural death rate. In (1.1), r is the coefficient of the growth rate of T cells, which is a logistic-type growth. This growth ensures that the T cells never grow larger than $T_{\max}$.

In (1.1) and (1.2), the term K_1VT models the rate that free virus infects $CD4^+$T cells. After a T cell becomes infected, it becomes a latently infected T cell. Hence the K_1VT term is subtracted from (1.1) and added to (1.2).

Equation (1.3) describes the actively infected $CD4^+$T cells. At the rate K_2, latently infected T cells become actively infected. The actively infected T cells manufacture virus and die at a rate per cell μ_b. Equation (1.4) models the free virus population. An assumption is made that when an actively infected $CD4^+$T cell becomes stimulated by antigen exposure, replication of the virus begins. Further, N viruses are formed before the host cell dies. Also, free virus is lost by connecting to $CD4^+$T cells at a rate K_1. The term $-\mu_v V$ takes into account loss of infectivity or removal from the body.

See the references [1, 6] for control problems on similar models of HIV infection and see [5] for background on treatment strategies. Note that this paper contains existence and uniqueness results with proofs for the optimal control, and such results are not given in [1] or [6]. Here, an optimal chemotherapy treatment is considered with the control affecting the interaction term K_1VT. This control represents the percentage of effect the chemotherapy has on interaction of T cells with the virus. The control for the chemotherapy, $u(t)$, multiplies the parameter K_1 in equations (1.1) and (1.2). Therefore, the control class is chosen to be measurable functions defined on $[t_0,\ t_1]$, with the condition $0 \le u(t) \le 1$. The interval of treatment is necessary since a plausible assumption is made that chemotherapy only has a certain designated time for allowable treatment. After some finite time frame, HIV is able to build up resistance to the treatment due to its mutation

ability. Also, chemotherapy has potentially hazardous side effects. Therefore, the length of treatment is restricted. For most HIV chemotherapy drugs, the length of treatment is less than 500 days. In addition, the optimal control will depend implicitly on the length of the treatment, and the general shape of the optimal control stays the same as the treatment interval changes. Hence, the state system is

$$\frac{dT}{dt} = \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T+T^*+T^{**}}{T_{\max}}\right) - (1-u(t))K_1 VT \tag{1.5}$$

$$\frac{dT^*}{dt} = (1-u(t))K_1 VT - \mu_T T^* - K_2 T^* \tag{1.6}$$

$$\frac{dT^{**}}{dt} = K_2 T^* - \mu_b T^{**} \tag{1.7}$$

$$\frac{dV}{dt} = N\mu_b T^{**} - K_1 VT - \mu_v V \tag{1.8}$$

with given initial values for T, T^*, T^{**}, and V at t_0.

The objective functional is defined as

$$J(u) = \int_{t_0}^{t_1} \left[T(t) - \frac{1}{2}Bu^2\right] dt.$$

The parameter B represents the "weight" on the benefit and cost. The benefit based on the T cell count is being maximized and the systemic cost based on the percentage effect of the chemotherapy given is being minimized. If $u(t) = 1$ represents maximal use of chemotherapy, then the maximal cost is represented by u^2. The goal is to characterize the optimal control u^* satisfying $\max_{0\le u\le 1} J(u) = J(u^*)$.

In section 2, a constraint on $T_{\max}$ is discussed, *a priori* estimates on the solutions are determined, and existence of an optimal control is investigated. In section 3, the aim is to seek to maximize the objective functional which is based on the benefit of the T cell count less the cost of the damage to the patient's body. The optimal control is characterized using Pontryagin's Maximum Principle. In section 4, uniqueness of the optimality system, which is the state system coupled with the adjoint system, is determined. In section 5, a numerical illustration for our problem is presented.

2. Existence of an optimal control

There are certain parameter restrictions that are imposed to ensure that this model is realistic. For the death rate at $T_{\max}$ to be greater than the supply rate, an assumption is that

$$\mu_T T_{\max} > s. \tag{2.5}$$

The steady state population size should be below $T_{\max}$ in order for the T cell population to expand when stimulated by the infection of HIV. Furthermore if the population ever gets near $T_{\max}$, it's growth should slow. See [9] for analysis of stability properties for this model.

Upper bounds are needed for the existence of an optimal control and in the uniqueness proof of the optimality system. Using $T(t) < T_{\max}$, upper bounds on

the solutions of the state system are determined.

$$\frac{d\hat{T}^*}{dt} = K_1\hat{V}T_{\max} \qquad \hat{T}^*(t_0) = \hat{T}_0^*$$
$$\frac{d\hat{T}^{**}}{dt} = K_2\hat{T}^* \qquad \hat{T}^{**}(t_0) = T_0^{**} \text{ where } K_1, K_2 > 0$$
$$\frac{d\hat{V}}{dt} = N\mu_b\hat{T}^{**} \qquad \hat{V}(t_0) = V_0$$

or

$$\begin{pmatrix} \hat{T}^* \\ \hat{T}^{**} \\ \hat{V} \end{pmatrix}' = \begin{pmatrix} 0 & 0 & T_{\max}K_1 \\ K_2 & 0 & 0 \\ 0 & N\mu_b & 0 \end{pmatrix} \begin{pmatrix} \hat{T}^* \\ \hat{T}^{**} \\ \hat{V} \end{pmatrix}$$

Since this is a linear system in finite time with bounded coefficients, then the supersolutions $\hat{T}^*$, $\hat{T}^{**}$, $\hat{V}$ are uniformly bounded.

To determine existence of an optimal control to our problem, we use a result from ([2, Thm 4.1, pg. 68-69]).

Theorem 2.1. *Under assumption (2.5), there exists an optimal control u^* that maximizes the objective functional $J(u)$.*

To prove this theorem, the following conditions must be satisfied.

i) The class of all initial conditions with a control u such that u is a Lebesgue-integrable function on $[t_0, t_1]$ with values in the admissible control set and such that the state system is satisfied is not empty.

ii) The admissible control set is closed and convex.

iii) The right hand side of the state system is continuous, is bounded above by a sum of the bounded control and the state, and can be written as a linear function of u with coefficients depending on time and the state variables.

iv) The integrand of the functional is concave on the admissible control set and is bounded above by $c_2 - c_1|u|^\beta$, where $c_1 > 0$, and $\beta > 1$.

First, an existence result in Lukes ([8], Theorem 9.2.1) for the state system (1.5)–(1.8) for bounded coefficients is invoked. The control set is closed and convex by definition. The right hand side of the state system (1.5)–(1.8) has at most linear growth since the state solutions are *a priori* bounded. In addition, the integrand in the functional, $T(t) - \frac{1}{2}Bu^2$, is concave on the admissible control set. To complete the existence of an optimal control, one uses that $T(t) - \frac{1}{2}Bu^2 \le c_2 - c_1|u|^\beta$, where $c_1 > 0$, and $\beta > 1$, since $T(t) < T_{\max}$.

3. Characterization of an optimal control

Since an optimal control exists for maximizing the functional subject to (1.5)–(1.8), then Pontryagin's Maximum Principle is used to derive necessary conditions on the optimal control[4].

Theorem 3.1. *Given an optimal control u^* and solutions of the corresponding*

state system (1.5)–(1.8), there exist adjoint variables λ_i, $i = 1, \dots, 4$ *satisfying*

$$\begin{aligned}
\lambda_1' &= -\frac{\partial \mathfrak{L}}{\partial T} = -\Big\{\Big[1 + \lambda_1\Big(-\mu_T + r(1 - \frac{T + T^* + T^{**}}{T_{\max}}) - \frac{rT}{T_{\max}} \\
&\quad -(1-u)K_1V\Big)\Big] + \lambda_2(1-u)K_1V - \lambda_4 K_1 V\Big\} \\
\lambda_2' &= -\frac{\partial \mathfrak{L}}{\partial T^*} = -\left(-\frac{\lambda_1 rT}{T_{\max}} - \lambda_2(\mu_T + K_2) + \lambda_3 K_2\right) \\
\lambda_3' &= -\frac{\partial \mathfrak{L}}{\partial T^{**}} = -\left(-\frac{\lambda_1 rT}{T_{\max}} - \lambda_3\mu_b + \lambda_4 N\mu_b\right) \\
\lambda_4' &= -\frac{\partial \mathfrak{L}}{\partial V} = -\Big(\frac{-s\lambda_1}{(1+V)^2} + (\lambda_2 - \lambda_1)K_1T(1-u) - \lambda_4(K_1T + \mu_v)\Big) \\
&\lambda_i(t_1) = 0 \quad \textit{for } i = 1, 2, 3, 4\,.
\end{aligned} \tag{3.1}$$

Further, u^* *is represented by*

$$u^* = \min(1, (\frac{(\lambda_2 - \lambda_1)K_1VT}{B})^+).$$

Proof. Define the Lagrangian as follows

$$\begin{aligned}
&\mathfrak{L}(T, T^*, T^{**}, V, u, \lambda_1, \lambda_2, \lambda_3, \lambda_4) \\
&= T - \frac{1}{2}Bu^2 + \lambda_1(\frac{s}{1+V} - \mu_T T + rT(1 - \frac{T + T^* + T^{**}}{T_{\max}}) \\
&\quad - (1-u(t))K_1VT) + \lambda_2((1-u(t))K_1VT - \mu_T T^* - K_2T^*) \\
&\quad + \lambda_3(K_2T^* - \mu_b T^{**}) + \lambda_4(N\mu_b T^{**} - K_1VT - \mu_v V) \\
&\quad + w_1(t)u(t) + w_2(t)(1-u(t))
\end{aligned} \tag{3.2}$$

where $w_1(t) \geq 0$, $w_2(t) \geq 0$ are penalty multipliers satisfying

$$w_1(t)u(t) = 0, \quad w_2(t)(1-u(t)) = 0 \text{ at the optimal } u^*.$$

In [4], the maximum principle gives the existence of adjoint variables satisfying (3.1).

Since,

$$\begin{aligned}
\mathfrak{L} = &-\frac{1}{2}Bu(t)^2 - \lambda_1(1-u(t))K_1VT + \lambda_2(1-u(t))K_1VT \\
&+w_1(t)u(t) + w_2(t)(1-u(t)) + \text{ other terms without } u\,,
\end{aligned}$$

then by differentiating this expression for $\mathfrak{L}$ with respect to u, we have

$$\frac{\partial \mathfrak{L}}{\partial u} = -Bu(t) + \lambda_1 K_1VT - \lambda_2 K_1VT + w_1(t) - w_2(t) = 0\,.$$

Solving for the optimal control yields

$$u^*(t) = \frac{(\lambda_2 - \lambda_1)K_1VT + w_1(t) - w_2(t)}{B}.$$

To determine an explicit expression for the optimal control (without w_1 and w_2), a standard optimality technique is utilized. One considers the following three cases to determine a specific characterization of an optimal control.

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

$$u^*(t) = \frac{(\lambda_2 - \lambda_1)K_1VT}{B}.$$

(ii) On the set $\{t|u^*(t) = 1\}$, $w_1(t) = 0$. Hence,

$$1 = u^*(t) = \frac{(\lambda_2 - \lambda_1)K_1VT - w_2(t)}{B}.$$

This implies that $0 \leq w_2(t) = (\lambda_2 - \lambda_1)K_1VT - B$ and $1 = u^*(t) \leq \frac{(\lambda_2 - \lambda_1)K_1VT}{B}$.

(iii) On the set $\{t|u^*(t) = 0\}$, $w_2(t) = 0$. Hence,

$$0 = u^*(t) = \frac{(\lambda_2 - \lambda_1)K_1VT + w_1(t)}{B}.$$

Since $w_1(t) \geq 0$, then $\frac{(\lambda_2 - \lambda_1)K_1VT}{B} \leq 0$. Notice

$$(\frac{(\lambda_2 - \lambda_1)K_1VT}{B})^+ = 0 = u^*(t)$$

in this case. Combining these three cases, the optimal control is characterized as

$$u^*(t) = \min(1, (\frac{(\lambda_2 - \lambda_1)K_1VT}{B})^+)$$

where s^+ is defined as

$$s^+ = \begin{cases} s, & \text{if } s > 0 \\ 0, & \text{if } s \leq 0\,. \end{cases}$$

If $\lambda_2 - \lambda_1 < 0$ for some t, then $u^*(t) \neq 0$. Hence, $0 < u^*(t) \leq 1$ for such t. $\lambda_2 < \lambda_1$ means the marginal valuation of the benefit functional with respect to the T cells is greater than the marginal valuation of the benefit functional with respect to the T^* cells. □

The optimality system consists of the state system coupled with the adjoint system with the initial conditions and transversality conditions together with the following relationship,

$$u^*(t) = \min(1, (\frac{(\lambda_2 - \lambda_1)K_1VT}{B})^+). \tag{3.3}$$

Utilizing (3.3), the following optimality system characterizes the optimal control.

$$\begin{aligned}
\frac{dT}{dt} &= \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T + T^* + T^{**}}{T_{\max}}\right) \\
&\quad - (1 - \min(1, (\frac{(\lambda_2 - \lambda_1)K_1VT}{B4})^+))K_1VT \\
\frac{dT^*}{dt} &= (1 - \min(1, (\frac{(\lambda_2 - \lambda_1)K_1VT}{B})^+))K_1VT - \mu_T T^* - K_2T^* \\
\frac{dT^{**}}{dt} &= K_2T^* - \mu_b T^{**} \\
\frac{dV}{dt} &= N\mu_b T^{**} - K_1VT - \mu_v V \\
&\quad T = T_0, \quad T^* = T_0^*, \quad T^{**} = T_0^{**}, \text{ and } V = V_0 \text{ at } t_0.
\end{aligned}$$

$$
\begin{aligned}
\lambda_1' &= -\Big\{\Big[1+\lambda_1\Big(-\mu_T + r(1-\frac{T+T^*+T^{**}}{T_{\max}}) - \frac{rT}{T_{\max}} \\
&\quad - (1-\min(1,(\frac{(\lambda_2-\lambda_1)K_1VT}{B})^+))K_1V\Big)\Big] \\
&\quad + \lambda_2(1-\min(1,(\frac{(\lambda_2-\lambda_1)K_1VT}{B})^+))K_1V - \lambda_4K_1V\Big\} \\
\lambda_2' &= -\left(-\frac{\lambda_1 rT}{T_{\max}} - \lambda_2(\mu_T+K_2) + \lambda_3K_2\right) \\
\lambda_3' &= -\left(-\frac{\lambda_1 rT}{T_{\max}} - \lambda_3\mu_b + \lambda_4N\mu_b\right) \\
\lambda_4' &= -\Big(\frac{-s\lambda_1}{(1+V)^2} + (\lambda_2-\lambda_1)K_1T(1-\min(1,(\frac{(\lambda_2-\lambda_1)K_1VT}{B})^+)) \\
&\quad - \lambda_4(K_1T+\mu_v)\Big) \\
&\quad \lambda_i(t_1) = 0 \quad \text{for } i=1,2,3,4
\end{aligned}
\tag{3.4}
$$

4. Uniqueness of Optimality System

Using $T(t) < T_{\max}$, the state system and adjoint system have finite upper bounds. These bounds are needed in the uniqueness proof of the optimality system.

Theorem 4.1. *For t_1 sufficiently small, the solution to the optimality system is unique.*

Proof. Suppose $(T, T^*, T^{**}, V, \lambda_1, \lambda_2, \lambda_3, \lambda_4)$ and $(\overline{T}, \overline{T}^*, \overline{T}^{**}, \overline{V}, \overline{\lambda}_1, \overline{\lambda}_2, \overline{\lambda}_3, \overline{\lambda}_4)$ are two solutions of the optimality system (3.4). Let $T = e^{\lambda t}p$, $T^* = e^{\lambda t}p^*$, $T^{**} = e^{\lambda t}p^{**}$, $V = e^{\lambda t}q$, $\lambda_1 = e^{-\lambda t}w$, $\lambda_2 = e^{-\lambda t}z$, $\lambda_3 = e^{-\lambda t}v$, $\lambda_4 = e^{-\lambda t}y$. Similarly let $\overline{T} = e^{\lambda t}\overline{p}$, $\overline{T}^* = e^{\lambda t}\overline{p}^*$, and so forth.

Let

$$
u = \min(1, (\frac{K_1e^{\lambda t}(w-z)qp}{B})^+)
$$

and

$$
\overline{u} = \min(1, (\frac{K_1e^{\lambda t}(\overline{w}-\overline{z})\overline{qp}}{B})^+).
$$

Substituting $T = e^{\lambda t}p$ into the first ODE of (3.4), the state equation becomes

$$
\begin{aligned}
e^{\lambda t}\dot{p} + \lambda e^{\lambda t}p &= \frac{s}{1+e^{\lambda t}q} - \mu_T e^{\lambda t}p + re^{\lambda t}p\left(1-\frac{e^{\lambda t}(p+p^*+p^{**})}{T_{\max}}\right) \\
&\quad - (1-\min(1,(\frac{K_1e^{\lambda t}(w-z)qp}{B_4})^+))K_1e^{2\lambda t}qp
\end{aligned}
\tag{4.1}
$$

where $\dot{p} = \frac{dp}{dt}$. Similarly, for $\lambda_1 = e^{-\lambda t}w$,

$$
\begin{aligned}
-\dot{w} + \lambda w &= e^{\lambda t} - \mu_T w + rw\left(1-\frac{e^{\lambda t}(2p+p^*+p^{**})}{T_{\max}}\right) - K_1e^{\lambda t}yq \\
&\quad + \left\{K_1e^{\lambda t}q(1-\min(1,(\frac{K_1e^{\lambda t}(w-z)qp}{B})^+))(-w+z)\right\}
\end{aligned}
\tag{4.2}
$$

The equations for T and $\overline{T}$, T^* and $\overline{T}^*$, T^{**} and $\overline{T}^{**}$, V and $\overline{V}$, λ_1 and $\overline{\lambda}_1$, λ_2 and $\overline{\lambda}_2$, λ_3 and $\overline{\lambda}_3$, λ_4 and $\overline{\lambda}_4$ are subtracted. Then each equation is multiplied by an appropriate function and integrated from t_0 to t_1. Next, all eight integral equations are added, and estimates to obtain the result are employed.

Some of the "integral equations" are listed below for illustration. Please note that u and $\overline{u}$ are used instead of their specific characterization.

$$\begin{aligned}
&\frac{1}{2}(p(t_1)-\overline{p}(t_1))^2+\lambda\int_{t_0}^{t_1}(p-\overline{p})^2\,dt\\
&\quad=\int_{t_0}^{t_1}\Big(\frac{s}{1+e^{\lambda t}q}-\frac{s}{1+e^{\lambda t}\overline{q}}\Big)e^{-\lambda t}(p-\overline{p})\,dt\\
&\quad\quad+(r-\mu_T)\int_{t_0}^{t_1}(p-\overline{p})^2\,dt+K_1\int_{t_0}^{t_1}e^{\lambda t}(qp-\overline{qp})(p-\overline{p})\,dt\\
&\quad\quad-\frac{r}{T_{\max}}\int_{t_0}^{t_1}e^{\lambda t}\big[(p^2-\overline{p}^2)+(pp^*-\overline{pp}^*)+(pp^{**}-\overline{pp}^{**})\big](p-\overline{p})\,dt\\
&\quad\quad-K_1\int_{t_0}^{t_1}e^{\lambda t}(uqp-\overline{uqp})(p-\overline{p})\,dt\,.
\end{aligned}\tag{4.3}$$

Also notice that

$$\begin{aligned}
&\frac{1}{2}(w(t_0)-\overline{w}(t_0))^2+\lambda\int_{t_0}^{t_1}(w-\overline{w})^2\,dt\\
&\quad=\int_{t_0}^{t_1}e^{\lambda t}\,dt+(r-\mu_T)\int_{t_0}^{t_1}(w-\overline{w})^2\,dt\\
&\quad\quad-\frac{r}{T_{\max}}\int_{t_0}^{t_1}\Big[e^{\lambda t}\big\{2(wp-\overline{wp})+(wp^*-\overline{wp}^*)\\
&\quad\quad\quad+(wp^{**}-\overline{wp}^{**})\big\}\Big](w-\overline{w})\,dt\\
&\quad\quad-K_1\int_{t_0}^{t_1}e^{\lambda t}\left\{(uwq-\overline{uwq})-(uzq-\overline{uzq})\right\}(w-\overline{w})\,dt\\
&\quad\quad+K_1\int_{t_0}^{t_1}e^{\lambda t}\left\{-(wq-\overline{wq})+(zq-\overline{zq})\right\}(w-\overline{w})\,dt\\
&\quad\quad-K_1\int_{t_0}^{t_1}e^{\lambda t}(yq-y\overline{q})(w-\overline{w})\,dt\,.
\end{aligned}\tag{4.4}$$

Several terms are estimated in these eight equations. First, notice

$$\int_{t_0}^{t_1}e^{\lambda t}\Big(\frac{1}{1+e^{\lambda t}q}-\frac{1}{1+e^{\lambda t}\overline{q}}\Big)(p^2-\overline{p}^2)\,dt\le C_1e^{\lambda t}\int_{t_0}^{t_1}((p-\overline{p})^2+(q^*-\overline{q}^*)^2)\,dt.$$

Below, four other estimates are presented that utilize upper bounds on the solutions. They involve separating terms that involve squares, several multiplied terms, and quotients.

$$\begin{aligned}
\frac{r}{T_{\max}}\int_{t_0}^{t_1}e^{\lambda t}(p^2-\overline{p}^2)(p-\overline{p})\,dt&\le\frac{r}{T_{\max}}\int_{t_0}^{t_1}e^{\lambda t}(p-\overline{p})^2 2e^{-\lambda t}T_{\max}\,dt\\
&=2r\int_{t_0}^{t_1}(p-\overline{p})^2\,dt
\end{aligned}\tag{4.5}$$

$$\begin{aligned}\frac{r}{T_{\max}}\int_{t_0}^{t_1} e^{\lambda t}(pp^*-\overline{p}\overline{p}^*)(p-\overline{p})\,dt &= \frac{r}{T_{\max}}\int_{t_0}^{t_1} e^{\lambda t}(pp^*-p\overline{p}^*+\overline{p}p^*\\ &\quad -\overline{p}\overline{p}^*)(p-\overline{p})\,dt\\ &\le C_2 e^{\lambda t_1}\int_{t_0}^{t_1}(p-\overline{p})^2+(p^*-\overline{p}^*)^2\,dt\end{aligned} \tag{4.6}$$

$$\begin{aligned}\int_{t_0}^{t_1}(u-\overline{u})^2\,dt &\le \int_{t_0}^{t_1}\Big(\frac{K_1e^{\lambda t}(w-z)qp}{B}-\frac{K_1e^{\lambda t}(\overline{w}-\overline{z})\overline{qp}}{B}\Big)^2\,dt\\ &= \frac{K_1^2e^{2\lambda t_1}}{B^2}\int_{t_0}^{t_1}\big[(w-z)qp-(\overline{w}-\overline{z})\overline{qp}\big]^2\,dt\\ &\le (\frac{K_1e^{\lambda t_1}}{B})^2\int_{t_0}^{t_1}\big[(z-w)^2q^2p^2-2(\overline{w}-\overline{z})\overline{qp}(w-z)qp\\ &\quad +(\overline{z}-\overline{w})^2\overline{q}^2\overline{p}^2\big]\,dt\\ &\le \widetilde{C}_4(\frac{K_1e^{\lambda t_1}}{B})^2\int_{t_0}^{t_1}\big[(z-\overline{z})^2+(w-\overline{w})^2\big]\,dt\end{aligned} \tag{4.7}$$

$$\begin{aligned}\int_{t_0}^{t_1} e^{\lambda t}(uqp-\overline{uqp})(p-\overline{p})\,dt &= \int_{t_0}^{t_1} e^{\lambda t}((u-\overline{u})qp+\overline{u}(qp-\overline{qp}))(p-\overline{p})\,dt\\ &\le \widetilde{C}_5e^{3\lambda t_1}\int_{t_0}^{t_1}(p-\overline{p})^2+(q-\overline{q})^2+(z-\overline{z})^2\\ &\quad +(w-\overline{w})^2\,dt\end{aligned} \tag{4.8}$$

To show uniqueness, the integral equations are combined. This combination produces

$$\begin{aligned}&\frac{1}{2}(p-\overline{p})^2(t_1)+\frac{1}{2}(p^*-\overline{p}^*)^2(t_1)+\frac{1}{2}(p^{**}-\overline{p}^{**})^2(t_1)+\frac{1}{2}(q-\overline{q})^2(t_1)\\ &+\frac{1}{2}(w-\overline{w})^2(t_0)+\frac{1}{2}(z-\overline{z})^2(t_0)+\frac{1}{2}(v-\overline{v})^2(t_0)+\frac{1}{2}(y-\overline{y})^2(t_0)\\ &+C_1\int_{t_0}^{t_1}\big[(p-\overline{p})^2+(w-\overline{w})^2+(z-\overline{z})^2\big]\,dt\\ &+C_2\int_{t_0}^{t_1}\big[(p^{**}-\overline{p}^{**})^2+(y-\overline{y})^2+(q-\overline{q})^2+(v-\overline{v})^2\big]\,dt\\ &\le C_1e^{3\lambda t_1}\int_{t_0}^{t_1}\big[(q-\overline{q})^2+(p-\overline{p})^2\big]+\big[(p^*-\overline{p}^*)^2+(p^{**}-\overline{p}^{**})^2\big]\\ &\quad +\big[(z-\overline{z})^2+(w-\overline{w})^2+(y-\overline{y})^2+(v-\overline{v})^2\big]\,dt\\ &+C_3\int_{t_0}^{t_1}\big[(p^*-\overline{p}^*)^2+(p^{**}-\overline{p}^{**})^2+(q-\overline{q})^2\big]\,dt.\end{aligned} \tag{4.9}$$

From (4.9) the simplification is

$$\begin{aligned}(\lambda-\widetilde{C}_1-\widetilde{C}_2e^{3\lambda t_1})\int_{t_0}^{t_1}\big[&(p-\overline{p})^2+(p^*-\overline{p}^*)^2+(p^{**}-\overline{p}^{**})^2+(q-\overline{q})^2\\ &+(w-\overline{w})^2+(z-\overline{z})^2+(v-\overline{v})^2+(y-\overline{y})^2\big]\,dt\le 0\end{aligned}$$

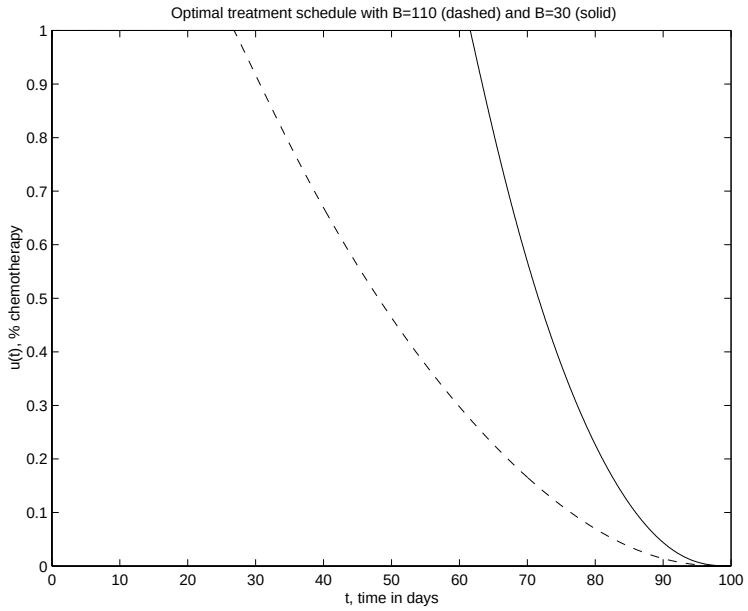
where $\widetilde{C}_1$, $\widetilde{C}_2$ depend on the coefficients and the bounds of p, p^*, p^{**}, q, w, z, v, y.

If λ is chosen such that $\lambda > \widetilde{C}_1 + \widetilde{C}_2$ and $t_1 < \frac{1}{3\lambda}\ln(\frac{\lambda-\widetilde{C}_1}{\widetilde{C}_2})$, then $p = \overline{p}$, $p^* = \overline{p}^*$, $p^{**} = \overline{p}^{**}$, $q = \overline{q}$, $w = \overline{w}$, $z = \overline{z}$, $v = \overline{v}$, $y = \overline{y}$. □

Uniqueness for a small time interval is not unusual in such a nonlinear boundary value problem. The unique optimal control u^* is characterized in terms of the unique solution of the optimality system. The optimal control u^* gives an optimal chemotherapy strategy for the HIV positive patient.

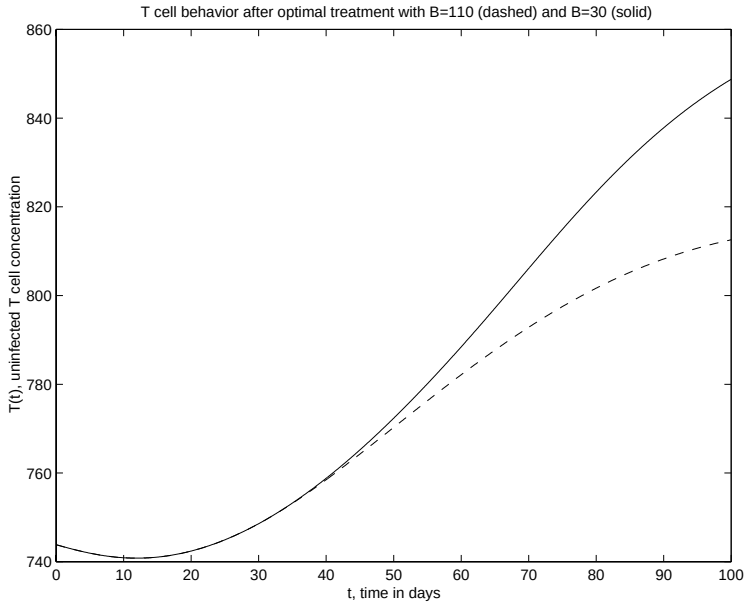
4. Numerical Illustration

Using two different weight factors of $B = 110$ and $B = 30$, numerical solutions for the uninfected T cells, virus concentration, and the optimal treatment strategy have been generated. The optimality system is solved using an iterative method with Runge-Kutta four scheme. Starting with a guess for the adjoint variables, the state equations are solved forward in time. Then those state values are used to solve the adjoint equations backward in time, and the iterations continue until convergence. See [3] for background on such iterative algorithms. The optimal treatment schedule is considered in the following picture. One notices that when B increases from 30 to 110 that the chemotherapy is given at the maximal level for a shorter period of time before decreasing in a continuous manner. Mathematically, this is due to the fact that the percentage chemotherapy given is inversely related to the weight factor, B. This says that if the systemic cost to the patient increases, then the patient receives the maximal chemotherapy for a shorter period of time.

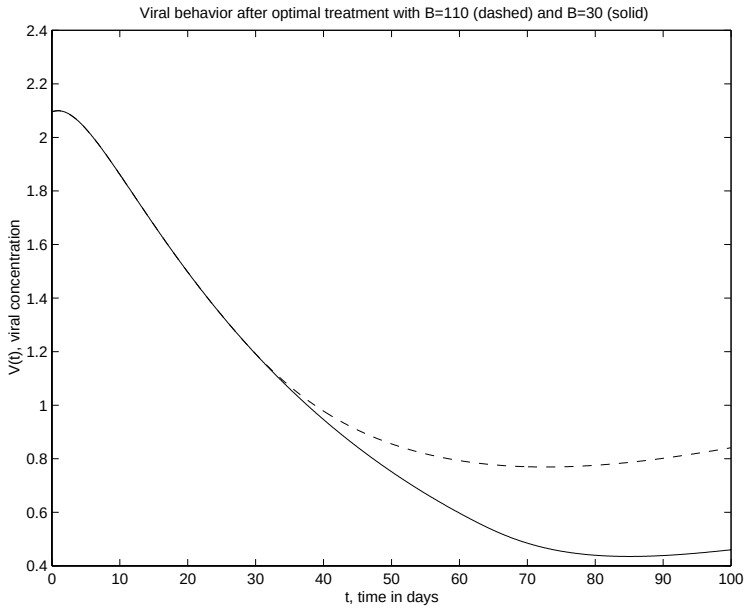


The graphs for the concentration of the uninfected T cells and the virus concentration are viewed on the next two pages. As the optimal chemotherapy is given, the T cell concentration increases in a logistic way. However, for a higher systemic cost, the T cell population increases at a slower rate. With both weight factors, the maximal chemotherapy is given for about the first thirty days. The T cell concentrations for these different factors produce similar graphs for the first thirty

days. However, after the first thirty days of treatment, the T cell concentration for $B = 110$ increases but at a slower rate than for the T cell concentration for $B = 30$.



If the systemic cost is greater, the body can not "fight off" the virus as effectively. Indeed, this idea is supported in the virus concentration graph. Therefore, for the higher systemic cost, the optimal chemotherapy given produces a lower T cell concentration and a higher virus concentration.



The following values were used for the constants in numerical calculations.

$\mu_T = 0.02/\text{d}$	Death rate of uninfected and latently infected $CD4^+$T cells.
$\mu_b = 0.24/\text{d}$	Death rate of actively infected cells.
$\mu_V = 2.4/\text{d}$	Death rate of free virus.

$K_1 = 0.000024\text{mm}^3/\text{d}$	Rate $CD4^+T$ cells become infected by free virus.
$K_2 = 0.003/\text{d}$	Rate T^* cells convert to actively infected.
$r = 0.03/\text{d}$	Rate of growth for the $CD4^+T$ cells.
$N = 1200$	Number of free virus produced by T^{**} cells.
$T_{\max} = 1500/\text{mm}^3$	Maximum $CD4^+T$ cell level.
$s = 10/\text{mm}^3$	Source term for uninfected $CD4^+T$.

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