Optimal Control of an HIV Immunology Model

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Abstract

A system of ordinary differential equations, which describes the interaction of HIV and T-cells in the immune system is utilized, and optimal controls representing drug treatment strategies of this model are explored. Two types of treatments are used, and existence and uniqueness results for the optimal control pair are established. The optimality system is derived and then solved numerically using an iterative method with Runge-Kutta fourth order scheme.

Key Words: HIV model, Optimal Control, Two treatments

AMS Classification: 49K15, 92D30

1 Introduction

AIDS - Acquired Immunity Deficiency Syndrome is the disease that has affected the whole world in the 20 years since it was first detected. It is caused by Human Immunodeficiency Virus (HIV). Of the 34.3 million people worldwide living with HIV infection today, more than 24 million are in the developing world.

There is still much work to be completed in the search for an anti-HIV vaccine. st of the chemotherapies are aimed at killing or halting the pathogen, but treatment which can boost the immune system can serve to help the body fight infection on its own [9]. The new treatments are aimed at reducing viral population and improving the immune response. This brings new hope to the treatment of HIV infection, and we are exploring strategies for such treatments using optimal control techniques.

An ordinary differential equation (ODE) model (taken from a Kirschner and Webb model [9]), which describes the interaction of $CD4^+T$ cells and HIV in the immune system is utilized, and optimal control of this ODE model is explored.

Once HIV enters the body, the human immune system tries to get rid of it. The invasion is reported to $CD4^+T$ cells. The $CD4$ is a protein marker in the surface of the T cell, and the letter T refers to thymus, the organ responsible for maturing these cells after they migrate from the bone marrow (where they are manufactured). The surface of $CD4^+T$ possesses a protein that can bind to foreign substances such as HIV. The HIV needs a host in order to reproduce and the above mentioned protein provides shelter. The HIV virus is a retrovirus, the RNA of virus is converted into DNA inside the $CD4^+T$ cell. Thus, when infected $CD4^+T$ cells begin to multiply to fight this pathogen, they produce more virus. See [3, 7, 8, 9, 11] for more details on disease progression.

Let T, V represent the concentration of the uninfected $CD4^+T$ cells and free infectious virus particles respectively, and u_1, u_2 represent two different treatment strategies. As our control classes we choose measurable functions defined on a fixed interval (as treatments can not be continued for infinite time period due to hazardous side effects) satisfying $0 \leq a_i \leq u_i(t) \leq b_i < 1$ for $i = 1, 2$. For most of HIV chemotherapy drugs, the length of treatment is less then 500 days [3].

The state system is

$$\frac{dT(t)}{dt} = s_1 - \frac{s_2 V(t)}{B_1 + V(t)} - \mu T(t) - kV(t)T(t) + u_1(t)T(t) \tag{1.1}$$

$$\frac{dV(t)}{dt} = \frac{g(1 - u_2(t))V(t)}{B_2 + V(t)} - cV(t)T(t) \tag{1.2}$$

satisfying $T(0) = T_0$ and $V(0) = V_0$, where T represents the concentration of $CD4^+T$

cells, V the concentration of HIV particles. The term $s_1 - \frac{s_2 V(t)}{B_1 + V(t)}$ is the source/proliferation of unaffected T cells , $\mu T(t)$ is the natural loss of uninfected T cells, $kV(t)T(t)$ is loss by infection, $\frac{gV(t)}{B_2+V(t)}$ is viral contribution to plasma and $cV(t)T(t)$ is the viral loss. Similarly, μ is death rate of T cells, k is infection rate of T cells, g is the input rate of an external virus source , c is the loss rate of virus and B_1, B_2 are half saturation constants. The controls u_1 and u_2 represent the immune boosting and viral suppressing drugs respectively. The definitions and numerical data for the parameters can be found in Kirschner and Webb [9, p. 74, Table 1].

The objective functional to be maximized is

$$J(u_1, u_2) = \int_0^{t_f} [T - (A_1 u_1^2 + A_2 u_2^2)]\, dt \tag{1.3}$$

The first term represent the benefit of T cells and the other terms are systemic costs of the drug treatments. The positive constants A_1 and A_2 balance the size of the terms, and u_1^2, u_2^2 reflect the severity of the side effects of the drugs. When drugs such as interleukin are administered in high dose, they are toxic to the human body, which justifies the quadratic terms in the functional. Our goal is maximizing the number of T cells and minimizing the systemic cost to the body. We seek an optimal control pair, u_1^*, u_2^* such that

$$J(u_1^*, u_2^*) = \max\{J(u_1, u_2) | (u_1, u_2) \in U\}$$

where $U = \{(u_1, u_2) | u_i \text{ measurable }, \ a_i \leq u_i \leq b_i, \quad t \in [0, t_f], \text{ for } i = 1, 2\}$ is the control set.

See Kirschner and Webb [9] for treatment strategies using immune boosting and delaying AIDS progression. They developed a mathematical model of dynamics of disease progression and IL-2 treatment of the HIV-infected immune system. Their model is based upon the key markers of HIV progression, $CD4^+T$ cell level and viral levels in the plasma, and the model agrees with preliminary results from clinical trials. They also predict that immunotherapy administered during the early stages of disease progression is most beneficial for raising $CD4^+T$ cell count.

See references [2], [3], and [7] for control problems on HIV infection in different types of models using treatment with a single drug and similar objective functional. In this paper we consider two controls, one boosts the immune system and other delays the HIV progression. This paper is the first one to address multiple controls for using more than one type of drug concurrently, which is the current practice in HIV treatment.

Tan and Xiang [13] have developed a stochastic model for the HIV pathogenesis under anti-viral drugs. They estimated the numbers of infectious free HIV and non-

infectious free HIV as well as the number of T cells through the extended Kalman filter method. Berman [1] also used a stochastic model with a three-stage diffusion process (pre-treatment interval, the control treatment interval and post treatment interval) for the T cell level of an HIV-infected individual. His goal was to determine the best time to intervene with an antiviral drug using a Brownian motion representation of the T cell level.

In section 2, we investigate the existence of an optimal control pair. In section 3, we derive the optimal control pair using Pontryagin's Maximum Principle [12]. In the same section we also derive the optimality system which characterizes the optimal control pair. The uniqueness of the optimality system is proved in section 4, and some numerical results are illustrated in the last section.

2 Existence of an Optimal Control Pair

The boundedness of solutions of the system (1.1) and (1.2) for the finite time interval is used to prove the existence of an optimal control pair. This can be proved using the fact that supersolutions $\overline{T}$ and $\overline{V}$ satisfying

$$\begin{aligned} \frac{d\overline{T}}{dt} &= s_1 + u_1(t)\overline{T} \\ \frac{d\overline{V}}{dt} &= \frac{g\overline{V}}{B_2 + \overline{V}} \end{aligned}$$

are bounded on a finite time interval.

The existence of the optimal control pair can be obtained by using a result by Fleming and Rishel ([4, Th. 4.1, p. 68-69]).

Theorem 2.1. *Consider the control problem with system equations (1.1), (1.2). There exists* $\vec{u}^* = (u_1^*, u_2^*) \in U$ *such that*

$$\max_{(u_1,u_2)\in U} J(u_1, u_2) = J(u_1^*, u_2^*).$$

Proof: To use an existence result, Theorem III.4.1 from [4], we must check the following properties:

1. The set of controls and corresponding state variables is nonempty.
2. The control U set is convex and closed.

3. The RHS of the state system is bounded by a linear function in the state and control variables.

4. The integrand of the objective functional is concave on U.

5. There exists constants $c_1, c_2 > 0$, and $\beta > 1$ such that the integrand $L(T, u_1, u_2)$ of the objective functional satisfies

$$L(T, u_1, u_2) \leq c_2 - c_1 \left(|u_1|^2 + |u_2|^2\right)^{\beta/2}.$$

In order to verify these conditions, we use a result by Lukes ([10, Th 9.2.1, p. 182] to give the existence of solutions of ODE's (1.1) and (1.2) with bounded coefficients, which gives condition 1. We note that the solutions are bounded. Our control set satisfies condition 2. Since our state system is bilinear in u_1, u_2, the RHS of (1.1) and (1.2) satisfies condition 3, using the boundedness of the solutions.

Note that the integrand of our objective functional is concave. Also we have the last condition needed

$$T - (A_1u_1^2 + A_2u_2^2) \quad \leq \quad c_2 - c_1(|u_1|^2 + |u_2|^2)$$

where c_2 depends on the upper bound on T, and $c_1 > 0$ since $A_1, A_2 > 0$. We conclude there exists an optimal control pair. □

3 Optimality System

In section 2, we proved the existence of an optimal control pair system for maximizing the functional (1.3) subject to (1.1)-(1.2). In order to derive the necessary conditions for this optimal control pair, we use Pontryagin's Maximum Principle [12].

The Lagrangian is defined as following:

$$\begin{aligned} L \;=\; & \left[T - (A_1u_1^2 + A_2u_2^2)\right] \\ & + \lambda_1 \left[s_1 - \frac{s_2V(t)}{B_1 + V(t)} - \mu T(t) - kV(t)T(t) + u_1(t)T(t)\right] \\ & + \lambda_2 \left[\frac{g(1-u_2(t))V(t)}{B_2 + V(t)} - cV(t)T(t)\right] \\ & + w_{11}(t)(b_1 - u_1) + w_{12}(t)(u_1 - a_1) \\ & + w_{21}(t)(b_2 - u_2) + w_{22}(t)(u_2 - a_2), \end{aligned}$$

where $w_{11}(t), w_{12}(t), w_{21}(t), w_{22}(t) \geq 0$ are penalty multipliers satisfying

$$w_{11}(t)(b_1 - u_1) = 0, w_{12}(t)(u_1 - a_1) = 0 \quad \text{at } u_1^*$$

and

$$w_{21}(t)(b_2 - u_2) = 0, w_{22}(t)(u_2 - a_2) = 0 \quad \text{at } u_2^*.$$

Theorem 3.1. *Given optimal controls u_1^*, u_2^* and solutions T^*, V^* of the corresponding state system (1.1)-(1.2), there exists adjoint variables λ_1, λ_2 satisfying*

$$\begin{aligned}
\lambda_1' &= -1 + \lambda_1 \left[\mu + kV^*(t) - u_1^*(t)\right] + \lambda_2 cV^*(t) \\
\lambda_2' &= \lambda_1 \left[\frac{B_1 s_2}{(B_1 + V^*(t))^2} + kT^*(t)\right] - \lambda_2 \left[\frac{B_2 g(1 - u_2^*(t))}{(B_2 + V^*(t))^2} - cT^*(t)\right]
\end{aligned}$$

and $\lambda_1(t_f) = \lambda_2(t_f) = 0$, the transversality conditions. Furthermore

$$\begin{aligned}
u_1^*(t) &= \min\left\{\max\left\{a_1, \frac{1}{2A_1}\left(\lambda_1 T^*(t)\right)\right\}, b_1\right\} \\
u_2^*(t) &= \min\left\{\max\left\{a_2, -\frac{\lambda_2}{2A_2}\frac{V^*(t)}{(B_2 + V^*(t))}\right\}, b_2\right\}
\end{aligned}$$

Proof: The form of the adjoint equations and transversality conditions are standard results from Pontryagin's Maximum Principle [12]. We differentiate the Lagrangian with respect to states, T and V respectively, and then the adjoint system can be written as:

$$\lambda_1' = -\frac{\partial L}{\partial T} = -1 + \lambda_1 \left[\mu + kV^*(t) - u_1^*(t)\right] + \lambda_2 cV^*(t) \tag{3.1}$$

$$\lambda_2' = -\frac{\partial L}{\partial V} = \lambda_1 \left[\frac{B_1 s_2}{(B_1 + V^*(t))^2} + kT^*(t)\right] - \lambda_2 \left[\frac{B_2 g(1 - u_2^*(t))}{(B_2 + V^*(t))^2} - cT^*(t)\right] \tag{3.2}$$

The optimality equations [6] are :

$$\begin{aligned}
\frac{\partial L}{\partial u_1} &= -2A_1 u_1^*(t) + \lambda_1 T^*(t) - w_{11}(t) + w_{12}(t) = 0 \qquad \text{at } u_1^* \\
\frac{\partial L}{\partial u_2} &= -2A_2 u_2^*(t) + \lambda_2 \left[-\frac{gV^*(t)}{B_2 + V^*(t)}\right] - w_{21}(t) + w_{22}(t) = 0 \quad \text{at } u_2^*.
\end{aligned}$$

Hence we obtain

$$u_1^*(t) = \frac{1}{2A_1}\left[\lambda_1 T^*(t) - w_{11}(t) + w_{12}(t)\right] \tag{3.3}$$

$$u_2^*(t) = \frac{1}{2A_2}\left[-\lambda_2 \frac{gV^*(t)}{B_2 + V^*(t)} - w_{21}(t) + w_{22}(t)\right]. \tag{3.4}$$

By standard control arguments involving the bounds on the controls, we conclude

$$u_1^* = \begin{cases} \frac{1}{2A_1}\lambda_1 T^*(t) & \text{if} \quad a_1 < \frac{1}{2A_1}\lambda_1 T^*(t) < b_1 \\ a_1 & \text{if} \quad \frac{1}{2A_1}\lambda_1 T^*(t) \leq a_1 \\ b_1 & \text{if} \quad \frac{1}{2A_1}\lambda_1 T^*(t) \geq b_1. \end{cases}$$

In compact notation, $u_1^*(t) = \min\left\{\max\left\{a_1, \frac{1}{2A_1}\left(\lambda_1 T^*(t)\right)\right\}, b_1\right\}$.

Similarly, we conclude

$$u_2^* = \begin{cases} -\frac{\lambda_2}{2A_2}\frac{V^*(t)}{B_2+V^*(t)} & \text{if} \quad a_2 < -\frac{\lambda_2}{2A_2}\frac{V^*(t)}{B_2+V^*(t)} < b_2 \\ a_2 & \text{if} \quad -\frac{\lambda_2}{2A_2}\frac{V^*(t)}{B_2+V^*(t)} \leq a_2 \\ b_2 & \text{if} \quad -\frac{\lambda_2}{2A_2}\frac{V^*(t)}{B_2+V^*(t)} \geq b_2. \end{cases}$$

In compact notation, $u_2^*(t) = \min\left\{\max\left\{a_2, -\frac{\lambda_2}{2A_2}\frac{V^*(t)}{B_2 + V^*(t)}\right\}, b_2\right\}$. □

The optimality system consists of the state system coupled with the adjoint system with the initial and transversality conditions together with the characterization of the optimal control pair

$$u_1^*(t) = \min\left\{\max\left\{a_1, \frac{1}{2A_1}\left(\lambda_1 T^*(t)\right)\right\}, b_1\right\} \tag{3.5}$$

$$u_2^*(t) = \min\left\{\max\left\{a_2, -\frac{\lambda_2}{2A_2}\frac{V^*(t)}{B_2 + V^*(t)}\right\}, b_2\right\}. \tag{3.6}$$

Utilizing (3.5) and (3.6), we have the following optimality system.

$$\frac{dT(t)}{dt} = s_1 - \frac{s_2 V(t)}{B_1 + V(t)} - \mu T(t) - kV(t)T(t)$$

$$
\begin{aligned}
&+\min\left\{\max\left\{a_1, \frac{1}{2A_1}\left(\lambda_1 T(t)\right)\right\}, b_1\right\} T(t) \\
\frac{dV(t)}{dt} &= \frac{g\left(1-\min\left\{\max\left\{a_2, -\frac{\lambda_2}{2A_2}\frac{V(t)}{B_2+V(t)}\right\}, b_2\right\}\right)V(t)}{B_2+V(t)} - cV(t)T(t) \\
\lambda_1' &= -1+\lambda_1\left[\mu + kV(t) - \min\left\{\max\left\{a_1, \frac{1}{2A_1}\left(\lambda_1 T(t)\right)\right\}, b_1\right\}\right] \\
&\quad +\lambda_2 cV(t) \qquad (3.7) \\
\lambda_2' &= \lambda_1\left[\frac{B_1 s_2}{(B_1+V(t))^2} + kT(t)\right] \\
&\quad -\lambda_2\left[\frac{B_2 g\left(1-\min\left\{\max\left\{a_2, -\frac{\lambda_2}{2A_2}\frac{V(t)}{B_2+V(t)}\right\}, b_2\right\}\right)}{(B_2+V(t))^2} - cT(t)\right] \\
\lambda_1(t_f) &= \lambda_1(t_f) = 0, \text{ and } T(0) = T_0, V(0) = V_0.
\end{aligned}
$$

4 Uniqueness of the Optimality System

We will state this simple lemma (without proof) needed for the proof of the uniqueness of solutions of the optimality system for the small time interval.

Lemma 4.1. *The function $u^*(s) = \min(\max(s,a),b))$ is Lipschitz continuous in s, where $a<b$ are some fixed positive constants.*

Theorem 4.1. *For t_f sufficiently small, bounded solutions to the optimality system are unique.*

Proof: Suppose $(T, V, \lambda_1, \lambda_2)$ and $(\overline{T}, \overline{V}, \overline{\lambda}_1, \overline{\lambda}_2)$ are two different solutions of our optimality system (3.7). Let $T = e^{\lambda t}p, V = e^{\lambda t}q, \lambda_1 = e^{-\lambda t}w, \lambda_2 = e^{-\lambda t}z$ and $\overline{T} = e^{\lambda t}\overline{p}, \overline{V} = e^{\lambda t}\overline{q}, \overline{\lambda}_1 = e^{-\lambda t}\overline{w}, \overline{\lambda}_2 = e^{-\lambda t}\overline{z}$, where $\lambda > 0$ is to be chosen. Further we let

$$
\begin{aligned}
u_1^*(t) &= \min\left\{\max\left\{a_1, \frac{1}{2A_1}\left(wp\right)\right\}, b_1\right\} \\
u_2^*(t) &= \min\left\{\max\left\{a_2, -\frac{z}{2A_2}\frac{q}{B_2+e^{\lambda t}q}\right\}, b_2\right\}
\end{aligned}
$$

and

$$\begin{aligned}\overline{u}_1^*(t) &= \min\left\{\max\left\{a_1, \frac{1}{2A_1}(\overline{w}\,\overline{p})\right\}, b_1\right\}\\ \overline{u}_2^*(t) &= \min\left\{\max\left\{a_2, -\frac{\overline{z}}{2A_2}\frac{\overline{q}}{B_2+e^{\lambda t}\overline{q}}\right\}, b_2\right\}.\end{aligned}$$

Now we substitute $T = e^{\lambda t}p$ in to the first ODE of (3.7) and get

$$\begin{aligned}p' + \lambda p &= e^{-\lambda t}s_1 - \frac{s_2 q}{B_1 + e^{\lambda t}q} - \mu p - ke^{\lambda t}pq\\ &\quad + \min\left\{\max\left\{a_1, \frac{1}{2A_1}(wp)\right\}, b_1\right\} p. \qquad (4.1)\end{aligned}$$

Similarly, for $V = e^{\lambda t}q, \lambda_1 = e^{-\lambda t}w, \lambda_2 = e^{-\lambda t}z$, we obtain

$$q' + \lambda q = \frac{g\left(1 - \min\left\{\max\left\{a_2, -\frac{z}{2A_2}\frac{q}{B_2+e^{\lambda t}q}\right\}, b_2\right\}\right)q}{B_2 + e^{\lambda t}q} - ce^{\lambda t}pq \qquad (4.2)$$

$$\begin{aligned}-w' + \lambda w &= e^{\lambda t} - w\left[\mu + ke^{\lambda t}q - \min\left\{\max\left\{a_1, \frac{1}{2A_1}(pw)\right\}, b_1\right\}\right]\\ &\quad -ce^{\lambda t}qz \qquad (4.3)\end{aligned}$$

$$\begin{aligned}-z' + \lambda z &= -w\left[\frac{B_1 s_2}{(B_1 + e^{\lambda t}q)^2} + ke^{\lambda t}p\right]\\ &\quad + z\left[\frac{B_2 g\left(1 - \min\left\{\max\left\{a_2, -\frac{z}{2A_2}\frac{q}{B_2+e^{\lambda t}q}\right\}, b_2\right\}\right)}{(B_2 + e^{\lambda t}q)^2} - ce^{\lambda t}p\right]. \qquad (4.4)\end{aligned}$$

Now we subtract the equations for T and $\overline{T}$, V and $\overline{V}$, λ_1 and $\overline{\lambda}_1$, λ_2 and $\overline{\lambda}_2$. Then multiply each equation by appropriate difference of functions and integrate from 0 to t_f. Next we add all four integral equations and will use estimates to obtain uniqueness.

Using Lemma 4.1, we have

$$|u_1^*(t) - \overline{u}_1^*(t)| \le \frac{1}{2A_1}|wp - \overline{wp}|$$

and

$$\begin{aligned} |u_2^*(t) - \overline{u}_2^*(t)| &\leq \left| \frac{1}{2A_2} \left(\frac{zq}{B_2 + e^{\lambda t} q} - \frac{\overline{zq}}{B_2 + e^{\lambda t}\overline{q}} \right) \right| \\ &\leq \frac{1}{2A_2} \left| \frac{B_2(zq - \overline{zq}) + e^{\lambda t}(z - \overline{z})}{(B_2 + e^{\lambda t} q)\,(B_2 + e^{\lambda t}\overline{q})} \right|. \end{aligned}$$

We illustrate one case of the estimate (which uses $|u_1^* - \overline{u}_1^*|$ estimate):

$$\begin{aligned} &\frac{1}{2}(p - \overline{p})^2(t_f) + \lambda \int_0^{t_f} (p - \overline{p})^2 \, dt \\ &\leq \int_0^{t_f} \left| \frac{s_2 q}{B_1 + e^{\lambda t} q} - \frac{s_2 \overline{q}}{B_1 + e^{\lambda t}\overline{q}} \right| |p - \overline{p}| \, dt + \int_0^{t_f} \mu |p - \overline{p}|^2 \, dt \\ &+ k \int_0^{t_f} e^{\lambda t} |pq - \overline{pq}| |p - \overline{p}| \, dt + \int_0^{t_f} |u_1^* p - \overline{u_1^*}\overline{p}| |p - \overline{p}| \, dt \\ &\leq C_1 \int_0^{t_f} \left[|p - \overline{p}|^2 + |q - \overline{q}|^2 + |w - \overline{w}|^2 \right] \, dt \\ &+ C_2 e^{\lambda t_f} \int_0^{t_f} \left[|p - \overline{p}|^2 + |q - \overline{q}|^2 \right] \, dt, \end{aligned}$$

where the constants C_1 and C_2 depend on the coefficients and the bounds on states and adjoints. Combining four of these estimates gives

$$\begin{aligned} &\frac{1}{2}(p - \overline{p})^2(t_f) + \frac{1}{2}(q - \overline{q})^2(t_f) + \frac{1}{2}(w - \overline{w})^2(0) + \frac{1}{2}(z - \overline{z})^2(0) \\ &+ \lambda \int_0^{t_f} \left[(p - \overline{p})^2 + (q - \overline{q})^2 + (w - \overline{w})^2 + (z - \overline{z})^2 \right] \, dt \\ &\leq \left(\tilde{C}_1 + \tilde{C}_2 e^{3\lambda t_f} \right) \int_0^{t_f} \left[(p - \overline{p})^2 + (q - \overline{q})^2 + (w - \overline{w})^2 + (z - \overline{z})^2 \right] \, dt. \end{aligned}$$

Thus from above equation we conclude that

$$\left(\lambda - \tilde{C}_1 - \tilde{C}_2 e^{3\lambda t_f} \right) \int_0^{t_f} \left[(p - \overline{p})^2 + (q - \overline{q})^2 + (w - \overline{w})^2 + (z - \overline{z})^2 \right] \, dt \leq 0$$

where $\tilde{C}_1, \tilde{C}_2$ depend on the coefficients and the bounds on p, q, w, z.

If we choose λ such that $\lambda > \tilde{C}_1 + \tilde{C}_2$ and $t_f < \frac{1}{3\lambda} \ln\left(\frac{\lambda - \tilde{C}_1}{\tilde{C}_2}\right)$, then $p = \overline{p}$, $q = \overline{q}$, $w = \overline{w}$, $z = \overline{z}$. Hence the solution is unique for small time. □

See Fister *et.al* [3] for proof of a similar uniqueness result. The uniqueness for a small time interval is usual in "two-point" boundary value problems due to opposite time orientations; the state equations have initial conditions and the adjoint equations have final time conditions. The optimal controls, u_1^*, u_2^* are characterized in terms of the unique solution of the optimality system. The above optimal controls give an optimal treatment strategy for the HIV infected patient under the scenario of these two types of drug treatments.

5 Numerical Illustration

The optimality system is solved using an iterative method with a Runge-Kutta fourth order scheme. The state system with an initial guess is solved forward in time and then the adjoint system is solved backward in time. The controls are updated at the end of each iteration using the formula for optimal controls, which we derived in section 3 (in the last part of Theorem 3.1). The iterations continue until convergence is achieved. See [5] for background on such iterative algorithms.

Using different combinations of weight factors (A_1, A_2) and upperbounds (b_1, b_2) for controls, one can generate several treatment schedules for various time periods. Here we illustrate a case for two different values of A_1 for a 50-day treatment schedule. Figures 1-4 are plotted using $A_1 = 250000, A_2 = 75, b_1 = 0.02, b_2 = 0.9$, Figures 5-8 are plotted using $A_1 = 500000$ and keeping the rest of the parameters unchanged. Note that due to the type of drugs administered, the upper bound b_1 of the u_1 control is much smaller than the upper bound b_2 of the u_2 control [9]. To balance the effect of these different sizes of b_1, b_2 in the objective functional, the balancing coefficient A_1 is taken much larger than A_2. Figure 1 and 2 represent the controls u_1^*, u_2^* for drug administration schedule for the first set of parameters. The immune boosting drug is administered in full scale nearly up to 40 days and then is tapered off. Similarly the viral suppression drug is administered in full scale nearly up to 5 days and then is tapered off. Figure 3 represents the number of T cells during our treatment period. The T cell population increases almost linearly up to 45 days and levels off after that time. Figure 4 represents the virus population during our treatment period. In the beginning, we see a sharp decrease in the virus population and after few days it starts to increase steadily with some fluctuations. Figure 5 and Figure 6 represent the optimal controls u_1^*, u_2^* for drug administration schedule for the

second set of parameters. The immune boosting drug is administered in full scale nearly up to 25 days and then tapers off. Similarly the viral suppression drug is administered in full scale nearly up to 4 days and then tapers off. When we compare Figures 7 and 8 for T and V with Figures 3 and 4, we see that higher A_1 values reduce the T cell population and increase the virus population.

After observing results of various combinations of parameters, we conclude that the higher the weight factor, the earlier we start tapering off the treatment. This higher weight factor means that the drug is more toxic and that drug is used less. Both drug treatments are given over the same interval but the time of giving the maximum level varies. The virus population drops for the first few days and starts to build up again. We can keep the virus population under a certain level but can not eradicate it.

Note that the format of the optimal controls do agree with those in the papers [2, 3, 7] with only one control. The interesting feature here is the interplay between the two controls, and the more lengthy treatment with immunotherapy (u_1 control) is recommended.

The results in these examples do not depend on the initial guess. The number of iterations required for these examples is about 10.

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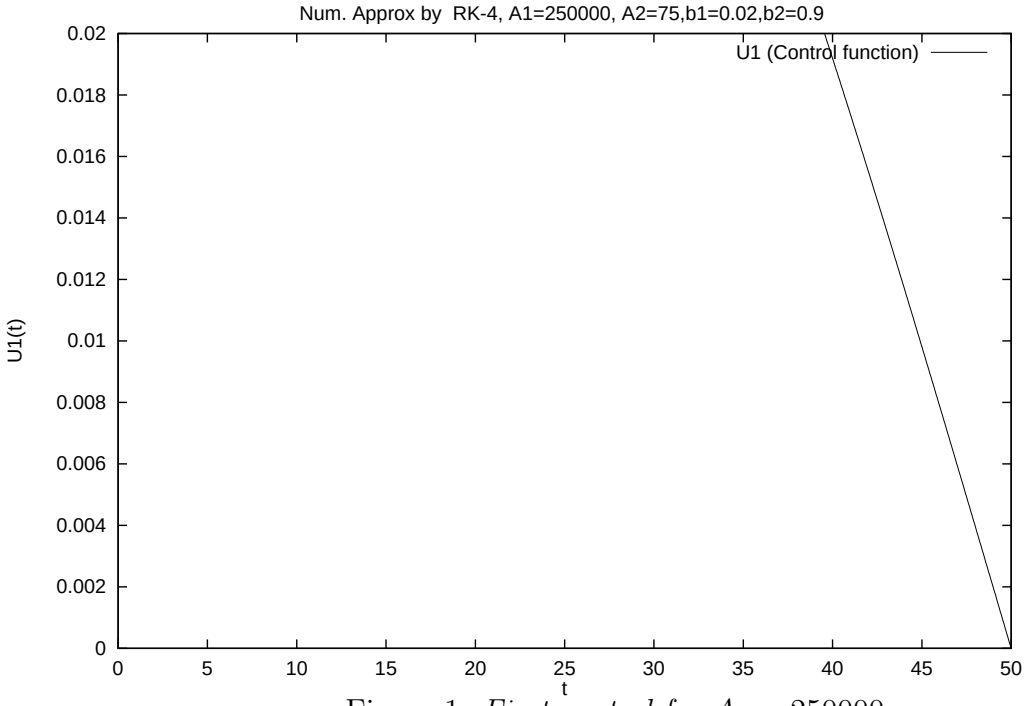

Figure 1: *First control for* $A_1 = 250000$

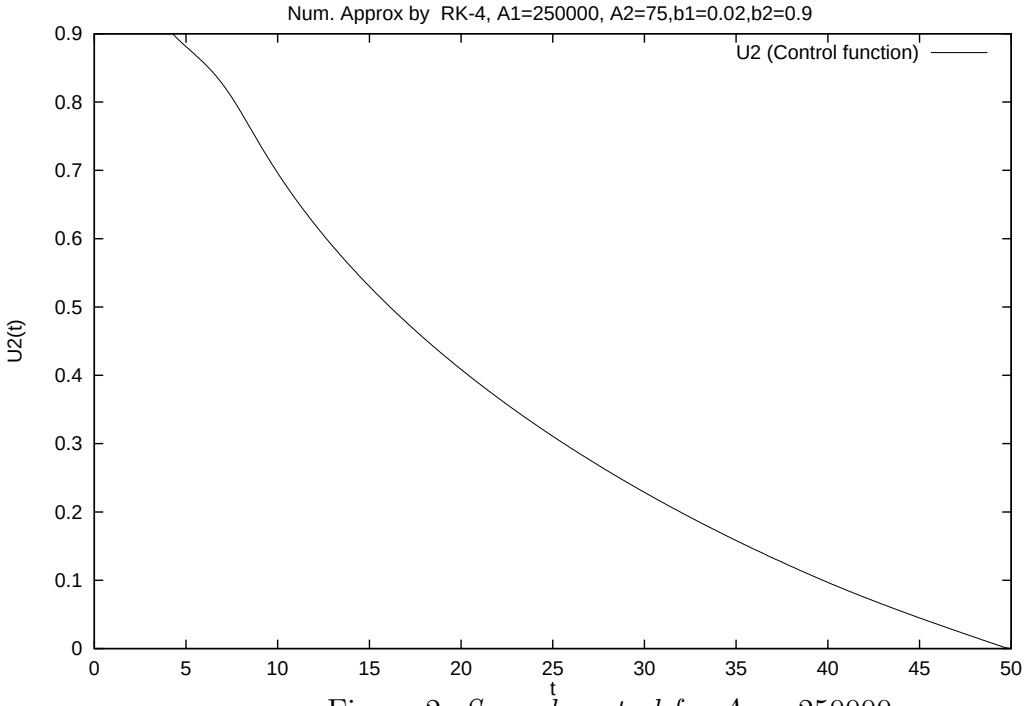

Figure 2: *Second control for* $A_1 = 250000$

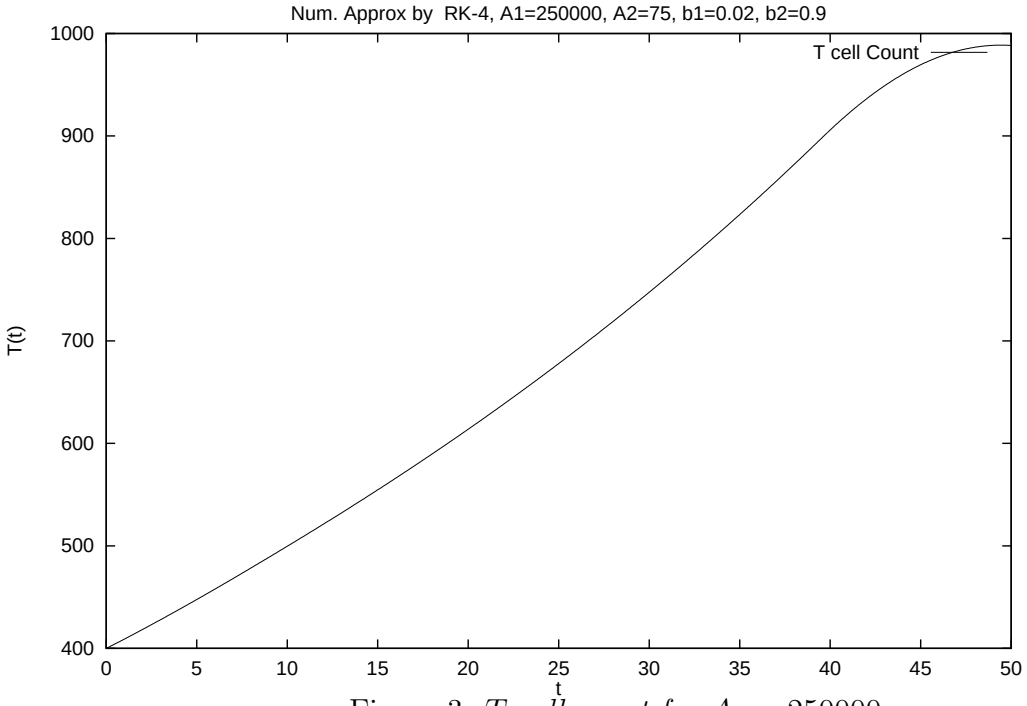

Figure 3: *T cell count for $A_1 = 250000$*

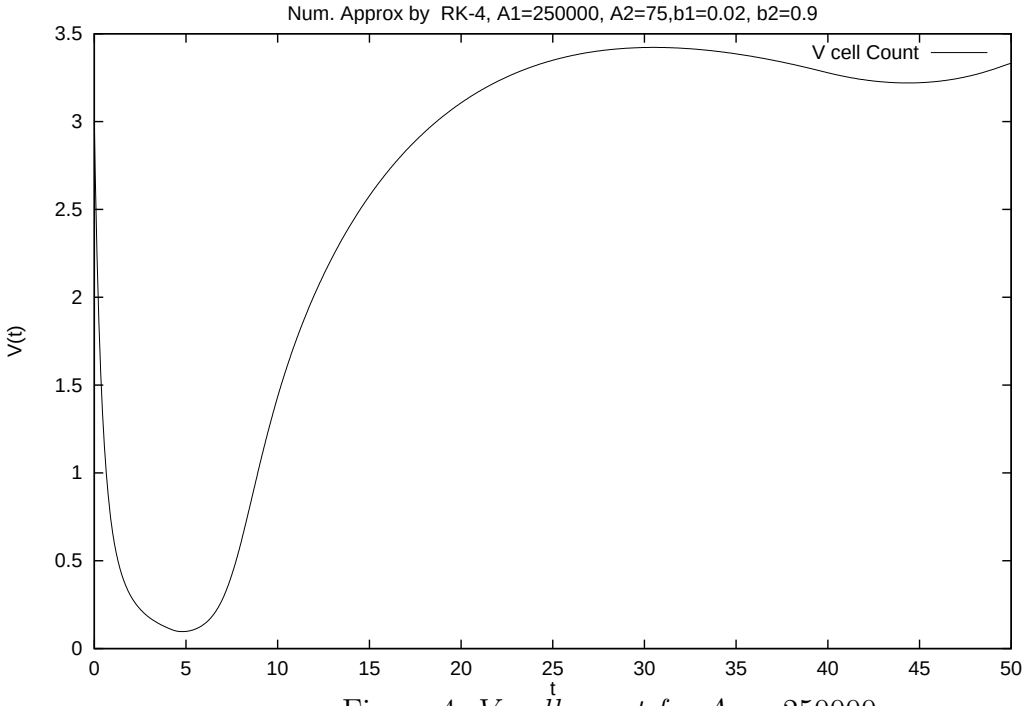

Figure 4: *V cell count for $A_1 = 250000$*

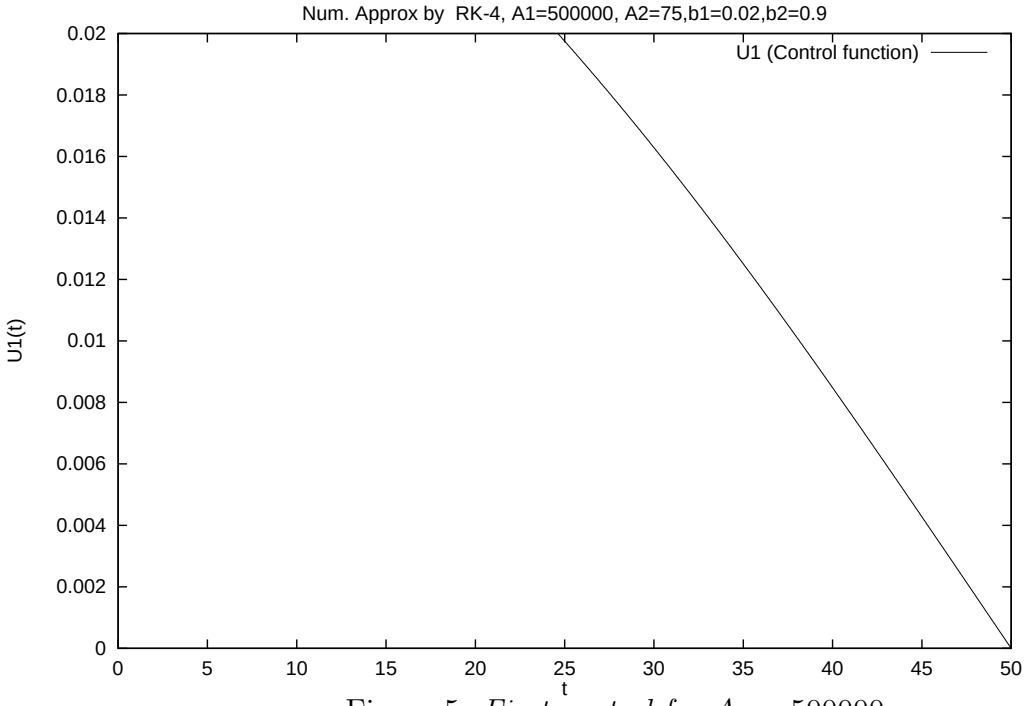

Figure 5: *First control for* $A_1 = 500000$

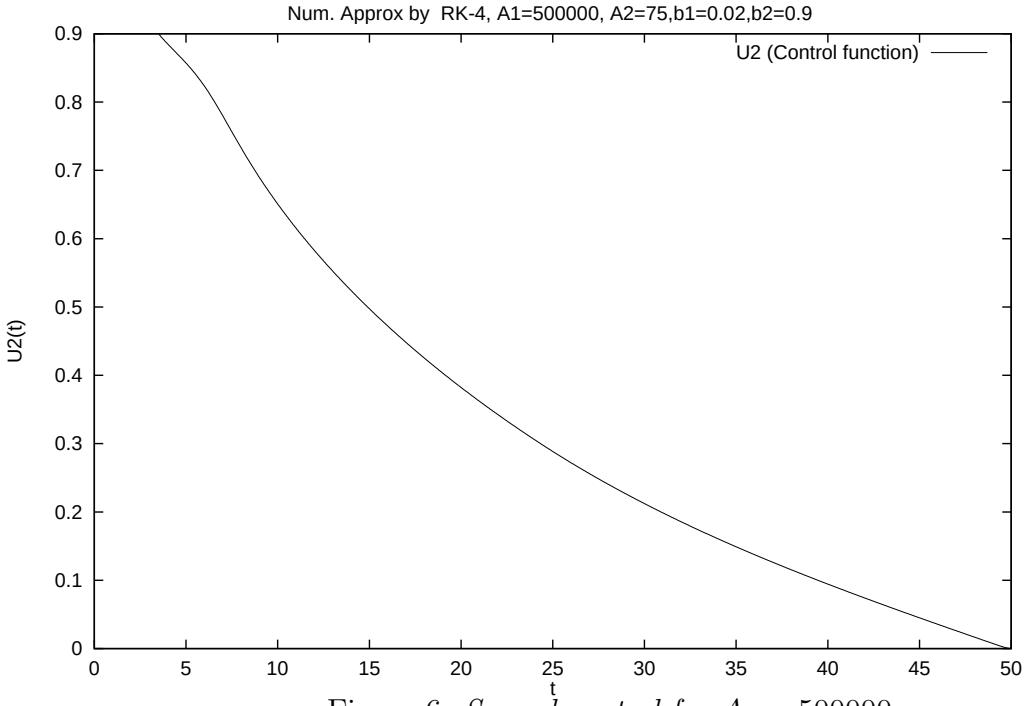

Figure 6: *Second control for* $A_1 = 500000$

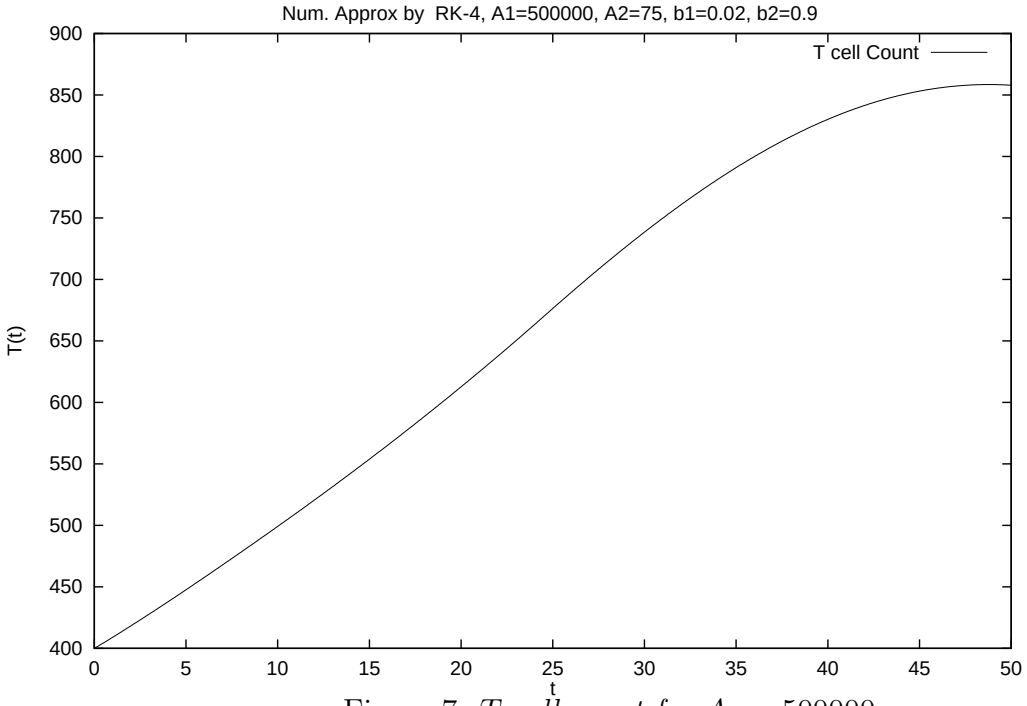

Figure 7: *T cell count for $A_1 = 500000$*

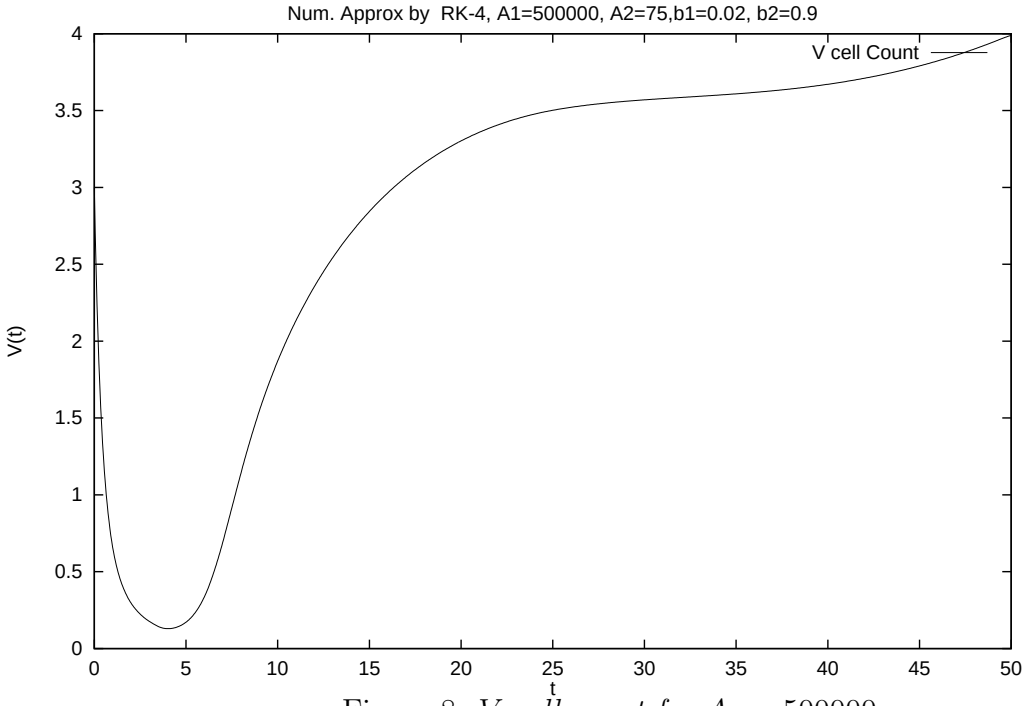

Figure 8: *V cell count for $A_1 = 500000$*

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