Chemotherapy in an HIV Model by a pair of Optimal Control

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Abstract: We introduce a medical control model, in the sense of an optimal control problem, which simulates the interaction of immune system with HIV. This model shows the strategy of chemotherapy treatment. In fact, the simulated optimal control pair, (u_1, u_2), represents the virus production and the percentage effect of the chemotherapy on the $CD4^+$ T cells. We define an objective function characterized based on maximizing T cells and minimizing the cost of the chemotherapy treatment.

In this paper, we introduce a new approach to find the optimal pair control for the simulated optimal control on treatment of HIV. By using an embedding method, optimal control problem transfers into a modified on the measure space, where now the existence of optimal pair is guaranteed by compactness of the space, and the metamorphosed problem in measure space is a kind of an infinite dimensional linear programming problem, whose solution can be approximated by that of a finite- dimensional one.

Key- Words: Measure theory, Optimal control, HIV, Linear programming,

1 Introduction

There are two kinds drugs for treatment of HIV infection ([1],[2]), the first kind effects on the virus production and reduces the virus production, the second kind effects on the $CD4^+$ T cells production and access $CD4^+$ T cells production.

In this paper, we present a control model which consists of two control function for medical control of the chemotherapy treatment that uses the above two kinds drugs. The first control, as in [3], represents the percentages of effect the chemotherapy has on the viral production and the next control represents the effect of the second drug chemotherapy on $CD4^+$ T cells access.

Pathologists attempt to obtain drugs that have capability both effects (reduce virus production and access $CD4^+$ T cells production). However some achievements obtained in this case, but still do not be yet drugs that have these two effects.

In this paper our purpose is the representation control mode3l that control both cases and minimizing the cost of treatment. To avoid harmful side effects, as in [1], we impose a condition called a *limited treatment window*, that is the treatment starts from time t_0 and lasts to final time t_1.

2 Two- control model

There are some simple control models study the effects of chemotherapy as an immune system infected with HIV, see for example [3,4,5]. We basically used the model and notations introduced in [1] and extended it as a two-control model.

Let T denote the uninfected $CD4^+$ T cells and T^* and T^{**} denote respectively the latently and actively infected $CD4^+$ T cells. The free infections virus particles are V. We assume that the ordinary differential equation model that describes the interaction of immune system with HIV virus is as follows:

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

$$\frac{dT^*}{dt} = u_1 k_1 VT - \mu_{T^*} T^* - k_2 T^* \quad (1)$$

$$\frac{dT^{**}}{dt} = k_2 T^* - \mu_{T^{**}} T^*$$

$$\frac{dV}{dt} = u_2 N \mu_{T^{**}} T^{**} - u_1 k_1 VT - \mu_V V$$

where the initial values of T, T^*, T^{**} and V are given at $t = t_0$. In this model, the control functions for the chemotherapy are $u_1(t)$ and $u_2(t)$. These are measurable functionals defined on $I = [t_0, t_1]$, which are bounded and assume:

$$0 \le u_i(t) \le 1, \qquad i = 1,2. \quad (2)$$

and in the medical model (1) Parameters and Constants are as follows

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μ_T = death rate of $CD4^+$ T cell population

μ_{T^*} = death rate of latently infected $CD4^+$ T cell population

$\mu_{T^{**}}$ = death rate of activity infected $CD4^+$ T cell population

μ_V = death rate of free virus

k_1 = rate $CD4^+$ T cell population becomes infected by free virus

k_2 = rate T^* cells convert to actively infected

r = rate of growth for the $CD4^+$ T cell population

N = number of free virus produced by T^{**} cells

T_{max} = maximum $CD4^+$ T cell population level

s = source term for uninfected $CD4^+$ T cells

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and

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

Numerical information for parameters is as in [1] and can be found in Table 1 of that article.

The objective function that to be maximized is defined as

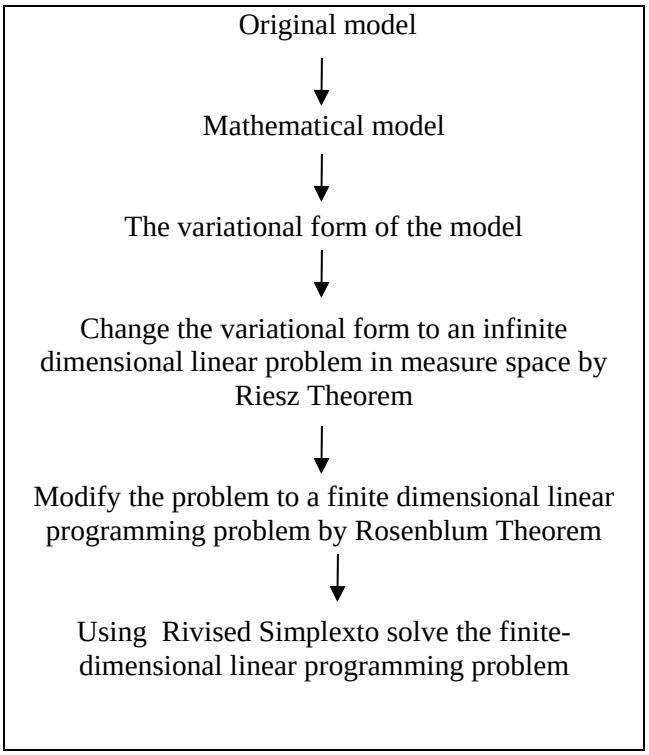
$$J(u_1, u_2) = \int_{t_0}^{t_1}\left[T(t) - \frac{1}{2}(\beta_1 u_1^2 + \beta_2 u_2^2)\right]dt \quad (3)$$

The desired weight on the benefit and cost are shown respectively by the parameters β_1 and β_2, where in our case we have chosen $\beta_1 = 100$ and $\beta_2 = 100$ (see [1]). In (3) we are maximizing the benefit on T cells count, and minimizing the systemic cost based the percentage effects of the chemotherapy given. The goal is to characterize the optimal pair $u_1^*(t)$ and $u_2^*(t)$, satisfying

$$J(u*) = J(u_1^*, u_2^*) = \max J(u_1, u_2) = J(u), \quad 0 \le u_i(t) \le 1, \ i = 1,2. \quad (4)$$

In this maximization problem, the necessary concavity of the objective functional in $u = (u_1, u_2)$ holds. The right hand sides of the equations in (1) are bounded, due to a priori bounds on the T variables, which imply the needed a priori bounds on the state variables. These bounds is needed to sure the compactness needed for the existence of the optimal control (see [6]).

In the next section we change the problem to a problem in measure space, where we interface with a linear programming problem, and can use all the prephonalia of the linear analysis. In fact our method based on the following diagram:



In the following we replace the problem by

another one in which the maximum of the objective functional (3) is calculated over a set of positive Radon measures to be defined as follows. Some authors have used this approach in a variety of optimal control problems, we mention only [9-11] and the pioneering work of Rubio [6] as well.

Let $\Omega = I \times A \times U$, and

$x=[x_1(t),x_2(t),x_3(t),x_4(t)]=[T(t),T^*(t),T^{**}(t),V(t)]\in A, \forall t \in I$

is the trajectory of the controlled system and A is a bounded, closed, pathwise connected set in $\mathbb{R}^4$, $u(t) = [u_1(t), u_2(t)] \in U, \forall t \in I$, where U is a bounded, closed subset of $\mathbb{R}^2$. We rewrite equations (3) and (1) as the following reduced form:

$$\text{Min } J(u) = J(u_1, u_2) = \int_{t_0}^{t_1} \left[x_1(t) - \frac{1}{2}(\beta_1 u_1^2 + \beta_2 u_2^2) \right] dt \quad (5)$$

s.t.

$$\dot{x}(t) = g\big(t, x(t), u(t)\big) \ , \ t \in I^{\circ}, (I^{\circ} \text{ is interior of } I) \quad (6)$$

We call the trajectory- control $p = [x(\cdot), u(\cdot)]$ *admissible pair*, if:

(i) The trajectory function $x(\cdot)$ is absolutely continuous, and $x(t) \in A$

(ii) the pair p satisfies (6) a.e. on I°.

We denote the set of admissible pairs by W. Now, we seek to find an optimal trajectory- control pair $p^* = [x^*(\cdot), u^*(\cdot)] \in W$ such that minimizes J(u) in (5). In general the minimization of the functional (5) over W is not possible. The set W may be empty: even if W is not empty, the functional measuring the performance of the system may not achieve its minimum in this set. It appears that the situation may become move promising if the set W could somehow be made larger. In the following we use a transformation to enlarge the set W. Let $p = [x(\cdot), u(\cdot)]$ be an admissible pair and B an open ball containing $I \times A$. We denote by $C'(B)$ the space of real- valued continuously differentiable functions on B. Let $\varphi \in C'(B)$ and define

$$\varphi^g = \nabla \varphi(x).g \quad (7)$$

The function φ^g is in the space $C(\Omega)$, the set of all continuous functions on the compact set Ω. For each admissible pair, we have (see [9])

$$\int_I \varphi^g(t,x,u) = \Delta\varphi, \forall \varphi \in C'(B) \quad (8)$$

Let $D(I^{\circ})$ be the space of infinitely differentiable real valued functions with compact support in I°. For each $\psi \in D(I^{\circ})$ define:

$$\psi^j(t, x(t), u(t)) = x_j \psi(t) + g_j \psi(t), j = 1, 2, \ldots, 4. \quad (9)$$

so we have (see [9])

$$\int_I \psi^j(t, x(t), u(t))dt = 0. \quad (10)$$

Now, assuming that B_1 is an open ball in R containing I, denote the space of all differentiable functions on B_1 by $C'(B_1)$, then

$$\theta^g(t,x,u) = \dot{\theta}(t), (t,x,u) \in \Omega$$

and

$$\int_I \theta^g(t,x,u)dt = \alpha_\theta, \theta \in C'(B_1). \quad (11)$$

The set of equalities (8) of which we singled out the special cases (10) and (11) are properties of admissible pairs in the classical formulation of optimal control problem in the following section, by suitable generalizing them, we shall effect the transformation of this into another, nonclassical problem which appear to have better properties in some respects (see Rubio [6] for details)

3 Optimization in measure space

For each admissible p, we corresponds the linear continuous functional Λ_p, as follows:

$$\Lambda_p : F(.,.,.) \in C(\Omega) \to \int_I F(t, x(t), u(t))dt. \quad (12)$$

This well defined mapping is linear, positive, continuous and injective (see [10]), Therefore, we can identify pairs p with the linear functional Λ_p. Using this approach, the above control problem with the objective functional (5) can be written as follows:

$$\text{Minimize } \Lambda_p(f_0) \quad (13)$$

Subject to:

$$\begin{aligned} &\Lambda_p(\varphi^g) = \Delta\varphi, \varphi \in C'(B) \\ &\Lambda_p(\psi^j) = 0, j = 1,2,3,4; \psi \in D(I^{\circ}) \quad (14) \\ &\Lambda_p(\theta^g) = \alpha_\theta, \theta \in C'(B_1), \end{aligned}$$

where $f_0 = x_1(t) - \frac{1}{2}(\beta_1 u_1^2 + \beta_2 u_2^2)$. Let $M^+(\Omega)$ denote the space of all positive Radon measures on Ω. By Riesz representation theorem (See Royden [7]), there is a one-to-one correspondence between functional $\Lambda_p \in C^*(\Omega)$ and a positive Borel measure on Ω such that;

$$\Lambda_p(F) = \int_\Omega F \, d\mu = \mu(F), F \in C(\Omega),$$

where $C^*(\Omega)$ is the dual space on Ω. Using these concepts, we change the space of optimization problem to the measure space. In other words the optimization problem in functional space (13)- (14) is equivalent to the following optimization problem in measure space:

$$\text{Minimize } \mu(f_0) \tag{15}$$

subject to:

$$\mu(\varphi^g) = \Delta\varphi, \varphi \in C'(B)$$
$$\mu(\psi^j) = 0, j = 1,2,3,4; \psi \in D(I^\circ) \tag{16}$$
$$\mu(\theta^g) = \alpha_\theta, \theta \in C'(B_1).$$

Define the set of all positive Radon measures satisfying (16) as Q, and *topologize* the space $M^+(\Omega)$ by the weak*- topology. One can prove the existence of an optimal measure in the set Q for the functional $\mu \to \mu(f_0)$ under the conditions imposed (see Rubio [6]).

4 Approximation of optimal control by optimal measure

The minimizing problem (15)-(16) is an infinite-dimensional linear programming problem and we are mainly interested in approximating it. It is possible to approximate the solution of the problem (15)-(16) by the solution of a finite dimensional linear program of sufficiently large dimension. Consider the first set of equalities in (16). Let the set

$$\{\varphi_i, i = 1,2,...\}$$

be total in $C'(B)$,i.e; be such that the linear combinations of the functions $\varphi_i \in C'(B)$ are uniformly dense in $C'(B)$, we can prove:

Proposition 1: Consider the linear programming consisting of the minimizing functional $\mu \to \mu(f_0)$ over the set Q_M of measures in $M^+(\Omega)$ satisfying $\mu(\varphi_b^g) = \Delta\varphi_b, b = 1,2,\ldots,M$, then if $M \to \infty$, $\lambda_M \equiv \inf_{Q_M} \mu(f_0)$ tends to $\lambda \equiv \inf_Q \mu(f_0)$.

Proof: See Appendix of [9].

It is possible to characterize a measure in the set Q_M at which the linear function $\mu(f_0)$ attains in minimum, it follows a result of Rosenbloom [8] that:

$$\mu^* \approx \sum_{k=1}^{N} \alpha_k^* \delta\left(y_k^*\right) , \tag{17}$$

where $y_k^* \in Y = \{y_1, y_2, ..., y_n\} \subseteq \Omega$, and $\alpha_k^* \geq 0, k = 1,2,\ldots,M$, and Y is an approximately dense subset of Ω. In (17) δ is an unitary atomic measure that is characterized by:

$$\delta(y)(F) = F(y), y \in \Omega.$$

By (17) and Proposition 1, the infinite- dimensional linear programming (15)-(16) can be approximated by the following linear programming problem, where y_k belongs to an approximately dense subset of Y.

$$\text{Minimize} \quad \sum_{k=1}^{N} \alpha_k f_0(y_k) \tag{18}$$

Subject to:

$$\sum_{k=1}^{N} \alpha_k \varphi_b^g(y_k) = \Delta\varphi_b, \quad b = 1,2,\ldots,M_1,$$
$$\sum_{k=1}^{N} \alpha_k \psi_r^j(y_k) = 0, \quad \begin{matrix} j = 1,2,3,4 \\ r = 1,2,\ldots,M_2/4 \end{matrix} \tag{19}$$
$$\sum_{k=1}^{N} \alpha_k \theta_s(y_k) = a_s, \quad s = 1,2,\ldots,L,$$
$$\alpha_k \geq 0,\ k = 1,\ 2,\ \cdots, N.$$

The set Ω will be covered with a grid, where the grid will be defined by taking all points in Ω as:

$$y_k = [t, x_{1_k}, x_{2_k}, x_{3_k}, x_{4_k}, u_{1_k}, u_{2_k}], \quad k = 1,\ 2,\ \cdots,\ N$$

The points in the grid will be numbered sequentially from 1 to N. We used a home-made Revised Simplex to solve the linear programming problem (18)-(19). The analysis of constructing control and trajectories follows from Rubio [6].

5 Numerical Results

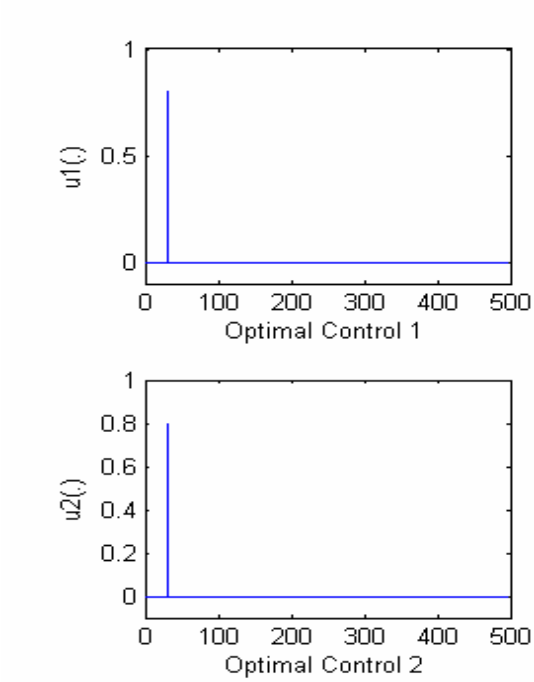
Example 1: In medical control problem (1), we assume the parameters as:

$k_1 = 2.4\times10^{-5}$	$r = .03$	$\mu_T = .02$
$k_2 = 3\times10^{-3}$	$N = 1200$	$\mu_{T^*} = .02$
$T_{max} = 1.5\times10^{3}$	$S = 10$	$\mu_{T^{**}} = .24$
		$\mu_V = 2.4$

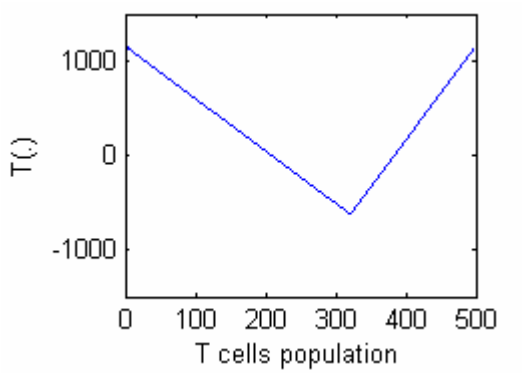
and

Intervals	Partitions
$A_T=[T_0, T_0+50]$	$P_T=5$
$A_{T^*}=[0,20]$	$P_{T^*}=5$
$A_{T^{**}}=[0,15]$	$P_{T^{**}}=5$
$A_V=[0,15]$	$P_V=5$
$A_{u_1}=[0,1]$	$P_{u_1}=5$
$A_{u_2}=[0,1]$	$P_{u_2}=5$
I=[0,500]	$P_t=10$

Also let $M_1=4$, $M_2=4$, and $L=10$ then by solving linear programming (18)-(19) we have the optimal T cell count as $T=1158$, and objective function value J* as 561,110 . The control functions $u_1(t)$ and $u_2(t)$ are shown in below. In fact they show the best policy of drugs treatment .



Also the optimal trajectory function T, is shown in below. This figure shows that under this kind of treatment, uninfected $CD4^+$ T cells decrease from the beginning up to 300 days, and after that they increase hopefully.



4 Conclusion

The method that we developed here for best chemotherapy in treatment of HIV is based on linear technique. This procedure might become a useful technique for the computation of a best treatment related to epidemiological disease with fully nonlinear model, of course, it in not necessary to impose any convexity on objective function.

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