Optimizing 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 Human Immunodeficiency Virus (HIV) . This model shows the strategy of chemotherapy treatment. In fact, the simulated optimal control pair, (u_1,u_2) control the percentage effect of the chemotherapy on the $CD4^+T$ cells and the virus production . An objective function is characterized based on maximizing T cells and minimizing the cost of chemotherapy treatment.
In this article, a new approach is introduced to find an optimal pair control for obtaining an optimal HIV treatment. By using an embedding method, optimal control problem transfers into a modified problem in an appropriate measure space, in which the existence of optimal pair is guaranteed by compactness of the space, and the metamorphosed problem in measure space is a type of an infinite dimensional linear programming problem, whose solution can be approximated by that of a finite-dimensional one.

Keywords: HIV, Linear programming, Measure theory, Optimal control.

1. INTRODUCTION

There are two kinds drugs for treatment of Human Immunodeficiency Virus (HIV) infection (Kirschner *et al*.(1997) and Renee *et al*. (1998)), 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 a control model is presented which consists of two control of the chemotherapy treatment that uses the above two kinds drugs. The first control, as in Mac Lan *et al*.(1992), represents the effect of the first drug chemotherapy on $CD4^+T$ cells access, and the next control presents of effect the chemotherapy has on the rival production.
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 regard, but such drugs which have these two effects together do not still exist.
In this paper, our purpose is the representation a control model that control both cases and minimizing the cost of treatment. To avoid harmful side effects, as in Kirschner *et al*. (1997), we impose a condition called a limited treatment window, meaning the treatment starts from t_0 and lasts to final t_1.

2. TWO-CONTROL MODEL

There are some control models study the effects of chemotherapy as an immune system infected with HIV, see for example Mc Lean *et al*. (1992), Perelson (1989), Perelson *et al*. (1993), and Xia (2003), Xia (2007) for latest models. We basically used the model and notations introduced in Kirschner *et al* .(1997), and extend 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 control model (governed by an ordinary differential equation) that describes the interaction of immune system with HIV virus is as follows:

$$\begin{aligned}
\frac{dT}{dt} &= \frac{s}{1+V} - \mu_T T + rT\left(1 - \frac{T+T^*+T^{**}}{T_{max}}\right) \\
&\quad - (1-u_1)k_1 VT \\
\frac{dT^*}{dt} &= (1-u_1)k_1 VT - \mu_{T^*} T^* - k_2 T^* \qquad (1) \\
\frac{dT^{**}}{dt} &= k_2 T^* - \mu_{T^{**}} T^{**} \\
\frac{dV}{dt} &= (1-u_2)N\mu_{T^{**}} T^{**} - (1-u_1)k_1 VT - \mu_V V
\end{aligned}$$

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 functional defined on I=$[t_0,t_1]$, which are bounded and assume:

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

In the medical model (1), parameters and constants, defined as follows:

μ_T = death rate of $CD4^+T$ cell population
μ_{T^*}= death rate of latently infected $CD4^+T$ cell population
$\mu_{T^{**}}$= death rate activity infected $CD4^+T$ cell population
μ_V = death rate free of 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

and

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

Numerical information for parameters is as in Kirschner *et al.* (1997) and can be found in Table 1 of that article.
The objective function that to be maximized is defined as

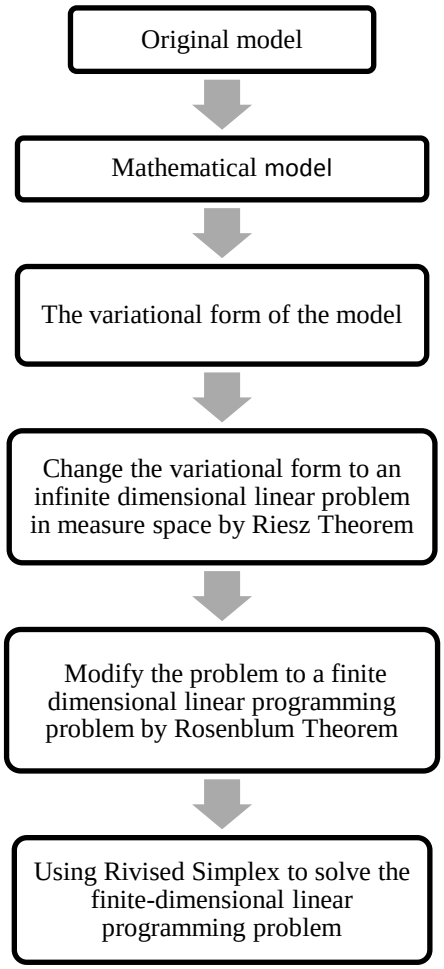
$J(x,u_1,u_2)=\int_{t_0}^{t_1}[T(t) - \frac{1}{2}(\beta_1 u_1^2 + \beta_2 u_2^2)]d$ (3)

The desired weight on the benefit and cost are shown respectively by the parameters β_1 and β_2 respectively, where in our case we have chosen β_1=100 and β_2=100 (see Kirschner *et al*. (1997)). In (3) we are maximizing the benefit on T cells count, and minimizing the systemic cost which is based on the percentage effects of the chemotherapy given. The goal is to characterize the optimal pair x*(t) and u*(t), satisfying

$J(x^*,u^*)=J(x^*,u_1^*,u_2^*)= \text{Max}J(x,u_1,u_2)$

$0 \le u_i(t) \le \quad i=1,2.$ (4)

In this maximization problem, the necessary concavity of the objective functional in x and u=(u_1,u_2) does not hold. The right hand sides of the equation 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 needed to guarantee the compactness of the domain which is needed for the existence of the optimal control (see Rubio (1986)).
In the next section the problem is changed to a problem in measure space, where we interface with a linear programming problem, and can use all the paraphernalia 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 Heydari *et al*. (2006), (2001), (1999), and the pioneering work of Rubio (1986) 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, path wise connected set in R^4 , $u(t) = [u_1(t), u_2(t)] \in U$, $\forall t \in I$, where U is a bounded, closed subset of R^2. One may rewrite optimization problem (3) and (1) as the following reduced form:

$\text{Max } J(x,u)=\text{Max } J(x,u_1,u_2) =$

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

s.t.

$$\dot{x}(t) = g(x(t),u(t)) \quad , \quad t \in I^0 \quad (6)$$

(I^0 is interior of I)

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

(i) the trajectory function x(.) is absolutely continuous, and x(t) ∈A

(ii) the pair p satisfies (6) a.e. on I^0.

The set of admissible pairs is denoted by W. Now, one seek to find an optimal trajectory-control pair p*=[x*(.),u*(.)]∈ W such that maximization J(x,u) in (5). In general the maximization 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 maximum in this set. It appears that the situation may become more 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(.),u(.)] be an admissible pair and B an open ball containing I × A. We denote by C'(B) the space of real-valued continuously differentiable functions on B. Let φ ∈ C' (B) and define

$$\varphi^g = \varphi_x g+\varphi_t = \Delta\varphi g + \varphi_t. \quad (7)$$

The function φ^g is in the space C(Ω), the set of all continuous function on the compact set Ω . For each admissible pair, we have (see Rubio (1986)),

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

Let $D(I^0)$ be the space of infinitely differentiable real valued functions with compact support in I^0. For each ψ ∈ $D(I^0)$ define:

$$\psi^j(t, x(t), u(t))= x_j\dot{\psi}(t)+g_j\psi(t), \ j=1, 2,3,4. \quad (9)$$

So we have (see[8])

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

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, non classical problem which appear to have better properties in some aspects (see Rubio (1986) for more details).

3. OPTIMIZATION IN MEASURE SPACE

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

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

This well defined mapping is linear, positive, continuous and injective (see Rosenbloom (1952)), 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:

Maximize $\Lambda_p(f_0)$ (13)

Subject to:

$$\Lambda_p(\varphi^g) = \Delta\varphi, \ \varphi \in C'(B)$$

$$\Lambda_p(\psi^j) = 0, \ j=1,2,3,4; \ \psi \in D(I^0) \quad (14)$$

$$\Lambda_p(\theta^g) = \alpha_\theta , \ \theta \in C'(B_1),$$

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 the Riesz representation theorem (see Royden (1970)), there is a one-to-one correspondence between functional $\Lambda_p \in C^*(\Omega)$ and a positive Borel measure on Ω such that;

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

where C*(Ω) 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:

Maximize $\mu(f_0)$ (15)

Subject to:

$$\mu(\varphi^g) = \Delta\varphi, \ \varphi \in C'(B)$$

$$\mu(\psi^j) = o, \ j=1, 2, 3, 3; \ \psi \in D(I^0) \quad (16)$$

$$\mu(\theta^g) = \alpha_\theta, \ \theta \in C'(B_1).$$

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 $\mu \rightarrow \mu(f_0)$ under the conditions imposed (see Heydari *et al* .(2001)).

4. APPROXIMATION OF OPTIMAL CONTROL BY OPTIMAL MEASURE

The maximization 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 maximizing functional $\mu \rightarrow \mu(f_0)$ over the set Q_{M_1,M_2,M_3} of measures in $M^+(\Omega)$ satisfying

$\mu(\varphi_b^g) = \Delta\varphi_b$, b=1,2,...,M_1,

$\mu(\psi_r^j) = 0$, r=1,2,...,M_2,

$\mu(\theta_s^g) = \alpha_s$ α=1,2,...,M_3

then if M_1, M_2, M_3 tend to infinity,

$\lambda_{M_1,M_2,M_3} \equiv sup\mu(f_0)$ tends to $\lambda \equiv \sup_Q \mu(f_0)$.

Proof: see Appendix of Heydari *et al* .(2006).

It is possible to characterize a measure in the set Q_{M_1,M_2,M_3} at which the linear function $\mu(f_0)$ attains in maximum, it follows from a result of Rosenbloom (1952) that:

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

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

δ (y)(F) = F(y), y $\in$ Ω.

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.

Maximize $\sum_{k=1}^{N} \alpha_k f_0(y_k)$ (18)

Subject to:

$$\sum_{k=1}^{N} \alpha_k \varphi_b^g(y_k) = \Delta\varphi_b, \quad b=1,2,...,M_1$$

$$\sum_{k=1}^{N} \alpha_k \psi_r^j(y_k)=0, \quad j=1,2,3,4 \quad (19)$$

$$r = 1, 2, ..., M_2$$

$$\sum_{k=1}^{N} \alpha_k \theta_s(y_k) = a_s, \quad s = 1, 2, .., L,$$

$$\alpha_k \geq 0,$$

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

$Y_k = [t, x_{1_k}, x_{2_k}, x_{3_k}, x_{14_k}, u_{1_k}, u_{2_k}]$, k=1, 2, ..., 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 (1986).

5. NUMERICAL RESULT

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

$k_1=2.4\times 10^{-5}$	r=0.03	$\mu_T = 0.02$
$k_2=3\times 10^{-3}$	N=1200	$\mu_{T^*} = 0.02$
$T_{max}=1.5\times 10^{3}$	s=10	$\mu_{T^{**}} = 0.24$
		$\mu_V = 2.4$

and

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

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=980. The control functions $u_1(t)$ and $u_2(t)$ can be obtained. In fact they show the best policy of drugs treatment. In the following, Figure 1 shows the uninfected T cells populations in absence of treatment. Figure 2 and 3, show the optimal control u_1 and u_2, respectively, and Figure 4 shows the uninfected T cells population during treatment time. It should be mentioned that the procedure is considered after 800 days of infection.

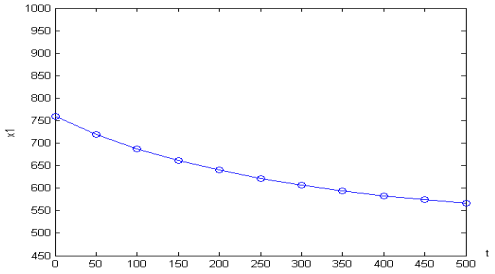


Figure 1. Uninfected T cells population in absence of treatment

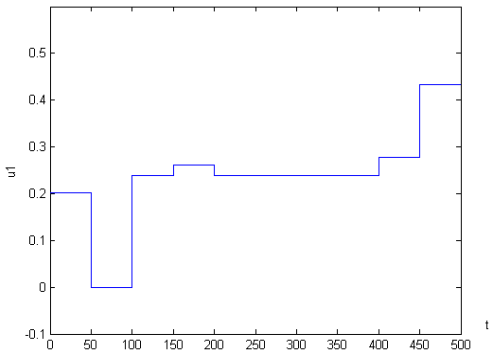


Figure 2. Optimal control u_1

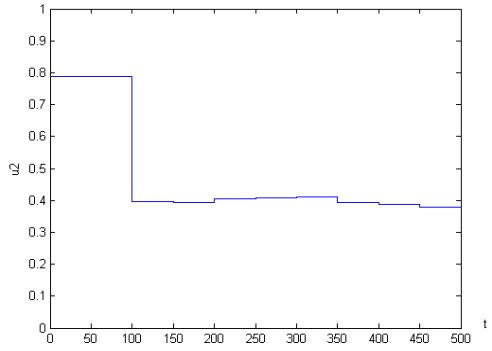


Figure 3. Optimal control u_2

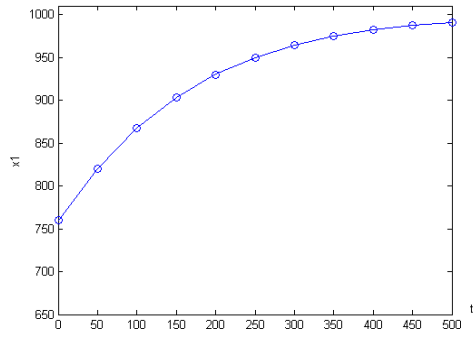


Figure 4. Uninfected T cells population during treatment time

6. 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 is not necessary to impose any convexity on objective function.

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