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OPTIMAL CONTROL OF AN HIV MODEL

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Abstract

We consider an HIV model, based on optimal control, for identifying the best treatment strategy in order to maximize the healthy cells by using chemotherapies with minimum side effects. In this paper, a new approach is introduced which transform the constraints of problem to the integral constraints. By an approximation, we obtain a finite dimensional linear programming problem which give us an approximate solution for original problem.

KeyWords: HIV Model, Optimal Control , Linear programming, Measure theory,Chemotherapy .

1- Introduction

One of the worst diseases in whole world is AIDS (Acquired Immunity Deficiency Syndrome). It is caused by the human immunodeficiency virus (HIV).

There is still much work to be completed in the search for an anti-HIV vaccine. Most 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. 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.
Once HIV enters the body, the human immune system tries to get rid of it. The invasion is reported to $CD_4^+T-cells$. The CD_4 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 CD_4^+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 the virus is converted into DNA inside the $CD_4^+T-cells$. Thus, when infected $CD_4^+T-cells$ begin to multiply to fight this pathogen, they produce more virus (see [1], [3], [5], [6]).

2. Statement of the Model

We consider a model which presented by Gumel et al.[3]describes the interaction of HIV and the immune system of the body. In this model, the variables are T_4,T_i and V present the number of healthy $CD_4^+T-cells$, infected $CD_4^+T-cells$ and free viruses respectively. The number of T_4 cells in the person is affected by the rate
of natural growth of T_4 cells, the rate of production of $CD_4^+T-cells$ due to the presence of the virus(note that if the virus gets into the body, T_4 cells multiply themselves to the maximum level to resist the virus), the natural death rate and rate of infection of healthy cells due to the presence of the virus.
The number of T_i cells depend on the rate of production of infected cells from actively infected $CD_4^+T-cells$, the rate at which the virus infects free cells, natural death, the action of anti-HIV cyto-toxic T lymphocyte cells and the viral lysis. Similarly, the population of the virus is determined by the production rate of viruses by actively infected T_4 cells, the rate at which the virus enters into the rested T_4 cells and the natural death rate.
In this model, the variables are T_4,T_i and V represent the number of healthy $CD_4^+T-cells$, infected $CD_4^+T-cells$ and free viruses, respectively.

$$\frac{dT_4(t)}{dt} = \rho s + rT_4(t)V(t) - \gamma_1 T_4(t) - \alpha k_v (1-u_1(t))T_4(t)V(t), \quad (1)$$

$$\frac{dT_i(t)}{dt} = \alpha k_v (1-u_1(t))T_4(t)V(t) + rk_v (1-u_1(t))T_4(t)V(t) - \gamma_2 T_i(t) \quad (2)$$
$$-\alpha k_c k_v T_4(t)V(t) - rk_c k_v T_4(t)V(t),$$

$$\frac{dV(t)}{dt} = N(1-L)(1-u_2(t))T_i(t) - \gamma_3 V(t) - (1-\alpha)k_t T_4(t)V(t), \quad (3)$$

with given initial values for T_4, T_i and V at t_0 respectively by T_4^0, T_i^0 and V^0.
Define the objective functional

$$J(u_1,u_2) = \int_{t_0}^{tf} (T_4(t) - (A_1(u_1(t))^2 + A_2(u_2(t))^2))dt. \quad (4)$$

In other words, we are maximizing the benefit based on the healthy T cells count and minimizing the cost based on the percentage effect chemotherapy given (i.e. u_1 and u_2). The parameters $A_1, A_2 \geq 0$ represent the weights on the benefit and cost.
The goal is to 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 is the control set defined by

$$U = \{u = (u_1,u_2) : u_i \text{ measurable}, \quad 0 \leq u_i(t) \leq 1, \quad t \in [t_0, t_f] \quad \text{for } i = 1,2\}.$$

In the above model, parameters and constants, defined as follows:

$\rho =$ the value of functioning thymus,

$s =$ rate of supply of $CD_4^+T - cells$

$r =$ rate of production of $CD_4^+T - cells$ due to the HIV,

$\gamma_1 =$ natural death rate of $CD_4^+T - cells$,

$k_v =$ rate of infection of activated $CD_4^+T - cells$,

$\gamma_2 =$ natural death rate of infected $CD_4^+T - cells$,

$\gamma_3 =$ natural death rate of free viruses,

$k_c =$ rate of Cyto-toxic T lymphocytes action viral lysis,

$N =$ rate of production of HIV from actively infected $CD_4^+T - cells$,

$k_t =$ rate of viral entry quiescent resting $CD_4^+T - cells$,

In the next section the problem is changed to a problem in measure space, where we interface with a linear programming problem.

In the following we replace the problem by another one in which the maximum of the objective functional (4) 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 [2],[7],[8],[10] and the pioneering work of Rubio ([9]) as well.

Let $\Omega = J \times A \times U$, where $J = [t_0, t_f]$ and $\forall t \in J, x = [x_1(t), x_2(t), x_3(t)]$ or $x = [T_4(t), T_i(t), V(t)] \in A$ is the trajectory of the controlled system and A is a compact set of $R^3, \forall t \in J, u(t) = [u_1(t), u_2(t)] \in U$ is the control and U is a compact set of R^2. we may rewrite optimization problem (1) -(4) as the following reduced form:

$$\max \quad J(x,u) = \int_{t_0}^{t_f} (x_1(t) - (A_1(u_1(t))^2 + A_2(u_2(t))^2))dt \tag{5}$$

$$s.t. \quad \dot{x}(t) = g(t,x,u) \quad , \quad t \in J^0 \tag{6}$$

3. Classical Control problems

We shall say that a trajectory-control pair $p = [x(.), u(.)]$, is admissible if the following conditions hold:

i) $x(t) \in A, \quad t \in J$.

ii) $u(t) \in U, \quad t \in J$.

iii) The boundary conditions $x(t_a) = x_a$ and $x(t_b) = x_b$ is satisfied, where x_b is unknown.

iv) The pair p satisfies the differential equation (6) *a.e.* on J^0.

Let B an open ball in R^4 containing $J \times A$. Let $C'(B)$ be the space of all real-valued continuously differentiable functions on B which are bounded on B together with their first derivatives. Let $\phi \in C'(B)$, and define function ϕ^g as follows:

$$\phi^g(t,x,u) = \phi_x(t,x)g(t,x,u) + \phi_t(t,x) \qquad (t,x,u) \in \Omega \tag{7}$$

The function ϕ^g is in the space $C(\Omega)$ of all real-valued continuous functions defined on the compact set Ω. Thus we have

$$\int_J \phi^g(t,x,u)dt = \int_J (\phi_x(t,x)\dot{x} + \phi_t(t,x))dt$$
$$= \int_J \dot{\phi}(t,x)dt = \phi(t_b,x_b) - \phi(t_a,x_a) \qquad (8)$$
$$= \Delta\phi \qquad ,\forall \phi \in C'(B)$$

Let $D(J^O)$ be the space of infinitely differentiable real-valued functions with compact support in J^O. Define

$$\psi_j(t,x,u) = x_j\psi'(t) + g_j(t,x,u)\psi(t) \qquad j = 1,2,...,n \quad \psi \in D(J^0). \qquad (9)$$

Then (see [9])

$$\int_J \psi_j(t,x,u) = 0 \qquad j = 1,2,...,n \quad \psi \in D(J^0).$$

Put

$$\phi(t,x,u) = \theta(t) \qquad (t,x,u) \in \Omega \qquad (10)$$

that is, a function which depends on the time variable only; then

$$\phi^g(t,x,u) = \dot{\theta}(t) \qquad ,(t,x,u) \in \Omega \qquad (11)$$

If p is an admissible pair, the equality (10) with the choice (11) for the function ϕ implies that

$$\int_J \phi^g(t,x,u)dt = a_\theta \qquad ,\theta \in C'(B) \qquad (12)$$

Where a_θ is the integral of f over J, independent of x and u. Now, the mapping

$$\Lambda_p : F \to \int_J F(t,x(t),u(t))dt, \quad F \in C(\Omega). \qquad (13)$$

Defines a positive, linear functional on $C(\Omega)$.
By the Riesz representation theorem, there exists a unique positive Radon measure μ on Ω which

$$\Lambda_p(F) = \int_\Omega F(t,x,u)dt = \int_\Omega Fd\mu = \mu(F), \quad F \in C(\Omega). \qquad (14)$$

Let $M^+(\Omega)$ be the set of all positive Radon measure on Ω. Define the positive Radon measure $\mu \in M^+(\Omega)$ such that maximizes the following linear functional

$$I(\mu) = \mu(f_0) \tag{15}$$

subject to

$$\mu(\phi^g) = \Delta\phi, \qquad \phi \in C'(B), \tag{16}$$

$$\mu(\psi_j) = 0, \qquad j = 1,2,...,n \qquad \psi \in D(J^0), \tag{17}$$

$$\mu(\theta^g) = a_\theta, \qquad \theta \in C_1(\Omega), \tag{18}$$

We define Q to be the set of all measures in $M^+(\Omega)$ that satisfy equalities (16)-(18) than we can show that there exists an optimal measure μ^* in the Q for which $\mu^*(f_0) \le \mu(f_0)$ for all $\mu \in Q$ (see [8]).
This problem is an infinite-dimensional linear programming problem and all the functions in (15)-(18) are linear with respect to measure μ. We obtain the approximate solution of this problem by the solution of a finite-dimensional linear program.

In this section, we are limiting constraint (15)-(18) as follows:
i) We choose the function $\phi(t,x) = x_i^r, r = 1,2,...,M_1$. and $i = 1,2,...,n$. Then we have $\phi^g = r x_i^{r-1} g_i(t,x,u)$.
ii) We consider

$$\psi_r(t) = \sin[\frac{2\pi r(t-t_a)}{\Delta t}], \qquad r = 1,2,...,M_{21},$$

$$\psi_r(t) = 1 - \cos[\frac{2\pi r(t-t_a)}{\Delta t}], \qquad r = M_{21}+1,...,2M_{21},$$

Where $\Delta t = t_b - t_a, M_2 = 2nM_{21}$. We shall call χ_h, h=1,2,..., the sequence of functions of the type

$$\psi_r(t,x,u) = x_r \dot{\psi}(t) + g_r(t,x,u)\psi(t), \qquad r = 1,2,...,M_2.$$

iii) For the third type of constraints, we choose

$$\theta_s = \begin{cases} 1 & t \in J_s \\ 0 & otherwise. \end{cases}$$

with $J_s = [\frac{t_a + (s-1)\Delta t}{L}, \frac{t_a + s\Delta t}{L}]$ $s = 1,2,....,L$ (see[9]).
In the previous section, we have limited the number of constraints in the original linear program; the underlying space is not, however, finite-dimensional.

Definition: Let A be borel set and z a point in the space Ω. The Radon measure δ_z will be called atomic measure if

$$\delta(z)(A)=\begin{cases}1 & z\in A\\ 0 & o.w\end{cases}$$

Now we approximate μ^* by a linear combination of atomic measure in following proposition of [9].

Proposition: Let ω be a countable dense subset of Ω. Given $\varepsilon>0$, a measure $\nu\in M^+(\Omega)$ can be found such that $|(\mu^*-\nu)f_0|<\varepsilon$, and $|(\mu^*-\nu)\phi_j^g|<\varepsilon$, $j=1,2,...,M$, and the measure ν has the form

$$\nu=\sum_{k=1}^{M}\alpha_k\delta(z^k),$$

where $\delta(z^k)$ is atomic measure, $z^k\in\omega,\alpha_k\geq 0,\quad k=1,2,...,M$. □

The infinite-dimensional linear programming problem in (15)-(18) can be approximated by the following linear programming problem in which $z_j, j=1,2,...,N$ belongs to a dense subset of Ω.

$$\max \quad \sum_{j=1}^{N}\alpha_j f_0(z_j), \tag{19}$$

$$s.t \quad \sum_{j=1}^{N}\alpha_j\varphi_i^g(z_j)=\Delta\varphi_i,\quad i=1,2,...,M_1, \tag{20}$$

$$\sum_{j=1}^{N}\alpha_j\chi_A(z_j)=0,\quad h=1,2,...,M_2, \tag{21}$$

$$\sum_{j=1}^{N}\alpha_j\theta_s(z_j)=a_f,\quad s=1,2,...,L, \tag{22}$$

$$\alpha_j\geq 0,\quad j=1,2,...,N,$$

where $z_j=(t_j,y_j,x_j)\in\omega, j=1,2,...,N$ are constructed by dividing the sets *J*, *A*, *U* into the number of equal subsets.

By using manner similar (see [9]) we can approximate the optimal pair $[x(.),u(.)]$ by considering $\lambda_k=\sum_{j\leq k}\alpha_j$ such that if we set $t\in(\lambda_{k-1},\lambda_k)$ then $u(t)\approx u_k$ and the trajectory $x(.)$ will be obtained by the equation (6).

4. Computational Results

We now present results from solving model which assumed the parameters and initial values the same Gumel [3] as follows:

s =10, r =0.03, $k_v = 0.4$, N=1000, $k_c = 0.5$, L=0.25, $\rho = 0.9, \alpha = 0.2, k_t = 0.8$, $\gamma_1 = \gamma_2 = 0.01, \gamma_3 = 3.07$ with $T_4(0) = 1000, T_i(0) = 10$ and $V(0) = 10000$.
For more clearness, it is better to present these results through graphs. Figures 1 and 2 show Healthy cells before and after treatment and Viral load before and after treatment, respectively. Figures 3 and 4 show the optimal control u_1 and u_2, respectively. In fact they show the best policy of drugs treatment.

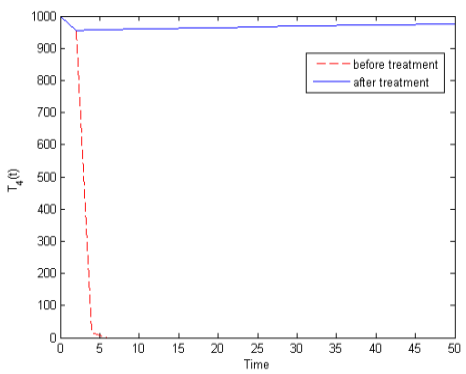

Fig.1. Healthy cells before and after treatment

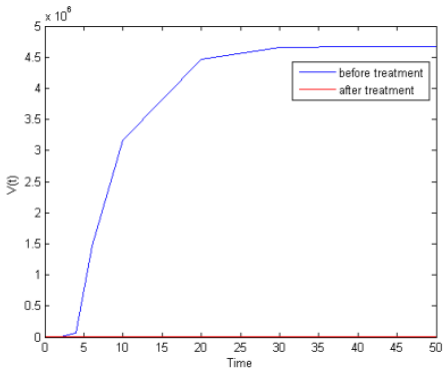

Fig.2.Viral load before and after treatment

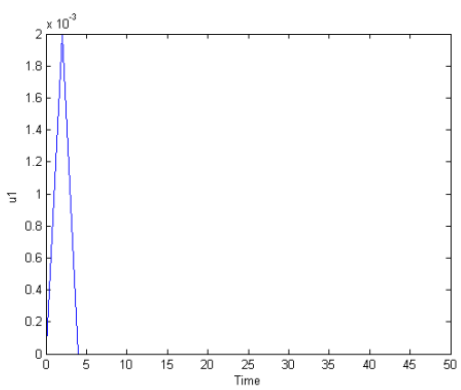

Fig.3.The first control

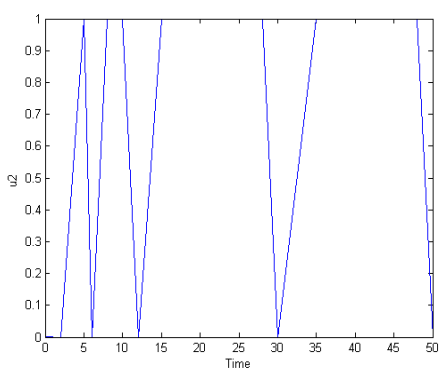

Fig.4. The second contro

5. Conclusion

In this paper an applicable and practical method for solving nonlinear optimal control problems is presented that we developed it for best chemotherapy in treatment of HIV which this method is based on linear technique. It seems that by using this method, we can obtain fine results by considering a linear treatment of the nonlinear differential equations. Moreover, it is not necessary to impose any restriction on objective function of model.

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