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A different approach of optimal control on an HIV immunology model

Masoud Roshanfekr [a,c,*], Mohammad Hadi Farahi [b,1], Raheleh Rahbarian [d,2]

[a] *Department of Mathematics, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran*
[b] *School of Sciences, Islamic Azad University, Mashhad branch, Mashhad, Iran*
[c] *Department of Science, Farhangian University, Daneshvar Tarbiat Moalem of Neyshabur, Iran*
[d] *Department of Science, Payame Noor University, Iran*

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Abstract A system of ordinary differential equation, which describes the interaction of HIV and T cells in the immune system, is utilized, and optimal representing drug treatment strategies of this model are explored. Control model, in the sense of an optimal control problem shows the strategy of chemotherapy treatment setting through a dynamic treatment. In this model, the optimal control pair represents the percentage effect the chemotherapy on the $CD4^+T$ cells and virus production. An objective function characterized based on maximizing T cells and minimizing the systemic cost of the chemotherapy. The optimal control could characterize by using Pontryagin's Maximum Principle. Then by using an embedding method, we transfer the problem in to a modified problem in measure space. This transformation is an injection; one-one mapping, so the optimal pair and its image under the transformation could be identified. New problem could be solved by a linear programming problem.

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). 34.3 million People live with HIV infection today that more than 24 million are in the developing world [1].

There is still much work to be completed in the search for an anti-HIV vaccine. Set 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 [2]. The new treatments are aimed at reducing viral population and improving the immune response [1,3]. This brings new hope to the treatment of HIV infection, and we

* Corresponding author at: Department of Mathematics, Neyshabur Branch, Islamic Azad University, Neyshabur, Iran. Tel.: +98 0915 1500968; fax: +98 0551 2224661.
E-mail addresses: ma_roshanfekr@yahoo.com (M. Roshanfekr), Farahi@math.um.ac.ir (M.H. Farahi), ra_rahbarian@yahoo.com (R. Rahbarian).
[1] Tel.: +98 0915 1114266.
[2] Tel.: +98 0915 3518157; fax: +98 0551 2224661.

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are exploring strategies for such treatments using optimal control techniques.

There are two kind drugs for treatment of HIV infection [1,4], the first kinds effect on the virus production and reduces the virus production, the second kinds effect on the $CD4^+T$ cells production and access $CD4^+T$ cells production [1,4]. In this paper, it is presented a control model for medical control of the chemotherapy treatment that uses the above two controls. Pathologists attempt to obtain drugs that have capability both works (access $CD4^+T$ cells production and reduce virus production). However some achievements obtained in this case, but still don't beget drugs that do this action [5].

Here our purpose was the representation control's model that control both cases and minimizing the cost of treatment.

2. The mathematical model

To begin the control procedure, it is necessary to have a model that describes the infected scenario. In [2] a simple model is given which simulates the interaction of immune system with HIV. This model is used here.

Let T; V represent the concentration of the uninfected CD_4^+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't be continued for infinite time period due to hazardous side effects) satisfying $0 \leqslant a_i \leqslant u_i \leqslant b_i < 1\, i = 1{,}2$ For most of HIV chemotherapy drugs, the length of treatment is less then 500 days [6].

The state system is

$$\begin{aligned}\frac{dT}{dt} &= s_1 - \frac{s_2 V(t)}{B_1 + V(t)} - \mu T(t) - kV(t)T(t) + u_1(t)T(t)\\ \frac{dV}{dt} &= \frac{g(1-u_2(t))V(t)}{B_2 + V(t)} - cV(t)T(t)\end{aligned} \tag{1}$$

Satisfying $V(0) = V_0$, $T(0) = T$, where T represents the concentration of CD_4^+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, $\frac{g(1-u_2(t))V(t)}{B_2+V(t)}$ 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 Table 1.

Table 1 The definitions and numerical data for the parameters [3].

Parameters and constant	Values
s_1	$2\ d^{-1}\ \mathrm{mm}^3$
s_2	$1.5\ d^{-1}\ \mathrm{mm}^3$
μ	$0.002\ d^{-1}$
k	$2.5\times10^{-2}\ d^{-1}\ \mathrm{mm}^3$
g	$30\ d^{-1}\ \mathrm{mm}^{-3}$
c	$0.007\ cd^{-1}\ \mathrm{mm}^{-3}$
b_1	14
b_2	1

The objective functional to be maximized is

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

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

Is recommend that the reader see [2–4] for a more complete background and analysis of the model.

3. Application of measure theory in optimal control problem

3.1. Further analysis of the classical control problem

In the section it is followed from Rubio [7].

Consider:

(i) A real closed interval $J = [t_a,\ t_b]$, with $t_a < t_b$. the interior of this interval in the real line will be denoted by $J^0 = (t_a,\ t_b)$.
(ii) A bounded, closed, path wise–connected set A in R^n.
(iii) Two elements of A, x_a and x_b, which are to be the initial and final states of the trajectory of the controlled system.
(iv) A bounded, closed subset U of R^m.
(v) Let $\Omega = J \times A \times U$, and f_0: $\Omega \to R$, g_i: $\Omega \to R$; $i = 1, 2, \ldots, n$. a continuous function.

Consider the differential equation $\dot{x}(t) = g(t, x(t), u(t)),\quad t \in J^0$,

Where the trajectory function $x(t) \in A$, $t \in J$ is a absolutely continuous and the control function $u(t) \in U$, $t \in J$ is Lebesgue-measurable.

Let $p = [x(.), u(.)]$ Be an admissible pair, and B an open ball in R^{n+1} containing $J \times A$; we denote by $C'(B)$ the space of real-valued continuously differentiable functions on B.

Let $\phi \in C'(B)$, and define

$$\begin{aligned}&\phi^g(t,x,u) = \phi_x(t,x)^t g(t,x,u) + \phi_t(t,x).\\ &\phi_x(t,x) = \left(\frac{\partial\phi}{\partial x_1}, \frac{\partial\phi}{\partial x_2}, \ldots, \frac{\partial\phi}{\partial x_n}\right), \quad (t,x,u) \in \Omega\end{aligned} \tag{3}$$

Since $p = [x(.), u(.)]$ is an admissible pair,

$$\begin{aligned}\int_J \phi^g[t,x(t),u(t)]dt &= \int_J \{\phi_x[t,x(t)]x'(t) + \phi_t[t,x(t)]\}dt\\ &= \int_J \dot{\phi}[t,x(t)]dt\\ &= \phi(t_b,x_b) - \phi(t_a,x_a) \equiv \Delta\phi,\end{aligned} \tag{4}$$

For all $\phi \in C'(B)$.

Let $D(J^0)$ be the space of infinitely differentiable real–valued functions with compact support in J^0.

Define

$$\psi_j(t,x,u) = x_j\psi'(t) + g_j(t,x,u)\psi(t), \quad j = 1,2,\ldots,n, \quad \psi \in D(J^0). \tag{5}$$

Then, if $p = [x(.), u(.)]$ is an admissible pair, we have, for $j = 1, 2, \ldots, n$ and $\psi \in D(J^0)$,

$$\int_J \psi_j[t,x(t),u(t)]dt = \int_J x_j\psi'(t)dt + \int_J g_j[t,x(t),u(t)]\psi(t)dt = x_j(t)\psi(t)|_J + \int_J \left\{x_j'(t) - g_j[t,x(t),u(t)]\right\}\psi(t)dt = 0. \tag{6}$$

Put $\phi(t, x, u) = \theta(t)$. $(t, x, u) \in \Omega$, that is a function which depends on the time variable only; then $\phi^g(t, x, u) = \theta'(t)$, if $p = [x(.), u(.)]$ is an admissible pair, then the equality (4) for the function ϕ implies that

$$\int_J f[t,x(t),u(t)]dt = a_f.$$

3.2. Transfer the problem into measure space

Now consider the mapping: Λ_p: $C(\Omega) \to R$

$$\Lambda_p(f) = \int_J f[t,x(t),u(t)]dt. \quad f \in C(\Omega) \tag{7}$$

This well defined mapping is linear, positive, continuous, and injection (see Rubio [6]) therefore, can be identified pairs $p = [x(.), u(.)]$ with the linear functional Λ_p.

Some authors define such a functional as positive Radon measure (see Rubio [7]),

Using this approach, the above optimal control now can be written as follows:

$$\begin{aligned} &\text{Minimize } \Lambda_p(f_0) \\ &\text{Subject to}: \Lambda_p(\phi^g) = \Delta\phi; \quad \phi \in C'(B). \\ &\qquad \Lambda_p(\psi_j) = 0; \quad j = 1,2,\ldots,n \quad \psi \in D(J^0) \\ &\qquad \Lambda_p(f) = a_f; \quad f \in C_1(\Omega) \end{aligned} \tag{8}$$

A Radon measure on Ω can be identified with a regular Borel measure on this set (see Rubio [6]), thus $\Lambda_p(f) = \int_\Omega f d\mu = \mu(f)$ $f \in C(\Omega)$.

The space of all positive Radon measures on $C(\Omega)$ will be denoted by $M^+(\Omega)$.

We seek a measure in $M^+(\Omega)$, to be normally denoted by μ^*, which minimizes

The functional

$$\mu \in M^+(\Omega) \to \mu(f_0) \in R \tag{9}$$

Subject to the constraints

$$\begin{aligned} &\mu(\phi^g) = \Delta\phi \quad \phi \in C'(B)\mu(\psi_j) = 0 \quad j = 1,2,\ldots,n \;\&\; \psi \in D(J^0). \\ &\mu(f) = a_f \quad f \in C_1(J^0). \end{aligned} \tag{10}$$

The existence of the optimal measure for problem (9) and (10) is based on analysis described in Farahi et al. [8].

3.3. Approximation

We considering the minimization of $\mu \to \mu(f_0)$ over a subset of $M^+(\Omega)$ defined by requiring that only a finite number of the constraints in (10) are satisfied.

Consider the first set of equalities in (10). Let the set $\{\phi_i| i = 1, 2, \ldots\}$ be such that the linear combinations of the function $\phi_i \in C'(B)$ are uniformly dense in the space

$C'(B)$. For instance, these functions can be taken to be monomials in the components of the n-vector x and the variable t.

Consider the function in $D(J^0)$ defined by

$$\psi(t) = \begin{cases} \sin[2\pi r(t-t_a)/\Delta t] & t \in J^0 \\ 0 & t \notin J^0 \end{cases}, \qquad \psi(t) = \begin{cases} 1-\cos[2\pi r(t-t_a)/\Delta t] & t \in J^0 \\ 0 & t \notin J^0 \end{cases} \tag{11}$$

where $\Delta t = t_b - t_a$ and $r = 1, 2, 3, \ldots$. We shall call $\{\chi_h| h = 1, 2, \ldots\}$ the sequence of functions of the type $\psi_j(t, x, u) = x_j\psi'(t) + g_j(t, x, u)\psi(t)$. $j = 1, 2, \ldots, n$, defined in (10), when the functions $\psi(t)$ are the sine and cosine functions (14) defined above and

$j = 1,2,\ldots,n$

Theorem 3.1. *Consider the linear program consisting in minimizing the function $\mu \to \mu(f_0)$ over the set $Q(M_1, M_2)$ of measures in $M^+(\Omega)$ satisfying*

$$\begin{aligned} &\mu(\phi_i^g) = \Delta\phi_i \quad i = 1,2,\ldots,M_1 \\ &\mu(\chi_h) = 0 \qquad h = 1,2,\ldots,M_2 \end{aligned} \tag{12}$$

As M_1 and M_2 tend to infinity, $\eta(M_1, M_2) = \inf \mu(f)_{Q(M_1,M_2)}$ tends to $\eta = \inf \mu(f_0)_Q$.

For proof see Farahi, et al. [8,9].

The number of constraints in the original linear program was limited; the underling space is not, however, finite-dimensional. It is possible, though, to develop a finite-dimensional linear program whose solution can be used to construct one for the problem of minimizing $\mu \to \mu(f_0)$ over the set (12).

z was written for the triple $(t, x, u) \in \Omega$. A unitary atomic measure with support the singleton set $\{z\}$, to be denoted by $\delta_z(A) = \begin{cases} 1 & z \in A \\ 0 & z \notin A \end{cases}$, is characterized by $\delta(z)(F) = F(z)$, $F \in C(\Omega)$, $z \in \Omega$.

It is possible to characterize a measure in the set $Q(M_1, M_2)$ at which the linear function $\mu \to \mu(f_0)$ attains its minimum.

Theorem 3.2. *The measure μ^* in the set $Q(M_1, M_2)$ at which the function $\mu \to \mu(f_0)$ attains its minimum has the form $\mu^* = \sum_{i=1}^{M_1+M_2} \alpha_i^* \delta_{z_i^*}$.*

With the triples $z_i^* \in \Omega$, and the coefficient $\alpha_i^* \geqslant 0,\ i = 1,2,\ldots,M_1+M_2$.

For proof see Rubio [7].

The measure–theoretical optimization problem is equivalent to a nonlinear optimization problem; we shall take a different *road this time, and try somehow to preserve the essential linearity of the problem. The answer lies in approximating this support, by introducing a set dense in Ω:*

Theorem 3.3. *Let ω be a countable dense subset of Ω. Given $\varepsilon > 0$, a measure $\bar{v} \in M^{+}(\Omega)$ can be found such that*

$$|(v^* - \bar{v})f_0| \leqslant \varepsilon$$
$$|(v^* - \bar{v})\phi_i^g| \leqslant \varepsilon \quad i = 1, 2, \ldots, M_1.$$
$$|(v^* - \bar{v})\chi_h| \leqslant \varepsilon \quad h = 1, 2, \ldots, M_2.$$

The measure $\bar{v}$ has the form $\bar{v} = \sum_{k=1}^{M_1+M_2} \alpha_i^* \delta(z_k)$. with the triples $z_i^* \in \omega$, and the coefficient $\alpha_i^* \geqslant 0, i = 1, 2, \ldots, M_1 + M_2$.

For proof see Rubio [7].

These results suggest that the following linear program should be considered. Given $\varepsilon > 0$ and z_k, $z_k \in \omega$, $k = 1, 2, \ldots, N$, where ω is a dense subset of Ω,

$$\begin{aligned} &Min \quad \sum_{j=1}^{N} \alpha_j f_0(z_j) \\ &\text{Subject to :} \quad -\varepsilon \leqslant \sum_{j=1}^{N} \alpha_j \phi_i^g(z_j) - \Delta\phi \leqslant \varepsilon \quad i = 1, 2, \ldots, M_1 \\ &\qquad\qquad\qquad -\varepsilon \leqslant \sum_{j=1}^{N} \alpha_j \chi_h(z_j) \leqslant \varepsilon \quad h = 1, 2, \ldots, M_2 \end{aligned} \tag{13}$$

Note that the elements $z_k \in \omega$, $k = 1, 2, \ldots, N$, are fixed; the only unknowns are the numbers α_i, $i = 1, 2, \ldots, N$. There are N unknowns and $2(M_1 + M_2)$ inequalities in this linear programming problem.

We have chosen functions, θ_s, $s = 0, 1, 2, \ldots, L$ as $\theta_s(t) = \begin{cases} 1 & t \in J_s \\ 0 & t \notin J_s \end{cases}$, with $J_s = [t_a + (s-1)(t_b - t_a)/L, t_a + s(t_b - t_a)/L]$

Now consider the optimal control problem

$$\begin{aligned} &\min \quad I = \int_{t_a}^{t_b} f_0[t, x(t), u(t)]dt \\ &\quad s.t \quad \dot{x}(t) = g_i[t, x(t), u(t)] \quad i = 1, 2, \ldots, n \end{aligned}$$

Let $\Omega = J \times A \times U$, divide the region Ω to N grids Ω_K, so we have: $\Omega = \bigcup_{K=1}^{N} \Omega_K$, and choose $z_K \in \Omega_K$, where $z_k = (t_k, x_k, u_k)$, $k = 1, 2, \ldots, N$. To define ϕ's, ψ's and θ's functions, we have chosen M_1, M_2 and L of these functions respectively, thus: $\phi_i^g(t, x, u) = \frac{\partial \phi_i(t,x)}{\partial x} \cdot g(t, x, u) \quad i = 1, 2, \ldots, M_1$

We define χ_h functions as follows:

$$\psi_j^r(t, x, u) = x_j \psi_r'(t) + g_j(t, x, u)\psi_r(t)$$

where $(t, x, u) \in \Omega$, $j = 1, 2, \ldots, n$, $r = 1, 2, \ldots, 2M_2$, and we have:

$$\begin{cases} \psi_r(t) = \sin[2\pi r(t - t_0)/\Delta t] & r = 1, 2, \ldots M_2 \\ \psi_r(t) = 1 - \cos[2\pi(r - M_{21})(t - t_0)/\Delta t] & r = M_{21} + 1, \ldots, 2M_2 \end{cases} \tag{14}$$

Where $M_2 = 2M_{21}$, $h = 1, 2, \ldots, M_2$, $\Delta t = t_1 - t_0$,

Now the optimal control problem (9) and (10) is approximated by the following finite-dimensional linear-programming problem:

$$\begin{aligned} &\min \quad \sum_{j=1}^{N} \alpha_j f_0(z_j) \\ &s.t: \quad \sum_{J=1}^{N} \alpha_j \phi_i^g(z_j) = \Delta\phi_i \quad i = 1, 2, \ldots, M_1 \\ &\qquad \sum_{j=1}^{N} \alpha_j \chi_h(z_j) = 0 \qquad h = 1, 2, \ldots, M_2 \\ &\qquad \sum_{j=1}^{N} \alpha_j \theta_s(z_j) = a_s \qquad s = 1, 2, \ldots, L \end{aligned} \tag{15}$$

where $\Delta\phi_i = \phi_i(t_b, x_b) - \phi_i(t_a, x_a)$

4. Computational method

In the following the problem (1) was replaced by another one in which the maximum of the functional (2) calculated over a set of positive Radon-measure to be defined as follows. We follow the analysis of the previous section.

We consider again state system (1) and for simplicity, it was assumed that:. $V = x_2$, $T = x_1$ Hence (1) change to:

$$\begin{aligned} \frac{dx_1}{dt} &= s_1 - \frac{s_2 x_2}{B_1 + x_2} - \mu x_1 - k x_2 x_1 + u_1(t) x_1 \\ \frac{dx_2}{dt} &= \frac{g(1 - u_2(t)) x_2}{B_2 + x_2} - c x_2 x_1 \end{aligned} \tag{16}$$

Putting parameters from Table 1 we have

$$\begin{aligned} \tfrac{dx_1}{dt} &= 2 - \tfrac{1.5x_2}{0.007 + x_2} - 0.002x_1 - 0.00025x_2x_1 + u_1(t)x_1 \\ \tfrac{dx_2}{dt} &= \tfrac{30(1 - u_2(t))x_2}{14 + x_2} - 0.007cx_2x_1 \end{aligned}$$

where the objective functional is as follows:

$$J(u_1, u_2) = \int_0^{t_f} \left[x_1 - \left(A_1 u_1^2(t) + A_2 u_2^2(t)\right)\right] dt. \\ A_1 = 250000, \ or\ 500000, \ and\ A_2 = 75 \tag{17}$$

The initial values of x_1, x_2 are given, while the final values of these variables are indefinite. Define $\dot{x} = g(t, x, u)$ where $x = \begin{bmatrix} x_1 \\ x_2 \end{bmatrix}$, $g = \begin{bmatrix} g_1 \\ g_2 \end{bmatrix}$ so we have

$$\begin{aligned} g_1(t, x, u) &= \frac{dx_1}{dt} = 2 - \frac{1.5x_2}{0.007 + x_2} - 0.002x_1 - 0.00025x_2x_1 + u_1(t)x_1 \\ g_2(t, x, u) &= \frac{dx_2}{dt} = \frac{30(1 - u_2(t))x_2}{14 + x_2} - 0.007x_2x_1 \end{aligned} \tag{18}$$

Here the optimal control problems (14) and (15) were approximated by a finite dimensional linear programming problem. Suppose $t \in J = [t_0, t_1]$, $x_i \in A_i$; $i = 1, 2 u_1 \in U_1$ and $u_2 \in U_2$. It was assumed that $m_1 = 10$, $m_2 = 5$, $m_3 = 5$, $m_4 = 6$ and $m_5 = 6$, are the number of partitions respect to J, A_1, A_2, U_1 and U_2, respectively. We define:

$$N = m_1 \times m_2 \times m_3 \times m_4 \times m_5 = 9000$$

Let $\Omega = J \times A_1 \times A_2 \times U$, where $U = (U_1, U_2)$ is control function pair and g: $\Omega \to R^5$ is the continuous function. Now divide the region Ω to N grids Ω_K, so we have:

$\Omega = \bigcup_{K=1}^{N} \Omega_K$, and choose $z_K \in \Omega_K$, where $z_k = \left(t_k, x_1^k, x_2^k, u_1^k, u_2^k\right)$, $k = 1, 2, \ldots, 9000$.

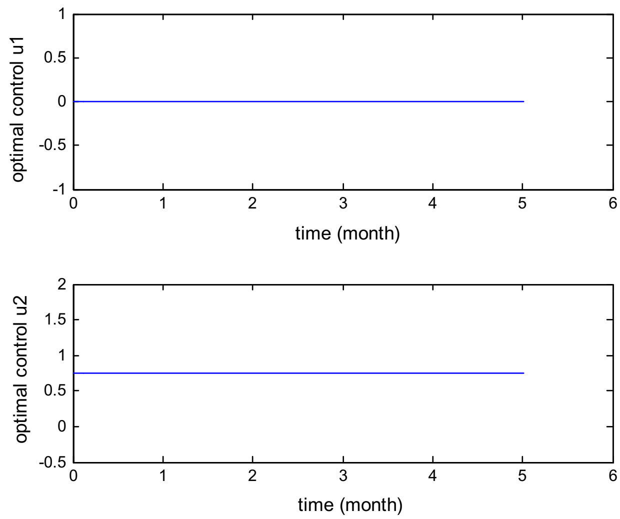

Figure 1 Optimal controls u_1, u_1 for $A_1 = 250000$.

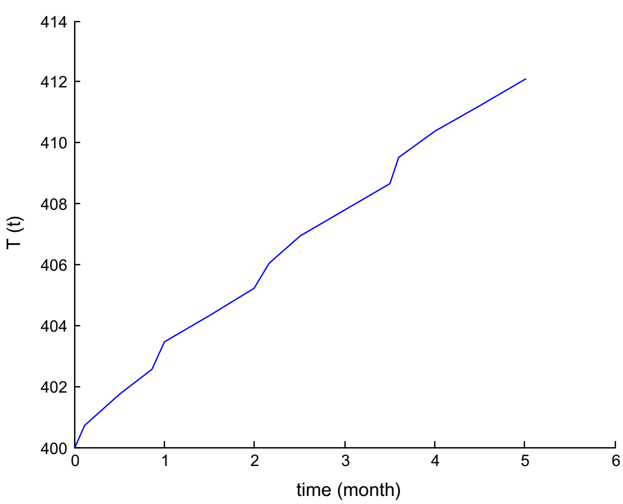

Figure 2 T cell count for $A_1 = 250000$.

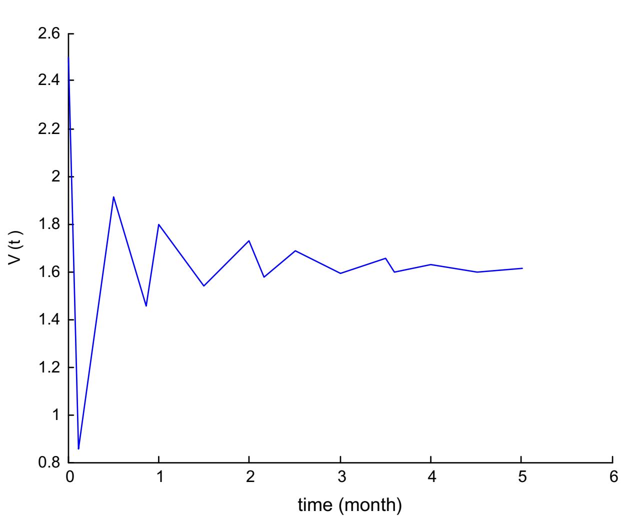

Figure 3 V cell count for $A_1 = 250000$.

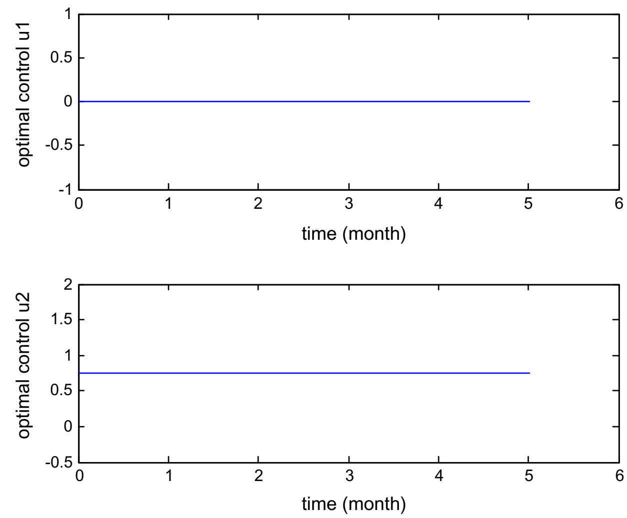

Figure 4 Optimal controls u_1, u_1 for $A_1 = 500000$.

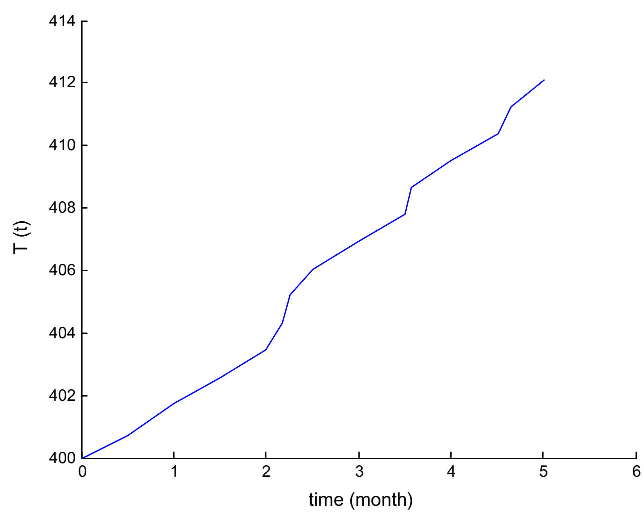

Figure 5 T cell count for $A_1 = 500000$.

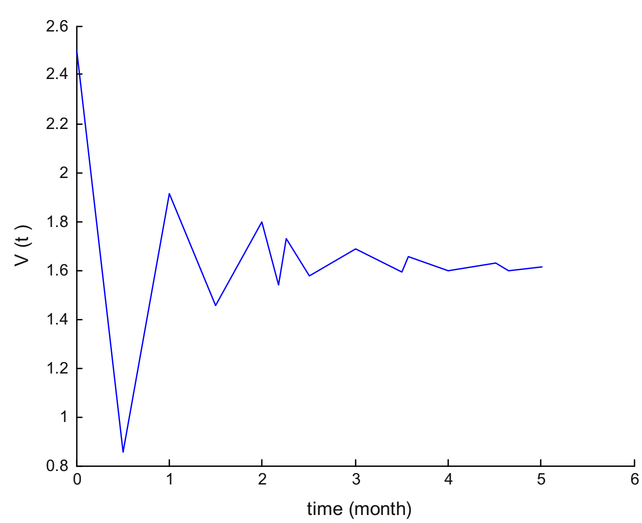

Figure 6 V cell count for $A_1 = 500000$.

The functions ϕ's, ψ's and θ's are defined as in [7].

So, the approximated linear programming problem which approximates the action of optimal control problem would be:

$$
\begin{aligned}
\max\ & \sum_{j=1}^{9000} \alpha_j \left[\int_0^{t_f} \left[x_1^j - \left(A_1 u_1^2(t) + A_2 u_2^2(t) \right) \right] dt \right] \\
\text{s.t}\ & -\sum_{j=1}^{9000} \alpha_j \left(2 - \frac{1.5 x_2^j}{0.007 + x_2^j} - 0.002 x_1^j - 0.00025 x_2^j x_1^j + u_1^j(t) x_1^j \right) + \beta_1^j = 400 \\
& -\sum_{j=1}^{9000} \alpha_j \left(\frac{30\left(1 - u_2^j(t)\right) x_2^j}{14 + x_2^j} - 0.007 x_2^j x_1^j \right) + \beta_2^j = 2.5 \\
& \sum_{j=1}^{9000} \alpha_j \left(\frac{2\pi i x_1^j}{5} \cos(2\pi i t_j/5) + g_1 \sin(2\pi i t_j/5) \right) = 0; \quad i = 1,2 \\
& \sum_{j=1}^{9000} \alpha_j \left(\frac{2\pi i x_1^j}{5} \sin(2\pi i t_j/5) + g_1 (1 - \cos(2\pi i t_j/5)) \right) = 0; \quad i = 1,2 \\
& \sum_{j=1}^{9000} \alpha_j \left(\frac{2\pi i x_2^j}{5} \cos(2\pi i t_j/5) + g_2 \sin(2\pi i t_j/5) \right) = 0; \quad i = 1,2 \\
& \sum_{j=1}^{9000} \alpha_j \left(\frac{2\pi i x_2^j}{5} \sin(2\pi i t_j/5) + g_2 (1 - \cos(2\pi i t_j/5)) \right) = 0; \quad i = 1,2 \\
& \sum_{j=1}^{900} \alpha_j = 1 \\
& \sum_{j=901}^{1800} \alpha_j = 1 \\
& \vdots \\
& \sum_{j=8101}^{9000} \alpha_j = 1 \\
& \alpha_j \geqslant 0; \quad j = 1,2,3,\ldots,9000
\end{aligned}
$$

The linear programming problem has 9000 variables and 20 constraints. This problem was solved for initial values, $A_1 = 250000$ and $A_2 = 500000$, by using MATLAB's software for the following defined intervals:

$$
A_1 = [400, 1000], \quad A_2 = [0, 3.5], \quad U_1 = [0, 0.2]\ U_2 = [0, 0.9], \quad J = [0, 9]
$$

The objective function's value is equal to 6139.69, and the piecewise constant controls u_1 and u_2 shown below.

4.1. Conclusion

There are generated several treatment schedules for various time periods. A case for two different values of A_1 for a 5-month treatment schedule is illustrated. Figs. 1–3 are plotted using $A_1 = 250000$; $A_2 = 75$; $b_1 = 0{:}02$; $b_2 = 0{:}9$,

Fig. 1 represents the controls u_1 and u_2 for drug administration schedule for these parameters.

Fig. 2 represents the number of T cells during our treatment period. The T cell population increases almost linearly up to5 month.

Fig. 3 represents the virus population during treatment period. In the beginning, a sharp decrease was showed in the virus population and after few days it started to increase steadily with some fluctuations.

Fig. 4 represents the optimal controls u_1 and u_2 for drug administration schedule for the second set of parameters.

In the compare of Figs. 5 and 6 for T and V with Figs. 2 and 3, it showed that higher A_1 values reduced the T cell population and increased the virus population.

Nowadays the dynamic behavior of the immune system in dealing with different diseases are expressed in equations and nonequations forms until the best way to control the immune system and treatment be resulted by mathematical science [6,10].

In the treatment of diseases Factors such as duration of therapy, the amount of prescribed medication, Intervals for drugs and treatment costs can form parts of the control of system [6].

Considering that the optimal control models made in most cases leads to the complex nonlinear with high Dimension, solving these models with the help of the classical methods optimal control or other numerical methods is very difficult. In addition in these methods restrictions are imposed on the system such as the derivative of the functions, which may be caused that the problem is not answer in the space of derivative functions [7].

Using of measure method for solving optimal control problems has some benefits such as using of this method for liner and nonlinear problems. This method can find the answer in the highest space size and then can be return the answer to the functions space using the approximation method. The complexity of problem and high dimension in measure space douse not so long the time of solution of problems. In measure method global answer can be found while in the most methods local answer can be found [7]. Therefore using of measure method in solving of these problems could be recommended.

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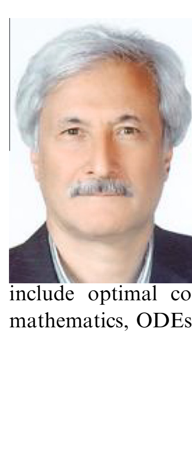

Mohammad H. Farahi is a Professor in Applied Mathematics at the Department of Applied Mathematics, Faculty of Mathematical Sciences, Ferdowsi University of Mashhad, Iran. He obtained his B.Sc., M.Sc. and Ph.D. from Ferdowsi University of Mashhad, Brunel University, UK and Leeds University, UK in 1972, 1978, and 1996, respectively. He has published more than 80 technical papers and 4 textbooks. His scientific interests include optimal control, optimization, sliding mode control, biomathematics, ODEs and PDEs, and approximation techniques.

Masoud Roshanfekr is a mathematics teacher in Islamic Azad University and Farhangian University, Daneshvar Tarbiat Moalem of Neyshabur, Iran. He obtained his B.Sc., from Ferdowsi university of Mashhad -Iran, M. Sc. from Islamic Azad university of Mashhad -Iran. He has published 4 technical papers. His scientific interests include optimal control, optimization and bio-mathematics.

Raheleh Rahbarian is an assistant Professor in biology at the Department of biology, Faculty of Sciences, Payame Noor University, Iran. She obtained her B.Sc., from Shahid Bahonar university of Kerman -Iran, M. Sc. from Ferdowsi university of Mashhad -Iran and Ph.D. from Kharazmi university of Tehran-Iran. She has published more than 20 technical papers.