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OPTIMAL CONTROL OF AN HIV MODEL

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Abstract: In this article we propose an optimal control problem, a drug regimen that inhibits the rate at which the uninfected cells become infected, inhibits the influx of the virus from the external lymphoid compartment and at the same time minimizing the drug cost. The model considered here has a different interpretation of the effects of treatment, since the production of virus from the external lymphoid compartment is not immediately blocked by treatment and thus influences the viral decay rate. The model utilizes a system of ordinary differential equations which describes the interaction of the immune system with the human immunodeficiency virus (HIV). The optimal control problem is transferred into a modified problem in measure space, one in which existence of the solution is guaranteed by compactness of space. By an approximation, we obtain a finite dimensional linear programming problem which gives an approximate solution to the original problem. Our numerical solutions obtained with the help of MATHCAD shows treatment protocols which could maximize the survival time of patients in the short and long term process. Simulations are given with the treatment parameter corresponding to suppression of virus influx from the lymphoid compartment.

Keywords: HIV model; $CD4^+T-cell$; treatment; optimal control; linear programming; simulation; measure theory; approximate solution; drug; MATHCAD.
2010 AMS Subject Classification: 97M10.

1. Introduction.

Since it was first detected about 30 years ago, AIDS - Acquired Immunodeficiency Syndrome as a disease has continued to affect the whole world. It is caused by Human Immunodeficiency Virus (HIV). According to WHO, of the 35 million people worldwide living with HIV infection today, more than 24 million are in low- and middle- income countries, particularly in sub-Saharan Africa [15].

Even though there have been advances in our scientific understanding of HIV and its prevention and treatment as well as years of significant effort by the global health community and leading government including civil society organizations, most people living with HIV or at risk for HIV do not have access to prevention, care, and treatment, and there is still no absolute cure. However, effective treatment with antiretroviral drugs can control the virus so that people with HIV can enjoy healthy lives and reduce the risk of transmitting the virus to others.

Once HIV infects the body, its target is CD4+Tcells, which are an important part of the human immune system. The infected cells produce a large number of new viruses. Highly active antiretroviral therapy (HAART) enables effective suppression of HIV-infected individuals and goes a long way to prolonging the time before the onset of acquired immune deficiency syndrome (AIDS). This could be for years or even decades and, therefore, increases life

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expectancy and quality to the patient. However, because of the long-lived infected cells and sites within the body where drugs may not achieve effective levels of penetration, antiretroviral therapy cannot eradicate HIV from infected patients [1]. Reverse transcriptase inhibitors (RTI) and Protease inhibitor (PI) are the two major constituents of HAART. RTIs act by preventing HIV from infecting cells by blocking the integration of the HIV viral code into the host cell genome while protease inhibitors prevent infected cells from replication of infectious virus particles, this enables it to reduce and maintain viral load below the limit of detection in many patients.

Until date, many of the host-pathogen interaction mechanisms during HIV infection and progression to AIDS remain unknown. Mathematical modeling of HIV infection is of interest since there are no adequate animal models to test the efficacy of drug regimes. These models provide the essential tool to capture a set of assumptions and provide new insights into questions that are difficult to answer by clinical or experimental studies. To describe various aspects of the interaction between the human immune system and HIV, a number of mathematical models have been formulated. For instance, modeling of the kinetics of HIV RNA under drug therapy has led to substantial insight into the dynamics and pathogenesis of HIV [14, 6, 16] and the existence of multiple reservoirs that have made eradication of the virus difficult. Wodaz and Nowak [10] presented the basic model of HIV infection, which contains three state variables: healthy CD4+ T-cells, infected CD4+ T-cells, and concentration of free virus. This model which has been modified offers important theoretical insights into the immune control of the virus, based on treatment strategies, while maintaining a simple structure [9].

In the first section of this article, a mathematical model of HIV dynamics that includes the effect of two treatments and analysis of optimal control is carried out with regards to appropriate goals.

The remaining part of this paper is organized as follows: in Section 2, the underlying HIV mathematical model is described with an increase phase space, Section 3 describes the formulation of the control problem. In section 4, we attempt to approximate the obtained optimal control problem by a linear programming problem. Numerical results using MATHCAD is the subject of Section 5. Section 6 is the conclusion.

2. Statement of the model

We consider a system of ordinary differential equation (ODE) presented by Kirschner and Webb [7] and used by Pritikin [4] which describes the interaction between HIV and the immune system of the body. In this model, $T(t)$ represents the uninfected $CD4^{+}T-cell$ population at the time t, $T_S(t)$ represents the drug-sensitive infected $CD4^{+}T-cell$ population at time t, $T_r(t)$ represents the drug-resistant CD4+T-cell population at time t, $V_S(t)$ represents the drug-sensitive virus population at time t, and $V_r(t)$ represent the drug resistant virus population at time t and $V(t) = V_S(t)+V_r(t)$ represent the total virus population at time t. All these populations are measured in the blood plasma, which constitutes only 2% of their total, the rest residing in the lymphatic tissue. The equations are as follows:

$$\frac{dT(t)}{dt} = S(t) - mT(t) + l_1(t)T(t)V(t) - (\eta_1(t)K_sV_s(t) + K_rV_r(t))T(t) \quad (2.1)$$

$$\frac{dT_s(t)}{dt} = \eta_1(t)K_sV_s(t)T(t) - m_1T_s(t) - l_2(t)T_s(t)V(t) \quad (2.2)$$

$$\frac{dT_r(t)}{dt} = K_rV_r(t)T(t) - m_1T_r(t) - l_2(t)T_r(t)V(t) \quad (2.3)$$

$$\frac{dV_s(t)}{dt} = (1-q)l_3T_s(t)V(t) - K_vT(t)V_s(t) + \eta_2(t)G_s(t) \quad (2.4)$$

$$\frac{dV_r(t)}{dt} = l_3T_r(t)V(t) + q\lambda_3T_S(t)V(t) - k_VT(t)V_r(t) + G_r(V)\frac{V_r(t)}{B+V(t)} \quad (2.5)$$

with given initial values.

The definitions and numerical values of the constants of equations (2.1) - (2.5) are listed in Table 1 [11, see Ogban and Lebedev]. They are as used for the model without treatment.

In these equations, treatment is modeled by the decreasing functions $\eta_1(t)$ and $\eta_2(t)$. The function $\eta_1(t)$ inhibits the rate at which uninfected $CD4^+T$ cells become infected and $\eta_2(t)$ inhibits the influx of virus from the external lymphoid compartment). The parameters c_1, c_2 and c_3 control the speed and strength of the drug-induced inhibitions). It is assumed that the functions $\eta_1(t)$ and $\eta_2(t)$ are determined by the expressions

$$\eta_1(t) = \exp(-c_1(t-t_0) \quad (2.6)$$
$$\eta_2(t) = \max\{\exp(-c_2(t-t_0), c_3)\}$$

3. Optimal control formulation

In this section, we formulate an optimal control problem in accordance with the recommendations developed by the committee of the international society for AIDS [2]. The committee in its recommendations pointed to the possibility of increasing the effectiveness of treatment by a strong combination of antiretroviral drugs. The model (2.4) -(2.6) meets this by the consideration of treatment with two different mechanisms of action. It is further reflected in the optimization problem by the introduction of two control variables. In particular, during medication, the dynamics of the source function is given as

$$\frac{d\eta_1(t)}{dt} = f_1^{trt} = -c_1\eta_1(t),\ \eta_1(0) = 1 \quad (3.1)$$

$$\frac{d\eta_2(t)}{dt} = f_2^{trt} = -c_2\eta_2(t),\ \eta_2(0) = 1 \quad (3.2)$$

We note that the second of the equation of (2.6) defined by the maximum does not meet the objective function of continuity and smoothness. To achieve this, $\eta_2(t)$ is written as

$$\frac{d\eta_2(t)}{dt} = f_2^{ntctrt} = \frac{c_2}{1-c_3}[\eta_2(t) - c_3],\ \eta_2(0) = 1 \quad (3.3)$$

Without loss of generality (3.3) preserves the characteristics of the function (2.6).

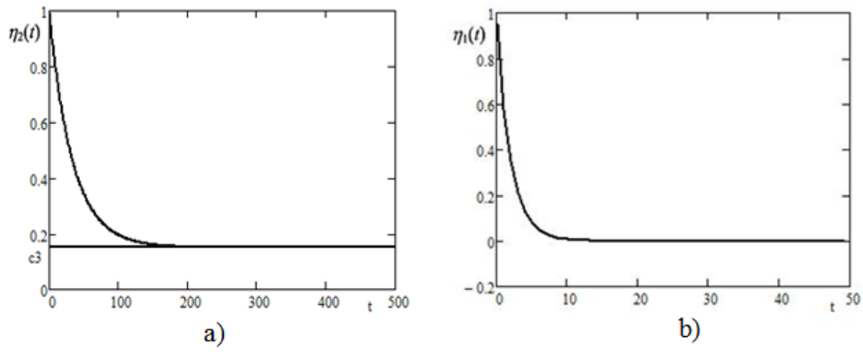

Figure 1. Graph of dynamics model of control functions with constant treatment

We write the growth equations for the modified functions at intervals of drug withdrawal as

$$\frac{d\eta_1(t)}{dt} = f_1^{wdr} = c_1[1-\eta_1(t)] \tag{3.4}$$

$$\frac{d\eta_2(t)}{dt} = f_2^{wdr} = \frac{c_2}{1-c_3}[1-\eta_2(t)] \tag{3.5}$$

Control variables, that is switches u_1 and u_2 are introduced and embedded into the treatment functions as follows: $u_1 = u_2 = 1$ corresponds to the process of treatment being on while $u_1 = u_2 = 0$ corresponds to discontinuation of treatment. This process is represented as

$$\frac{d\eta_1(t)}{dt} = u_1 f_1^{trt} + (1-u_1) f_1^{wdr} \tag{3.6}$$

$$\frac{d\eta_2(t)}{dt} = u_2 f_2^{trt} + (1-u_2) f_2^{wdr} \tag{3.7}$$

Substituting (3.1) and (3.4) in (3.6), and then(3.2) and (3.5) in (3.7)we have

$$\frac{d\eta_1(t)}{dt} = c_1[1-u_1-\eta_1(t)],\ \eta_1(0)=1,\ u_1 \in \{0,1\} \tag{3.8}$$

$$\frac{d\eta_2(t)}{dt} = \frac{c_2}{1-c_3}[1+(c_3-1)u_2-\eta_2(t)],\ \eta_2(0)=1,\ u_2 \in \{0,1\} \tag{3.9}$$

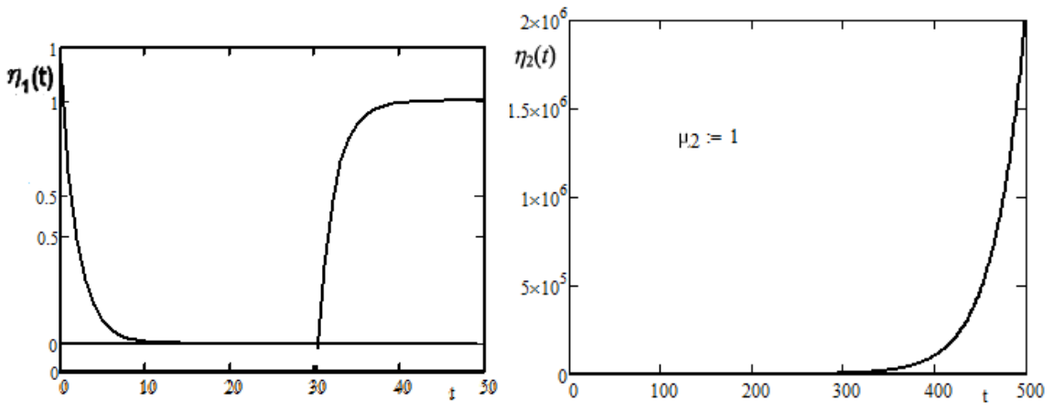

Figure 2. Dynamics of model showing structured treatment.

Thus, the system of differential equations(2.1)-(2.5) together with the controls is written as

$$\frac{dT(t)}{dt} = S(t) - mT(t) + l_1(t)T(t)V(t) - (\eta_1(t)K_sV_s(t) + K_rV_r(t))T(t)$$

$$\frac{dT_s(t)}{dt} = \eta_1(t)K_s V_s(t)T(t) - m_1 T_s(t) - l_2(t)T_s(t)V(t)$$

$$\frac{dT_r(t)}{dt} = K_r V_r(t)T(t) - m_1 T_r(t) - l_2(t)T_r(t)V(t)$$

$$\frac{dV_s(t)}{dt} = (1-q)l_3 T_s(t)V(t) - K_v T(t)V_s(t) + \eta_2(t)G_s(t) \qquad (3.10)$$

$$\frac{dV_r(t)}{dt} = l_3 T_r(t)V(t) + ql_3 T_s(t)V(t) - K_v T(t)V_r(t) + G_r(V)\frac{V_r(t)}{B+V(t)}$$

$$\frac{d\eta_1(t)}{dt} = c_1[1 - u_1 - \eta_1(t)]$$

$$\frac{d\eta_2(t)}{dt} = \frac{c_2}{1-c_3}[1 + (c_3 - 1)u_2 - \eta_2(t)]$$

This paper aims to propose a drug regimen that inhibits the rate at which the uninfected cells become infected and inhibits the influx of the virus from the external lymphoid compartment at the same time minimizing the drug cost. This can be modeled as follows. The main purpose of treatment is to prolong the life of a patient. There are three categories of disease severity which is determined by the level of concentration of $CD4^+T-cell$ present in the blood:

(i) greater than $500 unit/mm^3$

(ii) $200 \le T \le 500$

(iii) <200

The third category of patients develops the disease that is known as acquired immunodeficiency syndrome AIDS. The lower value of the concentration of T cells is a natural boundary of the studied processes in the immune system. This means that the phase space of the system (4.10) should consider its trajectory ending on the hypersurface

$$T(t) - T^* = 0 \qquad (3.11)$$

Here, T^* - some constant (for example, $T^* = 500 units/mm^3$ or $T^* = 200 units/mm^3$). The task of extending the life of the patient is that the immune system had reached the borders of (4.15) as late as possible.

Assume that at the beginning of treatment

$$T(t) \ge T^* \quad , \quad t \in [t_0, t_f], \quad T(t) = T^* \qquad (3.12)$$

A problem arising from the use of most chemotherapies is the multiple and sometimes harmful side effects as well as the ineffectiveness of treatment after a time due to the capability of the virus to mutate and become resistant to the treatment. Global effects of this phenomenon are considered by imposing limited treatment interval in line with the recommendations in [2], that is the treatment last for a given period of time t_0 to $t_0 + \tau$. Therefore, the treatment interval must contain the control function $u_i(.)$

$$\text{SUP}\, u_i \subseteq [t_0, t_0 + \tau]. \qquad (3.13)$$

Here, we follow [8] in assuming that the cost of the treatment is proportional to $u^2(t)$ at time t. Therefore the overall cost of treatment is $\int_{t_0}^{t_f} u^2(t)dt$. So the following functional should be maximized:

$$\nu(t_f, u) = t_f - \lambda \int_{t_0}^{t_f} u^2(t)dt. \tag{3.14}$$

The relative importance of maximizing the survival time t_f and minimizing the systemic cost to the body necessitate the use of the parameter λ.

The system of differential equations (3.10) can be represented in the generalized form as

$$\dot{x}(t) = g(x(t), u(t), t)\ ,\ x(0) = 0. \tag{3.15}$$

Assume that U denotes the set of all measurable control functions $u(.) \in [0,1]$, where $u(.)$ satisfies (3.13), and the corresponding solution of (3.15) at final time t_f satisfies [3.12]. Therefore, we are seeking for $u^*(.) \in U$ such that

$$\nu(t_f, u) \le \nu(t_f^*, u^*),\ \ \forall u \in U, \tag{3.16}$$

Setting $f_0(x(t), u(t), t) = 1 - \lambda u^2(t)$, then the optimal drug regimen problem, while ignoring t_0, can be represented as

$$\max_{t_f, u \in k} \int_{t_0}^{t_f} f_0(x(t), u(t), t)dt \tag{3.17}$$

Subject to

$$\dot{x} = g(x(t), u(t), t) \tag{3.18}$$

$$x(t_0) = x_0,\ T(t_f) = CD4^+_{crit}, \tag{3.19}$$

$$T(t) \ge CD4^+_{crit},\quad t \in [t_0, t_f], \tag{3.20}$$

This is an optimal control problem (OCP). The set U may be empty. If U is not empty, then the function measuring the performance of the system may not achieve its maximum in the set U. In order to overcome these difficulties, in the next section, we transfer the modified problem in measure space.

4. Approximation of OCP by Linear Programming Problem

We now use measure theory for solving optimal control problems based on the idea of Young [3] and applied by Rubio [5]. This method has been extended for approximating the time optimal problems by a Linear programming model [13].

4.1 We assume that the state variables $x(.)$ and the control variables $u(.)$, respectively get their values in the compact sets $B = B_1 * B_2 * ... B_7 \subset R^7$ and $U \subset R$. By setting $J = [t_0, t_f]$, we derive weak forms for (3.18) - (3.20).

Definition 1. A trajectory pair $p = [x(t), u(t), t)]$ is said to be admissible if the following conditions hold:

(i) $x(.) \in A \qquad \forall t \in J$ and is absolutely continuous.

(ii) $u(.) \in U \qquad \forall t \in J$ and is measurable on J.

(iii) p satisfies (3.18)-(3.20) everywhere on J^0

We assume that the set of all admissible triples is nonempty and denote it by H. Let p be an admissible triple, B an open ball in R^8 containing $J * A$, and let $C'(B)$ be the space of all real-valued continuous differentiable functions on it. Let $\gamma \in C'(B)$ and define γ^g as follow:

$$\gamma^g(x(t),u(t),t) = \gamma_x(x(t),t).g(x(t),u(t),t) + \gamma_t(x(t),t) \qquad (4.1.1)$$

for each $[x(t),u(t),t] \in \Omega$, where $\Omega = J * A * U$. The function γ^g is in the space of $C(\Omega)$, the set of all continuous functions on the compact set Ω. Since $p = [x,u,t_f]$ is an admissible triple, we have

$$\int_{t_0}^{t_f} \gamma^g(u(t),\xi(t),t)dt = \int_{t_0}^{t_f} \gamma_x(x(t),t).\dot{x}(t) + \gamma_t(x(t),t)dt$$

$$= \gamma(x(t_f),t_f) - \gamma(x(t_0),t_0) = \Delta\gamma \qquad (4.2)$$

for all $\gamma \in C'(B)$. Let $D(J^0)$ be the space of all infinitely differentiable real-valued functions with compact support in J^0. Define

$$\varphi^n(x(t),u(t),t) = x_n(t)\varphi'(t) + g_n(x(t),u(t),t)\varphi(t),$$

$$n = 1,2,...,7, \forall \varphi \in D(J^0) \qquad (4.1.3))$$

Since $p = [x,u,t_f]$ is an admissible triple, then the function $\varphi(.)$ has compact support in J^0, $\varphi(t_0) = \varphi(t_f) = 0$. Thus for $n = 1,2,...7$, and for all $\varphi \in D(J^0)$, from (4.3) and using integration by parts, we have

$$\int_{t_0}^{t_f} \varphi^n(x(t),u(t),t)dt = \int_{t_0}^{t_f} x_n(t)\varphi'(t)dt + \int_{t_0}^{t_f} g_n(x(t),u(t),t)\varphi(t)dt = 0 \qquad (4.1.4)$$

Also by choosing the functions which are dependent on time only, we have

$$\int_{t_0}^{t_f} \phi(x(t),u(t),t)dt = \alpha_\phi \quad \forall \phi \in C'(\Omega), \qquad (4.1.5)$$

where $C'(\Omega)$ is the space of all function in $C(\Omega)$ that depend only on time and α_ϕ is the integral of $\phi(.)$ on J.

Equations (4.2),(4.4) and (4.5) are the weak forms of (3.18)-(3.20).

Remark: The constraints (3.19) are considered on the right-hand side of (4.2) by choosing suitable functions $\gamma \in C'(B)$ which are monomials of $T(t)$. More so, the constant (3.20) is considered, by choosing an appropriate set A. Again by considering the mapping

$$\Pi_p : L \to \int_J L(x(t),u(t),t)dt, \quad \forall L \in C(\Omega) \qquad (4.1.6)$$

we note it is positive linear functional on $C(\Omega)$ and we can construct a 1-1 transformation

$p \to \Pi_p$ of admissible triples in H into the linear mapping Π_p.

Consequently, from (4.1.2), (4.1.4) and (4.1.5), we can conclude that maximizing the functional (3.17) over admissible space H, changes to the following optimization problem in functional space:

$$\max_{p \in H} \Pi_p(f_0) \tag{4.1.7}$$

Subject to

$$\Pi_p(\gamma^g) = \Delta\gamma, \quad \gamma \in C'(B) \tag{4.1.8}$$

$$\Pi_p(\varphi^n) = 0 \;\; n = 1,2,...,7, \;\; \varphi \in D(J^0), \tag{4.1.9}$$

$$\Pi_p(\phi) = \alpha_\phi, \;\; \phi \in C^1(\Omega) \tag{4.1.10}$$

4.2 Measure space. Let $M^+(\Omega)$ denote the space of all positive Radon measures on Ω. By the Riesz representation theorem [12], there exists a unique positive Radon measure $\mu \in \Omega$ such that

$$\Pi_p(L) = \int_J L(x(t), u(t), t)dt$$

$$= \int_\Omega L(x(t), u(t), t)d\mu \equiv \mu(L), \;\; L \in C(\Omega). \tag{4.2.1}$$

Thus, we may change the functional space of the optimization problem to measure space. This implies that the optimization problem (4.1.7)-(4.1.10) can be converted to the following optimization problem in measure space:

$$\max_{\mu \in M^+(\Omega)} \mu(f_0) \tag{4.2.2}$$

Subject to

$$\mu(\gamma^g) = \Delta\gamma, \quad \gamma \in C'(B), \tag{4.2.3}$$

$$\mu(\varphi^n) = 0, \quad n = 1,2,...,7, \varphi \in D(J^0), \tag{4.2.4}$$

$$\mu(\phi) = \alpha_\phi, \;\; \phi \in C^1(\Omega), \tag{4.2.5}$$

We now define Q to be the set of all measure in $M^+(\Omega)$ that satisfy (4.2.3)-(4.2.5) and then we can show that there exists an optimal measure μ^* in Q where the point may be studied without imposing conditions such as convexity. Formally, we state as follow:

Define the function $I : Q \to R$ as $I(\mu) = \mu(f_0)$.

Theorem. The measure theoretical problem of maximizing (4.2.2)-(4.2.5)has an optimal solution say $\mu^*, where \mu^* \in Q.$

Remarks: The above theorem guarantees the existence of an optimal solution.

Proof. See [ ] and note that the constraints (4.2.4) and (4.2.5) are special cases of (4.2.3). This implies that the set Q can be written as

$$Q = \bigcap_{\gamma \in C'(B)} \{\mu \in M^+(\Omega) : \mu(\gamma^g) = \Delta\gamma\}. \tag{4.2.6}$$

Suppose that $p=[x,u,t_f]$ is an admissible triple. Surely, $\{\mu\in M^+(\Omega):\mu(1)=t_f-t_0\}$ is compact in the weak topology. Moreover, the set Q as an intersection of the closed singleton sets $\{\Delta\gamma\}$ under the continuous function $\mu\to\mu(\gamma^g)$ is also closed. Hence, Q is a closed subset of a compact set. Since the functional I, mapping the compact set Q on the real line is continuous and takes its maximum from Q the compactness is proved.//

Obviously, the problem is an infinite dimensional linear programming problem, and all the functions (4.2.2) - (4.2.5) are linear in μ. We obtain an approximate solution of this problem by the solution of a finite-dimensional linear program.

Proposition. If the linear program problem consisting of maximizing the function I over the set Q_M of measures in $M^+(\Omega)$ satisfies

$$\mu(\gamma_i^g)=\Delta\gamma_i,\qquad i=1,...,M. \quad (4.2.7)$$

Then, Then, $J_M\equiv\max_{Q_M} I\to J=\max_{Q} I$ as $M\to\infty$

Proof. We have $Q\subseteq...\subseteq Q_M\subseteq...Q_2\subseteq Q_1$, it follows, therefore, that

$J\le...\le J_M\le...\le J_2\le J_1.$

The sequence $\{J_j\}_{j=1}^{\infty}$ is nonincreasing and bounded, so, it converges to a number ζ such that $\zeta\ge J$. We show that $\zeta=J$. Set $R=\bigcap_{M=1}^{\infty}Q_{M.}$ Then $Q\subseteq R$ and $\zeta\equiv\max_R I.$ It is sufficient to show $Q\subseteq R.$ Assume $\mu\in R$ and $\gamma\in C'(B).$ Since the linear combination of the function $\{\gamma_j, j=1,2,...\}$ is uniformly dense in $C'(B),$ there is a sequence $\{\tilde{\gamma}\}\in$ span$\{\gamma_j, j=1,2,,,,\},$ such that $\tilde{\gamma}_K$ tends to γ uniformly as $k\to\infty.$ Thus, S_1,S_2,S_3 tend to zero as $k\to\infty$ where $S_1=\sup|\gamma_x-\tilde{\gamma}_{K_x}|, S_2=\sup|\gamma_t-\tilde{\gamma}_{K_t}|,$

and $S_3=\sup|\gamma-\tilde{\gamma}_k|$. Since $\mu\in R$ and the functional $f\to\mu(f)$ is linear, $\mu(\tilde{\gamma}_K^g)=\Delta\tilde{\gamma}_K$ and

$$|\mu(\gamma^g)-\Delta\gamma|=|\mu(\gamma^g)-\Delta\gamma-\mu(\tilde{\gamma}_K^g)+\Delta\tilde{\gamma}_K|$$

$$=\left|\int_\Omega\{[\gamma_x(x,t)-\tilde{\gamma}_{K_x}(x,t)]g(x,u,t)+[\gamma_t(x,t)-\tilde{\gamma}_{kt}(x,t)]\}d\mu-(\Delta\gamma-\Delta\tilde{\gamma}_k)\right|$$

$$\le S_1\int_\Omega|g(x,u,t)|d\mu+S_2\int_\Omega d\mu+2S_3. \quad (4.2.8)$$

The right-hand side of the above inequality tends to zero as $k\to\infty,$ and the left-hand side is independent of $k;$ therefore $\mu(\gamma^g)=\Delta\gamma.$ Thus, $R\subseteq Q$ and $\zeta\le J,$ which implies $\zeta=J.//$

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Proposition 3. The measure μ^* in the set Q_M at which the functional I attains its minimum has the form

$$\mu^* = \sum_{j=1}^{M} \alpha_j{}^* \delta(z_j^*), \tag{4.2.9}$$

Where $\alpha^* \geq 0, z_j^* \in \Omega,$ and $\delta(z)$ is unitary atomic measure with the support being the singleton set $\{z_j^*\},$ characterized by $\delta(z)(F) = F(z), z \in \Omega.$

We, therefore, restrict ourselves to finding a measure in the form of (4.2.9) which maximizes the functional I and satisfies in M number of constraints (4.2.3)-(4.2.5). Thus by choosing the functions $\gamma_i, i = 1,2,...,M_1, \varphi_K, k = 1,...,M_2,$ and $\phi_S, s = 1,...,S,$ the infinite dimensional problem (4.2.2)-(4.2.5) is approximated by the following finite dimensional nonlinear programming problem:

$$\max_{\alpha_j \geq 0, z_j \in \Omega} imize \sum_{j=1}^{M} \alpha_j f_0(z_j) \tag{4.2.10}$$

Subject to

$$\sum_{j=1}^{M} \alpha_j \gamma_i^g(z_j) = \Delta\gamma, i = 1,...,M_1, \tag{4.2.11}$$

$$\sum_{j=1}^{M} \alpha_j \varphi_K^n(z_j) = 0, k = 1,...,M_2, n = 1,...,7, \tag{4.2.12}$$

$$\sum_{j=1}^{M} \alpha_j \phi_S(z_j) = b_{\phi_S}, s = 1,...,S \tag{4.2.13}$$

where $M = M_1 + 4M_2 + S.$ Obviously, (4.2.10)-(4.2.10) is a nonlinear programming problem with $2M$ unknowns: α_j and $z_j,$ $j = 1,...,M.$ We are interested in LP problem. The following proposition enables us to approximate the nonlinear programming problem (4.2.10)-(4.2.3) by a finite dimensional linear programming problem.

Proposition 4. Let $\Omega_N = \{y_1, y_2, ..., y_N\}$ be a countable dense subset of $\Omega.$ Given $\varepsilon > 0,$ a measure $v \in M^+(\Omega)$ can be found such that

$$\left|v(f_0) - \mu^*(f_{0)})\right| \leq \varepsilon,$$

$$\left|v(\gamma_i^g) - \mu^*(\gamma_i^g)\right| \leq \varepsilon, \quad i = 1,...,M_1,$$

$$\left|v(\varphi_k^n) - \mu^*(\varphi_k^n)\right| \leq \varepsilon, \quad k = 1,...,M_2, n = 1,2,...,7,$$

$$\left|v(\phi_S) - \mu^*(\phi_S)\right| \leq \varepsilon, \quad s = 1,...,S, \tag{4.2.14}$$

where the measure v has the form

$$v = \sum_{j=1}^{M} \alpha_j^* \delta(y_j), \tag{4.2.15}$$

And the coefficients $\alpha_j^*, j = 1,...,M,$ are the same as optimal measure (4.2.9), and $y_j \in \Omega_N, j = 1,...,M.$

Proof. Let us rename the functions $f_0, \gamma_i^g s, \varphi_k^n s,$ and ϕ_S's sequentially as h_j, $j = 1,2,...M+1.$ Then, for $j =,...,M+1,$

$$\left|(\mu^* - v)h_j\right| = \left|\sum_{i=1}^{M} \alpha_i^* [h_j(z_i^*) - h_j(y_i)]\right| \leq \left(\sum_{j=1}^{M^*} \alpha_i^*\right) \max_{i,j} \left|h_j(z_i^*) - h_j(y_i)\right| \quad (4.2.16)$$

where the $h_j s$ are continuous. Hence, by choosing $y_i, i = 1,...,M,$ sufficiently close to z_i^*, we have

$$\max_{i,j} \left|h_j(z_i^*) - h_j(y_i)\right| < \frac{\varepsilon}{\sum_{j=1}^{M} \alpha_j^*} .//$$

J is divided into S subintervals in order to construct a suitable set Ω_N as follows:

$$J_S = \left[t_0 + \frac{(s-1)\Delta T}{S-1}, t_0 + \frac{s\Delta T}{S-1}\right), \; s = 1,...,S-1, \quad J_S = [t_0, t_f), \quad (4.2.17)$$

where t_0 is a lower bound for the optimal time t_f.

Therefore, according to (4.2.15), the nonlinear programming problem (33)-(36) is converted to the following linear programming problem:

$$\max_{\alpha_j \geq 0} \sum_{j=1}^{M} \alpha_j f_0(y_j) \quad (4.2.18)$$

Subject to

$$\sum_{j=1}^{N} \alpha_j \gamma_i^g(y_j) = \Delta\gamma_i, \; i = 1,...,M_1, \quad (4.2.19)$$

$$\sum_{j=1}^{N} \alpha_j \varphi_k^n(y_j) = 0, \quad k = 1,...,M_2, n = 1,...,7, \quad (4.2.20)$$

$$\sum_{j=1}^{N} \alpha_j \phi_s(y_j) = b_{\phi_s}, s = 1,...,S. \quad (4.2.21)$$

Conclusion

In this paper, we proposed and constructed an optimal control problem. we considered a system of differential equations as a dynamic system which describes the various aspects of the interaction of HIV with the immune system. This control problem is a drug regimen that inhibits the rate at which the uninfected cells become infected, inhibits the influx of the virus from the external lymphoid compartment and at the same time minimizing the drug cost. A measure theoretical method is used to solve the problem. The method is not iterative and as such initial guess of the solution is not required. Numerical results with constant treatment are obtained.

Conflict of Interests

The authors declare that there is no conflict of interests.

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