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OPTIMAL CONTROL OF HIV-1 INFECTION MODEL WITH LOGISTIC GROWTH USING DISCRETE DELAY

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Abstract. We investigate an optimal treatment strategies with mathematical population model of HIV-1 infection dynamics. We establish the existence of an optimal control for this model and provide necessary conditions for the optimal treatment. Pontryagin's maximum principle is used to characterize these optimal controls, and the optimality system is derived. The optimal treatment strategy is obtained by solving the corresponding optimality system numerically. For the numerical simulation, we propose a new algorithm based on the Euler forward and backward difference approximation.

1. Introduction

Several drugs that substantially decrease morbidity and mortality in HIV-infected patients have been developed in the last few years. A number of researchers have searched for optimal treatment strategies that can decrease virus mutations, pharmaceutical side effects, and complex and expensive medication burdens. The structured model of HIV-1 dynamics has three state variables: $T(t)$ which represents the number of uninfected $CD4^+T$ cells at time t; $T^*(t)$ which represents the number of infected $CD4^+T$ cells at time t; and $V(t)$ which represents the number of virus particles at time t. The main

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target cell of HIV is the $CD4^+T$ helper cells. Now, we here introduce the control term η represents the effectiveness of the reverse transcriptase inhibitors (RTI), which block new infection. Hence, the equation become as follows,

$$\begin{aligned}
\frac{dT}{dt} &= \lambda - dT(t) + rT(t)\left(1 - \frac{T(t)}{K}\right) - \frac{(1-\eta)\beta T(t)V(t)}{1+\alpha T}, \\
\frac{dT^*}{dt} &= \frac{(1-\eta)\beta T(t-\tau)V(t-\tau)}{1+\alpha T} - \delta T^*(t), \\
\frac{dV}{dt} &= N\delta T^*(t) - cV(t). \qquad (1.1)
\end{aligned}$$

λ represents the rate at which new T cells are created from sources, r is the maximum proliferation rate of target cells. K is the T cell population density at which proliferation shuts off. Parameter d and δ are death rate of the T cells and infective cells (T^*), $\beta T(t)V(t)$ is the incidence of HIV-1 infection for $CD4^+T$ cells, each infected $CD4^+T$ cell is assumed to be produce N virus particles during its life time, including any of its daughter cells and c is the clearance rate constant of virions. α is the parameter that measure the inhibitory effect and the intracellular delay, τ represents the time needed for infected cells to produce virions after viral entry. Thus the infection rate, β, is reduced to $(1-\eta)\beta$, where $0 \le \eta_{\min} \le \eta \le \eta_{\max} < 1$. Here $\eta_{\min}$ and $\eta_{\max}$ represent minimal and maximal drug efficacy, respectively. when $\tau > 0$, the solution of the system (1.1) are defined in [1, 2] by the following initial conditions:

$$\begin{aligned}
&T(\theta) = \phi_1(\theta), \quad T^*(\theta) = \phi_2(\theta), \quad V(\theta) = \phi_3(\theta); \\
&\phi_1(\theta) \ge 0, \quad \phi_2(\theta) \ge 0, \quad \phi_3(\theta) \ge 0, \quad \theta \in [-\tau, 0]. \qquad (1.2)
\end{aligned}$$

System (1.1) has to be analyzed with the initial conditions $\phi = (\phi_1, \phi_2, \phi_3)$ defined in the space $C_\Omega^+ = \{\phi \in C([-\tau,0], \mathbb{R}_+^3) : \phi_1(\theta) = T(\theta), \phi_2(\theta) = T^*(\theta), \phi_3(\theta) = V(\theta)\}$, where $T(\theta) > 0$, $T^*(\theta) > 0$, $V(\theta) > 0, \theta \in C([-\tau,0], \mathbb{R}_+^3)$; is the Banach space of continuous functions and is a mapping from $[-\tau, 0]$ to $\mathbb{R}_+^3$, where

$$\mathbb{R}_+^3 = \{(T, T^*, V) : T, T^*, V > 0\}.$$

It can be shown that all solutions of the system (1.1) in C_Ω^+. Thus, C_Ω^+ is positively invariant and it is sufficient to consider solutions in C_Ω^+. From [3] standard existence and uniqueness results hold for system (1.1) in C_Ω^+.

2. An optimal control problem

In this section, we formulate an optimal control problem together with HIV-1 infection model (1.1) to derive the optimal treatment strategies. We minimize not only the virus population but also the systemic cost of drug

treatment. The cost of the treatment comes from both the actual treatment cost and the severity of the unintended side effects of the drugs. Therefore, our main objective is to optimize the functional as follows,

$$\max J(\eta) = \int_0^{t_f} \left(T(t) + V(t) - \left(\frac{B_\eta}{2} [\eta(t)]^2 \right) \right) dt, \tag{2.1}$$

where B_η is the weight constants to balance the quantity of virus particles and the control function, our control function η represents the drug (RTI) effectiveness satisfying $0 \leq \eta_{\min} \leq \eta \leq \eta_{\max} < 1$. The control class is chosen to be the measurable functions defined on $[0, t_f]$, with the initial condition $0 \leq \eta_{\min} \leq \eta \leq \eta_{\max} < 1$. In other words, we are seeking optimal control η^* such that

$$\max J(\eta^*) = \max \{ J(\eta) : \eta \text{ is Lebesque-integrable on } [0, t_f] \text{ with values } \in W = [\eta_{\min}, \eta_{\max}] \}$$

2.1. **Existence of an optimal control.** The approach to solve an optimal control problem is to first prove the existence of an optimal control and then characterize the optimal control by using the optimality system. We now prove that there exists an optimal control that minimizes the objective functional (2.1) subject to the HIV-1 dynamical model. The existence of an optimal control can be obtained by using a result from Fleming and Rishel [4] and by Lukes in [5].

Theorem 2.1. *There exists an optimal control $\eta^* \in W$ such that*

$$J(\eta^*) = \max_{\eta \in W} J(\eta). \tag{2.2}$$

According to [4]*, the solution exists if the following hypotheses are met:*

(1) *The set of controls and corresponding state variables is non-empty.*
(2) *The admissible control set W is closed and convex.*
(3) *The right-hand side of the state system is bounded by a linear combination of the state and control variables.*
(4) *There exists constants $h_1, h_2 > 0$ and $\beta > 1$ such that the integrand $L(T, T^*, V, \eta)$ of the objective functional satisfies*

$$L(T, T^*, V, \eta) \leq h_2 - h_1(|\eta|^2),$$

of the objective functional is a concave on W.

Proof. In order to verify the conditions, we should first prove the existence of the solution for the system (1.1), Since $\frac{\beta T}{1+\alpha T} < \beta$ and by neglecting the

negative terms in the model, we have

$$\frac{dT(t)}{dt} < \lambda + rT, \quad \frac{dT^*(t)}{dt} < (1-\eta)\beta V(t-\tau), \quad \frac{dV(t)}{dt} < N\delta T^*. \tag{2.3}$$

System (2.3), can be written in the matrix form as follows,

$$\begin{bmatrix} T(t) \\ T^*(t) \\ V(t) \end{bmatrix}' < \begin{bmatrix} r & 0 & 0 \\ 0 & 0 & 0 \\ 0 & N\delta & 0 \end{bmatrix} \begin{bmatrix} T(t) \\ T^*(t) \\ V(t) \end{bmatrix} + \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & (1-\eta)\beta \\ 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} T(t-\tau) \\ T^*(t-\tau) \\ V(t-\tau) \end{bmatrix}, \tag{2.4}$$

where $' = \frac{d}{dt}$. This system is linear in finite time with bounded coefficients. Then the solutions of this linear system are uniformly bounded. Therefore, the solution of the non-linear system (2.1) is bounded and exists by [5]. Hence the condition (1) is satisfied.

Secondly, we note that W is closed and convex by definition. For the third condition, the right hand side of system (1.1) is continuous, since the denominators of all fractions from the right hand side of this system consist solely of positive entities. Note that the integrand of our objective functional is concave. Also we have the last condition needed

$$L(T, T^*, V, \eta) \leq h_2 - h_1(|\eta|^2),$$

where h_2 depends on the upper bound on T and V and $h_1 > 0$ since $B_\eta > 0$. This completes the proof. □

2.2. **Optimality conditions.** In this section, we establish the necessary conditions for the optimal solution of the optimization problem (1.1), we use Pontrygian's minimum (maximum) principle is derived by

$$\mathrm{H} = T(t) + V(t) - \left(\frac{B_\eta}{2}[\eta(t)]^2\right) + \lambda_1 \frac{dT(t)}{dt} + \lambda_2 \frac{dT^*(t)}{dt} + \lambda_3 \frac{dV(t)}{dt} \tag{2.5}$$

and $\lambda_i,\ i = (1, 2, 3)$ are the adjoint variables that satisfy

$$\begin{aligned} \lambda_1'(t) &= -\frac{\partial H}{\partial T}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial H}{\partial T_\tau}(t+\tau); \ \ \lambda_1(t_f) = 0, \\ \lambda_2'(t) &= -\frac{\partial H}{\partial T^*}(t); \ \ \lambda_2(t_f) = 0, \\ \lambda_3'(t) &= -\frac{\partial H}{\partial V}(t) - \chi_{[0,t_f-\tau]}(t)\frac{\partial H}{\partial V_\tau}(t+\tau); \ \ \lambda_3(t_f) = 0. \end{aligned} \tag{2.6}$$

Here $\chi_{[0,t_f-\tau]}$ denotes the indicator function of the interval $[0, t_f - \tau]$ and defined by

$$\chi_{[0,t_f-\tau]} = \begin{cases} 1, & t \in [0, t_f - \tau], \\ 0, & \text{otherwise.} \end{cases} \tag{2.7}$$

To minimize the Hamiltonian functional, the Pontryagian's minimum principle [6] is used. Thus, we arrive at the following theorem.

Theorem 2.2. *Given an optimal control η^* and solutions of the corresponding state system* (1.1)*, there exist adjoint variable λ_i for $i = 1, 2, 3$ satisfy the following:*

$$\begin{aligned}
\lambda_1'(t) &= -\left(1 + \lambda_1\left(-d + r - \frac{2rT^*}{K} - \frac{(1-\eta)\beta V^*}{(1+\alpha T^*)^2}\right)\right. \\
&\qquad \left. +\lambda_2(t+\tau)\chi_{[0,t_f-\tau]}\frac{(1-\eta)\beta V^*}{(1+\alpha T^*)^2}\right), \\
\lambda_2'(t) &= -\left(\lambda_2(-\delta) + \lambda_3(N\delta)\right), \\
\lambda_3'(t) &= -\left(1+\lambda_1\frac{(1-\eta)\beta T^*}{(1+\alpha T^*)}+\lambda_3(-V)+\lambda_2(t+\tau)\chi_{[0,t_f-\tau]}\frac{(1-\eta)\beta T^*}{(1+\alpha T^*)}\right) \qquad (2.8)
\end{aligned}$$

with transversality conditions

$$\lambda_i(t_f) = 0; \quad i = 1, 2, 3. \qquad (2.9)$$

and the optimal control

$$\eta^* = \min\left(1, \max\left(0, \frac{1}{B_\eta}\left(\lambda_1\frac{\beta T^* V^*}{1+\alpha T^*} - \lambda_2\frac{\beta T^*(t-\tau)V^*(t-\tau)}{1+\alpha T^*(t-\tau)}\right)\right)\right). \qquad (2.10)$$

Proof. The optimal control η^* can be solved from the optimality condition $\left(\frac{\partial H}{\partial \eta}(t)\right) = 0$, By using the handedness of the control set W, it is easy to obtain η^* is in the form of (2.10). □

3. Numerical calculations

In this section, we give a numerical method to solve the optimality system (2.8), (2.9) and (2.10) are present the results. The optimal system is solved numerically and the results are presented graphically. Our findings leading to the approximation of the optimal controls (2.8-2.10) are carried out using the forward Euler method for the state system and backward difference approximation for the adjoint system. We assume that the step size h, such that $\tau = mh$ and $t_f - t_0 = nh$, where $(m, b) \in \mathbb{N}^2$. We define the state, adjoint and control variables at the mesh points. An initial guess is given for the control η which is then updated continuously untill the objective functional satisfies the conditions. However, there are several major problems to overcome when solving delay differential equations.

The different variables (cell populations and control functions) in the objective functional given in (2.1) have different scales. Hence they are balanced by choosing weight constants $B_\eta = 1$ and 2 in the objective functional given

in (2.1). The numerical results for the optimal problem are obtained by using the parameter values given in Table 1 ([7]).

By using the Theorem 2.2, for $\tau = 3$, the state equation (1.1) as follows:

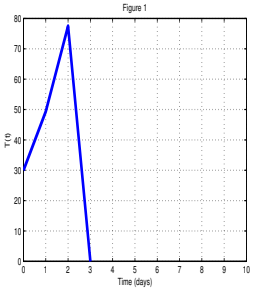
$$\begin{aligned}
\frac{dT}{dt} &= 5 - 0.01T(t) + 0.5T(t)\left(1 - \frac{T(t)}{1200}\right) - \frac{(1-\eta)0.0002T(t)V(t)}{1+0.01T}, \\
\frac{dT^*}{dt} &= \frac{(1-\eta)0.0002T(t-\tau)V(t-\tau)}{1+0.01T} - 1T^*(t), \\
\frac{dV}{dt} &= 800T^*(t) - 5V(t), \qquad (3.1)
\end{aligned}$$

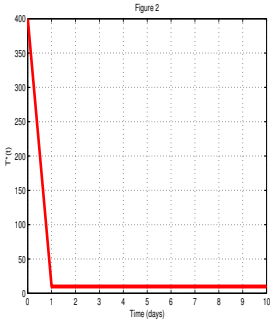
and using the parameter values from Table I, we obtain the optimal control variable $\eta = 0.5$ was followed from (2.10).

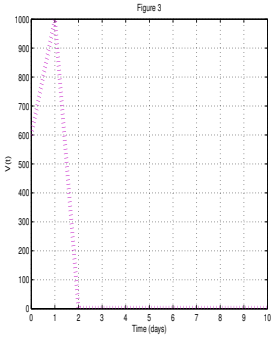
Table I. Parameters and Values

Parameter	**Units**	**Scaling values**
λ	$\text{day}^{-1}mm^{-3}$	5
d	day^{-1}	0.01
r	day^{-1}	0.5
K	mm^3day^{-1}	1200
β	mm^{-3}	0.0002
δ	day^{-1}	1
N	mm^3day^{-1}	800
c	day^{-1}	5
τ	day^{-1}	3

The graph from simulating the model, given below, help to compare the uninfected cells, the infected cells, and the viral load for using with no control and minimal level of control variables with the help of weight factor constants. Each control strategy can be calculated within 10 days.

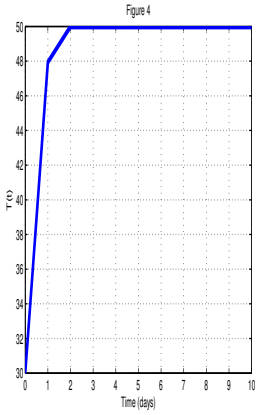


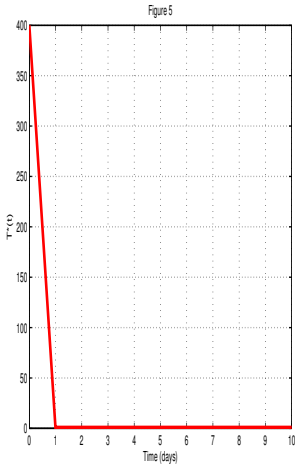


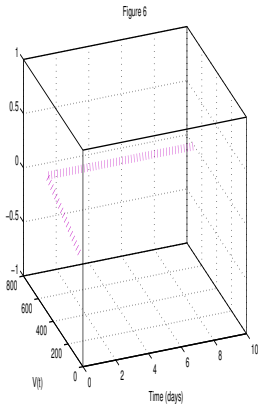


Figs: From figure (1)-(3) shows the simulation of the system (2.8)-(2.10) with RTI, using these initial conditions $T(0) = 30, T^*(0) = 400, V(0) = 600$, with $B_\eta = 1$ for $\tau = 3$.

Using the Table I values, we have noticed that the growth of uninfected cell decreased to a large level. In order to determine, under what level of control variable, the target cell of $CD4^+T$ cell has not to be infected may shown from the following figures. From the above figures (1)-(3) represent with using no control variable, since the growth of uninfected cell is decreasing the large level. For using the small level of control variable, the growth of the uninfected cells maintained a level of the growth. It may shown from the following figures.







Figs: Figure (4)-(6) shows the simulation of the system (2.8)-(2.10) with RTI, using these initial conditions $T(0) = 30, T^*(0) = 400, V(0) = 600$, with $B_\eta = 1$ for $\tau = 3$.

From the figures (4)-(6), we noticed that the small level of desirable control variable $\eta = 0.5$ can be easily control the growth rate of uninfected cells, infected cells and minimize the viral load. Based on the above simulation, we showed that small level of treatments, the $CD4^+T$ population grows significantly which improves the quality of life of the patient.

4. Conclusion

Firstly, we given a delay mathematical model with control that describe HIV infection of $CD4^+T$ cells during therapy. Hence, we presented an optimal therapy in order to minimize the cost of treatment, reduce the viral load, and improve immune response. For the comparison study of both without control and with control, the small level of control may lead to block new infection and prevent viral production by using drug therapy with minimum side effects. Our numerical results show that the optimal treatment strategies reduce viral load and increase the uninfected $CD4^+T$ cell count after two days of therapy intervention.

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