Optimal Control Theory Applied to the Anti-Viral Treatment of AIDS

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Abstract

This work concerns a particular application of the Optimal Control Theory to a model related to HIV infection dynamics. The mathematical model adopted in this work was proposed by Nowak et al., 1996 and describes the dynamics of viral concentration in terms of interaction with CD4 cells and the cytotoxic T lymphocytes, which are responsible for the immune defense of the organism. The control variable is the drug dose, which, in turn, affects the rate of infection of CD4 cells by HIV virus. The cost function to be minimized is a weighted sum of the final viral load and the accumulated side effects. Simulation results show that the optimal control scheme can achieve improved quality of the treatment in terms of reduction in the viral load and quantity of administered drugs, but has the inconvenience related to the necessity of frequent and periodic laboratory analysis to provide feedback information to adjust the doses.

1. Introduction

Mathematical and computational models have received growing recognition as a powerful tool for analysis in several branches of the human knowledge such as biology, economics and sociology and are no longer confined to traditionally quantitative fields of exact and technical sciences such as physics and engineering (LEVIN, 1997).
A number of works deal with the mathematical models for computer simulation of infectious diseases, particularly by viruses: NOWAK *et al.* 1991,1995,1996,1997; REGOES *et al.*, 1998; WEIN *et al.* 1998; ASACHENKOV *et al., 1994*; BRUNI *et al.*, 1975; CHERRUAULT *et al.*, 1986; MOHLER *et al.*, 1980; MURRAY, 1980. The mathematical models can be useful to describe situations that will be impossible to test in humans, such as required in 'what if' analysis and can also provide a basis for a quantitative approach, for instance, to optimize the administration of drugs.

In this work, the optimal control theory is used to reduce the final viral load while taking into account the accumulated side effect. The optimal control theory has been applied to many problems in engineering (CESARI, 1983; MOHLER *ET al.*, 1980) and there exist a number of efficient numerical methods to find the solution (STOER and BULIRSH, 1980).
The mathematical model is of crucial importance and the one proposed in NOWAK *et al.*, 1991, is used here. The model comprises a system of four non-linear ordinary differential equations that describe the number of uninfected CD4 cells, infected cells, free virus and cytotoxic T lymphocytes.

2. The Mathematical Model

The dynamic model proposed by NOWAK AND BANGHAM, 1996, consists of a system of four non-linear ordinary differential equations that specifically describe the variation of the variables x(t), y(t), v(t) and z(t) in function of the time $t \in R^+$. These variables represent, respectively, the amount of the healthy CD4 cells (x), infected CD4 cells (y), free virus (v) and the HIV-antigen specific cytotoxic T lymphocytes (z).

$$\begin{aligned}
\frac{dx(t)}{dt} &= \lambda - dx(t) - \beta x(t)v(t) \\
\frac{dy(t)}{dt} &= \beta(t)x(t)v(t) - ay(t) - py(t)z(t) \\
\frac{dv(t)}{dt} &= ky(t) - uv(t) \\
\frac{dz(t)}{dt} &= cy(t)z(t) - bz(t)
\end{aligned} \qquad \textbf{(1)}$$

Appropriate initial conditions are assumed to be given (boundary conditions) and in order to avoid numerical difficulties during the integration, a normalization of the variables are introduced.

The real parameters required in the model are: λ = rate of production of infected cells; D = mortality rate of the infected cells; a-rate of natural death of infected cells; β(t) = infection rate of healthy CD4 cells by HIV virus; p = rate of death of infected cells; b = rate of natural decline of CTL; c = rate of production of CTL; u-rate of natural decline of free virus; k = rate of production of free virus (which may be time variant).

In this model, the amount of healthy CD4 cells reproduce according to a fixed rate λ, but are attacked by the virus produced by other cells of its type, so that reproduction rate should decrease with to the existent amount of CD4, namely -Dx(t). Moreover, as those cells interact with the virus, its reproduction rate decreases according to the term - βx(t)v(t).

The infected cells depend on the density of cells in organisms that are amenable to be infected by the virus. Therefore, the growth of those cells y(t) will be proportional to the amount of healthy cells, which are succeptible to be infected x(t), and of the viral load v(t), with weighting factor β. This growth must be discounted by a term that represents the cells in terminal phase of destruction represented by ay(t) and also another term that is associated with the number of cells destroyed by the lymphocytes, py(t)z(t).

The density of virus v(t) increases in proportion to the infected cells once their replication depends essentially on the viral DNA code inside the cell, and this is represented in the model by k(t)y(t). However, the virus can be destroyed by the lymphocytes or suffer from erroneous decoding by *reverse transcriptase* enzyme (GALLO, 1994), which yields the term uv(t).

The model takes into account the production of cytotoxic T lymphocytes by the organism. This production depends on the antigenic characteristics of the viral particles, represented by cy(t)z(t) and a natural decline rate -bz(t).

3. The Optimal Control

The problem of drug administration in cast into the optimal control form, where the dose m(t) affect the infection rate of healthy CD4 cells β(t). The objective is to minimize the cost functional

$$J[m(.)] = \psi \frac{v^2(t_f)}{2} + \int_{t_0}^{t_f} \frac{m^2(t)}{2} dt \qquad \textbf{(2)}$$

subject to the state equations (1). The proposed cost functional J attempts to balance the accumulated side effect of the drug (the integral term) and the final viral load (the terminal cost). The choice of the weight Ψ depends on the subjective evaluation of the relative importance of the side effects and the reduction of the viral load over a fixed time horizon by the clinical staff.

It is assumed that the parameter β presents an exponential characteristic with respect to m,

$$\beta(t) = e^{-m(t)} \qquad \textbf{(3)}$$

where m(t) is the drug dose at time t, so that β becomes small when large doses m are used but can never become zero.

The boundary conditions are:

$$\begin{aligned} &x(0) = x_0 \\ &y(0) = y_0 \\ &v(0) = v_0 \\ &z(0) = z_0 \\ &x(t_f) = y(t_f) = v(t_f) = z(t_f) = \textit{free} \end{aligned} \qquad \textbf{(4)}$$

The Hamiltonian for this optimal control problem is:

$$\begin{aligned} H = {} & \lambda_x\left(\lambda - dx(t) - \beta x(t)v(t)\right) + \\ & + \lambda_y\left(\beta x(t)v(t) - ay(t) - py(t)z(t)\right) + \\ & + \lambda_v\left(k(t)y(t) - u(t)v(t)\right) + \\ & + \lambda_z\left(cy(t)z(t) - bz(t)\right) + \lambda_J\left(\frac{m^2(t)}{2}\right) \end{aligned} \qquad \textbf{(5)}$$

where the λ_x, λ_y, λ_v, λ_z are the adjoint variables or co-state variables and λ_J corresponds to the augmented state introduced to transform the original cost function in Bolza form into Mayer form (CESARI, 1983).

For the sake of simplicity of notation, the following shorthand will be used for the state variables x(t) ≡ x; y(t)≡y; v(t) ≡ v; z(t) ≡ z and the controls variables m(t) ≡ m (and, correspondingly, β(t) ≡ β)..

The differential equations governing the adjoint variables are obtained by differentiation of the Hamiltonian function,

$$\begin{aligned} \frac{d\lambda_x}{dt} &= -\frac{\partial H}{\partial x} \\ \frac{d\lambda_y}{dt} &= -\frac{\partial H}{\partial y} \\ \frac{d\lambda_v}{dt} &= -\frac{\partial H}{\partial v} \\ \frac{d\lambda_z}{dt} &= -\frac{\partial H}{\partial z} \end{aligned} \qquad \textbf{(6)}$$

which, in a more explicit form become:

$$\begin{aligned} \frac{d\lambda_x}{dt} &= \lambda_x d + \lambda_x \beta v - \lambda_y \beta v \\ \frac{d\lambda_y}{dt} &= \lambda_y a + \lambda_y pz - \lambda_v k - \lambda_z cz \\ \frac{d\lambda_v}{dt} &= \lambda_x \beta x - \lambda_y \beta x + \lambda_v u \\ \frac{d\lambda_z}{dt} &= \lambda_y py - \lambda_z cy + \lambda_z b \end{aligned} \qquad \textbf{(7)}$$

The value of the optimal control variable at each instant can be found by noting that it minimizes the Hamiltonian (Pontriagin's Minimum Principle, CESARI, 1983) and, therefore, must satisfy the necessary condition:

$$\frac{\partial H}{\partial m^*} = 0 \qquad \textbf{(8)}$$

yielding the expression for the optimal drug dose:

$$m^* + \lambda_x e^{-m^*} xv - \lambda_y e^{-m^*} xv = 0 \qquad \textbf{(9)}$$

Solutions to general non-linear optimal control problems may be difficult to be found and a numerical method must be invoked. The integration of the differential equations was carried out using the Runge-Kutta-Felberg 7/8 integrator with adaptive step-sizes (STOER *et al*, 1980), while the two point boundary value problem (TPBVP) corresponding to the present optimal control problem (equations 10 – 14) was solved by a *step descent* numerical method. The *step descent* method is fast at initial stages, presenting quadratic convergence, but when the iterations approach the optimum point, it becomes slower.

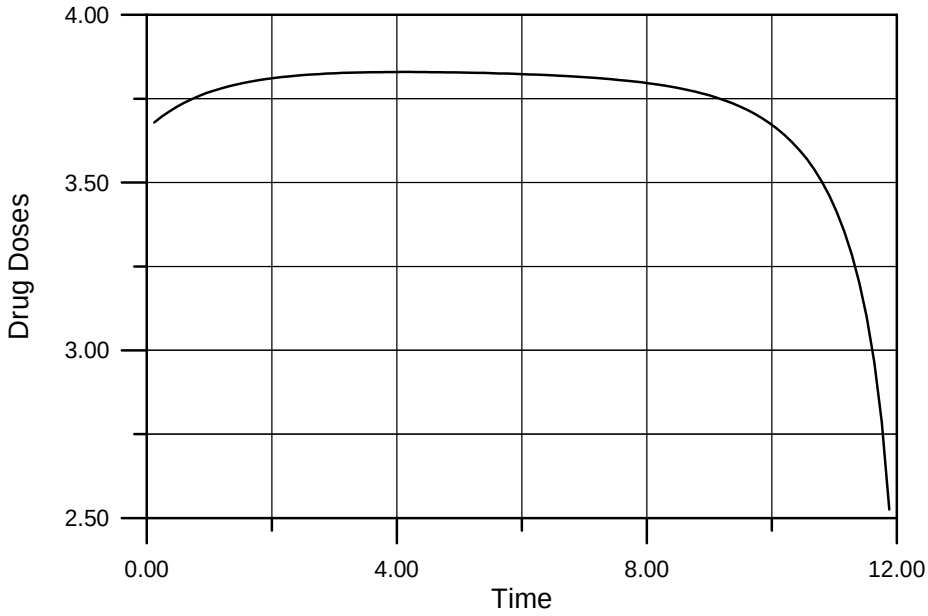

Figure 1 - Optimal Drug Doses (Optimal Control Law)

4. The Results

The state equations (1) were simulated for the cases $\beta = 1$ (no treatment) and $\beta = \beta^*(t)$ (optimal drug doses, Figure 1) using the initials conditions and the values of parameters obtained from NOWAK AND BANGHAM, 1996, presented in Table 1.

In Figure 1, the number of uninfected CD4 cells is seen to decay rapidly for non-treated patients (without control), while it is kept at an adequate level when optimal treatment scheme is used (optimal control). Figure 2 shows that the number of infected CD4 cells decline with treatment, while without treatment, it tends to increase. The same happens with the number of free virus, as shown in Figure 3. The initial increase in the number of lymphocytes in untreated patients in seen in Figure 4.

Modifications of the weight Ψ or moderate uncertainties in the model parameters (±10%) change the value of the optimal doses, but the overall shape of the curves (Figures 1-5) are preserved. Therefore, despite the difficulty with the estimation of the model parameters and the subjective nature of the choice of the cost functional, the proposed method provides some interesting insight into the dynamics of AIDS and may be a useful tool in medical training.

Parameters	***Values***
λ	1.0
d	1.0
a	0.8
β	1.0
p	0.05
b	0.01
c	0.1
u	0.01107
k	1.0

Variables	***Values***
x(0)	1.0
y(0)	0.2
v(0)	0.8
z(0)	0.03
t_f	12

Table 1 Values of the model parameters and initial condition used in the computer simulation

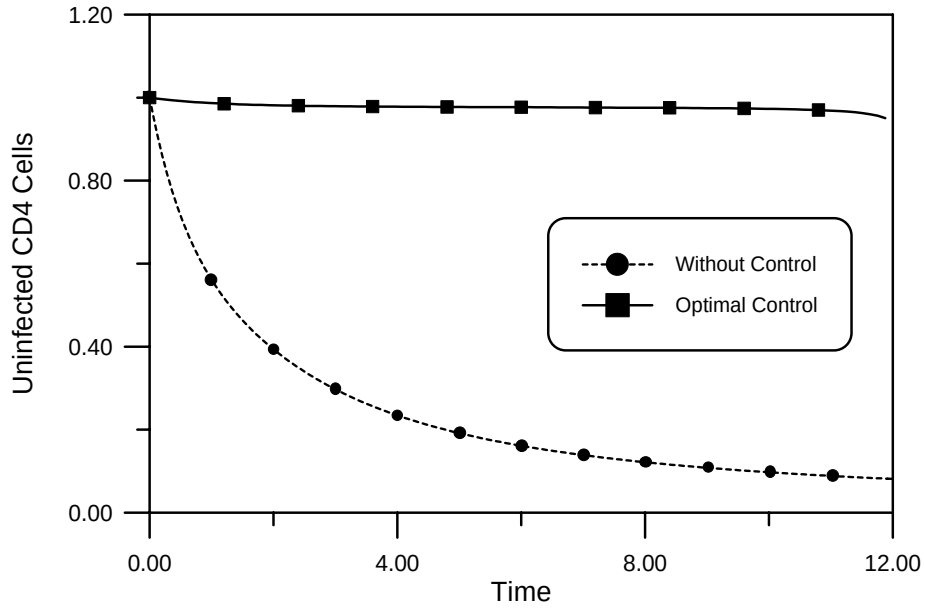

Figure 2 - Number of Uninfected CD4 Cells for the cases without control and with optimal control

5. Conclusions

The optimal control theory can be used to determine the optimal drug doses if a mathematical model of the infection and the values of the model parameters are available. In general, the task of estimating the model parameters for each patient may be very difficult to be carried out. However, the proposed methodology can still be useful in 'what if' type of analysis, where the medical staff can evaluate the effects of the alternative treatment schemes such as pulsed control (high doses applied at spaced intervals in time), constant control (moderate doses kept constant during a long period), adaptive control (one such scheme could be the use of doses that are proportional to some easily measurable variable) and others. The optimal control scheme yields the best results in terms of the chosen cost functional, as verified by extensive simulations, if the model is accurate (the model parameters are known and effects such as the presence of mutant virus are absent).

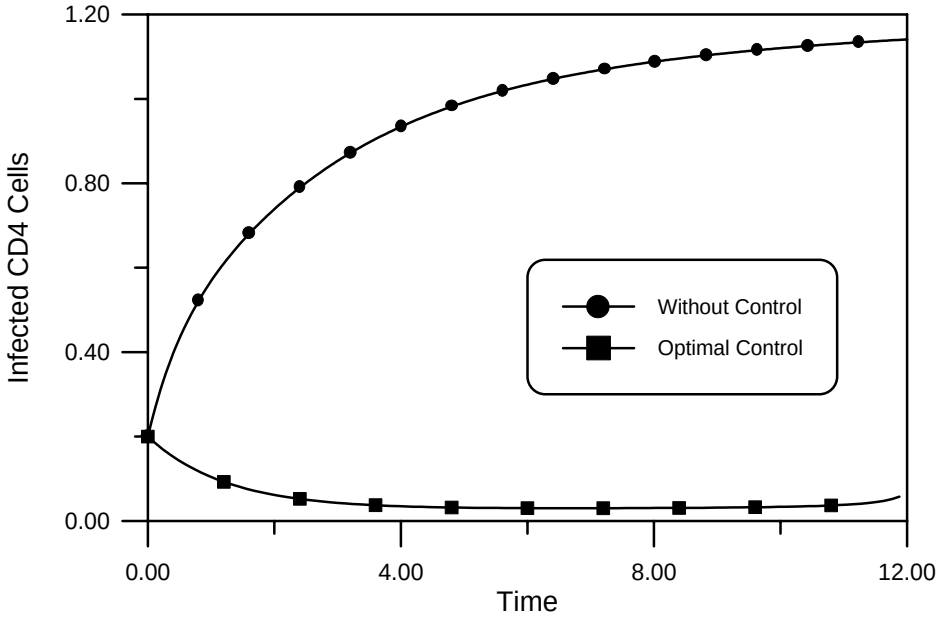

Figure 3 - Number of CD4 Cells infected by HIV virus for the cases without control and with optimal control

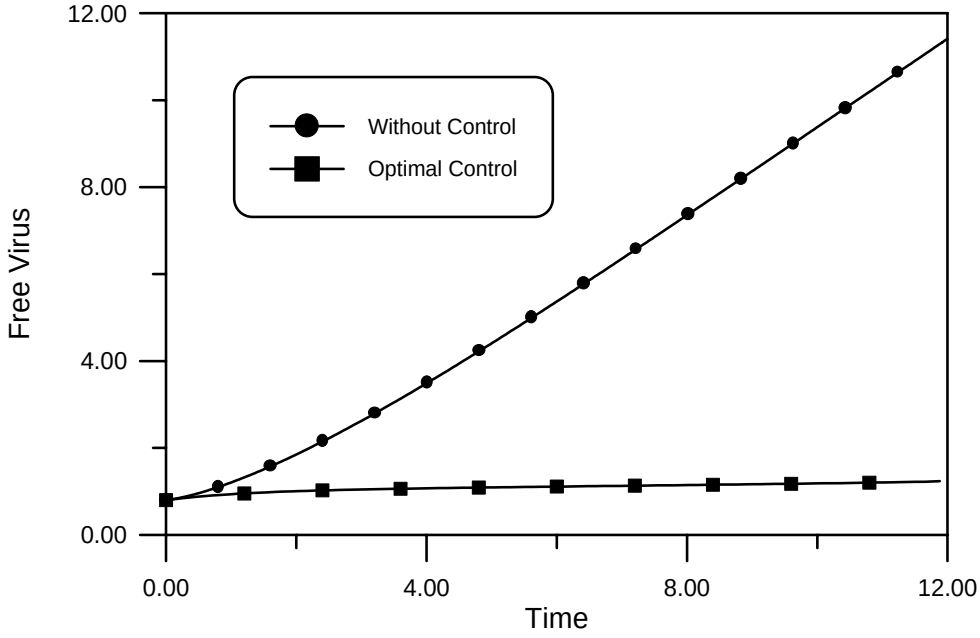

Figure 4 - Number of Free Virus for the cases without control and with optimal control

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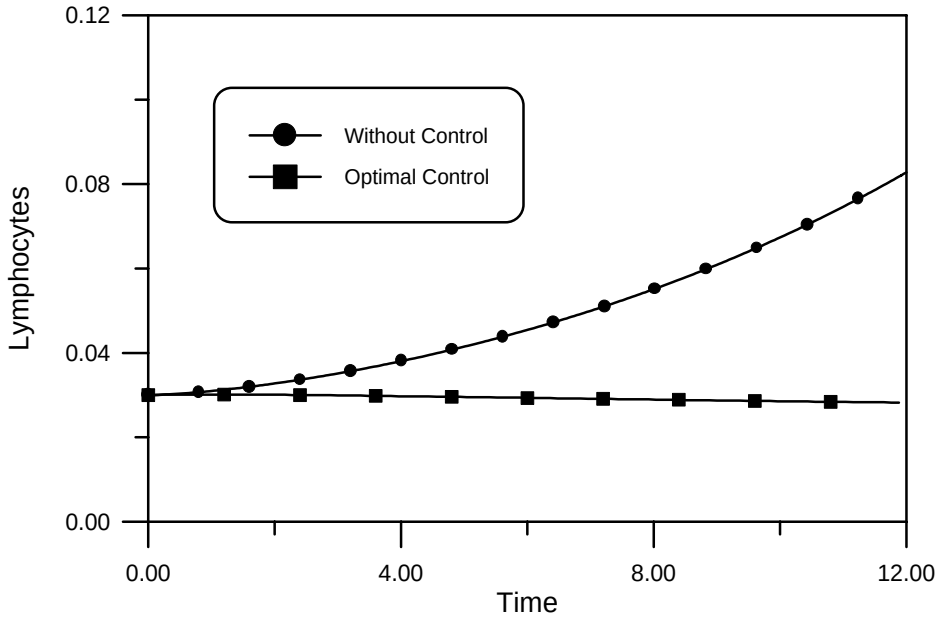

Figure 5 - Number of Lymphocytes for the cases without control and with optimal control

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