A Quantitative Analysis of Optimal Treatment Schemes for AIDS

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Abstract

The present work presents some numerical procedures in order to estimate the right drug doses in the treatment of AIDS based on the Optimal Control Theory and using a mathematical model for the viral load and the number of CD4+ T cells. The optimal solution is then compared in terms of the clinical response obtained using sub-optimal doses and fixed doses. The sub-optimal doses are found by a search method applied to the coefficients of a series approximation of the admissible doses function. The parameters of the mathematical model used in the computer simulations were adjusted to fit actual clinical data. The sensitivity of the proposed procedure is evaluated by a Monte Carlo type method where random uncertainties of up to 10% are added to the model parameters.

1. INTRODUCTION

Mathematical models have been extremely valuable in the research of dynamical phenomena related to a variety of biological systems. The increase in the cases of AIDS has brought a lot of effort to find new mathematical models in order to try to describe the temporal variation of the HIV load or the number of CD4+ T cells. Works on this topic have focused on analyzing the effects of the drug administration strategies [Mittler *et al*. 1998, Murray *et al*. 1998 and Wick 1999] along the time.

Mathematical models that provide quantitative descriptions of the dynamics exhibited by AIDS were, among others, derived by Nowak [Nowak and Bangham 1996], Phillips [Phillips 1996], Perelson [Perelson and Nelson 1993] and Tan [Tan and Wu 1998]. Extended versions of these mathematical models have been used to optimize the drug doses required in the treatment. The particular model used in this work was originally proposed by Tan [Tan and Wu 1998], and is similar to that appearing in Perelson [Perelson and Nelson 1993].

Previous work [Caetano and Yoneyama 1999a] has shown that it is possible to improve the effectiveness of the treatment by using a closed loop drug administration strategy. The improvements were related to the fact that more information was used in the process of tuning the drug doses, when compared to standard constant dose treatment schemes. Moreover, it was also shown (by computer simulation) that it is possible to use the optimal control theory to take into account the adverse side effects during a short term treatment scheme [Kirschner *et al* 1997, Joshi 2002, Caetano and Yoneyama 1999b]. Also, in another work, a locally optimal control, using a linearized model and the linear-quadratic regulator theory, was combined with standard fixed dose treatment to achieve an improved balance between the therapeutic and side effects [Caetano and Yoneyama 2002].

The aim of the present study is to analyze the dynamics of the viral load and the number of CD4+ T cells under different treatment schemes, including the optimal one, using a dynamic model fitted to actual data. The actual data used to tune the model parameters were provided by the Centro de Referência e Treinamento em *DST-AIDS* at São Paulo. The mathematical model comprises four differential equations representing the dynamics of uninfected CD4+ T cells, latently infected CD4+ T cells, actively infected CD4+ T cells and free viruses. A cost function was proposed to express, in a quantitative manner, the compromise between the therapeutic outcomes and the intensity of side-effects. A numerical technique was then used to solve the optimal control problem. The optimal results were compared to those corresponding to the suboptimal solution, where a series expansion type approximation is used, and to the constant-doses treatment scheme.

2. METHODS

2.1. The Mathematical Model

The model in Tan [Tan and Wu 1998] describes the clinical evolution of patients infected by HIV. The original model comprises four differential equations involving variables with stochastic terms. Here, the mathematical model was simplified by eliminating these stochastic terms. The dynamics is then described by the differential equations

$$\begin{cases} \dot{x}_1 = S(x_4) + \lambda(x_1, x_2, x_3)x_1 - x_1[\mu_1 + k_1(m_1)x_4] \\ \dot{x}_2 = \omega k_1(m_1) \cdot x_4 x_1 - x_2[\mu_2 + k_{20}] \\ \dot{x}_3 = (1-\omega)k_1(m_1)x_4 x_1 + k_{20}x_2 - \mu_3 x_3 \\ \dot{x}_4 = N(t)\mu_3 x_3 - x_4[k_1(m_1) \cdot x_1 + \mu_v] \end{cases} \quad (1)$$

where $\dot{x} = dx/dt$ represents the time derivative and the values from parameters of dynamic system are obtained by relations:

$$S(x_4) = \frac{s\theta}{\theta + x_4} \quad (2)$$

$$\lambda(x_1, x_2, x_3) = r\left[1 - \frac{(x_1 + x_2 + x_3)}{T_{max}}\right] \quad (3)$$

$$N(t) = \beta_2 - (\beta_2 - N_0)\, e^{-\beta_1 t} \quad (4)$$

with

$x_1 = x_1(t) \equiv$ uninfected CD4+ T cells;

$x_2 = x_2(t) \equiv$ latently infected CD4+ T cells;

$x_3 = x_3(t) \equiv$ active infected CD4+ T cells; and

$x_4 = x_4(t) \equiv$ free virus HIV;

The parameters are s = the rate of generation of x_1 from precursors; r = rate of stimulated growth of x_1; T_{max} = maximum T cells population level; μ_i = death rate of x_i ; N = the number of infectious virions produced by an actively infected T cell; θ = viral concentration needed to decrease s. The function $k_1(\,)$ depend on the drug doses m

$$k_1(m) = k_{10}\, e^{-\alpha m}$$

and is related to the conversion rate of uninfected CD4+ T cell to latently infected CD4+ T cell by contact with viruses.

Examples of drugs that affect the dynamics via function k_1 are the reverse transcriptase inhibitors: *zidovudine, ddI, 3TC* and *lamivudine*.

Intuitively, one can say that x_1 cells are stimulated to proliferate with rate $\lambda(x_1, x_2, x_3)$ in the presence of antigen and HIV.

Without the presence of HIV, the rate of generation is $S(x_4)$. In the presence of free HIV (x_4), uninfected cells x_1 can be infected to become x_2 cells or x_3 cells, depending on the probability of these cells (x_1) to become actively (x_3) or latently infected (x_2) cells with rate ω.

However, the x_2 cells can also be activated to become x_3 cells. The x_3 cells are short living and will normally be killed upon activation with death rate μ_3. The x_1, x_2 cells and x_4 free viruses have finite life and the death rates in this model are μ_1, μ_2 and μ_3 respectively. The x_3 cells release free viruses x_4 with rate $N(t)$ as described by equation (4).

2.2. The Optimal Control

The standard treatment schemes use constant drug doses according to tables recommended by the World Health Organization. The doses are adjusted from time to time depending on the clinical evolution of the particular patient.

Here, in the present work the doses are to be adjusted dynamically using optimal control theory.

The main problem of optimal control is to find a control input $m(t)$ that minimizes the cost function

$$J(m) = h(x(t_f), t_f) + \int_{t_0}^{t_f} g(x(t), m(t), t)dt$$

where t0 and tf are the initial and final times, respectively, fixed *a priori*. The functions h and g are required to be bounded and positive. The state $x(\,)$ and $m(\,)$ are required to satisfy the state equations

$$\dot{x} = f(x(t), m(t))$$

In the specific problem treated here, $f(\,)$ is given by the equations (1-4).

The cost function try to quantify the side-effects that are related to the drug doses while also taking into account the clinical conditions as reflected by the values of CD4 counts and viral load. An index that was used in previous work by the authors [Caetano and Yoneyama 2002] with satisfactory results is given by

$$J(m) = \int_{t_o}^{t_f} \left\{ \phi\left(1 - \varepsilon_1 m(t) e^{-\alpha_1 m_1(t)}\right) + \frac{\gamma_1}{x_1^2(t)} + \gamma_2 x_4^2(t) \right\} dt \quad (5)$$

An heuristic interpretation of the proposed cost functional is that the first term in the integral represents the side-effects. When $m = 0$,

$$\phi\left(1 - \varepsilon_1 m(t) e^{-\alpha_1 m_1(t)}\right) = 1$$

and the side effect is proportional to ϕ, while for large values of *m*,

$$\phi\left(1-\varepsilon_1 m(t)e^{-\alpha_1 m_1(t)}\right)\cong 0$$

and thus the side effect is neglected. The coefficients ϕ are a weight that reflects the importance of the side-effects, when compared to the clinical state which are represented by the other two terms in the integral.

The term in x_1 (uninfected CD4+ T cells) is clearly small (*a favorable situation*) when x_1 is large (that is, an elevated number of CD4+ T cells). The term in x_4 (viral load) is in a quadratic form, so that it is small (again, *a favorable situation*) when x_4 is also small. The choices of the values of the weights ϕ, γ_1, and γ_2, are subjective and require controlled experiments.

The optimal control problem is to find *m(t)* that minimizes equation (5), subject to restrictions represented by the state equations (1-4) with fixed final time and free final state variables. Using the Pontryagin's Maximum Principle (see, for instance [Kirk 1970] or [Lewis 1986]), the adjoint variables should satisfy *

$$\lambda = -\frac{\partial H}{\partial x} \qquad (6)$$

where H is the Hamiltonian function, which in the present case is given by

$$\begin{aligned} H = {} & \lambda_1\left(\frac{s\theta}{\theta+x_4}+r\left(1-\frac{x_1+x_2+x_3}{T_{max}}\right)x_1-x_1\left(\mu_1+k_1x_4\right)\right)+\\ & +\lambda_2\left(\omega k_1x_4x_1-x_2\left(\mu_2+k_2\right)\right)+\\ & +\lambda_3\left(\left(1-\omega\right)k_1x_4x_1+k_2x_2-\mu_3x_3\right)+\\ & +\lambda_4\left(\left(\beta_2-\left(\beta_2-N_0\right)e^{-\beta_1 t}\right)\mu_3x_3-x_4\left(k_1x_1+\mu_v\right)\right)+\\ & +\phi\left(1-\varepsilon_1 m(t)\,e^{-\alpha_1 m(t)}\right)+\frac{\gamma_1}{x_1^2(t)}+\gamma_2x_4^2(t) \end{aligned}$$

Substituting the expression of the Hamiltonian function H into the equation (6), one gets

$$\dot{\lambda}_1=\frac{2\lambda_1 r x_1}{T_{max}}+\lambda_1\left(\mu_1+k_1x_4\right)-\lambda_2\omega k_1x_4-\lambda_3\left(1-\omega\right)k_1x_4+$$
$$+\lambda_2 x_4 k_1+\frac{2\gamma_1}{x_1^3}$$

$$\dot{\lambda}_2=\frac{\lambda_1 r x_1}{T_{max}}+\lambda_2\left(\mu_2+k_2\right)-\lambda_3k_2$$

$$\dot{\lambda}_3=\frac{\lambda_1 r x_1}{T_{max}}+\lambda_3\mu_3-\lambda_4\mu_3\left(\beta_2-\left(\beta_2-N_0\right)e^{-\beta_1 t}\right)$$

$$\dot{\lambda}_4=\frac{\lambda_1 s\theta}{\left(\theta+x_4^2\right)}+\lambda_1x_1k_1-\lambda_2\omega k_1x_1-\lambda_3\left(1-\omega\right)k_1x_1+$$
$$+\lambda_4\left(k_1x_1+\mu_v\right)-2\gamma_2x_4$$

The optimal *m* should minimize the Hamiltonian function, so that

$$\frac{\partial H}{\partial m}=0$$

which, in the expanded version is

$$\lambda_1x_1k_{10}\alpha_1e^{-\alpha_1 m}-\lambda_2\omega k_{10}x_4x_1e^{-\alpha_1 m}+$$
$$+-\lambda_3\left(1-\omega\right)k_{10}\alpha_1x_4x_1e^{-\alpha_1 m}+\lambda_4x_4k_{10}x_1\alpha_1e^{-\alpha_1 m}+$$
$$+\phi\alpha_1\varepsilon_1me^{-\alpha_1 m}-\phi\varepsilon_1e^{-\alpha_1 m}=0$$

which clearly becomes

$$\begin{aligned} e^{-\alpha_1 m}\big[& \lambda_1x_1k_{10}\alpha_1-\lambda_2\omega k_{10}x_4x_1+\\ & -\lambda_3\left(1-\omega\right)k_{10}\alpha_1x_4x_1+\\ & +\lambda_4x_4k_{10}x_1\alpha_1+\phi\alpha_1\varepsilon_1m-\phi\varepsilon_1\big]=0 \end{aligned}$$

and the optimal drug doses are given by

$$m^+=\left(\frac{-\lambda_1+\lambda_2\omega+\lambda_3\left(1-\omega\right)-\lambda_4}{\varepsilon_1\phi}\right)+\frac{1}{\alpha_1}$$

The numerical values of the weights adopted in this work, for illustration purposes, are:

$$\gamma_1=2.5\cdot10^5 \qquad \phi=100$$
$$\gamma_2=1.0\cdot10^{-8} \qquad \varepsilon_1=0.01$$

The solutions of Optimal Control Problems are generally based either on the Pontryagin's Maximum Principle or Dynamic Programming (see Kirk 1970, Lewis 1986). However, solutions of optimal control problems are rarely provided in a explicit closed form, because of the difficulty to solve the TPBVP (Two Point Boundary Value Problem) or the HJBE (Hamilton-Jacobi-Bellman Equation).

In the present work, the numerical solution was obtained by solving the TPBVP using the Collocation Method on Matlab 6.5 with routine bvp4c.m. The convergence for solution was fast and good.

2.3. The Sub-Optimal Control

An alternative to solving the TPBVP\ or the HJBE equation is to optimize directly the cost function by using a search method after parameterization of the admissible controls. Hence, if $\{u_i\}_{i=1,2,...}$ is a basis for the class *M* of admissible functions m(t), one can make the approximation

$$m(t) \approx c_1 u_1(t) + \ldots + c_p u_p(t) = m^c(t)$$

assuming that the expansion considers only terms up to order p. The restated problem is to find (c_1, ... ,c_p) such that

$$J(c_1, \ldots, c_p) = J[m^c]$$

is minimized.

The parameterization of the input functions *m(t)*, in the present work, involves a subset of the coefficients in the series expansion employing sinusoidal functions, as proposed by Jacob (Jacob 1972). The approximations provide sub-optimal solutions, in the sense that the cost achieved is generally greater when the higher terms of the series expansion are neglected compared to the case resulting from use of the actual optimal control. However, sub-optimal inputs may be far easier to compute than the actual optimal control.

Following Jacob (Jacob 1972), a convenient expansion is in terms of sin ( ) and cos ( )

$$\begin{aligned} m(t) = {} & c_1 + c_2 t + c_3 \sin(c_0 t) + c_4 \cos(c_0 t) + \\ & + c_5\left[3\sin(c_0 t) - 4\sin^3(c_0 t)\right] + \\ & + c_6\left[8\sin(c_0 t) - 4\sin(c_0 t)\cos(c_0 t)\right] + \\ & + c_7\left[16\sin(c_0 t)\cos^4(c_0 t) - 12\sin(c_0 t)\cos^2(c_0 t)\right] + \\ & + c_8\left[6\sin(c_0 t)\cos^5(c_0 t) - 20\sin^3(c_0 t)\cos^3(c_0 t) + \right. \\ & \left. + 6\sin^5(c_0 t)\cos(c_0 t)\right] \end{aligned}$$

2.4. The Clinical Data

The clinical data used in this work were provided by the Centro de Referência e Treinamento em DST-AIDS in São Paulo city, Brazil, after proper authorization from the Ethics Committee. From the approximate total of 5.000 medical records, 43 were selected to be included in the database used here. The selection procedure was carried out in order to retrieve only those records pertaining to patients who did not undergo severe opportunistic infections that required aggressive treatment, intermittent treatment programs involving many interruptions and returns or frequent changes of the administered drugs among other factors. Moreover, in order to adjust the model parameters, the patient records were required to include adequately long periods of fixed treatment scheme, so that identification techniques could be applied.

The model parameters for each specific patient were obtained by combining published values with those found by fine tuning by an iterative procedure. The parameters in the model were first initialized with values presented in Tan [Tan and Wu 1998] and Perelson [Perelson and Nelson 1999]. Then, iteratively, small corrections were added to those parameters until the simulation results using the updated model would agree with the real clinical data, up to a pre-specified tolerance level. Table 1 presents typical numerical values (actually record 002) which are used in the results appearing hereafter. Considering that the number of data points for a specific patient is rather small, the uncertainty in determining the model parameters might be significant. Therefore, in order to verify robustness of the solution, the sensitivity of the results was evaluated by introducing random perturbations (±10%) on the nominal parameter values of the model, under the action of the computed sub-optimal control.

Table 1. Model parameters

s	R	T_{max}	μ_1	μ_2	μ_3
0.01	0.102	1500	0.05	0.014	0.3

μ_v	k_{10}	k_{20}	N_0	θ	ω
2	3E-5	0.007	1400	1	0.97

β_1	β_2	α_1	α_2
0.01	1000	0.002	0

Table 2. Initial conditions

x_1	x_2	x_3	x_4	t_f
28	300	110	407,000	340

3. RESULTS

The numerical simulations were performed using the initial conditions shown in Table 2.
Figure 1 shows the response of the component $x_1(t)$, density of CD4+ T cells to treatments with optimal, suboptimal and constant doses. Figure 2 shows the corresponding $x_2(t)$ component, namely the viral load. Although the achieved level of CD4 is lower with the optimal doses when compared to those obtained by using either suboptimal or constant doses (figure 1), the viral load is significantly smaller when the administered doses are optimal (figure 2). Figure 3 shows the drug doses. It can be noticed that the optimal doses tends to be higher than either suboptimal or constant doses in the initial phase of the treatment. However, the optimal doses tend to decay faster than the sub-optimal doses. The sharp drop in the value corresponding to optimal doses in the last phase is related to the\ effect of adopting a fixed final time (border effect). In a practical application, one could compute the optimal doses for a slightly longer time horizon and discard the last periods. In figures 1 and 2, the actual clinical data corresponding to constant dose treatment offered to the specific patient (indicated by the symbol +) show that the mathematical model had been fitted adequately.

Figure 4 shows the variation of the integral term in the cost functional with time. In terms of the proposed cost function, the optimal doses yield a significantly lower cost, indicating that an improved balance between the therapeutic and side effects and are achieved.

In order to investigate the sensitivity of the sub-optimal solution (first form of m^c, random perturbations were added to the parameters s, r, k_{10} and μ_1, while undergoing treatment using the constant dose scheme. The perturbations were multiplicative factors of type $(1+0.1\Delta)$ where Δ is a uniformly distributed random variable assuming values between [-1 , 1]. The results are shown in figure 5. It can be noted that the perturbed trajectories in the CD4 × Viral Load plane remain within a vicinity of the nominal trajectory (without perturbations). The adjoint variable for CD4 is shown in figure 6 with terminal condition equal zero.

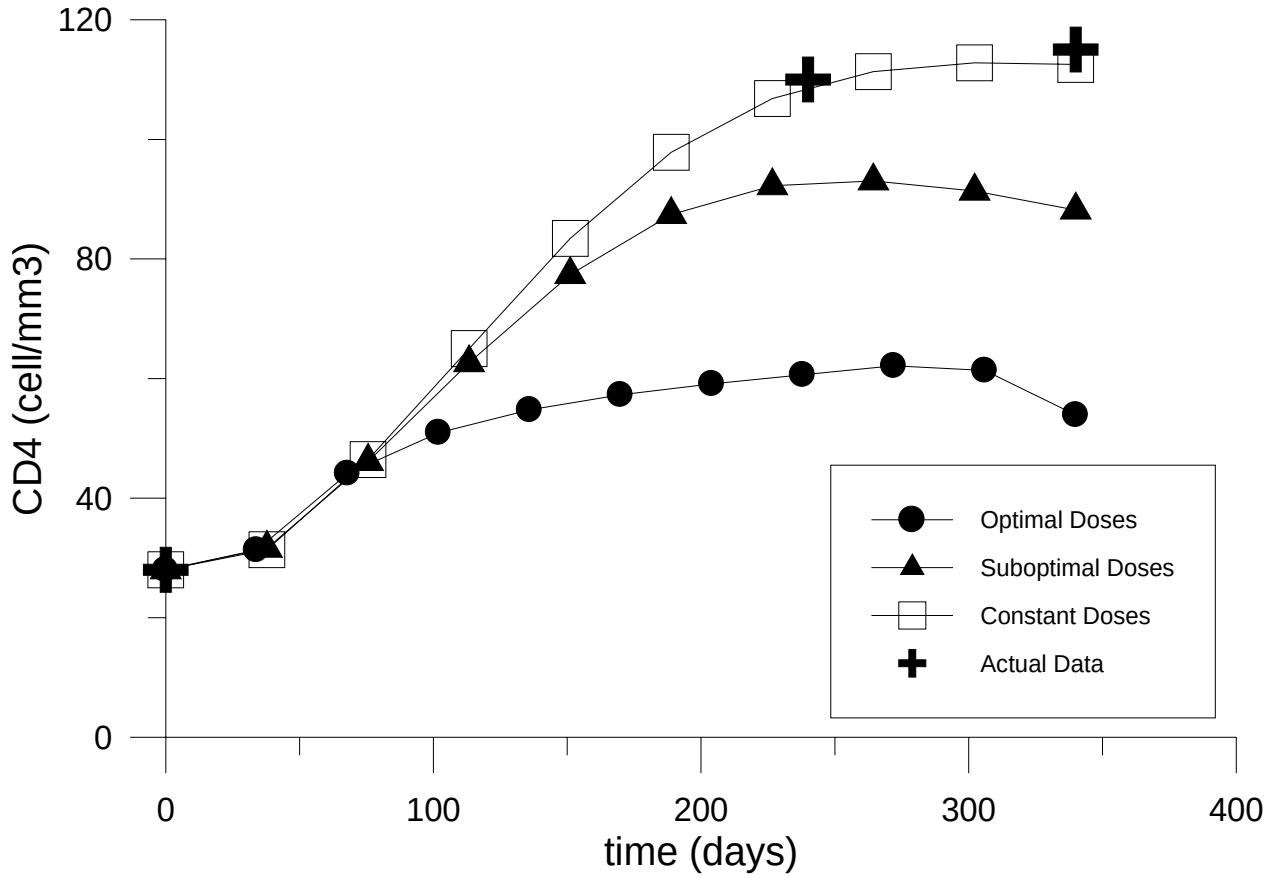

Figure 1. Effects of the various forms of treatment on the number of CD4 cells.

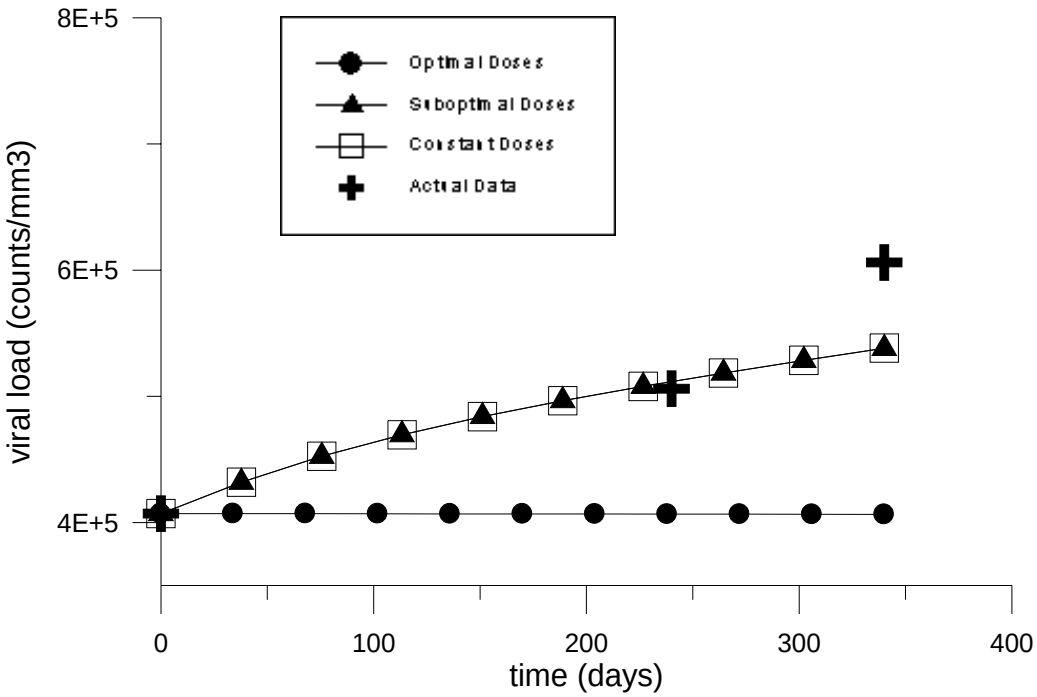

Figure 2. Response of the viral load to treatments using varied drug doses.

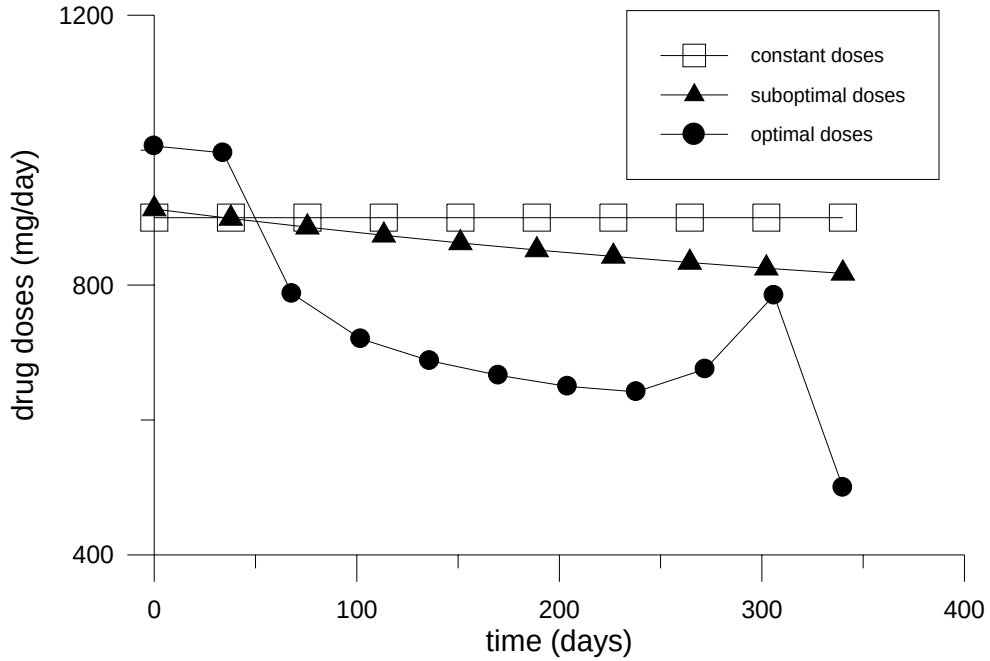

Figure 3. Comparison of doses computed using optimal, sub-optimal (sin-cos expansion) and constant schemes.

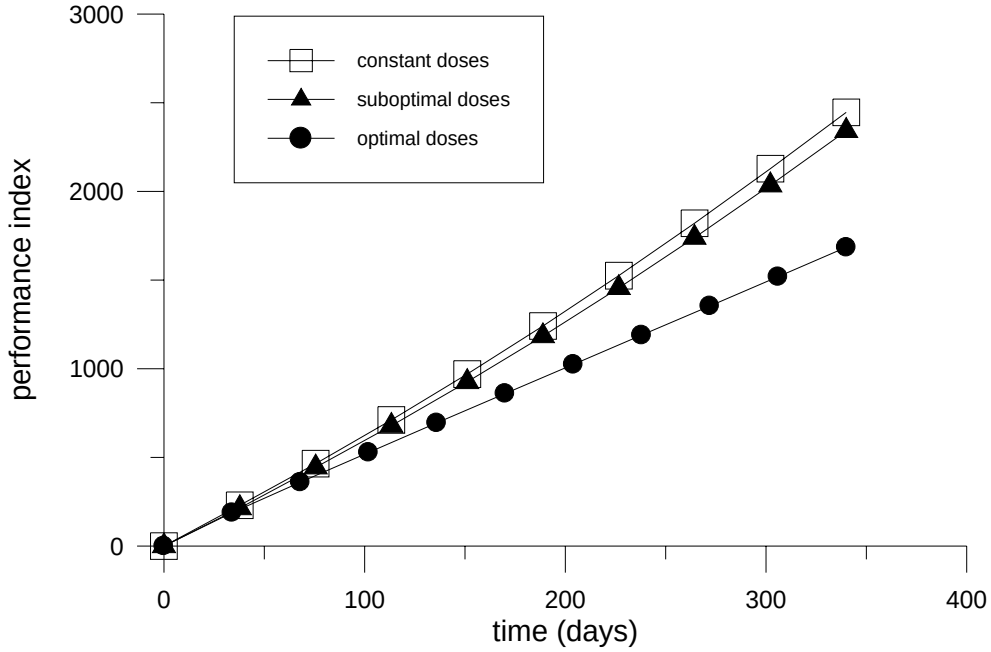

Figure 4. Integral term of the performance index. The actual cost corresponds to the value at time = t_f = 340 days.

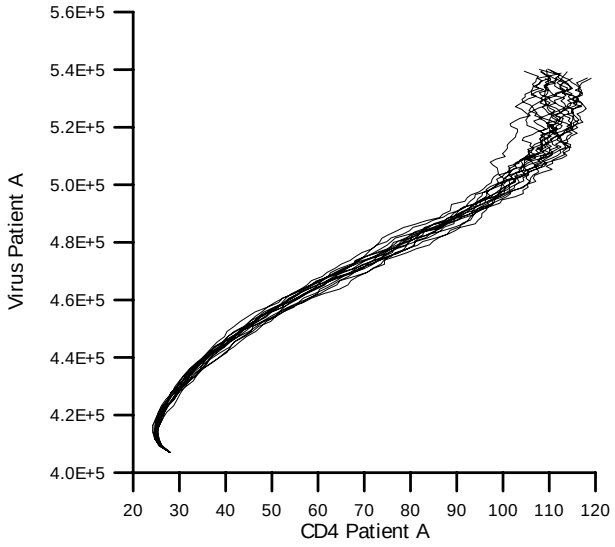

Figure 5. Sensitivity analysis considering 10% random variations on the model parameters and under sub-optimal control.

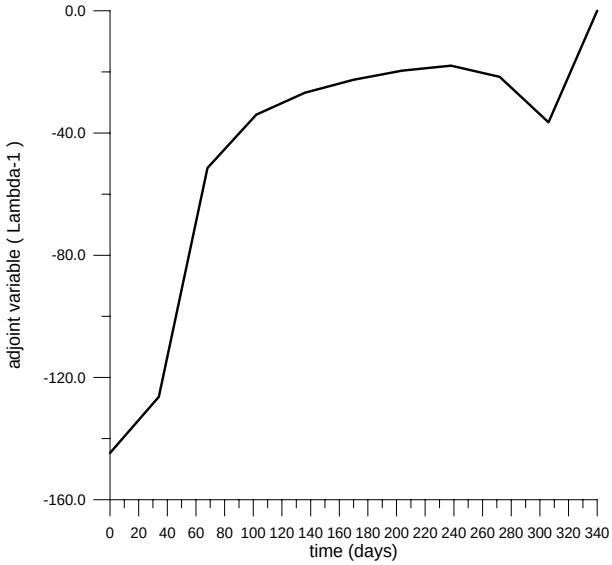

Figure 6. Adjoint variables for CD4 variable.

4. CONCLUSIONS

This work dealt with the problem of optimizing the drug doses in the treatment of AIDS using optimal control theory. A sub-optimal control scheme that requires much less computational effort to yield the solution was also proposed. However, at least in terms of the proposed cost function, the optimal doses calculated by solving the state and co-state equations was found to be significantly better. Although the results depend on the choice of the cost function J(m), which involves subjective factors, the use of optimal drug doses resulted in an improved compromise between the side effects, reduction of the viral load and increase in the CD4+ T cells. A Monte Carlo type method with parametric perturbations of up to 10% variation around

the nominal values showed that the proposed method has adequate robustness against modelling uncertainty. The results obtained here can be extended by considering multi-drug treatment (such as HAART) using $k_1(m_1)$ and $k_2(m_2)$ functions. However, this can cause several difficulties for identifying the model parameters, since one would require patient data with a significant period of treatment under a fixed treatment scheme.

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