NUMERICAL OPTIMIZATION APPLIED TO THE TREATMENT OF AIDS IN THE PRESENCE OF MUTANT HIV VIRUS

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Abstract: Here is presented an application of Optimal Control to a model describing the dynamics of an infection by HIV where mutant forms are present. It extends authors' previous results where mutant drug-resistant HIV virus were absent. The model adopted, proposed in (Nowak, *et al*., 1997) deals with the dynamics of viral concentrations. The control is the dose of an alternative drug exhibiting different activity from the primitive and mutant HIV viruses. The cost function is a weighted sum of the total viral load at a fixed time horizon and the accumulated side effects. Simulation results show that the optimal control scheme can achieve improved quality of the treatment.

Keywords: Biomedical system, Differential equations, Nonlinear equations, Numerical simulation, Optimal control.

1. INTRODUCTION

A number of mathematical models have already been developed to describe the population dynamics of HIV in patients under drug treatment including the case of the presence of drug-resistant mutants (Nowak, *et al*., 1991, 1995, 1996, 1997; Regoes, *et al*., 1998; Wein, *et al*., 1998; Asachenkov, *et al*, 1994; Bruni, *et al*, 1975; Cherruault, 1986).

In this work, the optimal control theory is applied to a mathematical model proposed in (Nowak, *et al*., 1997) comprising five non-linear ordinary differential equations that specifically describe the variation of the amount of healthy CD4 cells, infected CD4 cells, free virus, cells infected by mutant virus and mutant virus particles.

The model takes into account the basic dynamics of virus-host cell interactions as well as the effects of the immune response on the viral load under

treatment with a drug that affects the rate of infection of CD4 cells by the mutant form of the virus.
The cost functional has a terminal cost involving the total number of HIV virus and an integral term involving the dose of the administered drug, so that the optimal control problem tends to make a compromise between the efficacy of the treatment scheme (final viral load) and the side effects (accumulated effects of the drug along the time horizon).

The optimal drug administration strategy is computed using a numerical method and the results for a typical patient (model parameters obtained from the current literature) is compared to a classical constant-dose therapy.

It might be very difficult to obtain the numerical values of the parameters involved in the model, for each patient, and also the weights used in the cost functional may depend on subjective evaluation of the clinical staff.

However, the developed numerical tools may be very useful as a tool for 'what if' type of analysis, where sensitivity to a specific drug, magnitude of the side effect, the actual cost of the drug, rate of viral reproduction and other variables can be adjusted and the effects evaluated by computer simulation.

2. THE MODEL

The model used in this work was proposed in (Nowak, *et al.*, 1997) and comprises the following non-linear ordinary differential equations:

$$\begin{aligned} \dot{x} &= \lambda - dx - \beta xv - \beta_m x v_m \\ \dot{y} &= \beta(1-\varepsilon)xv - ay \\ \dot{v} &= ky - uv \\ \dot{y}_m &= \beta\varepsilon xv + \beta_m x v_m - a y_m \\ \dot{v}_m &= k_m y_m - u v_m \end{aligned} \qquad (1)$$

where the variables are the number of uninfected CD4 cells (x), infected CD4 cells (y), free virus (v), mutant infected cells (y_m) and mutant free virus (v_m).

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

The parameters required in the model are:

- λ = rate of production of uninfected cells;
- d = rate of death of uninfected cells;
- a = rate of natural death of infected cells;
- β = rate of production of infected cells;
- β_m = rate of production of infected cells by mutant free virus;
- u = rate of natural decline of free virus;
- k = rate of production of free virus (which may be time variant);
- k_m = rate of production of free virus (which may be time variant);
- ε = probability of mutation from primitive to resistant mutant during reverse transcription of viral RNA into viral DNA.

The rate of production of infected cells by mutant free virus $\beta_m(t)$ will be controlled by drugs with activity of form

$$\beta_m(t) = \beta_{m_0} e^{-\alpha m(t)}$$

with β_{mo} the natural rate of production of infected cells by mutant free virus and α is related to the activity of the drug used.

In this model, 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 decreases with the current quantity of CD4 cells, namely -dx(t).

Moreover, as those cells interact with the virus, its reproduction rate further decreases according to the term

$$-\beta x(t)v(t)$$

and with mutant free virus

$$-\beta_m x v_m.$$

The quantity of infected CD4 cells depends on the availability of cells in the organism, which are amenable to be infected by the virus.

Therefore, the growth of those cells y(t) will be proportional to the existent amount of healthy cells x(t) and of free virus v(t), with weighting factor

$$\beta(1-\varepsilon).$$

This growth must be discounted by a term that represents the cells in terminal phase of destruction represented by ay(t).

The increase of the viral load v(t) is proportional to the quantity of infected cells since the replication depends essentially on the reverse transcripted viral DNA code inside the cell, and this is represented in the model by ky(t).

However, the virus can be destroyed by the lymphocytes or suffer from erroneous decoding (Gallo, 1994), which yields the term uv(t).

3. THE FORMULATION OF THE OPTIMAL CONTROL

The optimal control theory is used to find the solution that minimize (or maximize) a cost (or payoff) functional.

In the present case the cost functional is chosen to be a compromise between the viral load at a certain final time t_f and the accumulated cost related to the amount of administered drug, which in turn is related to the severity of side effects and also the actual cost of the treatment.

Denoting by J[m(·)] the cost achieved by using a drug administration policy m(·), the objective is :

$$\min_{m(.)} J[m(.)] = \frac{1}{2}(\psi_1 y^2(t_f) + \psi_2 y_m^2(t_f) + \psi_3 v_m^2(t_f) + \int_{t_0}^{t_f} m^2(\tau)d\tau)$$

where ψ_1, ψ_2 and ψ_3 are the weights that tend to force the final states of interest to be close to zero, in this case

$$y(t_f),\ y_m(t_f) \text{ and } v_m(t_f).$$

The variable m(t) is a function $m:[0,t_f] \rightarrow R$ that should be selected in such a way as to minimize J[m(·)] and, in the specific case, represents the drug dose administered to the patient.

The minimization of the cost functional should also take into account the dynamics constraints on state, given by equations (1).

The boundary conditions for the components of the state are

$$x(0) = x_0$$
$$y(0) = y_0$$
$$v(0) = v_0$$
$$y_m(0) = y_0$$
$$v_m(0) = v_{mo}$$
$$x(t_f) = y(t_f) = v(t_f) = y_m(t_f) = v_m(t_f) = \text{free}$$

The Hamiltonian corresponding to the present optimal control problem is:

$$H = \lambda_x(\lambda - dx - \beta xv - \beta_m xv_m) + \lambda_y(\beta(1-\varepsilon)xv - ay) + \lambda_v(ky - uv) + \lambda_{y_m}(\beta\varepsilon xv + \beta_m xv_m - ay_m) + \lambda_{v_m}(k_m y_m - uv_m) + \lambda_m\left(\frac{m^2}{2}\right)$$

The variables λ are the co-state variable or adjoint variables and the dynamic system that it represents is

$$\dot{\lambda}_x = -\frac{\partial H}{\partial x} = \lambda_x d + \lambda_x\beta v + \lambda_x\beta_m v_m - \lambda_y\beta(1-\varepsilon)v - \lambda_{y_m}\beta\varepsilon v - \lambda y_m\beta_m v_m$$

$$\dot{\lambda}_y = -\frac{\partial H}{\partial y} = \lambda_y a - \lambda_v k$$

$$\dot{\lambda}_v = -\frac{\partial H}{\partial v} = \lambda_x\beta x - \lambda_y\beta(1-\varepsilon)x + \lambda_v u - \lambda_{y_m}\beta\varepsilon x$$

$$\dot{\lambda}_{y_m} = -\frac{\partial H}{\partial y_m} = \lambda_{y_m} a - \lambda_{v_m} k_m$$

$$\dot{\lambda}_{v_m} = -\frac{\partial H}{\partial v_m} = \lambda_x\beta_m x - \lambda_{y_m}\beta_m x + \lambda_{v_m} u$$

The optimal control law minimizes the Hamiltonian at each time (Pontriagin's Minimum Principle, Cesari, 1983) and a necessary condition is

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

which in the specific problem can be written in a more explicit way as

$$\lambda_x\beta_{m_0}\alpha e^{-\alpha m}xv_m - \lambda_{y_m}\beta_{m_0}\alpha e^{-\alpha m}xv_m + m = 0$$

The Two-Point Boundary Value Problem (TPBVP), initial conditions for the state equations and terminal conditions for the co-state equations) that must be solved may be hard to tackle analytically.

Hence, the TPBPV is solved here using an iterative numerical method.

It is assumed that the patient has already started an initial treatment so that the replication of the primitive virus is null (β = 0) and also, it is expected that by the end of the control horizon, $v(t_f) << v_m(t_f)$.

However, a number of researchers have shown (Nowak, 1997) that free mutant HIV virus can begin to attack the uninfected cells and the therapy using the initial drug may be ineffective.

Therefore, the present optimization problem considers only the doses of an alternative drug that acts on the replication of the mutant virus through β_m.

4. NUMERICAL RESULTS

The numerical method used to solve the present optimal control problem is Steepest Descent (Stoer and Bulirsh, 1980). The numerical values of the model parameters and the initial values for the state

Table 1 Parameters of Simulation

Parameters	Values
λ	10
d	0.01
β	0.00 (hypothesis)
β_{m0}	0.005
ε	0.0001
a	0.5
k	10
u	3
k_m	10

Table 2 Initials Conditions to State Variable

State Variables	Initial Values
x(0)	30
y(0)	10
v(0)	100
$y_m(0)$	0.001
$v_m(0)$	0.1
Final Time	40 days

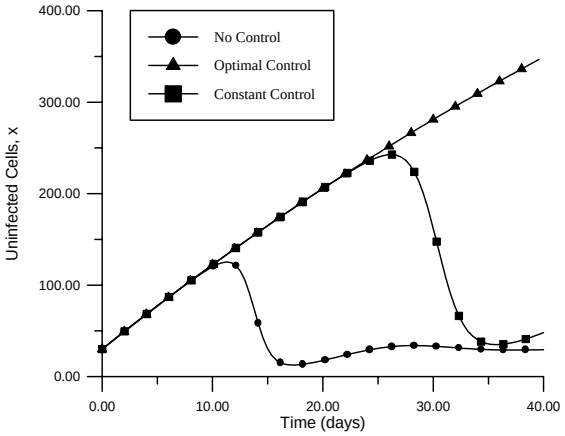

Fig. 1. Uninfected Cells

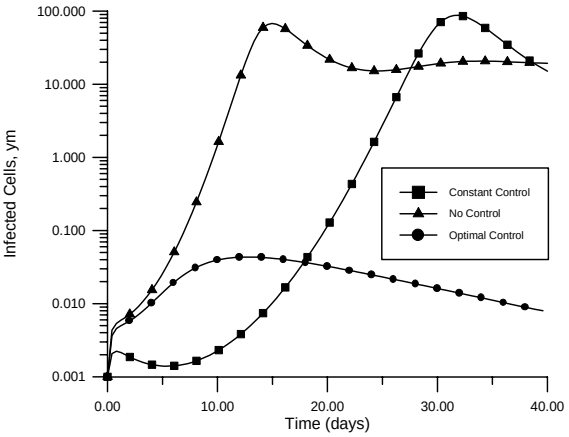

Fig. 2. Infected Cells

were obtained from (Nowak, 1997). The parameters used in the numerical example are shown in the Table 1 and the initial conditions are in the Table 2.

Fig. 1-3 present three situations that were simulated: (i) the case without the alternative drug, (ii) administration of the alternative drug at a constant dose and (iii) drug doses computed using the optimal control theory.

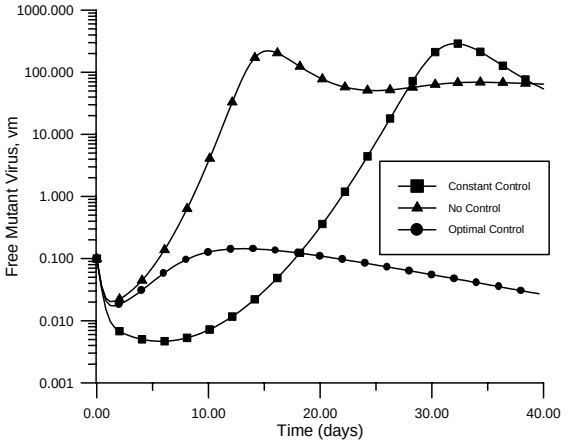

Fig. 3. Free Mutant Virus

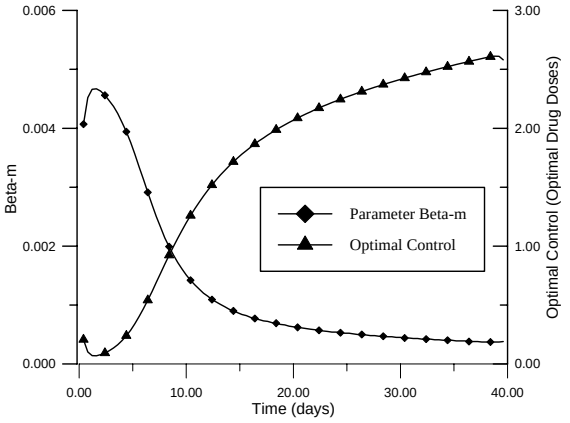

Fig. 4. Optimal Control and the corresponding virus growth rate

The curves for the case without control coincide with those presented in Nowak, 1997.

Fig. 4 shows the action of optimal control law. As a form of choosing the numerical value for the dose in the case of constant control (dose kept constant during the whole time horizon), one could use, for instance, the maximum value obtained in the optimal control strategy (about 2.5, in the specific case).

However, it can be observed in Fig. 5 that the use such doses during the whole of the control horizon amounts to a significantly larger value of the accumulated side effects.

Fig. 5 present the integral term of the cost functional, which represents the accumulated side-effects and expenses with the actual cost of the drugs, for the cases of constant control and optimal control.

5. CONCLUSION

The optimal control theory is a powerful tool to solve many interesting problems, and here an application to the optimization of drug administration policies for AIDS patients was proposed.

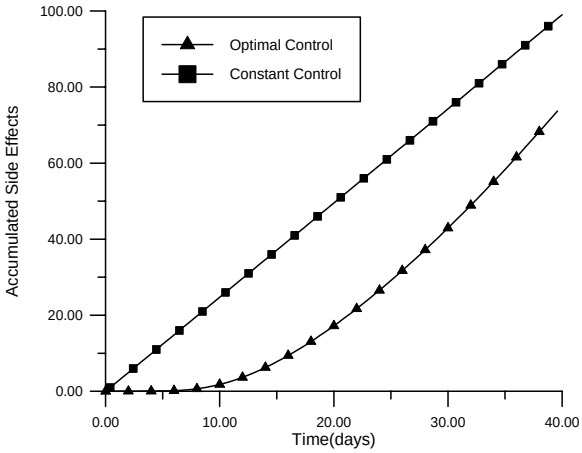

Fig. 5. Integral term of the cost functional, which represents the side-effects of the drug

The results were compared to a conventional clinical treatment scheme where the drug dose is constant for long time intervals.

Although the actual numerical values for the model parameters are difficult to be identified in actual clinical situations (and for each new patient), the developed numerical tools allow 'what if' type of analysis, where sensitivity to the drug, magnitude of the side effect, cost of the drug, rate of viral reproduction and other variables can be adjusted and the effects evaluated by computer simulation.

REFERENCES

Asachenkov, A., G. Marchuk, R. Mohler, S. Zuev (1994). *Disease Dynamics*, Birkhäuser, Boston.

Bruni, C., M.A. Giovenco, G. Koch, R. Strom (1975). A Dynamical Model of Humoral Immune Response. *Math. Biosciences*, **27**, 191-221.

Cesari, L. (1983). *Optimization: Theory and Applications*. Springer Verlag, New York.

Cherruault, Y. (1986). *Mathematical Modelling in Biomedicine*, D. Reidel, Dordrecht.

Gallo, R. (1994). *Caça ao Vírus, AIDS-Câncer e Retrovírus Humano, a História de uma Descoberta Científica.* Editora Siciliano, São Paulo, Brazil.

Levin, S.A., B. Grenfell, A. Hastings, A.S. Perelson (1997). Mathematical and computational challenges in population biology and ecosystems science. *Science*, **275**, 334-343.

Mohler, R.R., C. Bruni, A. Gandolfi (1980). A systems approach do immunology. In: *Proc. IEEE*, Vol. 68, No 8, pp. 964-990.

Murray, J.D. (1989). *Mathematical Biology*. Springer Verlag, New York.

Nowak, M.A., R.M. Anderson, A.R. McLean, T.F.W. Wolfs, J. Goudsmit, R.M. May (1991). Antigenic diversity thresholds and the development of AIDS. *Science*, **254**, 963-969.

Nowak, M.A., S. Bonhoeffer, G.M. Shaw, R.M. May (1997). Anti-viral treatment dynamics of resistance in free virus and infected cell populations. *Journal of Theoretical Biology*, **184**, 203-217.

Nowak, M.A., R.M. May, R.E. Phillips, S.R. Jones, D.G. Lallo, S. McDam, P. Klenerman, B. Köppe, K. Sigmund, C.R.M. Banghan, A.J. McMichael (1995). Antigenic oscillations and shifting immunodominance in HIV infections. *Nature*, **375**, 606-611.

Nowak, M.A. and R.M. Bangham (1996). Population dynamics of immune responses to persistent viruses. *Science*, **272**, 74-79.

Regoes, R.R., D. Wodarz, M.A. Nowak, (1998). Virus dynamics: the effect of target cell limitation and immune response on virus evolution. *Journal of Theoretical Biology*, **191**, 451-462.

Stoer, J. and R. Bulirsch, (1980). *Introduction to Numerical Analysis*. Springer Verlag, New York.

Wein, M. L., R.M. D'Amato, A.S. Perelson, (1998). Mathematical analysis of antiretroviral therapy aimed at HIV-1 eradication or maintenance of low viral loads. *Journal of Theoretical Biology*, **192**, 81-98.