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HIV infection control: a constructive algorithm for a state-based switching control

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Abstract: The control of the HIV infection is considered in the framework of the optimal control theory within the problem of resource allocation. A control action, changing the intervention strategy on the basis of the updated situations, is proposed. The switching instants are not fixed in advance but are determined along with the final control time. A constructive algorithm to compute iteratively the switching control is outlined. The solutions obtained provide interesting and promising results.

Keywords: state-based switching cost function, piece-wise constant control, epidemic models, HIV model

1. INTRODUCTION

In this paper the control of an epidemic disease is faced in the framework of optimal control theory: a cost index weighting differently the control depending on the varied conditions is introduced, thus changing the intervention strategy on the basis of the updated situations. The switching instants between such different strategies are not fixed in advance, but are determined on the basis of the dynamics evolution and on the optimization process. The epidemic disease here considered is the human immunodeficiency virus (HIV). One kind of approach considers the dynamics among categories of populations (subjects in the susceptible or infected status, patients in the pre-AIDS or the AIDS one are the most common), as in [1,2]. Differently, the point of view here assumed refers to the dynamics of the infection at a cellular level. In an HIV positive subject the virus infects the CD4 T-cells in the blood; when the number of these cells is below 200 in each mm^3 the HIV patient has AIDS. Many different models have been proposed to describe the HIV/AIDS infection. In [3], the model includes the uninfected and the infected CD4 T-cells, the concentration of helper-independent and of the helper-dependent and the concentration of the precursors. This model has two equilibrium points, one corresponding to the AIDS status and the other to the Long-Term nonprogressor (LTNP) one. In [4], this model is simplified, considering only the dynamics of the uninfected and the infected CD4 T-cells but taking into account the effects of cytotoxic T lymphocyte, in order to drive the HIV patient state into the LTNP region of attraction, instead to progress to the AIDS one. In [5], the variables introduced are the uninfected CD4 T-cells, the infected CD4 T-cells, the infectious virus, the noninfectious virus and the immune effectors, aiming at determining an optimal feedback control to drive the system to a stationary state with low viral load and strong immune response. A simple model considering only the concentration of CD4 T-cells and the concentration of the HIV particles is presented in [6]; two different treatment strategies are introduced: one aiming at delaying the virus progression and the other at boosting the immune system. Among all the proposed strategies, the policy using two drug controls appeared to be the best one, since it reduced the number of virus particles, beyond the increase of the number of uninfected CD4 T-cells, [7]. Also the problem of the HIV mutation is considered in [8, 9]; this could cause resistance to specific drug therapies. In [8], it is shown that the model predictive control has the best performance among the ones based on the use of a switched linear system for a nonlinear mutation model. In [9], the introduction of a suitable observer for the parameter estimation is proposed for a better behaviour of the control action. In [10], it is suggested the use of the fractional-order HIV model as a more realistic description than the traditional ones, thus obtaining very low levels dosage of the anti-HIV drugs. As well known, in optimal control the central aspect, beyond the choice of the model, is the definition of the cost index, i.e. what is required to be minimized: the control effort and/or the number of infected subjects, for example. Another aspect to be considered is the problem of resources allocation, especially when they are limited. For example, in [11] the problem of optimal resource allocation is faced when a limited quantity of vaccine has to be

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distributed between two non-interactive populations, assuming a stochastic epidemic model. The minimization of the control effort, i.e. the input amplitude, is also considered in [12]. In this paper, the HIV model proposed in [4] is adopted. The problem of controlling the HIV epidemic spread is faced in Section 2, starting from a cost index in which the control effort is weighted taking into account the number of infected cells; the weight coefficient is therefore state dependent. A constructive algorithm is proposed to provide an efficient resource allocation, by solving iteratively optimal control problems. In Section 3 the numerical results obtained for the case study here considered are presented and discussed. Conclusions and future work are outlined in Section 4.

2. THE CONSIDERED HIV MODEL AND THE PROPOSED CONTROL

In this paper, the model adopted in [4] is considered; the state variables are the uninfected CD4 T-cells, denoted by x, and the infected CD4 T-cells, denoted by y. The equations describing the relationships among these variables are:

$$\dot{x}(t) = \gamma - dx(t) - \beta(1-u(t))x(t)y(t) \quad (1)$$

$$\dot{y}(t) = -\beta x(t)y(t)u(t) + \pi(y(t)) \quad (2)$$

with $\pi(y(t)) = a + By(t) + Cy^2(t) + Dy^3(t)$ and initial conditions $x(t_0) = x_0$, $y(t_0) = y_0$. The meaning of the real parameters γ, d, β, α, B and C is illustrated in [3, 4]. The control u is assumed bounded by U.

In a classical optimal control design approach, the problem is to determine the control able to minimize the number of infected cells keeping the control effort within acceptable values. This goal is obtained defining a cost function in which the designer fixes the weights on the different terms, for example the errors, the state variables and the inputs. In this case, the cost function

$$J(u(t),T) = \int_{t_0}^{T} [K_1 + K_2 x(t)y(t)u(t) + K_3 y(t) + Pu^2(t)]\, dt, \qquad K_1, K_2, K_3, P \in \Re_+ \quad (3)$$

could be defined, where the time, the number of infected and non-infected cells, and the control are considered. Under these considerations, the optimal control problem can be formulated and solved. The choice of the weights is guided by considerations on the conditions under which the system evolves.

The idea here proposed is to define the cost index with one or more weights state dependent, so that different values can be assumed.

The presence of state functions as weights increases the complexity of the procedure for the optimal control problem solution. In order to overcome such a problem still maintaining the state dependency, the solution here proposed makes use of a state space partition into regions with consequent piecewise constant functions assumed for the weights, constant when the state belongs to each region. Without loss of generality, the partition of the state space considered hereafter is referred to only one component; specifically, the number of infected cells $y(t)$, the ones that, according to their number, can be associated to different levels of critical issues. Moreover, only the weight P of the control term is defined as a function of the state, $P(x(t),y(t)) = P(y(t))$. So, be $y^f \geq 0$ the minimum threshold under which the control action is assumed not necessary; then, the interval $[y^f, +\infty)$ is divided into N subintervals $I^i = [\xi^i, \xi^{i+1})$, $i = 1,2,\ldots,N$, with $\xi^1 = y^f$, once $\xi^{N+1} = +\infty$ is set for uniformity of notation. Consequently, the weight $P(y(t))$ can be rewritten as

$$P(y(t)) = \alpha_i \quad \text{for} \quad y(t) \in I^i, \quad \alpha_i \in \Re_+ \quad (4)$$

Under the assumption that a low cost for the control must be assumed if a strong action is wanted, that is for high values of infected CD4 T-cells $y(t)$, the relationship $\alpha_h \leq \alpha_k$ for $h > k$ will be chosen. The consequence of these choices is the definition of N optimal control problems, in which the cost function is of the form of (3) with the weight of the control term as in (4). The control u is in the class of bounded functions continuous almost everywhere satisfying

$$q_i(t) = -u(t) \leq 0, \quad q_2(t) = u(t) - U \leq 0, \quad U > 0 \quad (5)$$

The solution of the optimal control problem for system (1)-(2), under conditions (5) on the input and $\chi(y(T),T) = y(T) - y^f = 0$ on the final state, are the control $u(t)$ and the time $T > 0$,along with the corresponding state evolution, which minimize the cost index (3) with (4). To avoid the trivial case, it will be assumed that $y(t_0) = y_0 > y^f$, so that $y_0 \in I^i$ for some i. The constructive algorithm proposed requires to solve, iteratively, such an optimal control problem in each subinterval, according to the actual state evolution. More precisely, for the interval I^i, the Hamiltonian is

$$\begin{aligned} &H_{\alpha_i}(x(t),y(t),\lambda_1(t),\lambda_2(t),u(t)) = \\ &= K_1 + \alpha_i u^2(t) + K_2 x(t)y(t)u(t) + K_3 y(t) + \\ &+\lambda_1(\gamma - dx(t) - \beta(1-u(t))x(t)y(t)) + \\ &+\lambda_2(-\beta x(t)y(t)u(t) + \pi(y(t))) \end{aligned} \quad (6)$$

and the necessary optimality conditions are [13]

$$\begin{aligned} \dot{\lambda}_1(t) &= -\frac{\partial H_{\alpha_i}}{\partial x} = -K_2 y(t)u(t) + d\lambda_1(t) + \\ &+\beta(1-u(t))y(t)\lambda_1(t) + \beta y(t)\lambda_2(t)u(t) \end{aligned} \quad (7)$$

$$\begin{aligned} \dot{\lambda}_2(t) &= -\frac{\partial H_{\alpha_i}}{\partial y} = -K_2 x(t)u(t) - K_3 + \\ &+\beta(i-u(t))x(t)\lambda_1(t) + \beta x(t)\lambda_2(t)u(t) + \\ &-\lambda_2(t)\left[B + 2Cy(t) + 3Dy^2(t)\right] \end{aligned} \quad (8)$$

$$0 = \frac{\partial H_{\alpha_i}}{\partial u} + \frac{\partial q_1}{\partial u}\eta_1 + \frac{\partial q_2}{\partial u}\eta_2 = 2\alpha_i u(t) + \\ + K_2 x(t) y(t) + \beta x(t) y(t) \lambda_1(t) - \beta x(t) y(t) \lambda_2(t) + \\ + \eta_1(t) + \eta_2(t) \quad (9)$$

$$\eta_i(t) q_i(t) = 0,\ \eta_i(t) \geq 0, \quad i = 1,2 \quad (10)$$

$$H_{\alpha_i}|_T = 0,\ \lambda_1(T) = 0,\ \lambda_2(T) = -\zeta,\ \zeta \in \Re \quad (11)$$

Be $\left(T^1, x^1(t), y^1(t), u^1(t)\right)$ the solution, if it exists, over the interval $\left[t_0, T^1\right)$ obtained at the first step. If $y^1(t) \in I^i$ $\forall t \in \left[t_0, T^1\right)$, then the algorithm stops.

Otherwise, it happens that, during the evolution, there exists a time instant t_1 such that $y^1(t_1) \in I^i$ and $y^1(t_1^+) \notin I^i$, say, for example, $y^1(t_1^+) \in I^{i-1}$: then t_1 is the first switching instant. So, the solution of the switching problem for $t \in [t_0, t_1)$ is given by $\left(T^1, x^1(t), y^1(t), u^1(t)\right)$ and a new cycle starts with a new optimization problem under initial condition $y^1(t_1) = \xi^{i-1}$, with the same cost index where t_0 is replaced by t_1, and with the weight $P(y(t)) = \alpha_{i-1}$, according to (4).

At the generic j–th step, introducing the quantity

$$W_j(t) = x(t) y(t) \left(-K_2 - \beta \lambda_1(t) + \beta \lambda_2(t)\right) \quad (12)$$

the optimal solution in the time interval $\left[t_{j-1}, T^j\right)$ is

$$u^j(t) = \begin{cases} 0 & \text{if} \quad -W_j(t) > 0 \\ \frac{W_j(t)}{2\alpha_i} & \text{if} \quad 0 < \frac{W_j(t)}{2\alpha_i} < U \\ U & \text{if} \quad \frac{W_j(t)}{2\alpha_i} > U \end{cases} \quad (13)$$

In the solution (13), $\lambda_1(t)$ and $\lambda_2(t)$, along with the state $x(t)$ and $y(t)$, appear explicitly; they can be determined by considering the dynamics (1)-(2) together with the conditions (7)-(11). In each region, the solution obtained is optimal with the specific boundary conditions.

The final solution provided by the algorithm is then computed as the composition of the M partial solutions obtained at each step according to the expression

$$u^0(t) = u^1(t)\big|_{[t_0,t_1]} \circ u^2(t)\big|_{(t_1,t_2]} \circ \cdots \circ u^M(t)\big|_{(t_{M-1},t_M]} \quad (14)$$

where M is the number of cycles involved.

It is worth to note that in the solution, the control is not impulsive and the dynamics of the system is not a discontinuous one. The switching in the control occurs since the weight in the cost index changes depending on the decisions of the control designer. This is the main difference with respect to the approach used for multi-agent systems in [14], where the Razumikhin technique is adopted, and to switching systems, as in [15], where the stability analysis is addressed by the Lyapunov functions theory.

3. NUMERICAL RESULTS AND DISCUSSION

In this Section the behaviour of the considered HIV system with the proposed control approach is studied to put in evidence the differences and the advantages with respect to a traditional optimal control formulation with constant weights.

In all the simulations performed, the following parameters, taken from [3,4], have been used for the model (1)-(2): $\gamma = 1$, $d = 0.1$, $\beta = 1$, $\alpha = 0.0668$, $B = -3.1540$, $C = 2.9402$, $D = -0.6$; as in [4], the initial conditions are set as $x_0 = 0.2$ and $y_0 = 3$. For all the simulations, the coefficients $K_1 = 10$, $K_2 = 1$, $K_3 = 20$ in the cost function have been chosen, of almost the same order of magnitude, with the exception of K_2 since it weights a cubic term; the upper bound $U = 0.9$ for the control has been fixed.

An optimal control approach demands to the cost function the ability to modulate the control according to all the variables involved. For a choice of the cost index as in (3), the solution depends on the values given to the weights assigned to each term. In fact, consider, for example, the choice $P = 1$, i.e. a fixed constant value.

In Figure 1 the corresponding control action $u_\alpha(t)$ is depicted, whereas in Figure 2 the time histories of the uninfected $x_\alpha(t)$ and the infected $y_\alpha(t)$ cells are presented.

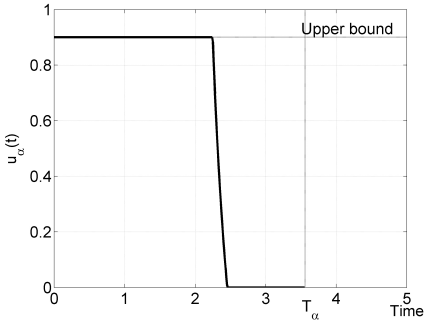

Fig. 1. Time history of the drug therapy $u_\alpha(t)$ for $P = 1$.

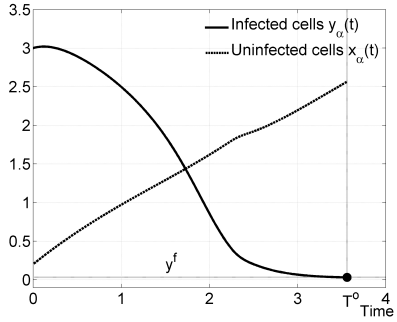

Fig. 2. Time histories of infected $y_\alpha(t)$ and uninfected $x_\alpha(t)$ cells for $P = 1$.

The control $u_\alpha(t)$ is up to its maximum value for a certain time and then, since its effectiveness starts to be much

lower than its cost, goes rapidly to zero.

The result of this test looks like the therapy-based choice, as also found in [4], with a limited time assumption of the drug; the main difference is that the duration is not fixed in advance but it is given as part of the solution of the optimal control problem, depending on the evolution of the dynamics and the associated cost.

For the solution proposed in this paper, the interval $[\xi^1, +\infty)$, with $\xi^1 = y^f = 0.03$, has been divided into $N = 2$ subintervals, $I_y^1 = [\xi^1, \xi^2)$ and $I_y^2 = [\xi^2, \xi^3)$, with $\xi^2 = 2$ and $\xi^3 = +\infty$, aiming at associating a dangerous and critical level for the infection to the interval I_y^2 and a lower level of severity to I_y^1.

Intuitively, one imagines the necessity of a stronger control action in the first case than in the second one. On the basis of the previous considerations, this result can be obtained associating a low control cost when a higher control seems to be required and a high control cost in the other case. Then, $\alpha_1 = 100$ and $\alpha_2 = 1$ are set in (4) and the solution obtained yields the results depicted in Figures 3 and 4.

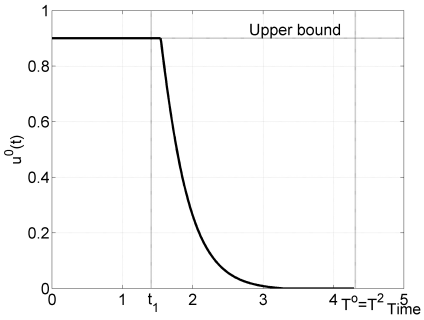

Fig. 3. The proposed switching control action $u^0(t)$.

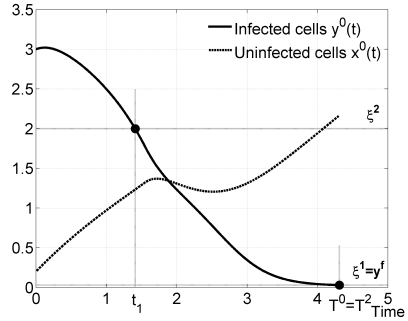

Fig. 4. Time history of the infected $y^0(t)$ and uninfected $x^0(t)$ cells.

Figure 3 shows the control action $u^0(t)$for the switching case and in Figure 4 the time histories of the uninfected CD4 T-cells $x^0(t)$ and the infected ones $y^0(t)$ are reported.

In order to put in evidence the relationships between the results of the two approaches, the one in Figure 1, with constant weight $P = 1$, and the switching control of Figure 3, it may be useful to plot them together in Figure 5, as well as the corresponding evolutions of the number of infected cells in Figure 6. The two figures well describe and support the contribution of the proposed approach: thanks to the fact that the number of infected cells reaches the limit value $\xi^2 = 2$ at time $t_1 = 1.39$, the change of the control weight in the cost function produces a new behaviour. It is characterized by a shorted saturated action and a smoother decreasing shape, with the state still reaching the final condition, despite the global lower effort of the control, as can be noted in Figure 6.

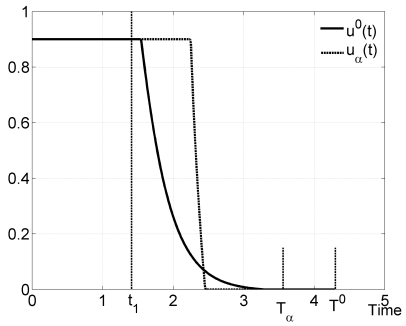

Fig. 5. Control effort: comparison between classical ($P = 1$) and switching cases

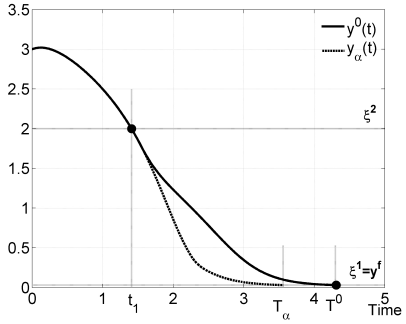

Fig. 6. Infected cells: comparison between classical ($P = 1$) and switching cases.

The only disadvantage is, obviously, a slight increment of the final control time $T^0 = T^2$. Nevertheless, this apparent drawback is fully compensated by the fact that the control, over the whole time interval during which the drug is provided, requires a lower effort. This can be shown computing and plotting the function $\int_0^t u(\tau)d\tau$, that is proportional to the global control effort required, i.e. a form of

energy.

Figure 7 is then obtained, showing that until both solutions require the full control action, the functions are obviously coincident; then, the decrement of the control amplitude in the switching case, starting when the classical one is still at maximum, produces a reduction of the total amount of energy related to the therapy cost.

Clearly, changing the values for the α_i, the solution changes and different behaviours are obtained.

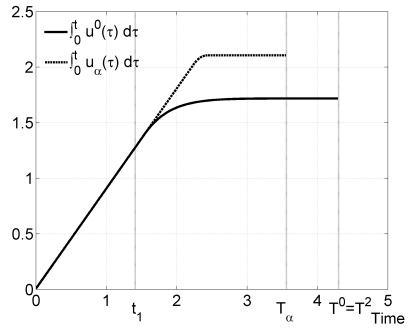

Fig. 7. Control effort: comparison between classical and switching cases.

4. CONCLUSIONS

A model of the HIV is considered, proposing an action in which the control effort takes into account the number of infected cells, giving higher attention when they are dangerously over a fixed critical value and considering the infection not much severe below. This goal is obtained proposing a constructive iterative algorithm in the framework of optimal control theory. Obviously, the result can be easily generalized to the case of more than one critical value and with a more complex decomposition of the state space. The results obtained show that this approach provides an efficient resource allocation, so being more efficient, for example from an economical point of view, than the one from classical theory where constant weights are chosen. The idea here proposed for the specific example of the HIV will be developed in a forthcoming work, within a methodological framework, in which all the dynamic characteristics will be formally investigated.

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