Optimal Control to reduce the HIV/AIDS spread

Paolo Di Giamberardino
Dept. Computer, Control and Management Engineering Antonio Ruberti
Sapienza University of Rome
Rome, Italy
paolo.digiamberardino@uniroma1.it

Daniela Iacoviello
Dept. Computer, Control and Management Engineering Antonio Ruberti
Sapienza University of Rome
Rome, Italy
daniela.iacoviello@uniroma1.it

***Abstract*—In this paper the problem of the HIV/AIDS spread reduction is addressed in the framework of optimal control theory. A model recently proposed has been adopted; it considers two classes of susceptible subjects, the wise people and the people with incautious behaviours, and three classes of infected, the ones still not aware of their status, the pre-AIDS patients and the AIDS ones. The control actions involve prevention by information campaign, to reduce the category of subjects with unwise behaviour, by test campaign, to reduce the number of subjects not aware of having the virus, and medication on patients with a positive diagnosis. A cost index aiming at the reduction of patients with positive diagnosis is introduced with the conflicting requirements of using as less resources as possible.**

***Index Terms*—epidemic modeling, optimal control, HIV-AIDS spread**

I. Introduction

In this paper, an optimal control approach to determine the interventions to face the HIV/AIDS spread is proposed. HIV stands for Human Immunodeficiency Virus and it is responsible of the Acquired Immune Deficiency Syndrome (AIDS) that can be reached in 10-15 years from the infection [1]–[3]. The virus infects cells of the immune system that becomes weaker, so that the possibility of infections increases; the HIV is mainly transmitted through body fluids exchange between individuals.

Despite the well-known modalities of its diffusion, it is still one of the most diffuse disease; the most alarming aspect is that there is still a serious delay for the infected subjects to become aware of their status. All the subjects of the populations are susceptible but with wise behaviour the spread would stop; no vaccine exists up to now, only medication after the positive response to HIV- test. An information campaign could induce people to have cautious behaviours and to periodically test their negativeness to the HIV/AIDS. Moreover, medication is included in the control actions since new drug therapies help the patients in remaining in the HIV situations without reaching the AIDS status. These three levels of intervention are suggested by the World Health Organization (WHO).

Mathematical modelling of the HIV/AIDS diffusion has been faced in [2]–[9], by considering, as in this paper, the dynamics between subjects, thus introducing:

This work was supported by Sapienza University of Rome, Grants No. 191/2016 and No. RP11715C82440B12.

- the class of susceptible subjects (S) that are the healthy individuals that may contract the virus;
- the class of the infected individuals (I) not aware of their condition;
- the class of the pre-AIDS patients (P);
- the class of the AIDS patients (A).

The importance of prevention has been stated in [5], [6], where the attention is devoted to risky subjects, drug users and sex workers, showing with simulation the effects of prevention.

Another approach, described in [10], focuses on the CD4 T-cells, the essential components of the immune system. An HIV patient is classified as an AIDS one if he has less than 200 CD4 T-cells in mm^3 of blood. In this case the analysis shows the existence of two equilibrium points: the long term non-proliferative (LTNP) condition and the AIDS one; therefore, the medication strategy aims at driving the patient into the LTNP region of attraction [2], [3].

The natural framework to study epidemic problems and, in particular HIV/AIDS spread, is the optimal control, aiming at determining the best control action with respect to conflicting requirements, such as using as less resources as possible while minimizing the number of infected patients, [8], [11]–[14].

In this paper, the approach considering the dynamics of the interactions between subjects [1], [4], [5] is adopted. The susceptible individuals S are divided into two categories, considering people adopting wise behaviours and the ones that do not consider adequately the dangerousness of this disease. Therefore, five categories are present: two classes of healthy subjects and three classes of subjects with HIV/AIDS. It is worth to be noted that only the pre-AIDS subjects and the AIDS patients are actually aware of their status. The external actions introduced are an effective information campaign, a test campaign and the virus therapy.

The control laws are computed to minimize a cost index to reduce the number of infected subjects with positive diagnosis of HIV/AIDS, using less resources as possible. The chosen goal has consequences in all the control actions introduced above, the increase of the information, the test campaign and the medication. The minimum Pontryagin principle is applied obtaining the optimal controls along with the corresponding state evolutions.

The paper is organized as follows. In Section II the adopted model is briefly recalled and the controls are introduced. In

978-1-5386-4444-7/18/$31.00 ©2018 IEEE

Section III, the optimal control is determined and in Section IV, numerical results are presented and discussed. Conclusions and future work are outlined in Section V.

II. The HIV/AIDS model

The model of the HIV/AIDS diffusion presented in [5], [6] is here briefly recalled. This disease is particularly dangerous since there is a period, also ten years long, in which its symptoms are not evident and therefore a subject could, unconsciously, infect other people. Nevertheless, it could be transmitted only by specific risky contacts; despite the fact that all the subjects could contract the virus, with wise behaviours the infection could be stopped. These two characteristics have been considered in the WHO suggestions of intervention and have guided the choices of the proposed modelling.

In particular, the healthy subjects are divided into two categories: the unwary subjects, denoted by S_1 and the wise ones that adopt safe behaviours, named S_2. The infected subjects may be distinguished into three kinds of patients: the ones that still do not know to be infected, I, the subjects with a positive HIV diagnosis, P, and the ones with AIDS, A. The control actions introduced are the prevention with information campaign inducing subjects to wise behaviours and to improve a test campaign (primary and secondary preventions, respectively); moreover, the medication is applied on the patients with positive HIV/AIDS diagnosis (third action). The costs of primary and secondary preventions represent an immediate economic effort, whereas the effects could be noted only in the future: a schedule of the control action is advisable.

Let $\begin{pmatrix} S_1(t) & S_2(t) & I(t) & P(t) & A(t) \end{pmatrix}$ denote the number of individuals in each of the previous catecory. It is useful to introduce also the quantity $N_c(t) = S_1(t) + S_2(t) + I(t)$, representing the part of the population for which no diagnosis has been produced; it is the sum of the healthy people and the unaware ones.

In Fig. 1, the block diagram representing the interactions described above is depicted.

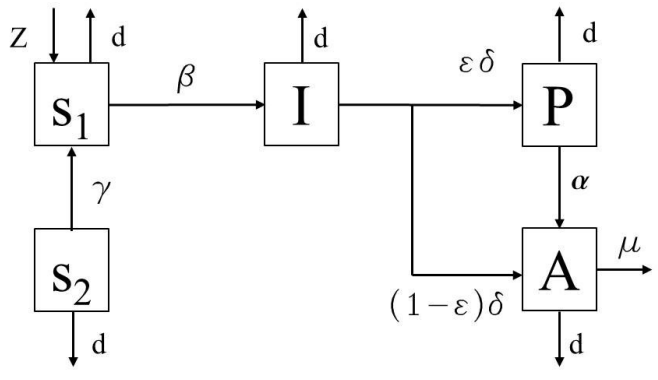

Fig. 1. Block diagram of the considered model.

The control actions introduced are: $u_1(t)$, corresponding to the effort placed in the information campaign (for the $S_1(t)$ reduction); $u_2(t)$, that is related to a test campaign to reduce the unaware infected individuals and, consequently, to reduce the interaction responsible of the epidemic spread; $u_3(t)$, the therapy, which reduces the transition of the known infected individuals $P(t)$ to the more deadly group $A(t)$.

Therefore, the final model is:

$$\begin{aligned}
\dot{S}_1(t) &= Z - dS_1(t) - \beta\frac{S_1(t)I(t)}{N_c(t)} + \gamma S_2(t) \\
&\quad -S_1(t)u_1(t) && (1)\\
\dot{S}_2(t) &= -(\gamma + d)\, S_2(t) + S_1(t)u_1(t) && (2)\\
\dot{I}(t) &= \beta\frac{S_1(t)I(t)}{N_c(t)} - (d+\delta)\, I(t) - \psi\frac{I(t)}{N_c(t)}u_2(t) && (3)\\
\dot{P}(t) &= \varepsilon\delta I(t) - (\alpha + d)\, P(t) + \phi\psi\frac{I(t)}{N_c(t)}u_2(t) \\
&\quad +P(t)u_3(t) && (4)\\
\dot{A}(t) &= (1-\varepsilon)\,\delta I(t) + \alpha P(t) - (\mu + d)\, A(t) \\
&\quad -(1-\phi)\,\psi\frac{I(t)}{N_c(t)}u_2(t) - P(t)u_3(t) && (5)
\end{aligned}$$

where Z denotes the rate of increment of the population, assumed as the newborn individuals and excluding infectious transmission from mother to son.

All the parameters appearing in (1)–(5) represent the coefficients which weight each contribution to the correspondent rate of variables change. In particular

- β regulates the interaction responsible of the infectious propagation;
- γ takes into account the fact that a wise individual in $S_2(t)$ can, accidentally, assume a incautious behaviour as the $S_1(t)$ persons;
- δ weights the natural rate of $I(t)$ subjects becoming aware of their status;
- α characterises the natural rate of transition from $P(t)$ to $A(t)$ due to the evolution of the infectious disease;
- ψ determines the effect of the test campaign on the unaware individuals $I(t)$;
- ϕ is the fraction of individuals in $I(t)$ which become, after test, classified as $P(t)$ (ϕ) or $A(t)$ ((1-ϕ));
- ε is the fraction of individuals $I(t)$ which discover to be in the pre-AIDS condition or in the AIDS one;
- d is responsible of the natural death rate, assumed the same for all the classes, while μ is the additional death factor for the individuals $A(t)$.

III. The optimal control

In the model (1)–(5), the number of subjects $P(t)$ with positive diagnosis of HIV and the one $A(t)$ with AIDS is an information that could be reasonably assumed known, resulting after specific tests. A cost index aiming at the minimization of the number of patients $P(t)$ and $A(t)$ is then introduced; this should imply an indirect effect also on the unknown number $I(t)$ and on the number of $S_1(t)$ subjects, by introducing effective control actions. Realistic considerations suggest the introduction of a limitation on the resources needed. The final time t_f is assumed fixed, whereas the final state is free. The following problem can be stated.

Problem formulation: consider the dynamical system (1)–(5) and assume that the initial and the final time instants, t_0 and t_f, are fixed; for sake of simplicity $t_0 = 0$ is set. The final state is left free, while the initial state is assumed fixed and known

$$\begin{aligned} S_1(0) = S_{10} \quad S_2(0) = S_{20} \quad I(0) = I_0 \\ P(0) = P_0 \quad A(0) = A_0 \end{aligned} \tag{6}$$

The control actions $u_i(t)$, $i = 1, 2, 3$, are continuous almost everywhere and bounded by given upper limits

$$0 \leq u_i(t) \leq M_i, \quad M_i \in R, \quad i = 1, 2, 3 \tag{7}$$

Assuming $a_1, a_2 \geq 0$, $r_i \geq 0$ for $i = 1, 2, 3$, be

$$\begin{aligned} &J\left(P, A, u_1, u_2, u_3\right) = \\ &\frac{1}{2}\int_0^{t_f} \left(a_1 P^2(t) + a_2 A^2(t) + \sum_{i=1}^{3} r_i u_i^2(t) \right) dt \end{aligned} \tag{8}$$

the cost index.

The goal is to determine the controls $u_i(t)$, $i = 1, 2, 3$ and the state evolution that minimize the cost index (8) and satisfy the system (1)–(5) with the initial conditions (6) under conditions (7). To solve the minimization problem, we first introduce the Hamiltonian

$$\begin{aligned} H = &\frac{\lambda_0}{2}\left(a_1 P^2(t) + a_2 A^2(t) + \sum_{i=1}^{3} r_i u_i^2(t) \right) \\ &+\lambda_1(t)\left(Z - dS_1(t) - \beta\frac{S_1(t)I(t)}{N_c(t)} + \gamma S_2(t) \right. \\ &\left. -S_1(t)u_1(t) \right) - \lambda_2(t)\left(\left(\gamma + d\right) S_2(t) - S_1(t)u_1(t) \right) \\ &+\lambda_3(t)\left(\beta\frac{S_1(t)I(t)}{N_c(t)} - \left(d + \delta\right) I(t) - \psi\frac{I(t)}{N_c(t)}u_2(t) \right) \\ &+\lambda_4(t)\left(\varepsilon\delta I(t) - \left(\alpha + d\right) P(t) + \phi\psi\frac{I(t)}{N_c(t)}u_2(t) \right. \\ &\left. +P(t)u_3(t) \right) + \lambda_5(t)\left(\left(1 - \varepsilon\right)\delta I(t) + \alpha P(t) \right. \\ &\left. - \left(\mu + d\right) A(t) - \left(1 - \phi\right)\psi\frac{I(t)}{N_c(t)}u_2(t) - P(t)u_3(t) \right) \end{aligned} \tag{9}$$

where

$$\lambda(t) = \begin{pmatrix} \lambda_1(t) & \lambda_2(t) & \lambda_3(t) & \lambda_4(t) & \lambda_5(t) \end{pmatrix}^T \in R^5 \tag{10}$$

is the costate function and $\lambda(0) \in R$.

The necessary conditions of the control may be derived by using the Pontryagin minimum principle [15]; more precisely, the following result holds.

Theorem: the above optimal control problem admits the normal solution:

$$u_i^*(t) = \begin{cases} 0 & \Omega_i \leq 0 \\ \Omega_i & 0 \leq \Omega_i \leq M_i \\ M_i & \Omega_i \geq M_i \end{cases} \quad i = 1, 2, 3 \tag{11}$$

with

$$\begin{aligned} \Omega_1(t) &= \frac{2\left(\lambda_1^*(t) - \lambda_2^*(t)\right) S_1^*(t)}{r_1} \\ \Omega_2(t) &= \frac{2\psi\left(\lambda_3^*(t) - \lambda_4^*(t) - (1 - \phi)\right) I^*(t)}{r_2 N_c^*(t)} \\ \Omega_3(t) &= \frac{2\left(\lambda_5^*(t) - \lambda_4^*(t)\right) P^*(t)}{r_3} \end{aligned}$$

where $\lambda_i^*(t)$, $i = 1\ldots, 5$, are the adjoint variables satisfying

$$\begin{aligned} \dot{\lambda}_1^*(t) = &-\frac{\partial H}{\partial S_1}\bigg|^* = d\lambda_1^*(t) + \left(\lambda_1^*(t) - \lambda_2^*(t)\right) u_1^* \\ &\left(\lambda_1^*(t) - \lambda_3^*(t)\right)\frac{\beta I^*(t)\left(S_2^*(t) + I^*(t)\right)}{N_c^*(t)} \\ &\psi\frac{I^*(t)u_2^*}{N_c^*(t)}\left(\lambda_3^*(t) - \phi\lambda_4^*(t) - (1 - \phi)\lambda_5^*(t)\right) \end{aligned} \tag{12}$$

$$\begin{aligned} \dot{\lambda}_2^*(t) = &-\frac{\partial H}{\partial S_2}\bigg|^* = \gamma\lambda_3^*(t) + \gamma\left(\lambda_1^*(t) - \lambda_2^*(t)\right) \\ &\beta\left(\lambda_1^*(t) - \lambda_3^*(t)\right)\frac{S_1^*(t)I^*(t)}{N_c^{*2}(t)} \\ &\psi\frac{I^*(t)u_2^*}{N_c^{*2}}\left(\lambda_3^*(t) - \phi\lambda_4^*(t) - (1 - \phi)\lambda_5^*(t)\right) \end{aligned} \tag{13}$$

$$\begin{aligned} \dot{\lambda}_3^*(t) = &-\frac{\partial H}{\partial I}\bigg|^* = (d + \delta)\lambda_3^*(t) \\ &\beta\left(\lambda_1^*(t) - \lambda_3^*(t)\right)\frac{S_1^*(t)\left(S_1^*(t) + S_2^*(t)\right)}{N_c^{*2}(t)} \\ &\psi\frac{\left(S_1^*(t) + S_2^*(t)\right)u_2^*}{N_c^{*2}}\left(\lambda_3^*(t) - \phi\lambda_4^*(t) - (1 - \phi)\lambda_5^*(t)\right) \end{aligned} \tag{14}$$

$$\begin{aligned} \dot{\lambda}_4^*(t) = &-\frac{\partial H}{\partial P}\bigg|^* = d\lambda_4^*(t) + \alpha\left(\lambda_4^*(t) - \lambda_5^*(t)\right) \\ &a_1 P^*(t) - \left(\lambda_4^*(t) - \lambda_5^*(t)\right) u_3^* \end{aligned} \tag{15}$$

$$\dot{\lambda}_5^*(t) = -\frac{\partial H}{\partial A}\bigg|^* = (d + \mu)\lambda_4^*(t)A^*(t) - a_2 A^*(t) \tag{16}$$

with final conditions

$$\lambda_i^*(t_f) = 0, \quad i = 1, \ldots, 5 \tag{17}$$

Proof: the solution comes directly from the application of the minimum Pontryagin principle. Let $\Xi^* = \begin{pmatrix} S_1^*(t) & S_2^*(t) & I^*(t) & P^*(t) & A^*(t) \end{pmatrix}$ satisfy the system (1)–(5) and the initial state conditions (6). The necessary conditions for Ξ^* to be a minimum for the cost index (8) are the following: defined H as in (9), there exists a constant $\lambda_0 \geq 0$ and a function $\lambda^*(t) \in R^5$, $\lambda^* \in \bar{C}^1\left[t_i, t_f\right]$ (first

derivatives continuous almost everywhere) not simultaneously null, such that

$$\dot{\lambda}^*(t) = -\left.\frac{\partial H}{\partial \Xi}\right|^{*T} \tag{18}$$

and

$$H\left(S_1^*(t), S_2^*(t), I^*(t), P^*(t), A^*(t), u_1^*(t), u_2^*(t), u_3^*(t)\right) \leq$$
$$H\left(S_1^*(t), S_2^*(t), I^*(t), P^*(t), A^*(t), \omega_1(t), \omega_2(t), \omega_3(t)\right) \tag{19}$$

for any admissible control functions ω_i, $i = 1, 2, 3$.

From (19) the control law (11) is obtained; for its computation the equations (12)–(16), coming from (18) must be solved; being the final state not fixed, one has the boundary condition $\lambda^*(t_f) = 0$. This condition also implies that $\lambda_0 > 0$ and therefore the normality of the solution.

IV. Numerical results and discussion

As noted, in real situation the unique available data is the one related with the number of subjects with positive HIV diagnosis, $P(t)$, and the number of subjects with an AIDS diagnosis, $A(t)$. This consideration determined the choice of the cost index (8); aiming at reducing the number of $P(t)$ and $A(t)$ subjects should involve all the control actions, but in different ways. The first control (the information campaign) should reduce the new infections, and therefore reduce the total number of infected $I(t)+P(t)+A(t)$. The second control (the test campaign) should reduce the number of unaware infected subjects $I(t)$, thus increasing the number of aware infected patients $P(t) + A(t)$. Finally, the medication should aim at reducing the number of subjects with an AIDS diagnosis, thus avoiding, as much as possible, the transition of subjects from the condition of pre-AIDS status to the AIDS one. As can be noted, these actions appear to be in some way competitive and in contradiction one to each other in the short period. Therefore, the choice of the weights in the cost index could enhance one strategy versus the others. As far as the model parameters is concerned, the following values are assumed, according to the literature, [1]:

$$d = 0.02; \quad Z = 10^4; \quad \beta = 1.5; \quad \gamma = 0.2; \quad \psi = 10^5;$$
$$\delta = 0.4; \quad \phi = 0.95; \quad \varepsilon = 0.6; \quad \alpha = 0.5; \quad \mu = 1.$$

The initial conditions

$$(S_{10}, S_{20}, I_0, P_0, A_0) = \left(10^5, 10^4, 5 \cdot 10^3, 0, 0\right)$$

are assumed.

A first test is performed assuming in the cost index the same weights $a_1 = a_2 = 10^{-5}$ for both patients $P(t)$ and $A(t)$, weighting more the first control action than the other two: $r_1 = 1$, $r_2 = r_3 = 10^{-3}$. The final time $t_f = 50$ is chosen. The obtained optimal control functions significantly influence the evolution of the state variables.

In Figs. 2–6 the controlled state variables are shown along with the free evolutions for comparative purpose. It could be appreciated that the number of susceptible subjects increases, Figs. 2 and 3, thanks to the optimal combination of the control effort u_1 and u_2 that concur in avoiding incautious behaviours of susceptible subjects and having a fast diagnosis, thus again avoiding dangerous contacts. The control u_2 concurs in decreasing the number of infected subjects $I(t)$, Fig. 4, since it is devoted to help the subjects to discover, as soon as possible, the illness and if they belong to the $P(t)$ or $A(t)$ groups.

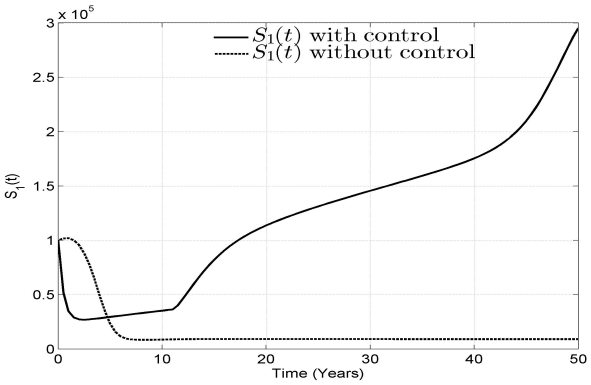

Fig. 2. Test 1: time evolution of the $S_1(t)$ subjects with and without optimal control actions .

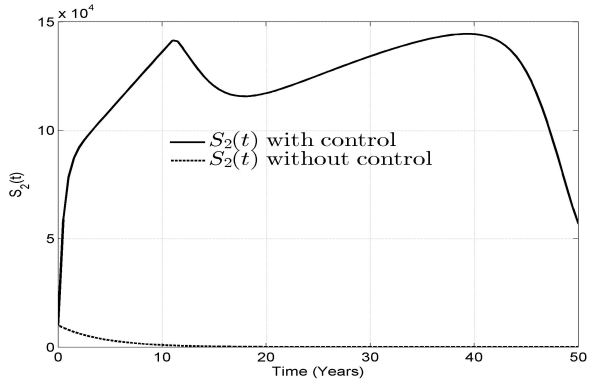

Fig. 3. Test 1: time evolution of the $S_2(t)$ subjects with and without optimal control actions

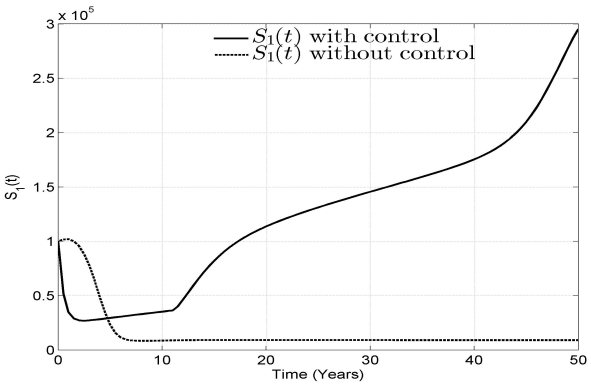

Fig. 4. Test 1: time evolution of the $I(t)$ subjects with and without optimal control actions

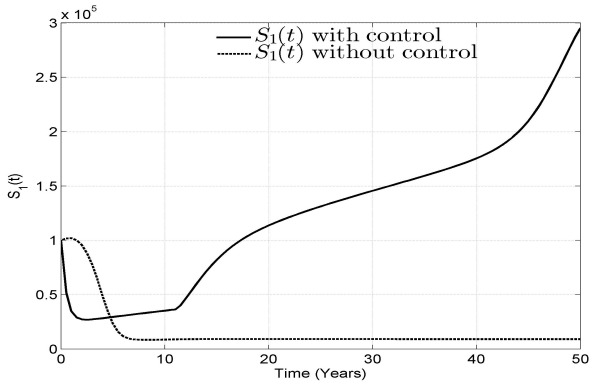

Fig. 5. Test 1: time evolution of the $P(t)$ subjects with and without optimal control actions

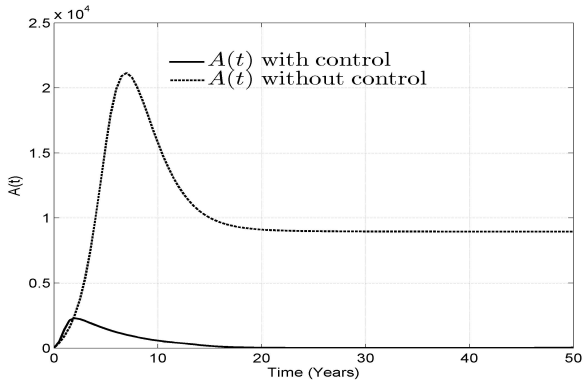

Fig. 6. Test 1: time evolution of the $A(t)$ subjects with and without optimal control actions

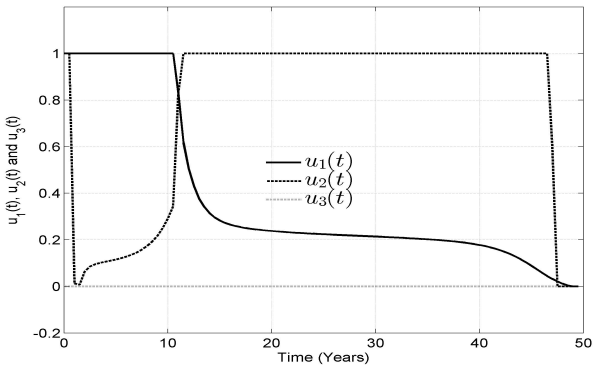

Fig. 7. Test 1: time evolution of the optimal control actions

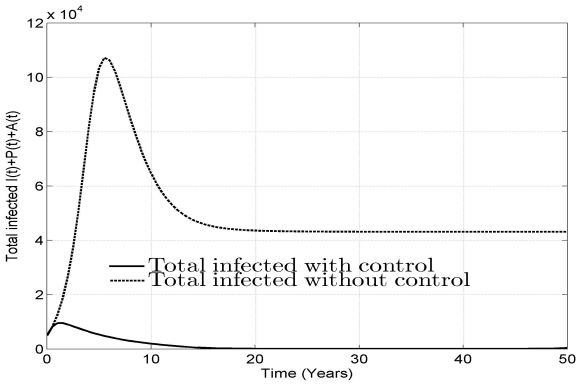

Fig. 8. Test 1: time evolution of the total number of infected, with and without the control actions

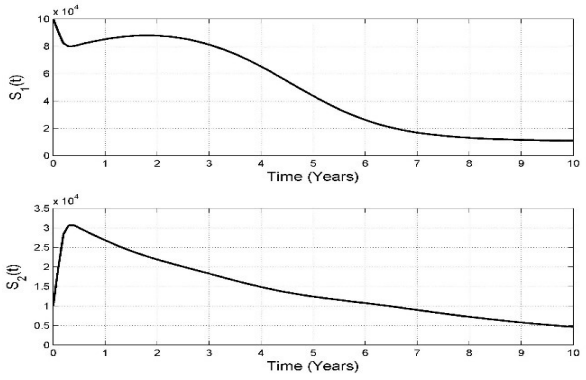

Fig. 9. Test 2: time evolutions of the $S_1(t)$ and $S_2(t)$ subjects

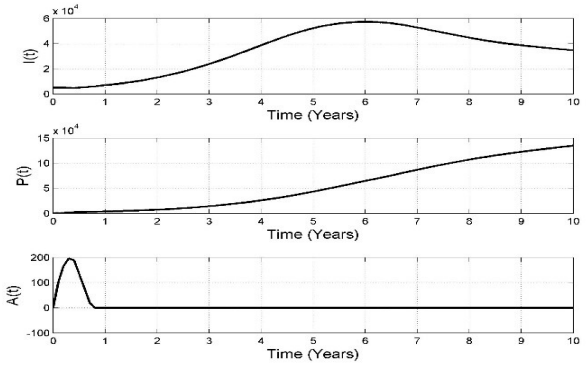

Fig. 10. Test 2: time evolutions of the $I(t)$, $P(t)$ and $A(t)$ subjects

The number of subjects in the pre-AIDS condition $P(t)$ at the beginning increases (but less than in the case of absence of control) and then it significantly decreases almost to zero, Fig. 5. The same happens for $A(t)$: while in the non-controlled condition it goes to a value of about 10000 subjects, with a controlled situation it definitely decreases to almost zero, Fig. 6. It is interesting to note that these results do not require the third control action; it confirms the importance of the optimal combination of the prevention actions. In the case considered, the medication seems not useful to the total reduction of both $P(t)$ and $A(t)$. This is actually true for the cynical reason that there is a higher mortality in $A(t)$ than in $P(t)$ and then any action which keeps subjects in $P(t)$ is in contrast with the minimization requirements.

Then, in order to put in evidence the importance and the role of each control action and to show how to get a more humane

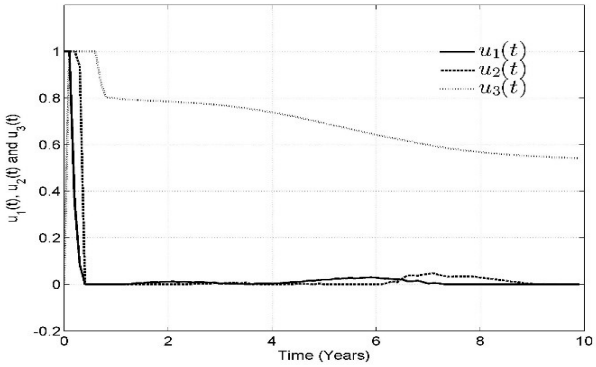

Fig. 11. Test 2: time evolutions of the optimal control actions

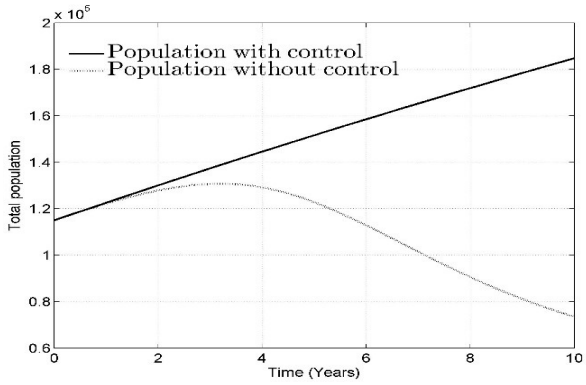

Fig. 12. Test 2: time evolution of the total population, with and without the control actions

behavior, a second test is performed aiming at stressing the conditions, which enhance the contribution of medication. Clearly, the reduction of the number of patients with AIDS should imply a rise in the number of patients in the pre-AIDS status. So, in the cost function (8), only the state $A(t)$ is considered, along with the controls. A consequent choice for the weights is $a_1 = 0$, $a_2 = 10^{-2}$, $r_1 = 10$, $r_2 = 10$ and $r_3 = 0$, with $t_f = 10$ to stress the short term action. In this case, in which the aim is to decrease the number of AIDS patients, the combination of the controls enhances the contribution of all the efforts, obtaining a significant decrease of the number of AIDS patients, due also to the medication, a decrease of the unaware infected and an increase in the number of subjects in the pre-AIDS status, the LTNP patients. In Figs. 9 and 10 these behaviours of the state variables are shown, whereas in Fig. 11 the three control actions are proposed.

The overall effectiveness of the optimal control action also for this choice of cost function weights is well evidenced in Fig. 12, where the time history of the total population under the control action is compared with the same evolution without control.

V. Conclusion

The paper investigates the possibility of controlling the HIV/AIDS infection diffusion. The dynamical model adopted includes three control actions corresponding to different strategies of intervention. An optimal control problem formulation is used for the reduction of the number of infected subjects under an efficient resources allocation. Unfortunately, being known only the number of the diagnosed individuals, they are the only one considered in the definition of the cost function, but it is shown through numerical simulations, that this limitation does not affect the high effectiveness of the control action. The result obtained shows how feasible controls for the prevention of the HIV/AIDS infection effects can be obtained by means of suitable optimal control problem formulations.

References

[1] R. Nareshn, A. Tripathi, and D. Sharma, "Modeling and analysis of the spread of aids epidemic with immigration of hiv infectives," *Mathematical and computer modelling*, vol. 48, pp. 800–892, 2009.

[2] D. Wodarz and M. Nowak, "Specific therapy regimes could lead to long-term immunological control of hiv," *in Proc. Nat. Acad. Sci.*, vol. 96, pp. 14464–14469, 1999.

[3] H. Chang and A. Astolfi, "Control of hiv infection dynamics," *IEEE Control Systems*, 2009.

[4] C. Pinto and D. Rocha, "A new mathematical model for co-infection of malaria and hiv," *in Proc. 4th IEEE International Conference on Nonlinear Science and Complexity*, 2012.

[5] P. Di Giamberardino, L. Compagnucci, C. D. Giorgi, and D. Iacoviello, "A new model of the hiv/aids infection diffusion and analysis of the intervention effects," *in Proc. of 25th Mediterranean Conference on Control and Automation*, 2017.

[6] P. Di Giamberardino, L. Compagnucci, C. D. Giorgi, and D. Iacoviello, "Modeling the effects of prevention and early diagnosis on hiv/aids infection diffusion," *IEEE Transactions on Systems, Man and Cybernetics: Systems*, 2018.

[7] P. Di Giamberardino and D. Iacoviello, "An optimal control problem formulation for a state dependent resource allocation strategy," *in Proc. 14th Int. Conf. on Informatics in Control, Automation and Robotics*, 2017.

[8] P. Di Giamberardino and D. Iacoviello, "Optimal control of SIR epidemic model with state dependent switching cost index," *Biomedical Signal Processing and Control*, vol. 31, 2017.

[9] A. R. Rutherford, B. Ramadanovic, W. Michelow, B. D. L. Marshall, W. Small, K. Deering, and K. Vasarhelyi, "Control of an hiv epidemic among injection drug users: simulations modeling on complex networks," *in Proceedings of the 2016 Winter Simulations Conference*, 2016.

[10] M. Nowak and R. May, *Virus Dynamics*.

[11] E. A. Bakare, A. Nwagwo, and E. Danso-Addo, "Optimal control analyis of an sir epidemic model with constant recruitment," *International Journal of Applied Mathematical Research*, vol. 3, no. 3, pp. 273–285, 2014.

[12] F. Lin, K. Muthuraman, and M. Lawley, "Optimal control theory approach to non-pharmaceutical interventions," *International Journal of Applied Mathematical Research*, vol. 10, no. 32, pp. 1–13, 2010.

[13] D. Iacoviello and N. Stasio, "Optimal control for sirc epidemic outbreak," *Computer Methods and Programs in Biomedicine*, vol. 110, 2013.

[14] O. N. Owuor, M. Johannes, and M. S. Kibet, "Optimal vaccination strategies in an sir epidemic model with time scales," *Applied Mathematics*, vol. 4, 2013.

[15] B. D. O. Anderson and J. B. Moore, *Optimal control*. 1989.