LQ control design for the containment of the HIV/AIDS diffusion

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***Abstract* – An optimal control design approach is applied to a novel HIV/AIDS model to reduce the infection diffusion. Two classes of susceptible subjects, the wise one and the incautious ones, and three classes of infectious subjects, the ones not aware of their condition and the subjects in the pre-aids or in the aids status, are considered. The control input, represented by information campaigns and the medication action, is designed by means of a linear quadratic approach on the linearized model. Moreover, a preliminary state observer for the unmeasurable number of the unconscious infectious subjects is introduced. Numerical results show the effectiveness of the solution, and its robustness with respect to the approximations introduced by the linearization.**

***Index Terms*: HIV/AIDS epidemic model, system analysis, optimal control, linear quadratic regulator, separation principle**

I. Introduction

In the last three decades, much progress has been made in the attempts to eradicate the Human Immunodeficiency Virus (HIV) responsible of the Acquired Immune Deficiency Syndrome (AIDS), [1-3]. The virus infects cells of the immune system, destroying or impairing their function: the immune system becomes weaker, and the person is more susceptible to infections. It can be transmitted by body fluids such as blood, semen, pre-seminal fluid, rectal fluid, vaginal fluid, and breast milk; therefore, it is mainly transmitted by a subject during unprotected sex, sharing needles or syringes and, less commonly, by oral sex, blood transfusion or from mother to child during pregnancy or breastfeeding. The AIDS is the most advanced stage of the HIV infection and can be reached in 10-15 years from the infection. Up to now, no vaccine exists and the control actions are the prevention and the medication after a positive diagnosis. Despite the well-known modalities of its transmission, it is still one of the most diffused disease; the recent data of the World Health Organization (last update 2016) report that there are more than 36 million of people with a positive diagnosis of HIV. There is still a serious delay for the infectious subjects to become aware of their status: it is estimated that in Europe more than 122000 subjects are HIV positive without knowing.

The World Health Organization (WHO) suggests three levels of intervention:

i. the first level is designed for healthy people to reduce the possibility of new infections; it corresponds to increase the effort to induce the subjects to adopt cautious behaviors;

ii. the second level of prevention aims at a fast identification of new infections and risky conditions, thus reducing the percentage of subjects that are not aware of their illness (and therefore to reduce new infections);

iii. the third level is the medication to the aware infectious subjects.

Mathematical modeling of the HIV/AIDS diffusion may be grouped in two main approaches: one focuses on the dynamic at subjects' interactions level [2, 4, 5]. Generally, four main classes are introduced: the Susceptible subjects (S) that are the healthy people that may contract the virus; the Infectious one (I) that are not aware of their condition; the pre-AIDS patients (P); the AIDS patients (A). In this framework, the control action is mainly focused on the prevention; for example, in [6] the attention is devoted to risky subjects, drug users and sex workers, showing, by means of simulations, the effects of prevention; in particular, the Authors studied the consequences of the reduction of syringe sharing and of the reduced time to diagnosis, stressing the relations among these factors and the HIV prevalence.

The second approach 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 [7]; he could try to reach the long-term non-progression (LTNP) status that allows him to contrast the HIV and other infections. It is shown that two equilibrium points are present: the LTNP and the AIDS condition; the medication strategy aims at driving the patient into the LTNP region of attraction [2,3].

The natural framework to study the control of the epidemic models is the optimal control theory in which conflicting issues can be addressed [8]; in epidemic spread, the control represents the general prevention effort (in particular the vaccine action, if possible), the medication, the quarantine, allowing to face with limitations of resources.

Optimal control has been applied referring to the classical SIR model (susceptible-infectious-removed subjects) [9-11], to the influenza [12-14], to the Dengue disease [15], to schedule vaccination strategies [16, 17], to study complex networks and identify spread process [18].

In this paper, following the first approach that considers the dynamics of the interactions between subjects, the model in [5] presenting a new HIV/AIDS description is assumed.

The susceptible individuals, S, are divided into two categories, the one that adopts wise behaviors and the one that does not take into account the dangerousness of this disease. This distinction appears particularly useful if one takes into account the trivial fact that if all the people assumed wise behavior no spread would occur. Therefore, five categories are present: along with the subjects with HIV/AIDS (i.e. classes *I, P, A*), two classes of susceptible subjects are considered. The control actions introduced are:

i. an effective information campaign, inducing all the people to wise behaviors;
ii. a test campaign to reduce the time in which an infectious subject *I* is not aware of his status and could infect an unwary one;
iii. the medication applied on the patients with positive diagnosis of HIV/AIDS.

In this paper, the control actions are chosen in order to minimize a cost index aiming at reducing the number of infectious subjects with as less resources as possible. These goals appear in line with the spread characteristics of the HIV virus: the reduction of the number of infectious subjects implies both the increase of the information and the test campaign. The third level of intervention, the medication on the patients, cannot influence the HIV/AIDS spread; however, it is preserved in the paper for completeness. The dynamical model is nonlinear, whereas for the cost index a quadratic lagrangian is chosen. A linearization of the model in the neighborhood of an equilibrium point is discussed, aiming at applying the linear quadratic (LQ) regulator theory, [19], which provides a state feedback control law. Since only the number of the patients with HIV (P) or AIDS (A) is available, an observer is determined to estimate the full state and, in particular, the number of the subjects *I*, infectious but not aware of their status.

The paper is organized as follows. In Section II the adopted nonlinear model is briefly recalled and the optimal control problem is formulated. In Section III the control design is proposed; three subsections are introduced: in the first one the linear approximation of the model is discussed; then the regulator is determined in the linear quadratic framework; finally, the state estimator design, along with the full control action, are determined. In Section IV numerical results are presented and discussed, showing the effectiveness of the proposed control law. Conclusions and future work are outlined in Section V.

II. MODEL DESCRIPTION AND OPTIMAL CONTROL PROBLEM FORMULATION

In this paper, the model of the HIV/AIDS diffusion presented in [5] is adopted and is here briefly recalled. It suitably models the two main particularities of the HIV/AIDS spread that significantly distinguish this disease from the others:

- there is a period, more or less long, in which the symptoms of the infection are not evident;
- the HIV can be transmitted only by some body fluids and sharing needles or syringes.

The first characteristic is responsible of the dangerousness of HIV/AIDS since an infectious individual could be unaware of his status for a long time and could infect unwise susceptible subjects. Therefore, it is useful to stress (and to model) the second characteristic described: the infection can be transmitted when unsafe behaviors are adopted. In fact, everyone is susceptible, but one can distinguish between the category of wise people that adopt safe behaviors, and the one of unwary subjects that could become infectious because they share syringes or needles, or for unprotected sex. These two particularities of the HIV/AIDS spread are modeled in this paper, where control actions consistent with the three levels of intervention previously recalled are introduced.

The effort to induce the population to participate to test campaign should reduce the risky time in which an infectious subject, not aware of his status, could infect healthy unwise susceptible ones, being able, of course, also to start a medication program.

A schedule of the control action is advisable, since the costs of primary and secondary preventions represent an immediate economic effort, whereas their effects could be appreciated only in the future, as will be discussed later.

Taking into account all these aspects, the variables introduced in the model are the following:

- $S_1(t)$ represents the number of healthy people that are not aware of dangerous behaviors and then can contract the virus;
- $S_2(t)$ represents the number of healthy people that, suitably informed, gives great attention to the protection;
- $I(t)$ represents the number of infectious subjects who are still not aware of their status;
- $P(t)$ represents the number of patients which have received a diagnosis of HIV;
- $A(t)$ represents the number of the patients which have received a diagnosis of AIDS positiveness.

As far as the control actions is concerned, they are:

- $u_1(t)$, related to the information campaign (thus reducing $S_1(t)$);
- $u_2(t)$, denoting the effort to improve a test campaign to the discovery of the infection as soon as possible (thus reducing the interactions between I and S_1);
- $u_3(t)$, representing a therapy, aiming at reducing the transition from P to A.

Therefore, the final model is:

$$\dot{S}_1(t) = Z - dS_1(t) - \frac{\beta S_1(t)I(t)}{N_c(t)} + \gamma S_2(t) - S_1(t)u_1(t) \tag{1}$$

$$\dot{S}_2(t) = -(\gamma + d)S_2(t) + S_1(t)u_1(t) \tag{2}$$

$$\dot{I}(t) = \frac{\beta S_1(t)I(t)}{N_c(t)} - (d+\delta)I(t) - \psi \frac{I(t)}{N_c(t)} u_2(t) \tag{3}$$

$$\dot{P}(t) = \varepsilon\delta I(t) - (\alpha + d)P(t) + \phi\psi \frac{I(t)}{N_c(t)} u_2(t) + P(t)u_3(t) \tag{4}$$

$$\dot{A}(t) = (1-\varepsilon)\delta I(t) + \alpha P(t) - (\mu + d)A(t) + (1-\phi)\psi \frac{I(t)}{N_c(t)} u_2(t) - P(t)u_3(t) \tag{5}$$

where:

- $N_c(t) = S_1(t) + S_2(t) + I(t)$ denotes the number of subjects that actually are ($S_1(t)$ and $S_2(t)$) or think $(I(t))$ to be healthy;

- d denotes the rate of natural death;
- Z denotes the flux of new subjects in the class S_1;
- β is related to the dangerous interactions between the S_1 and the I categories;
- γ is the rate of wise subjects that could change, incidentally, their status increasing $S_1(t)$;
- ψ is related to the control action aiming at helping the individuals in I to discover their infectious condition, and therefore to be assigned to the P or the A class;
- ϕ is the ratio of subjects that transit to P after positive test;
- δ is the rate of transition from I to P or A without any external action;
- ε is the ratio of subjects that transit to P by natural evolution;
- α is the rate of the natural transition from P to A;
- μ is the rate of death in A, directly caused by the infection.

In Fig. 1 the block diagram describing the interactions illustrated above is shown. Note that the control actions are indicated with dotted arrows as inputs of the blocks of the categories of subjects over which they act directly.

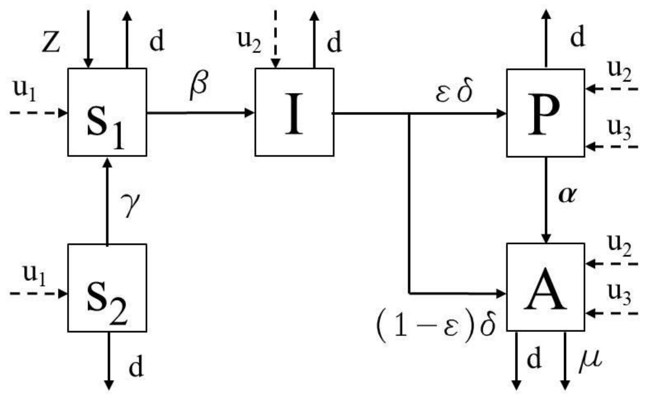

Figure 1. Block diagram of the HIV-AIDS scheme introduced.

Introducing the five dimensional state vector $X = \begin{pmatrix} S_1 & S_2 & I & P & A \end{pmatrix}^T$ and the functions

$$f(\cdot) = \begin{pmatrix} Z - dS_1 - \dfrac{\beta S_1 I}{N_C} + \gamma S_2 \\ -(\gamma + d)S_2 \\ \dfrac{\beta S_1 I}{N_C} - (d + \delta)I \\ \varepsilon\delta I - (\alpha + d)P \\ (1-\varepsilon)\delta I + \alpha P - (\mu + d)A \end{pmatrix} \quad g_1(\cdot) = \begin{pmatrix} -S_1 \\ S_1 \\ 0 \\ 0 \\ 0 \end{pmatrix}$$

$$g_2(\cdot) = \begin{pmatrix} 0 \\ 0 \\ -\psi \dfrac{I}{N_c} \\ \phi\psi \dfrac{I}{N_c} \\ (1-\phi)\psi \dfrac{I}{N_c} \end{pmatrix} \quad g_3(\cdot) = \begin{pmatrix} 0 \\ 0 \\ 0 \\ P \\ -P \end{pmatrix}$$

the system (1)-(5) can be re-written in the compact form:

$$\dot{X} = f(X) + g_1(X)u_1 + g_2(X)u_2 + g_3(X)u_3 = F(X,U) \quad (6)$$

where $U = (u_1 \; u_2 \; u_3)^T$.

As far as the output is concerned, the physically and realistically available measurements of the dynamics are represented by the number of the subjects with a positive diagnosis of HIV and /or AIDS, i.e. $P(t)$ and $A(t)$, also separately. Then, the measurable output can be assumed as:

$$y(t) = CX(t) = \begin{pmatrix} 0 & 0 & 0 & 1 & 1 \end{pmatrix} \begin{pmatrix} S_1(t) \\ S_2(t) \\ I(t) \\ P(t) \\ A(t) \end{pmatrix} \quad (7)$$

Note that it is impossible to know the number of unaware infectious subjects $I(t)$ as well as it is not possible to quantify $S_1(t)$ and $S_2(t)$ separately.

The aim is to minimize the number of infectious subjects $I(t)$ by using as less resources as possible; then, the following quadratic cost index is assumed:

$$\begin{aligned} J(X,U) &= \frac{1}{2}\int_{t_0}^{\infty} \left[X^T(t)QX(t) + \hat{U}^T(t)R\hat{U}(t) \right] dt \\ &= \frac{1}{2}\int_{t_0}^{\infty} \left[qI^2(t) + r_1 u_1^2(t) + r_2 u_2^2(t) \right] dt \end{aligned} \quad (8)$$

with

$$Q = \begin{pmatrix} 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & q & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}, \; q > 0 \qquad R = \begin{pmatrix} r_1 & 0 \\ 0 & r_2 \end{pmatrix}, \; r_i > 0, \; i = 1,2$$

and $\hat{U}(t) = \begin{pmatrix} u_1(t) & u_2(t) \end{pmatrix}^T$.

It is worth to be noted that the control $u_3(t)$ has not been introduced in the cost index (8) since it does not affect the $I(t)$ dynamic, as evident from the model (1)-(5).

The solution of the minimization problem (8) cannot be easily obtained if the variables involved ($I(t)$ in the present case) are not measurable and, at the same time, a desirable goal is to design a feedback control law.

As far as the first point is concerned, the problem of state variables estimation introduces an error that affects the cost index value, yielding a solution which cannot be optimal. For the control law design, a possible choice is the linear quadratic approach on the linearized system, thanks also to the quadratic structure of the cost index; this choice guarantees a priori the closed form implementation.

Then, the global control design proposed is composed by two main steps:

- the LQ regulator: a linear approximation of (6) is preliminary required; then the classic LQ solution is found as a linear state feedback;
- the state estimation: the linear approximation adopted suggests to use a linear observer which simplifies the whole design allowing the application of the separation principle.

III. THE CONTROL DESIGN

In this Section the proposed control design procedure is described. The nonlinear system is firstly linearized, as described in Subsection 3.1; this aspect is quite crucial and requires a preliminary analysis for the choice of the working point around which the linearization is computed.
Thanks to the choice of a quadratic cost index, the linear quadratic regulator theory is applied to the linearized system in Subsection 3.2, aiming at a solution in closed form. Since the state is not available, an estimation is required; then, in Subsection 3.3 a linear observer is determined. It guarantees the application of the separation principle so allowing the use of the feedback control law, determined by the LQ regulator, with the state estimation. Clearly, in the numerical simulations the linear approximated control law is used with the nonlinear system.

3.1 The linear approximation

According to the control design proposed, a linear approximation in the neighborhood of an equilibrium point is required. Following a classical approach, the computation of the state space points which verify the equation $F(X^e,0)=0$ is performed, yielding the solutions [5]

$$X_1^e=\begin{pmatrix}1/d\\0\\0\\0\\0\end{pmatrix}Z \qquad X_2^e=\begin{pmatrix}1/H\\0\\ \dfrac{H-d}{(d+\delta)H}\\ \dfrac{\varepsilon\delta(H-d)}{(\alpha_1+d)(d+\delta)H}\\ \dfrac{\delta(H-d)\left[(1-\varepsilon)d+\alpha_1\right]}{(\alpha_1+d)(\alpha+d)(d+\delta)H}\end{pmatrix}Z \tag{9}$$

where $H=\beta-\delta$.

The positiveness of the elements in the vector state X_2^e implies the conditions: $H>0$ and $H>d$; therefore the second equilibrium point X_2^e is a feasible one only if

$$H>d \tag{10}$$

If $H=d$, X_2^e coincides with X_1^e .

Assume condition (10) satisfied, for a more general analysis of both the points and for the fact that in the present case the parameter values make (9) verified. So, two possible linearized dynamics can be computed in the neighborhood of the two points, recalling that, in any case, C is given by (7).
The state matrix, i.e. the Jacobian matrix evaluated at the equilibrium point X_i^e

$$A_i=\left.\frac{\partial F}{\partial X}\right|_{X=X_i^e,U=0} \tag{11}$$

and the input matrix

$$B_i=\left.\frac{\partial F}{\partial U}\right|_{X=X_i^e,U=0} \tag{12}$$

must be computed, for $i=1,2$.
The stability analysis gives that, under condition (10), the equilibrium point X_1^e is unstable, due to the presence of one real positive eigenvalue, whereas the equilibrium point X_2^e is locally asymptotically stable, since all the eigenvalues of A_2 have negative real part [5].
Since the aim of the control problem is to minimize the value of $I(t)$, so leading it as close as possible to zero, the choice of working in a neighborhood of X_1^e , for which $I^e=0$, seems effective. Unfortunately, the properties of controllability and observability for the linear approximation are not fulfilled, as shown in the Appendix for the general case of equilibrium points with $I^e=0$. This fact prejudices the control design and, consequently, X_1^e does not represent a practicable choice for the system linearization.
On the other hand, once the equilibrium point X_2^e is considered, the controllability and observability properties for A_2 , B_2 and C are both satisfied, as shown in the Appendix for the case of case of equilibrium points with $I^e\neq 0$; consequently, X_2^e represents a suitable choice. The condition $I^e\neq 0$ has a drawback is the fact that in this equilibrium point $I^e=\dfrac{H-d}{(d+\delta)H}$ can be far from zero; this would force the linear approximation to be valid in a quite large neighborhood of the equilibrium point, with all the consequent approximation errors.
Since all these considerations arise from the classical analysis of the equilibria $F(X^e,0)=0$, a possible extension of such concept can bring to study a more general condition $F(X^e,U^e)=0$ in which forced equilibria are considered under a constant input action U^e . This idea, applied in the present case, can be used to increase the possibility of finding suitable forced equilibrium points, which present controllable and observable linear approximations and, in addition, are characterized by $I^e=0$.
The results of the computation of such new set of equilibrium points is reported in the Appendix, where it is shown that the two conditions, on I^e and on the structural properties, cannot be satisfied contemporarily. So, the use of generalized forced equilibrium points does not help in the present control design; on the contrary, it may introduce some complications in the evaluation of the ranges and of the bounds of the control values.
Then, in the sequel, the choice of X_2^e as the linearization point is performed. Therefore, the system (6)–(7) is linearized in the neighborhood of such a point; denoting with

$$\widetilde{X}(t) = X(t) - X_2^e \tag{13}$$

the new variables, one has:

$$\begin{aligned}\dot{\widetilde{X}}(t) &= A_2\widetilde{X}(t) + \hat{B}_2\hat{U}(t)\\ \widetilde{y}(t) &= C\widetilde{X}(t)\end{aligned} \tag{14}$$

with A_2 as in (11) while $\hat{B}_2$ represents the first two columns of B_2 given in (12) .

3.2 The LQ solution

The system (6) is nonlinear and the cost index (8) is quadratic in the state and in the control; aiming at determining a control in the linear quadratic regulator framework, the linearized system (14), determined in the previous Subsection 3.1, is herein considered. As already discussed, the aim is to determine a control action able to minimize the number of infectious subjects $I(t)$ not aware of their status, using as less resources as possible, and the choice of the cost index (8) well describes these two contrasting requirements.

Since the state variables may be expressed, from (13), as $X(t) = X_2^e + \widetilde{X}(t)$, the cost index (8) must be rewritten putting in evidence the new variable $\widetilde{X}(t)$, whose estimation will be computed by the observer. Then:

$$\begin{aligned}J(\widetilde{X},\hat{U}) &= \frac{1}{2}\int_{t_i}^{\infty}\left[\left(X_2^e + \widetilde{X}(t)\right)^T Q\left(X_2^e + \widetilde{X}(t)\right) + \hat{U}^T(t)R\hat{U}(t)\right]dt\\ &= \frac{1}{2}\int_{t_i}^{\infty}\left[q\left(\frac{H-d}{(d+\delta)H}Z + \widetilde{I}(t)\right)^2 + r_1u_1^2(t) + r_2u_2^2(t)\right]dt\end{aligned} \tag{15}$$

where $\widetilde{I}(t)$ is the third component of the state $\widetilde{X}(t)$.

The minimization of the cost index (15) for the linear dynamical system (14) is equivalent to solve an LQ tracking problem where the reference $\bar{r}_{\widetilde{I}}$ for $\widetilde{I}(t)$ is the constant value

$$\bar{r}_{\widetilde{I}} = -\frac{H-d}{(d+\delta)H}Z \tag{16}$$

The existence and uniqueness of the solution of the stationary tracking problem on infinite time interval is in general guaranteed only if the matrix Q is positive definite; however, with Q semidefinite positive, as in the present case, the existence of a stabilizing feedback control law is still guaranteed.

The state feedback optimal control law for the problem (14)-(15) is given by [8]:

$$\hat{U}^o(t) = -R^{-1}\hat{B}_2^T K\widetilde{X}^o(t) + R^{-1}\hat{B}_2^T g_{\bar{r}} \tag{17}$$

where

- $\widetilde{X}^o(t)$ is the optimal evolution solving the equation (14) with control (17):

$$\dot{\widetilde{X}}^o(t) = \left[A_2 - \hat{B}_2R^{-1}\hat{B}_2^T K\right]\widetilde{X}^o(t) + \hat{B}_2R^{-1}\hat{B}_2^T g_{\bar{r}} \tag{18}$$

- $g_{\bar{r}}$ is given by:

$$g_{\bar{r}} = \left[K\hat{B}_2R^{-1}\hat{B}_2^T - A_2^T\right]^{-1}Q\bar{r} \tag{19}$$

with $\bar{r} = \begin{pmatrix} * & * & \bar{r}_{\widetilde{I}} & * & * \end{pmatrix}^T$, which gives $Q\bar{r} = \begin{pmatrix} 0 & 0 & q\bar{r}_{\widetilde{I}} & 0 & 0 \end{pmatrix}^T$

- K is the solution of the algebraic Riccati equation (ARE):

$$0 = K\hat{B}_2R^{-1}\hat{B}_2^T K - KA_2 - A_2^T K - Q \tag{20}$$

As previously discussed, the state $X(t)$, and consequently $\widetilde{X}(t)$, is not fully available; in particular the number $I(t)$ of the infectious subjects non aware of their status is not known.

Then, the linear observer is designed in the next subsection. In fact, once the system (6) has been linearized and the choice of a linear quadratic regulator is assumed to obtain an easy feedback control law, a linear observer appears advisable also in view of the possibility of using the separation principle, as it will be outlined in the next subsection.

3.3. The state estimator and the control law design

To complete the solution of the problem (14)-(15), the separation principle approach is applied; a state observer is designed determining an estimation ξ of the non-available state of the linearized system (14).

The separation principle allows to apply the control law (17) with the estimated state; this implies the separated determination of the gain of the observer and of the gain of the linear quadratic tracking controller in (17).

In the numerical results section, it will be assessed that for the values of the parameters chosen in [1, 5], reasonable for describing the HIV/AIDS spread and adopted in this paper, the system (14) is observable.

Then, it is possible to design the local state observer:

$$\dot{\xi}(t) = (A_2 - GC)\xi(t) + \hat{B}_2\hat{U}(t) + G\widetilde{y}(t) \tag{21}$$

obtaining the gain G in order to place the eigenvalues of $A_2 - GC$ in the left side of the complex plane.

Therefore, $\widetilde{X}^o(t)$ can be substituted in (17) by its estimation ξ given by (21). The control law (17) becomes:

$$\hat{U}^o(t) = -R^{-1}\hat{B}_2^T K\xi^o(t) + R^{-1}\hat{B}_2^T g_{\bar{r}} \tag{22}$$

with ξ^o satisfying:

$$\dot{\xi}^o(t) = \left[A_2 - GC - \hat{B}_2R^{-1}\hat{B}_2^T K\right]\xi^o(t) + \hat{B}_2R^{-1}\hat{B}_2^T g_{\bar{r}} + G\widetilde{y}(t) \tag{23}$$

The feedback law which solves the original optimal control problem, minimizing the cost index (8) for the nonlinear system (6)-(7), is therefore given by (22)-(23).

IV. NUMERICAL RESULTS

In this Section, numerical computations are performed to show the feasibility of the proposed control scheme.
The values chosen for the parameters in the dynamics (1)-(5) are the ones used in [1] and [5]:

$d = 0.02;\ \beta = 1.5;\ \delta = 0.4;\ \varepsilon = 0.6;\ \phi = 0.95;\ \gamma = 0.2;$
$\psi = 10^5;\ \alpha = 0.5;\ \mu = 1;\ Z = 1000.$

Consequently, $H = \beta - \delta = 1.1 > 0$ and then the equilibrium point X_2^e exists and is locally asymptotically stable:

$$X_2^e = \begin{pmatrix} 0.91 \\ 0 \\ 2.34 \\ 1.08 \\ 0.90 \end{pmatrix} 10^3 \quad (24)$$

The linear approximation in the neighborhood of this equilibrium point yields the following matrices:

$$A_2 = \begin{pmatrix} -0.7976 & 0.2 & -0.1176 & 0 & 0 \\ 0 & -0.22 & 0 & 0 & 0 \\ 0.7776 & 0 & 0.3024 & 0 & 0 \\ 0 & 0 & 0.24 & -0.52 & 0 \\ 0 & 0 & 0.16 & 0.5 & -1.02 \end{pmatrix} \quad (25)$$

$$\hat{B}_2 = \begin{pmatrix} -3.57 & 0 \\ 3.57 & 0 \\ 0 & -3.82 \\ 0 & 3.63 \\ 0 & 0.19 \end{pmatrix} \quad (26)$$

The output matrix C is the one in (7). It is easy to verify that the linear system (14), with numerical values (25) and (26) and position (13) is both observable and controllable; then all the computations described in the previous Section can be performed.
The offset (16) assumes the value $\bar{r}_{\tilde{I}} = -2.34 \cdot 10^3$.
With a first choice for the weights in the cost index as $q = 10^{-4}$, $r_1 = 1$, $r_2 = 1000$, the solution of the ARE $K\hat{B}R^{-1}\hat{B}^T K - KA - A^T K - Q = 0$ gives

$$K = \begin{pmatrix} 6.19 \cdot 10^{-10} & 4.86 \cdot 10^{-10} & 2.81 \cdot 10^{-9} & 0 & 0 \\ 4.86 \cdot 10^{-10} & 4.42 \cdot 10^{-10} & -1.38 \cdot 10^{-11} & 0 & 0 \\ 2.82 \cdot 10^{-9} & -1.38 \cdot 10^{-11} & 4.36 \cdot 10^{-6} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

from which

$$g_{\bar{r}} = \begin{pmatrix} -1.13 \cdot 10^{-4} \\ -1.06 \cdot 10^{-4} \\ -1.03 \cdot 10^{-2} \\ 0 \\ 0 \end{pmatrix}$$

and the optimal control, which should drive the state variable $\tilde{I}(t)$ of the linearized system to the reference value $\bar{r}_{\tilde{I}}$, and therefore, once applied to the nonlinear dynamics, the state variable $I(t)$ to zero, is

$$\hat{U}^o(t) = \begin{pmatrix} 1.21 \cdot 10^{-7} & 4.01 \cdot 10^{-7} & 2.57 \cdot 10^{-6} & 0 & 0 \\ 2.03 \cdot 10^{-7} & -9.96 \cdot 10^{-10} & 3.14 \cdot 10^{-4} & 0 & 0 \end{pmatrix} \tilde{X}^o(t) + \\ + \begin{pmatrix} 6.34 \cdot 10^{-3} \\ 7.39 \cdot 10^{-1} \end{pmatrix} \quad (27)$$

Recalling the hypothesis assumed on $u_3(t)$, the complete control law is:

$$U^o(t) = \begin{pmatrix} \hat{U}^o(t) \\ 0 \end{pmatrix} \quad (29)$$

Simulations can be performed applying the control law (29) to the linear system used for design purpose and to the nonlinear initial system.
Figure 2 shows the comparison between the time history of the number of infectious individuals $I(t)$ with the corresponding evolution for the linearized dynamics $\tilde{I}(t)$ (dotted line) shifted by the equilibrium value I^e.
The effectiveness of the procedure here proposed and adopted for the design of the optimal state feedback control law for nonlinear dynamics (1)-(5), making use of a local linearized approximation, is then well evident, being the two time evolution comparable.
Note that the result shown is obtained under the simplifying hypothesis of state measure availability.

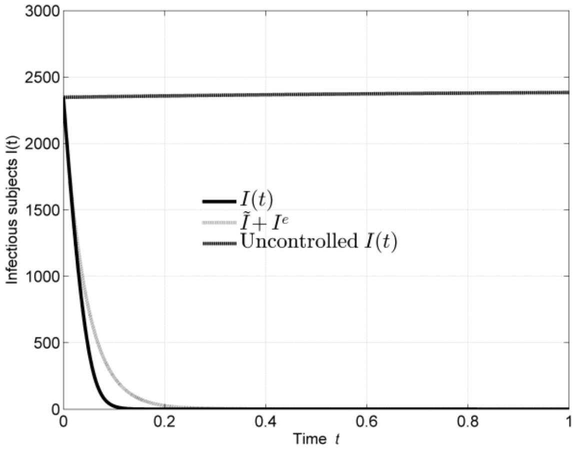

Figure 2. Time history of the number of the infectious subjects $I(t)$ (solid), compared with the same for the linear approximation translated by the equilibrium value I^e (dotted), and with the uncontrolled case (dashed).

As discussed in the previous Sections, the unavailability of a direct measurement for the number of the subjects infectious but not aware of such a condition, the $I(t)$, makes impossible the direct use of (29). The solution here proposed is based on the use of a linear state observer to produce an estimation of the real value of $I(t)$.

The choice of a linear observer, designed on the basis of the linear approximation (26) of the nonlinear dynamics (1)-(5), is also supported by the encouraging results obtained for the control computed on the linear approximation shown in Figure 2, thus suggesting that the convergence region may be quite large.

Then, starting from the linear approximation (14), a linear state observer of the form (21) is computed.

A crucial aspect is the choice of the velocity of convergence of the estimation error. The effects of the linear observer applied to the linear dynamics is reported in Figure 3 for the set of eigenvalues

$\Lambda = \{-1.0, -1.1, -1.2, -1.3, -1.4\}$

Note that I^e is added to both $\tilde{I}(t)$ and its estimation to refer them to the state variable $I(t)$.

The eigenvalues are chosen of the same order of magnitude as the given linear dynamics. In order to stress the importance of the observer dynamic, the input $U(t) = 0$ has been considered. The overall control law (22) is constituted by the state feedback (17), optimal according to (15) for the local linear approximated dynamics, feeded by the linear state estimator (21).

The effect of the state estimation performed by applying the linear observer to the nonlinear dynamics is illustrated in Figure 4, showing a satisfactory behavior.

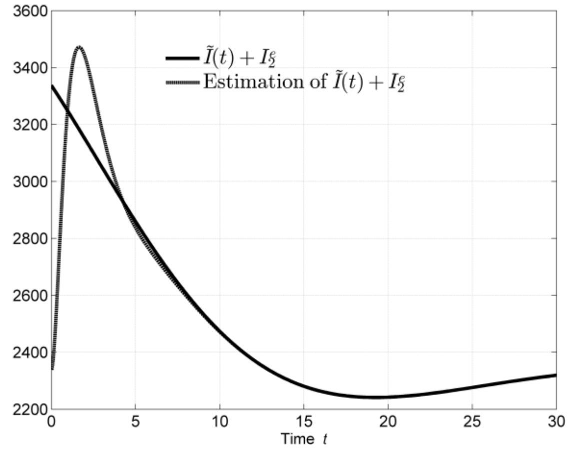

Figure 3. Comparison between the state $\tilde{I}(t)$ of the linear approximation (solid line) and its estimation (dashed line), both shifted by I^e, performed by the state observer applied to the linearized system.

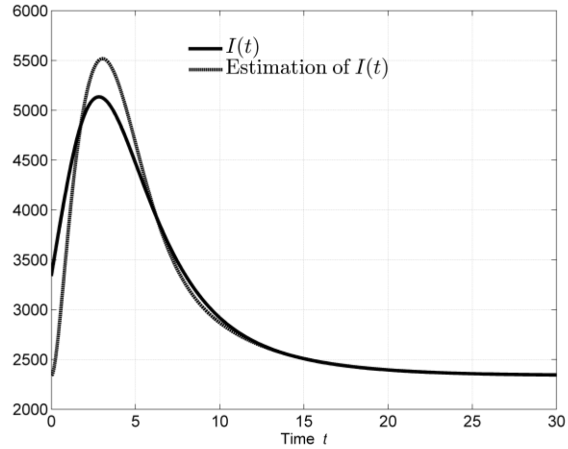

Figure 4: Comparison between actual state $I(t)$ of the nonlinear dynamics (solid line) and its estimation (dashed line) obtained by shifting the output of the linear state observer by I^e.

The control scheme proposed is applied to the original nonlinear system (1)-(5); the simulation results are reported in Figures 5-11. In particular, Figures 5-9 show the results for the five state components, depicting each variable with and without control along with the equilibrium value, while in Figures 10-11 the resulting control inputs are plotted.

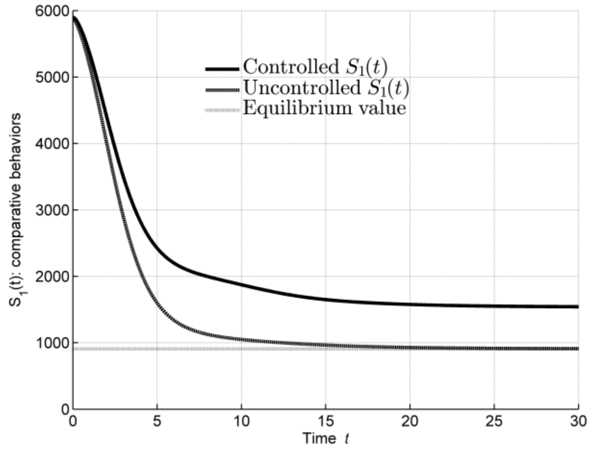

Figure 5. Time history of the number of unwise population members $S_1(t)$, comparing the cases with and without control action.

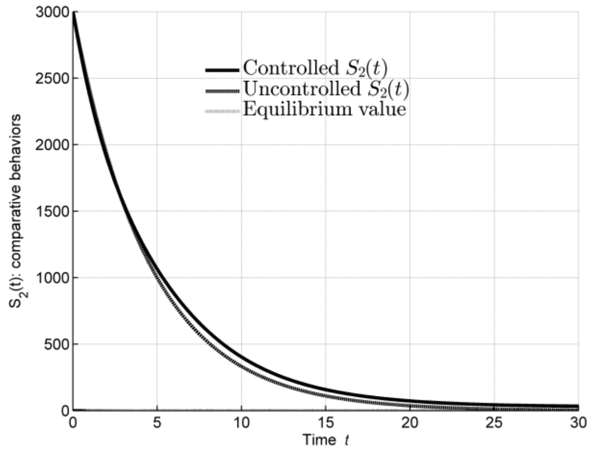

Figure 6. Time history of the number of wise population members $S_2(t)$, comparing the cases with and without control action.

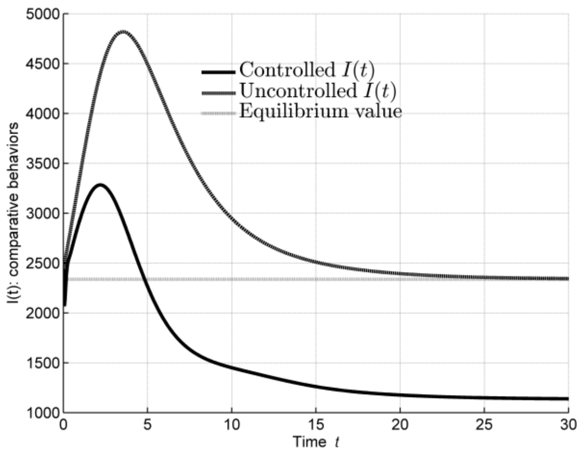

Figure 7. Time history of the number of infectious individuals $I(t)$ responsible of the epidemic diffusion, comparing the cases with and without control action.

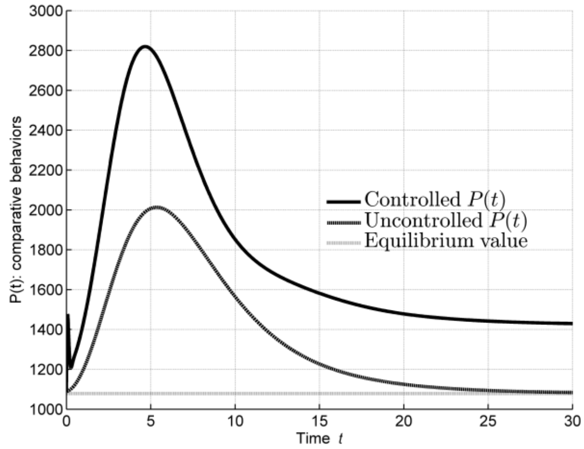

Figure 8. Time history of the number of diagnosed subjects in the pre-AIDS phase $P(t)$, comparing the cases with and without control action.

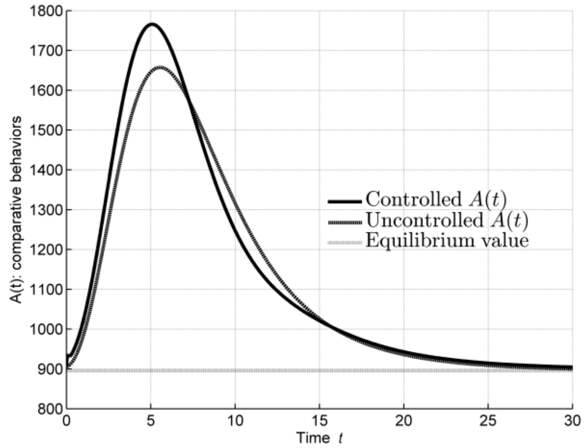

Figure 9. Time history of the number of AIDS diagnosed subjects $A(t)$, comparing the cases with and without control action.

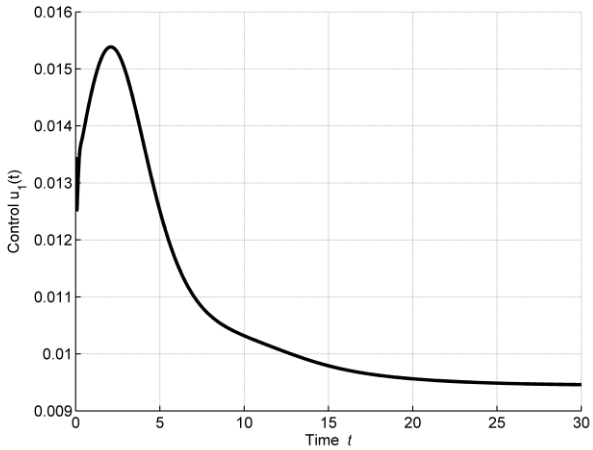

Figure 10. Time evolution of the prevention control action $u_1(t)$.

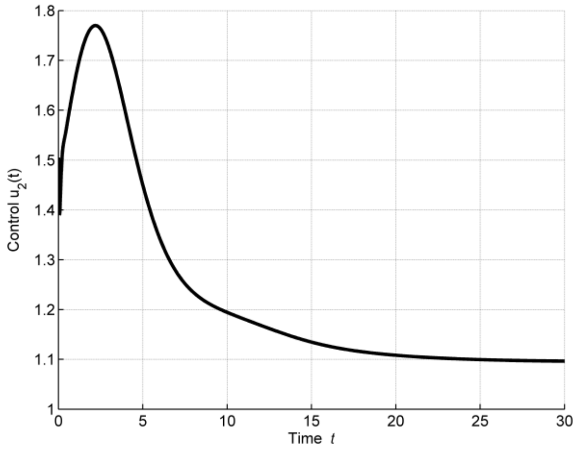

Figure 11. Time evolution of the diagnostic control action $u_2(t)$.

The overall effect of the control is also summarized in Figures 12 and 13, where the time history of the total number of non-infectious subjects, given by $S_1(t)+S_2(t)$, and the number of known and unknown infectious ones, $I(t)+P(t)+A(t)$, are reported respectively.

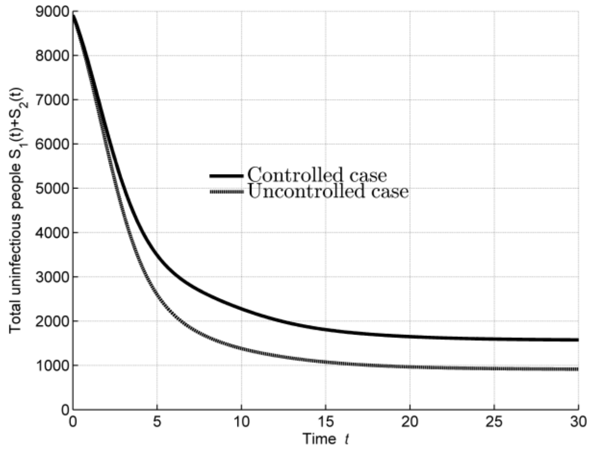

Figure 12. Time history of the number of total uninfectious individuals with (solid) and without (dashed) the infection spread control action

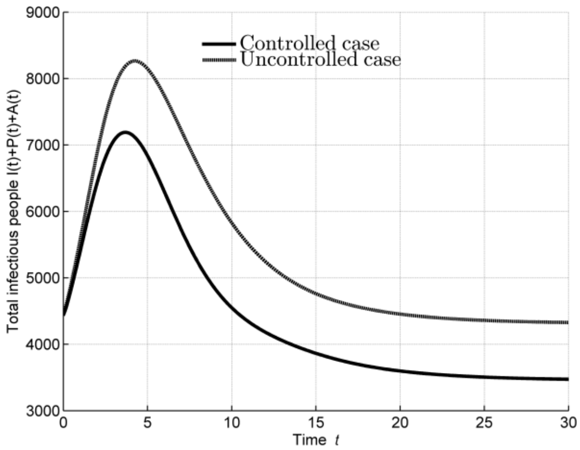

Figure 13. Time history of the number of total infectious individuals, with (solid) and without (dashed) the infection spread control action.

The positive effects of the control actions can be observed in the time hystories of the state components. The number of uninfectious subjects increases, more sensibly for the unwise group, $S_1(t)$, than for the wise one, $S_2(t)$. This behavior is due to the small action of the first control, as seen in Figure 12, which moves individuals from S_1 to S_2 , combined with the action of the control $u_2(t)$, which, aiming to empty the group I , reduces the possibility of contagious interaction between S_1 and I , leaving a larger number of subjects in S_1 . As already said, the number of unaware infectious individuals introduced in the cost function, $I(t)$, strongly decreases; since such reduction is not due to a change in the illness conditions but only in a change of awareness of the individual illness status, one evident effect is the increment of the number of the diagnosed infectious $P(t)$ and $A(t)$.

Despite the choice of the weights $r_1=1$ and $r_2=1000$ which impose a higher cost for the second input, the higher magnitude of the control $u_2(t)$ shows the great importance of the diagnosis in the epidemic control. It is a consequence of the impossibility, according to the considered model, of any contagious actions between the known infectious subject and all the others.

One more interesting observation, arising from the time histories of the two controls, is that they show the classical shape that usually can be met when dealing with optimal control of epidemic diffusion: an initial high effort to bring the number of the contagious individuals below a certain level and then an almost constant action to keep the situation at acceptable values according to the costs introduced.

The positive global effects of the control actions are easily understood once the time evolution of the number of total safe individuals (Figure 12) and of infectious individuals (Figure 13), compared to the case of absence of control, is considered. Figure 12 shows a total increment of uninfectious persons, as it is expected. The reduction of the total amount of infectious subjects, Figure 13, proves that the increment of the number of individuals in $P(t)$ and $A(t)$ are highly compensated by the reduction of the dangerous components of $I(t)$.

In any optimal control problem, a peculiar aspect is represented by the choices of the weights in the cost function: different relevance can then be given to the control and to the errors, and between each control or each error component.

A characterization of the contribution of the weight parameter defined in (15) can be performed by means of some simulations for different values.

So, in Figures 14-15-16 the effects of the weight q is evidenced by means of the corresponding state evolutions: the sum of the susceptible subjects, $S_1(t)+S_2(t)$, the unaware infectious people, $I(t)$, and the patients $P(t)+A(t)$, respectively . The different values for q are used while the two weights on the control are kept fixed to the main case: $r_1=1$ and $r_2=1000$.

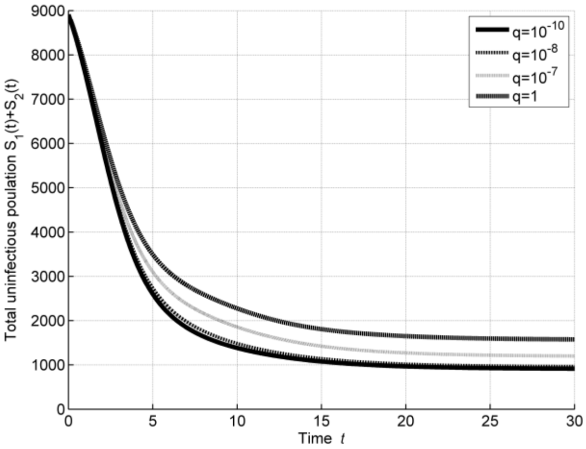

Figure 14. Time history of the total uninfectious individuals for different choices of the weight q.

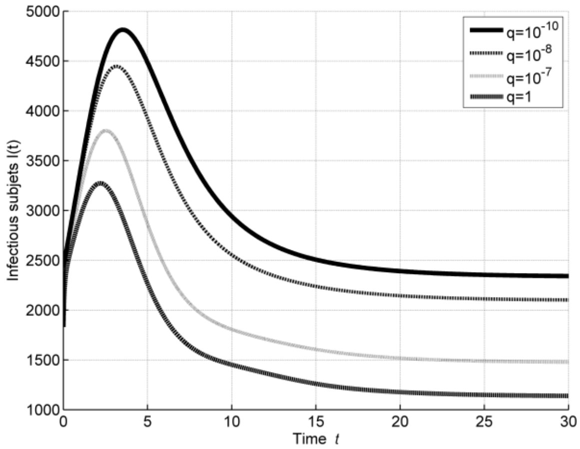

Figure 15. Time history of the infectious individuals in $I(t)$ for different choices of the weight q.

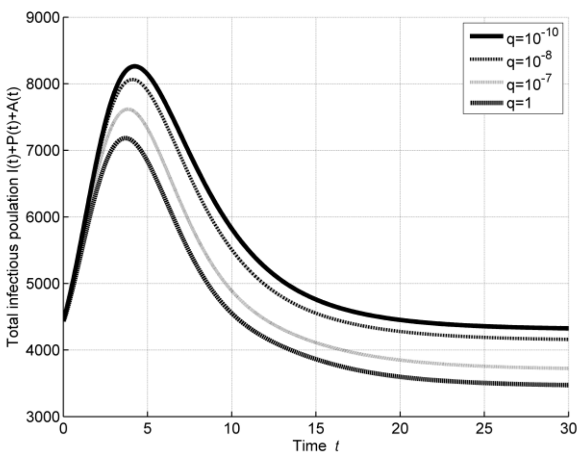

Figure 16. Time history of the total infectious individuals for different choices of the weight q.

The general effects are obvious: the higher is the value of the weight q, the more important are the positive effects of the control action. An interesting observation can arise once the increment of the beneficial effects is compared to the increment of the q value. While this effect is verifiable on these Figures, the more evident contribution can be noted in Figure 15. Starting with the small value $q=10^{-10}$, an increment of three order of magnitude, $q=10^{-7}$, produces a steady state reduction of infectious subjects $I(t)$ from 2300 to less than 1500, while a further increment up to seven order of magnitude, using $q=1$, produces a decrement of about 300 units.

A different comparative analysis can be performed studying the effects of changes in r_1 and r_2 values on the amplitude of the control inputs. Figures 17 and 18 show how much the input $u_1(t)$ is dependent on the changes in r_1 and r_2 respectively. Also in this case it can be important to stress the fact that increments in case of small values produce more relevant effects than in case of higher ones. For example, comparing the case of $r_1=1$ and $r_2=1$, solid line in Figure 18, with the case of $r_1=5$ and $r_2=1$, solid line on Figure 17, a difference of three orders of magnitude in $u_1(t)$ amplitude can be appreciated. However, for any couple of values considered for r_1 and r_2, the order of the amplitudes of $u_1(t)$ is equal or less than 10^{-3}.

When the second input is considered, a first relevant result that can be observed is the one evidenced in Figure 19: the small effects of input $u_1(t)$, and then of its changes, makes input $u_2(t)$ almost independent from the choice of r_1.

In Figure 20 the more intuitive relationship between the cost of input $u_2(t)$ and its amplitude is present, the greater the cost, the lower the amplitude.

In any case, for the different choices adopted for r_1 and r_2, the contribution of $u_2(t)$ is always much greater than the one of $u_1(t)$. This suggests that, if the control $u_1(t)$ is set equal to zero as done for $u_3(t)$ (canceled for different general considerations), and in the cost function the corresponding term is neglected, the solution so obtained should be quite similar to the present one.

However, the choice of maintaining $u_1(t)$ has been adopted since it can be more interesting once the actual cost, in terms of economical budget required for actuation, is introduced.

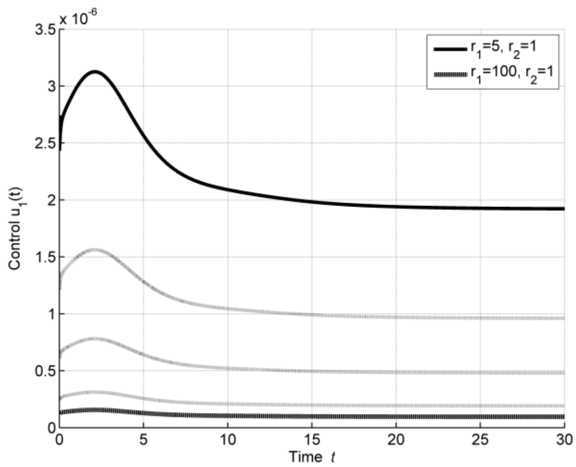

Figure 17. Time evolution of the control $u_1(t)$ for different values of weight r_1. The dotted curves correspond to intermediate values of the parameter.

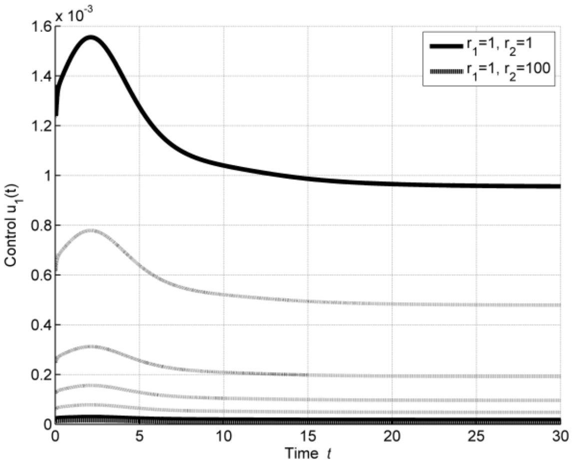

Figure 18. Time evolution of the control $u_1(t)$ for different values of weight r_2. The dotted curves correspond to intermediate values of the parameter.

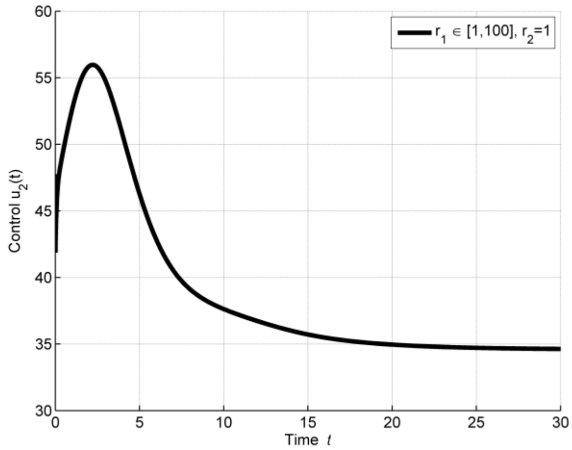

Figure 19. Time evolution of the control $u_2(t)$ for different values of weight r_1.

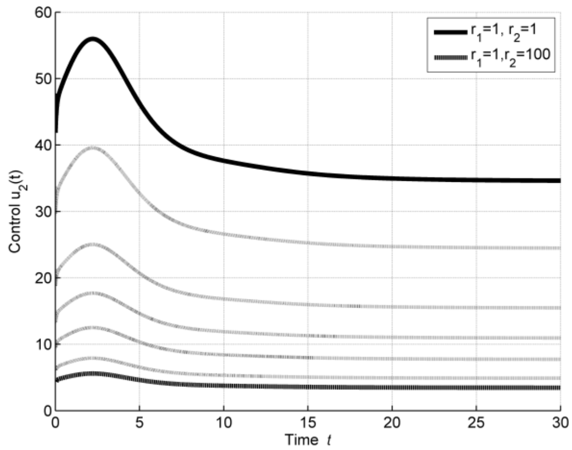

Figure 20. Time evolution of the control $u_2(t)$ for different values of weight r_2. The dotted curves correspond to intermediate values of the parameter.

V. CONCLUSION AND FUTURE DEVELOPMENTS

In this paper the model of HIV/AIDS spread is faced proposing a state feedback control scheme using a novel nonlinear model that considers five classes of population, two for the susceptibles and three for the infectious subjects.

The problem is formulated in the framework of the optimal control theory, defining a quadratic cost index aiming at the reduction of the number of infectious individuals not aware of their status, using as less resources as possible.

The design approach is based on the linearization in the neighborhood of a suitable equilibrium point, obtaining a system that is both controllable and observable.

The consequently transformed cost index and the linearized system could be studied in the framework of linear quadratic tracking problem. The state variable to be minimized is not measurable and it has been estimated using a linear observer. The choice of operating in a linearized contest makes the separation principle hold, simplifying the design and guarantying the feedback control structure for the original nonlinear system.

The results obtained, the contribution of each control action and the importance of a suitable choice for the weight coefficients in the cost function are all discussed by means of different simulations results.

The problem faced in this paper can be extended in the following directions. From the modeling point of view, generalizations could include: i. other possible interactions, like incautious unaware contacts with subjects in the pre-AIDS condition; ii. the flux of new subjects can affect more classes; iii. noise and uncertainties in the state variable dynamics, which for example suggest the use of an extended Kalman filter (EKF) or the unscented one (UKF).

As far as the control design approach, different choices for the cost index can be introduced, for example to activate all the three levels of intervention. In addition, a nonlinear control strategy designed directly on the original system could be introduced as well as a nonlinear observer.

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APPENDIX

Computation of the equilibrium points.

The traditional definition of equilibrium points for time invariant nonlinear dynamics of the form $\dot{X}(t) = F(X(t), U(t))$ with $X \in R^n$, $U \in R^m$ refers to the state space points X^e which constitute invariant conditions under no external action, satisfying $F(X^e, 0) = 0$, for which the condition $X(0) = X^e$ implies $X(t)|_{U(t)=0} = X^e \ \forall t \geq 0$.

Sometimes it can be useful to extend such concept assuming a constant input and computing the equilibria under external action, i.e. determining forced equilibria. The formulation of the extended problem is quite straightforward, since a forced equilibrium point $X^e(U^e) \in R^n$, with $U^e \in R^m$, must satisfy the condition $F(X^e(U^e), U^e) = 0$, which gives $X(t)|_{U(t)=U^e} = X^e \quad \forall t \geq 0$, once $X(0) = X^e(U^e)$ is set.

Since the classical formulation can be obtained setting $U^e = 0$, the extended case is firstly studied, and the consequences of the choice $U^e = 0$ are successively addressed.

For the given system (6), the condition $F(X^e(U^e), U^e) = 0$ assumes the explicit form

$$Z - dS_1^e - \frac{\beta S_1^e I^e}{N_c^e} + \gamma S_2^e - S_1^e \bar{u}_1 = 0 \qquad \text{(A1)}$$

$$-(\gamma + d)S_2^e + S_1^e \bar{u}_1 = 0 \qquad \text{(A2)}$$

$$\frac{\beta S_1^e I^e}{N_c^e} - (d + \delta)I^e - \psi \frac{I^e}{N_c^e}\bar{u}_2 = 0$$

(A3)

$$\varepsilon\delta I^e - (\alpha + d)P^e + \phi\psi \frac{I^e}{N_c^e}\bar{u}_2 + P^e \bar{u}_3 = 0 \qquad \text{(A4)}$$

$$(1-\varepsilon)\delta I^e + \alpha P^e - (\mu + d)A^e + (1-\phi)\psi \frac{I^e}{N_c^e}\bar{u}_2 - P^e \bar{u}_3 = 0 \qquad \text{(A5)}$$

once $U^e = (\bar{u}_1 \quad \bar{u}_2 \quad \bar{u}_3)^T$ is set and $X^e(U^e)$ is shortened as X^e.

The attention will be focused on the first three equations only, since P^e can be easily obtained from (A4) once the first three components are found:

$$P^e = \frac{\varepsilon\delta N_c^e + \phi\psi\bar{u}_2}{N_c^e(\alpha + d - \bar{u}_3)} I^e \qquad \text{(A6)}$$

and the same holds for A^e given the other state variables:

$$A^e = \frac{(1-\varepsilon)\delta N_c^e + (1-\phi)\psi\bar{u}_2}{N_c^e(\mu + d)} I^e + \frac{\alpha - \bar{u}_3}{\mu + d} P^e \qquad \text{(A7)}$$

Moreover, the main interest is in I^e, being directly involved in the control problem addressed in the paper.

From (A3) one gets the solution

$$I^e = 0 \qquad \text{(A8)}$$

holding for any choice of the control actions, and the input dependent solution

$$I^e = \frac{\beta - (d + \delta)}{d + \delta} S_1^e - S_2^e - \frac{\psi}{d + \delta}\bar{u}_2 \qquad \text{(A9)}$$

The two cases are now investigated.

Case 1: $I^e = 0$

From (A8), (A1) and (A2) give

$$S_1^e = \frac{1}{(1 + \frac{\bar{u}_1}{\gamma + d})} \frac{Z}{d} \qquad \text{(A10)}$$

$$S_2^e = \frac{\frac{\bar{u}_1}{\gamma + d}}{(1 + \frac{\bar{u}_1}{\gamma + d})} \frac{Z}{d} \qquad \text{(A11)}$$

while (A6) and (A7), with (A8), give $P^e = 0$ and $A^e = 0$ for any value of U^e.

Therefore, the complete solution is

$$X_1^e(\bar{u}_1) = \frac{Z}{d} \begin{pmatrix} \frac{1}{(1 + \frac{\bar{u}_1}{\gamma + d})} & \frac{\frac{\bar{u}_1}{\gamma + d}}{(1 + \frac{\bar{u}_1}{\gamma + d})} & 0 & 0 & 0 \end{pmatrix}^T,$$

$$\forall U^e \geq 0 \qquad \text{(A12)}$$

For $\bar{u}_1 = 0$, corresponding to $U^e = (0 \quad \bar{u}_2 \quad \bar{u}_3)^T$, one has

$$X_1^e = X_1^e(0) = \frac{Z}{d}(1 \quad 0 \quad 0 \quad 0 \quad 0)^T, \ \forall \bar{u}_2, \bar{u}_3 \geq 0 \qquad \text{(A13)}$$

Increasing the value of $\bar{u}_1$, the point moves in the $S_1 - S_2$ plane, keeping all the other three components identically equal to zero.

Since

$\lim_{\bar{u}_1 \to +\infty} X_1^e(\bar{u}_1) = \frac{Z}{d}(0 \quad 1 \quad 0 \quad 0 \quad 0)^T$ and $S_1^e + S_2^e = \frac{Z}{d}$,

the effect of the control $\bar{u}_1$ is to move individuals, at the equilibrium conditions, from $S_1^e = \frac{Z}{d}$, $S_2^e = 0$ to $S_1^e = 0$, $S_2^e = \frac{Z}{d}$.

The relationship between the two state variables at the equilibrium point is evident also from (A2), which gives

$$S_2^e = \frac{\bar{u}_1}{\gamma + d} S_1^e \qquad \text{(A14)}$$

verified $\forall U^e \geq 0$.

Case 2: $I^e = \frac{\beta - (d+\delta)}{d+\delta} S_1^e - S_2^e - \frac{\psi}{d+\delta}\bar{u}_2$

Expression (A9), making use of (A2), can be rewritten as

$$I^e = \frac{\beta - (d+\delta)}{d+\delta} S_1^e - \frac{\bar{u}_1}{\gamma + d} S_1^e - \frac{\psi}{d+\delta}\bar{u}_2 \quad \text{(A15)}$$

and the expression for N_c^e is

$$N_c^e = \frac{\beta}{d+\delta} S_1^e - \frac{\psi}{d+\delta}\bar{u}_2 \quad \text{(A16)}$$

which must be positive and then $\beta S_1^e - \psi \bar{u}_2 > 0$

Moreover,

$$\frac{\beta S_1^e I^e}{N_c^e} = \frac{\beta S_1^e \left[\left(\beta - (d+\delta)\left(1 + \frac{\bar{u}_1}{\gamma + d}\right)\right) S_1^e - \psi \bar{u}_2 \right]}{\beta S_1^e - \psi \bar{u}_2} \quad \text{(A17)}$$

Then, from (A1), one has

$$Z - dS_1^e - \frac{\beta S_1^e I^e}{N_c^e} + \gamma S_2^e - S_1^e \bar{u}_1 =$$
$$= (\delta(1+\hat{u}_1) - \beta)(S_1^e)^2 + (Z + (\beta + d(1+\hat{u}_1))\hat{u}_2) S_1^e - Z\hat{u}_2 = 0$$

(A18)

with $\hat{u}_1 = \frac{\bar{u}_1}{\gamma + d}$ and $\hat{u}_2 = \frac{\psi}{\beta}\bar{u}_2$.

The two solutions, functions of the constant inputs, depend on the values of the parameters. They have the expressions

$$S_1^e = \frac{-(Z + (\beta + d(1+\hat{u}_1))\hat{u}_2)}{2(\delta(1+\hat{u}_1) - \beta)} \pm \frac{sqrt\{(Z + (\beta + d(1+\hat{u}_1))\hat{u}_2)^2 + 4Z\hat{u}_2(\delta(1+\hat{u}_1) - \beta)\}}{2(\delta(1+\hat{u}_1) - \beta)} \quad \text{(A19)}$$

However, according to the Descartes' rule of signs applied to (A18), if $(\delta(1+\hat{u}_1) - \beta) > 0$ there is one real positive solution and one negative. Then, one feasible solution exists and its expression is

$$S_1^e(\bar{u}_1, \bar{u}_2)) = S_1^e(\hat{u}_1, \hat{u}_2)) = \frac{-(Z + (\beta + d(1+\hat{u}_1))\hat{u}_2)}{2(\delta(1+\hat{u}_1) - \beta)} + \frac{sqrt\{(Z + (\beta + d(1+\hat{u}_1))\hat{u}_2)^2 + 4Z\hat{u}_2(\delta(1+\hat{u}_1) - \beta)\}}{2(\delta(1+\hat{u}_1) - \beta)} \quad \text{(A20)}$$

By substitution into (A2), (A15), (A6) and (A7), one obtains the equilibrium point $X_2^e(\bar{u}_1, \bar{u}_2) = X_2^e(\hat{u}_1, \hat{u}_2)$

If the condition $(\delta(1+\hat{u}_1) - \beta) > 0$ is not satisfied, both the solutions have positive real part, but it must be checked whether they are real; the corresponding condition is

$$(Z + (\beta + d(1+\hat{u}_1))\hat{u}_2)^2 + 4Z\hat{u}_2(\delta(1+\hat{u}_1) - \beta) > 0 \quad \text{(A21)}$$

With (A21) satisfied, let $S_1^{e1}(\hat{u}_1, \hat{u}_2))$ and $S_1^{e2}(\hat{u}_1, \hat{u}_2))$ be such solutions computed taking the minus and the plus sign respectively; again, by substitution into (A2), (A15), (A6) and (A7), one obtains the two equilibrium points $X_2^{e1}(\bar{u}_1, \bar{u}_2) = X_2^{e1}(\hat{u}_1, \hat{u}_2)$ and $X_2^{e2}(\bar{u}_1, \bar{u}_2) = X_2^{e2}(\hat{u}_1, \hat{u}_2)$, corresponding to the solutions $S_1^{e1}(\hat{u}_1, \hat{u}_2))$ and $S_1^{e2}(\hat{u}_1, \hat{u}_2))$ of (A19), respectively.

Some additional considerations can be performed setting one or both the input equal to zero.

i. $\bar{u}_2 = 0$ ($\hat{u}_2 = 0$)

In this case the equation (A18) becomes

$$(\delta(1+\hat{u}_1) - \beta)(S_1^e)^2 + ZS_1^e = 0$$

and gives only one feasible solution

$$S_1^e = \frac{Z}{\beta - \delta(1+\hat{u}_1)} \text{ if } \hat{u}_1 < \frac{\beta - \delta}{\delta}.$$

From S_1^e, one can compute

$$S_2^e = \frac{\bar{u}_1 Z}{(\gamma + d)(\beta - \delta(1+\hat{u}_1))}$$

using (A2),

$$I^e = \frac{(\beta - (d+\delta))(\gamma + d) - \bar{u}_1(d+\delta)}{(d+\delta)(\gamma + d)(\beta - \delta(1+\hat{u}_1))} Z$$

using (A15), $P^e = P^e(S_1^e, S_2^e, I^e)$ by means of (A6) and $A^e = A^e(S_1^e, S_2^e, I^e, P^e)$ thanks to (A7), so obtaining all the components of the equilibrium point

$X_2^{e1}(\bar{u}_1, 0) = X_2^{e1}(\hat{u}_1, 0)$

ii. $\bar{u}_1 = 0$ ($\hat{u}_1 = 0$)

Under this assumption, equation (A18) assumes the simplified expression:

$$(\delta - \beta)(S_1^e)^2 + (Z + (\beta + d)\hat{u}_2) S_1^e - Z\hat{u}_2 = 0 \quad \text{(A22)}$$

and the solutions for S_1^e can be obtained directly from (A19); one has

$$S_1^e = \frac{-(Z + (\beta + d)\hat{u}_2)}{2(\delta - \beta)} \pm \frac{sqrt\{(Z + (\beta + d)\hat{u}_2)^2 + 4Z\hat{u}_2(\delta - \beta)\}}{2(\delta - \beta)}$$

If $(\delta - \beta) > 0$ only one positive real solution can be found:

$$S_1^e = \frac{-(Z + (\beta + d)\hat{u}_2) + qrt\{(Z + (\beta + d)\hat{u}_2)^2 + 4Z\hat{u}_2(\delta - \beta)\}}{2(\delta - \beta)}$$

Then, from (A2), (A15), (A6) and (A7), the equilibrium point $X_2^e(0, \bar{u}_2) = X_2^e(0, \hat{u}_2)$ is computed.

In case of $(\delta - \beta) < 0$, (A22) has two real positive roots, and then, physically acceptable, only if condition (A20), simplified as $(Z + (\beta + d)\hat{u}_2)^2 + 4Z\hat{u}_2(\delta - \beta) > 0$, holds. Denote by S_1^{e1} and S_1^{e2} such solutions, if they exist. Referring once again to (A2), (A15), (A6) and (A7), the two equilibrium points $X_2^{e1}(0, \bar{u}_2) = X_2^{e1}(0, \hat{u}_2)$ and $X_2^{e2}(0, \bar{u}_2) = X_2^{e2}(0, \hat{u}_2)$ can be obtained.

iii. $\bar{u}_1 = \bar{u}_2 = 0$ ($\hat{u}_1 = \hat{u}_2 = 0$)

Under zero input one obtains the classical unforced equilibrium points. To compute them, equation (A18) becomes, in the present case, $\left((\delta - \beta)S_1^e + Z\right)S_1^e = 0$ and the only acceptable solution is:

$S_1^e = \dfrac{Z}{\beta - \delta}$;

therefore, the other components are:

$S_2^e = 0$, $\quad I^e = \dfrac{\beta - (d+\delta)}{(d+\delta)(\beta-\delta)} Z$,

$P^e = \dfrac{\varepsilon\delta\left(\beta - (d+\delta)\right)}{(\alpha + d)(d+\delta)(\beta-\delta)} Z$,

$A^e = \dfrac{\delta\left(\alpha + d(1-\varepsilon)\right)\left(\beta - (d+\delta)\right)}{(\mu + d)(\alpha + d)(d+\delta)(\beta-\delta)} Z$.

The equilibrium point so obtained is denoted by $X_2^e = X_2^e(0,0)$.

iv. $\psi\bar{u}_2 = \dfrac{\left(\beta - (d+\delta)\right)(\gamma + d) - (d+\delta)\bar{u}_1}{d(\gamma + d + \bar{u}_1)}$

In this case, expression (A9) gives the forced solution $I^e = 0$, and the system has only one equilibrium point, whose expression is the same as in (A12).

In conclusion, the classical equilibrium points computation gives the two solutions X_1^e and X_2^e.

If forced equilibrium points are looked for, the system has one solution

$X_2^e(\bar{u}_1, \bar{u}_2) = X_2^e(\hat{u}_1, \hat{u}_2)$ if $\left(\delta(1+\hat{u}_1) - \beta\right) > 0$,

while it has two solutions

$X_2^{e1}(\bar{u}_1, \bar{u}_2) = X_2^{e1}(\hat{u}_1, \hat{u}_2)$ and $X_2^{e2}(\bar{u}_1, \bar{u}_2) = X_2^{e2}(\hat{u}_1, \hat{u}_2)$,

if $\left(\delta(1+\hat{u}_1) - \beta\right) < 0$

and $\left(Z + \left(\beta + d(1+\hat{u}_1)\right)\hat{u}_2\right)^2 + 4Z\hat{u}_2\left(\delta(1+\hat{u}_1) - \beta\right) > 0$.

Otherwise, no solution exists.

Structural properties analysis

The results of the previous computation of the equilibrium points for the given system (1)-(5), both in the classical unforced case, i.e. $U^e = 0$, and in the presence of constant inputs, $U^e \neq 0$, can be divided into two groups: one in which, directly or under forced behavior, $I^e = 0$, and one in which $I^e \neq 0$. The structure of an equilibrium point in the first group is

$$X_a^e = X^e\Big|_{I^e=0} = \begin{pmatrix}\bar{S}_1 & \bar{S}_2 & 0 & 0 & 0\end{pmatrix}^T$$

while for the second one the form is

$$X_b^e = X^e\Big|_{I^e\neq 0} = \begin{pmatrix}\bar{S}_1 & \bar{S}_2 & \bar{I} & \bar{P} & \bar{A}\end{pmatrix}^T$$

The computation of the linear approximations in the neighborhood of each type of equilibrium point is performed in order to analyze the controllability and the observability properties, whose fulfillment are necessary conditions for the control design proposed in the paper.

To this aim, the first step is the computation of the linear state matrix A as the Jacobian matrix $J(X,U) = \dfrac{\partial F(X,U)}{\partial X}$ evaluated at each equilibrium point, and the input matrix B as the matrix $\dfrac{\partial F(X,U)}{\partial U}$ computed in the same points. The output of the system is already in linear form, so that $C = \begin{pmatrix}0 & 0 & 0 & 1 & 1\end{pmatrix}$ is known.

In the following matrices, for sake of simplicity, only the terms which are always equal to zero are evidenced, denoting with the character '*' all the other ones.

Case $X_a^e = X^e\Big|_{I^e=0} = \begin{pmatrix}\bar{S}_1 & \bar{S}_2 & 0 & 0 & 0\end{pmatrix}^T$

The form of the matrices is

$$A_a = \frac{\partial F}{\partial X}\Big|_{X=X_a^e, U=\bar{U}} = \begin{pmatrix} * & * & * & 0 & 0 \\ 0 & * & 0 & 0 & 0 \\ 0 & 0 & * & 0 & 0 \\ 0 & 0 & * & * & * \\ 0 & 0 & * & * & * \end{pmatrix}$$

$$B_a = \frac{\partial F}{\partial U}\Big|_{X=X_a^e, U=\bar{U}} = \begin{pmatrix} * & 0 & 0 \\ * & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix} = \begin{pmatrix} b_{a,1} & 0 & 0 \end{pmatrix}$$

that give the reachability matrix:

$$R_a = \begin{pmatrix} b_{a,1} & A_a b_{a,1} & A_a^2 b_{a,1} & A_a^3 b_{a,1} & A_a^4 b_{a,1} \end{pmatrix} = \begin{pmatrix} * & * & * & * & * \\ * & * & * & * & * \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

and the controllability one

$$O_a = \begin{pmatrix} C \\ CA_a \\ CA_a^2 \\ CA_a^3 \\ CA_a^4 \end{pmatrix} = \begin{pmatrix} 0 & 0 & 0 & * & * \\ 0 & 0 & * & * & * \\ 0 & 0 & * & * & * \\ 0 & 0 & * & * & * \\ 0 & 0 & * & * & * \end{pmatrix}$$

which show that neither controllability nor observability hold.

Case $X_b^e = X^e\big|_{I^e \neq 0} = \left(\bar{S}_1 \quad \bar{S}_2 \quad \bar{I} \quad \bar{P} \quad \bar{A}\right)^T$

The form of the matrices are

$$A_b = \frac{\partial F}{\partial X}\bigg|_{X = X_b^e, U = \bar{U}} = \begin{pmatrix} * & * & * & 0 & 0 \\ * & * & 0 & 0 & 0 \\ * & * & * & 0 & 0 \\ * & * & * & * & 0 \\ * & * & * & * & * \end{pmatrix}$$

$$B_b = \frac{\partial F}{\partial U}\bigg|_{X = X_b^e, U = \bar{U}} = \begin{pmatrix} * & 0 & 0 \\ * & 0 & 0 \\ 0 & * & 0 \\ 0 & * & * \\ 0 & * & * \end{pmatrix}$$

The determinants of the reachability and observability matrices R_b and O_b are functions of all the inputs and the model parameters. The can be equal to zero only for particular combinations of such values; their ranks must be verified for any given particular case.