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A ROBUST OUTPUT–FEEDBACK TREATMENT SCHEDULING FOR HIV-1

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Abstract: In this paper an anti–retroviral supply treatment scheduling for a dynamical model of the HIV-1 is proposed. This therapy design problem is approached from an equilibrium point stabilization perspective by viewing the drug treatment as a control law. The main feature of the proposed controller is threefold, namely: It exploits the natural properties, for stabilization purposes, of the HIV-1 model leading to a quite simple structure. It is an output–feedback scheme in the sense that for achieving the desired stability properties it is not required neither feedback nor estimation of the unmeasurable state. It is robust against both parametric and structural uncertainties. The usefulness of the presented control scheme is illustrated via numerical simulations.

1. INTRODUCTION

In the last decades, the immunological response of the body against the Human Immunodeficiency Virus (HIV) has received a lot of attention from both an analysis and a therapy design perspectives. Hence, the achieved advances in understanding the interaction between the human immune system and the virus are remarkable. This knowledge has lead, in consequence, to also quite important results in recognizing the best anti–retroviral substances for reducing the effect of the HIV and the way they must be supplied to infected patients with the aim of improving their quality of life. Perhaps the most currently accepted solution is the so–called Highly Active Anti-Retroviral Therapy (HAART).

Unfortunately and in spite of the aforementioned notable results, one of the main drawbacks of the policies for supplying the medication in present practice is that they are not completely systematized, leading to several undesirable situations, e.g. medicine waste and cost increment, among other.

In order to deal with this systematization problem, one alternative that has given very interesting results is to represent the dynamic behavior of the disease in terms of a mathematical model to later on approach the treatment scheduling design as a control problem, i.e. by viewing the drug supply policy as a control law. The main limitation of this approach is that the available models are based only on the qualitative description of the major elements evolution involved in the disease, due to the impossibility for obtaining a treatable representation that describes the virus behavior in a complete way. Nevertheless, it is widely accepted

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that the results obtained from this systems theoretic approach establish very valuable guidelines for the medicine practice.

From the control perspective, the treatment scheduling design can be viewed as a stabilization problem. Specifically, for a given dynamical model the equilibrium points that correspond both to a healthy and an infected behavior are identified, then looking at the anti–retroviral supply as a control input, the objective is to design a control law that stabilizes the healthy equilibrium point. The problem is further complicated since actually it must be formulated as a robust output–feedback design due to necessity of including several constraints imposed by practical considerations about the disease treatment, namely: it is well known that there exists a significant uncertainty on the value of the parameters involved in the available models since they vary from patient to patient, although some bounds have been also identified. Regarding models structure, the qualitative description of the virus behavior is also (depending on the chosen model) a source of considerable uncertainty. Finally and in spite of the fact that some alternatives are at disposition for measuring the variables involved in the models (Bentwich, 2005), the quite high cost for obtaining the CTL count cells leads to the assumption that this variable can not be measured.

At this point it is important to remark that the proposition of a control scheme in this context must not be considered as a solution that pursues the elimination of the disease, as would be interpreted the objective of stabilizing the healthy equilibrium point. Evidently reaching this point in an infected patient is far from the reality. Instead of this interpretation, the obtained result must be considered as a guide that can be followed in the practical treatment application with the aim to supply the drug in an efficient way expecting, at the same time, to minimize the effect of the virus.

Although several mathematical models for the HIV have been reported and different approaches have led to a variety of control laws (Perelson and Nelson, 1999), (Zurakowski and Teel, 2004), (Campello de Souza, 1999), (Ko *et al.*, 2006), (Biafore and D'Attellis, 2005), (Brandt and Chen, 2001), (Yadav and Balakrishnan, 2006), (Melgarejo *et al.*, 2006), (Palacios *et al.*, 2007) the representation introduced in (Campello de Souza, 1999) has attracted the attention since it describes in a precise way the interaction between the immune system and the HIV-1 inside the body by means of a relatively simple structure that includes the evolution of the CD4 T-helper cells, the CTL cells and the viral load. Paradoxically and in spite of this simplicity, the reported controllers obtained using this model show (at some extent) a complex structure, see for example (Ge *et al.*, 2005), (Culshaw *et al.*, 2004).

The main contribution of this paper is to show that considering the model presented in (Campello de Souza, 1999), the problem of stabilizing the equilibrium point corresponding to a healthy behavior can be solved in a quite simple way, without appealing to complex control algorithms, if the intrinsic stability properties exhibited by the system model are exploited. Actually, it is shown that due to structure and associated stability properties of the dynamic equations that describe the behavior of the CD4 T-helper and the CTL cells, stability is achieved by only controlling the viral load, via the drug supply, and leaving to evolve in a natural way the other variables.

The simplicity of the proposed solution is enlightened by the fact that the stabilization objective is achieved considering both parametric and structural uncertainties without requiring neither the feedback nor the estimation of the CTL cells, according to the practical limitation for measuring this variable. In this sense, the proposed controller exhibits the required robust output–feedback structure.

In a technical setting, the control problem is solved by identifying that the dynamic behavior of the CD4 cells enjoy some Input–to–State Stability (ISS) properties (Sontag, 2001) while the corresponding equation for the CTL cells satisfy some Convergence–Input Convergence–State (CICS) conditions (Sontag, 2003). This scenario is complemented with the design of a control law that compensates the destabilizing effect produced by the viral load on the CD4 cells. The usefulness of this controller is numerically validated.

The rest of the paper is organized as follows: In Section 2 the model considered for the HIV-1, some of its properties that are useful for the controller design and the formulation of the approached problem are presented. The main result of the paper, together with a detailed discussion about its structure, are included in Section 3 while its numerical evaluation is presented in Section 4. Section 5 is devoted to some concluding remarks.

2. PROBLEM FORMULATION

In this section the problem approached in this paper is presented. First, the considered mathematical model for the HIV-1 is introduced together with a brief description and some of its properties. After this, the control problem is mathematically formalized in terms of this representation.

It is considered the HIV-1 model, first reported in (Campello de Souza, 1999), given by

$$\dot{x}_1 = \alpha_1(x_{10} - x_1) - \beta_1 x_1 x_3 \quad (1)$$
$$\dot{x}_2 = \alpha_2(x_{20} - x_2) + \beta_2 x_2 x_3 \quad (2)$$
$$\dot{x}_3 = \beta_3 x_1 x_3 - \beta_4 x_2 x_3 - u \quad (3)$$

where x_1, x_2 and x_3 are the CD4 T-helper cells, the CTL cells and the viral load, respectively. The *all positive* parameters α_1, α_2, β_1, β_2, β_3 and β_4 are defined in Table 1 while x_{10} and x_{20} stand for the values of x_1, x_2 corresponding to a healthy condition. The control input u is the anti-retroviral treatment pre-established for a particular patient.

The main feature of model (1)–(3) comes from the widely recognized fact that it describes in a precise way the interaction between the immune system and the HIV-1 inside the body. However, from a control point of view the complications are evident, namely, the nonlinear nature of the dynamic behavior and the underactuated structure of the system (there are more degrees of freedom than control inputs). Moreover, it is well known that there exist limitations for measuring the number of CTL cells (x_2) and that the value of the model parameters involves a large uncertainty.

Fortunately enough, and in spite of the aforementioned complications, the introduced model presents some particular properties that are useful for solving the problem of designing a control scheme. Some that are particularly important for developing the proposed control scheme in this paper are the following:

P.1. The first property is related with the equilibria of the system with no input. It is well-known that the system has two equilibrium points. The first one is given by $x_1^* = x_{10}$, $x_2^* = x_{20}$, $x_3^* = 0$ and corresponds to the non infection condition. The second equilibrium point is

$$x_1^* = \frac{\beta_2\beta_3\alpha_1 x_{10} + \beta_1\beta_4\alpha_2 x_{20}}{\beta_3(\beta_1\alpha_2 + \beta_2\alpha_1)}$$
$$x_2^* = \frac{\beta_2\beta_3\alpha_1 x_{10} + \beta_1\beta_4\alpha_2 x_{20}}{\beta_4(\beta_1\alpha_2 + \beta_2\alpha_1)} \quad (4)$$
$$x_3^* = \frac{\alpha_1\alpha_2(\beta_3 x_{10} - \beta_4 x_{20})}{\beta_2\beta_3\alpha_1 x_{10} + \beta_1\beta_4\alpha_2 x_{20}}$$

which is obtained by assuming a viral load (x_3) different from zero, i.e. considering that the patient is infected. Here the CD4 cell count decreases while the CTL cell count increases with respect to the noninfected condition.

P.2. Concerning the system parameters, a second well established property of the model (1)–(3) is that, although unknown, there exist some limit values for them. In this sense, the numerical values included in Table 1 what illustrate are average values found in infected patients.

P.3. A third important system feature concerns the fact that its state trajectories are always positive. This can be easily shown by noting that the vector field defined by the right hand side of equations (1)–(3) never points outwards of the first octant of the Cartesian coordinate system.

P.4. A last characteristic that must be mentioned is that, besides their positiveness, the CD4 and CTL count cells trajectories are bounded by the non infected condition of the patient. Indeed, x_1 always describes trajectories under the maximum value x_{10} while the trajectories of x_2 are bounded from below by x_{20}.

Once the structure of the model and its properties have been established, the control problem can be formulated in the following way:

Consider the HIV-1 model (1)–(3). Assume that

A.1 *The only available states are x_1 and x_3.*
A.2 *All the system parameters are unknown.*

Under these conditions, design a control law u such that $\lim_{t\to\infty}(x - x^*) = 0$, where x^* is equilibrium point that corresponds to a healthy condition, while preserving the strict positivity of both the system state and the control input.

3. MAIN RESULT

In this section the main result of the paper is presented, namely, a Robust Output–feedback control law that solves the problem formulated in Section 2.

Before presenting this result in a technical way, it is interesting to motive the rational behind its design in terms of the following structural properties:

• The HIV model can be decomposed into two subsystems Σ_1 and Σ_2 composed by equations (1)–(2) and (3), respectively.

• Looking only at Σ_1 it can be noticed that this subsystem consists of two decoupled equations that share the same input x_3.

• The two equations involved in Σ_1 enjoy some natural stability properties, as will be shown below. The CD4 count cell equation is ISS, by considering x_3 as input and x_1 as output, while the corresponding to the CTL count cells is CICS, considering again x_3 as input. The important implication of this facts is that if x_3 tends to zero, then x_1 and x_2 converge to x_{10} and x_{20}, respectively, in a natural way.

• Regarding subsystem Σ_2, besides the fact that it directly involves the control input u, it is possible to see that the dynamic behavior of x_3 depends on two terms, one depending on x_1 and

Table 1. Parameters description of HIV model

Parameter	Description	Value
α_1	Death rate of CD4 T-cells	0.25 1/year
β_1	Infection rate of CD4 T-cells by HIV	50 $ml/10^7$ $copies \cdot year$
α_2	Death rate of CTL cells	0.25 1/year
β_2	Growth rate of CTL cells in response to HIV load	10 $ml/10^7$ $copies \cdot year$
β_3	Growth rate of HIV load due to infected CD4 T-cells	0.01 $mm^3/$ $cells \cdot year$
β_4	Death rate of HIV load due to CTL cells	0.0045 $mm^3/$ $cells \cdot year$

other depending on x_2. Moreover, due to the positivity of the state, the x_1 dependent term has a destabilizing effect on x_3, i.e. it produces an increment on the viral load, while the x_2 dependent term is a stabilizing one producing a decrement on x_3. Since the control objective is to steer x_3 to zero, then it is clear that the control input u must only compensate the destabilizing term.

• It must be noticed that the compensation of the destabilizing term in subsystem Σ_2 can be achieved without a precise knowledge of the parameter β_3. Actually, this task can be done assuming only that an upper bound of this parameter is known, since both x_1 and x_3 are measurable, providing with a robust structure to the control law.

• Since the stabilizing, x_2 dependent, term does not need to be neither compensated nor eliminated, the control law does not require knowledge of the unmeasurable state x_2. This fact establishes the output–feedback structure of the proposed scheme.

All these conditions are included in the formulation of the main result of this paper and which is presented in the next

Proposition 1. Consider the HIV-1 model (1)–(3). Assume that

A.1 The only available states are x_1 and x_3.

A.2 All the system parameters are unknown except β_3 which belongs to the set $\left[\underline{\beta_3}, \bar{\beta}_3\right]$ with $\bar{\beta}_3$ known.

Under these conditions the control law given by

$$u = Kx_3 + \bar{\beta}_3 x_1 x_3 \tag{5}$$

guarantee that $\lim_{t\to\infty}(x - x^*) = 0$ where $x^* = (x_{10}, x_{20}, 0)$, preserving the strict positivity of both the system state and the control input.

PROOF. The closed loop system is given by

$$\dot{x}_1 = \alpha_1(x_{10} - x_1) - \beta_1 x_1 x_3 \tag{6}$$

$$\dot{x}_2 = \alpha_2(x_{20} - x_2) + \beta_2 x_2 x_3 \tag{7}$$

$$\dot{x}_3 = -\beta_4 x_2 x_3 + \left[\left(\beta_3 - \bar{\beta}_3\right) x_1 - K\right] x_3 \tag{8}$$

The first important characteristic of this system that must be noticed is that the proposed control law does not destroy the positivity of x_3 since preserves the slope field. Thus, due to the fact that equations for the first two states are the same, the positivity of x_1 and x_2 are also preserved.

Consider now the following positive definite function

$$V = \frac{1}{2}x_3^2$$

whose time derivative along (8) is given by

$$\dot{V} = -\left[\beta_4 x_2 - \left(\beta_3 - \bar{\beta}_3\right) x_1 + K\right] x_3^2$$

Taking into account that x_1 and x_2 are positive for all time, it is clear that it is possible to obtain that $\dot{V} \leq -Kx_3^2$ showing that x_3 exponentially tends to zero.

On the other hand, defining $z_2 = x_2 - x_{20}$ equation (7) can be equivalently written as

$$\dot{z}_2 = -\left(\alpha_2 - \beta_2 x_3\right) z_2 + \beta_2 x_{20} x_3$$

which can be viewed as a linear time–varying system with input $\beta_2 x_{20} x_3$. Considering first the case of zero input, the solution of this equation is given by

$$z_2 = \mathbf{e}^{-\int_0^t (\alpha_2 - \beta_2 x_3) d\tau} x_2(0)$$

From this expression it can be obtained that $z_2 \to 0$, i.e. $x_2 \to x_{20}$, since

$$\int_0^t \left(\alpha_2 - \beta_2 x_3\right) d\tau = \alpha_2 t - \beta_2 \int_0^t x_3(\tau) d\tau \to \infty$$

due to the fact

$$\int_0^t x_3(\tau) d\tau \to constant$$

when x_3 exponentially tends to zero. This converge property is preserved when the input is not zero since it has been shown that this variable tends exponentially to zero. Hence, equation (7) is CICS.

The proof is completed by noting that the same procedure as the one followed for x_2 can be repeated with equation (6) in order to show that $x_1 \to x_{10}$. In this case, however, due to the negative sign of the input $\beta_1 x_{10} x_3$ it is possible to prove not only CICS but also, considering x_3 as

input and x_1 as state, that this equation exhibits ISS properties. □

The following remarks are in order about the presented result:

i) The proposed controller has a quite simple structure. In fact, the term $\bar{\beta}_3 x_1 x_3$ is not (theoretically) necessary, although it is introduced with the aim of improving the dynamic response of the closed loop system.

ii) Notice that, besides β_3 it is not required any knowledge on the system parameters. This feature makes the controller highly robust against parametric uncertainty.

iii) The purpose of the proposed controller is compensate the destabilizing term $\beta_3 x_1 x_3$. This task can be carried out even if there exist some uncertainty in the structure of this term, i.e. if it is modeled as a function $\phi(x_1, x_3)$ that depends on x_1 and x_3. In this case the control law would take the form $u = Kx_3 + \bar{\phi}(x_1, x_3)$ where the function $\bar{\phi}(\cdot)$ is an upper bound of the term that must be compensated. This situation allows for considering also structural uncertainty.

4. SIMULATION RESULTS

The performance of the proposed controller was investigated via numerical simulations. The particular values considered for the system parameters are shown in Table 1, while the healthy condition was given by $x_{10} = 1000\ cells/mm^3$ and $x_{20} = 550\ cells/mm^3$. With the aim to further enlight the usefulness of the proposed controller, in Figure 1 the open–loop behavior of the system is presented when $x_1(0) = x_{10}$, $x_2(0) = x_{20}$ and $x_3(0) = 0.1$. In this figure it can be noticed how corresponding to a quite rapid increment of the viral load, there is a decrement in the CD4 cells and an increment in the CTL cells. Based on this graphical description, the control objective is to reduce the decrement of the CD4 cells and the increment of the CTL cells while steering the value of the viral load to zero.

Concerning the behavior of the closed–loop scheme, in Figure 2 it is depicted the evolution of the viral load (x_3) when $x_3(0) = 1$, and the controller was tuned considering $K = 100$ and $\bar{\beta}_3 = 0.0125$, i.e. assuming a 25% of uncertainty on this parameter.

It can be noticed how the stabilization objective on this variable was achieved in a very fast way. Evidently, once the system is contaminated the other two state, although also convergent, show a convergence rate greater than the viral load.

In Figure 3 the CD4 count cells trajectory is presented while the CTL evolution is illustrated

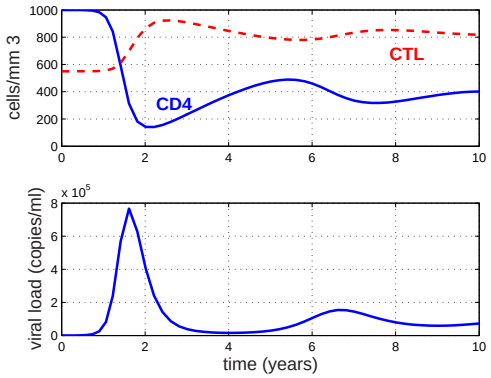

Fig. 1. Open–loop behavior of the HIV-1 dynamical model.

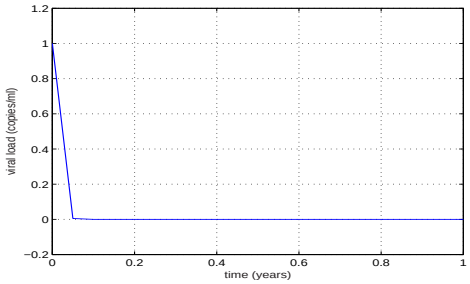

Fig. 2. Closed–loop behavior of the viral load.

in Figure 4. In both figures it is clear that they spend around 25 years to completely arrive to the desired value. This period of time is determined by the natural convergence properties of the systems given (basically) in terms of α_2.

On the other hand, it must be noticed as a remarkable feature, how the trajectories for x_1 and x_2 do not considerable diverge from the healthy equilibrium point. In the case of x_1 the minimum achieved value is around 630 $cells/mm^3$ while for the CTL the maximum value achieved by this variable is around 605 $cells/mm^3$.

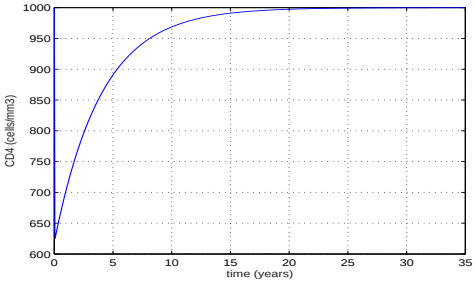

Fig. 3. Closed–loop behavior of the CD4 count cells.

With the aim to completely illustrate the controller performance, in Figure 5 it is included the trajectory described by the control input. As can be noticed, its convergence to zero is also achieved very fast, reaching a maximum value of 110 $copies/ml$.

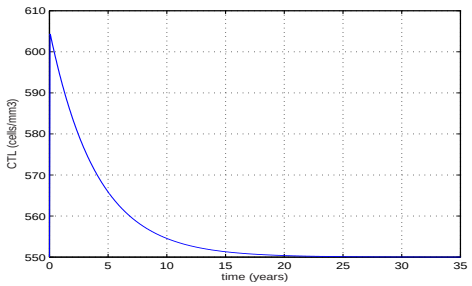

Fig. 4. Closed–loop behavior of the CTL count cells.

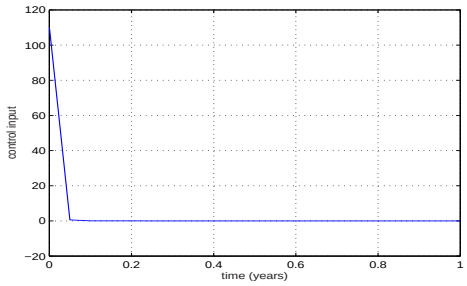

Fig. 5. Closed–loop behavior of the control input.

5. CONCLUSIONS

In this paper a quite simple controller that achieves stabilization of the healthy equilibrium point of a HIV-1 dynamical model is presented. The considered (third order) model involves as state variables the evolution of the CD4 T-helper and the CTL count cells together with the viral load. The control input is the anti–retroviral treatment scheduling. The simplicity of the controller is obtained by exploiting the natural stability properties of the system. Actually, the viral load is directly (exponentially) stabilized to zero via the control input, while (due to the natural stable structure) the other variables evolve to reach the desired operation conditions in a natural way. The numerical results show that the control scheme can produce high performance responses. It is the authors belief that these results can state a very valuable guide for the practical medicine application.

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