Nonlinear Control Techniques for an HIV-1 Model

Ioannis P. Kordonis
National Technical University of Athens
PhD. Candidate
jkordonis1920@yahoo.com

Alexandros C. Charalampidis
National Technical University of Athens
PhD. Candidate
alexchar@central.ntua.gr

George P. Papavassilopoulos
National Technical university of Athens
Professor
yorgos@netmode.ntua.gr

Abstract

This paper applies nonlinear control methods to an HIV - 1 model describing the interaction among CD4+ T cells, CD8+ T cells and HIV - 1. The problem is stated as an output feedback stabilization problem. At first a nonlinear observer is designed for the non measureable state variable of the model. Then two state feedback controllers are designed: the first is based on sliding mode control and the second on the receding horizon control. Practical forms of the output feedback schemes are finally tested via simulation in order to illustrate the robustness of the proposed methods.

1. Introduction

Human Immunodeficiency Virus (HIV) is the virus causing Acquired Immune Deficiency Syndrome (AIDS), a disease which compromises the immune system. The major target of HIV is a class of lymphocytes called CD4+ T cells and as a result their number is decreased, leading to the deficiency of the immune system. Thus, a patient is vulnerable to opportunistic infections. Normally, the number of the CD4+ cells is around 1000 mm^{-3} and when it drops below 200 mm^{-3} the patient is classified as having AIDS [1],[2].

Currently, the most commonly applied treatment is HAART (Highly Active AntiRetroviral Therapy), a therapy consisting of a mixture of more than three antiretroviral drugs of at least two types: the protease inhibitors and the reverse transcriptase inhibitors. This treatment suppresses HIV viral replication and maintains high the CD4 counts, prolonging the patient's life expectancy. However, there are some drawbacks; the high cost and the possible side effects.

An important part during the therapy is measuring the concentrations of CD4, CD8 and viral load. The most typical measuring methods for the viral load are the polymerase chain reaction (PCR), the viral load assays and branches deoxyribonucleic acid test. Regarding the lymphocyte measurements, the most common technique is flow cytometry which can distinguish and count CD3, CD4, and CD8 T cells simultaneously. However, due to its high cost, laboratories often measure only the CD4 concentration [3], [4].

Several dynamic models for HIV have been proposed including [1], [5], [6], [7] and [8]. These models aim to describe, with different accuracy, the interaction between the immune system and HIV. In this paper the model of [8] is used due to its simplicity and the relatively precise way of describing the interaction between the immune system and HIV. Several control methods have been used for the antiretroviral drug scheduling problem. In [9] several linear time delay control schemes are investigated, in [10] a backstepping controller is designed, in [11] a passivity based approach is used, in [12],[13] and [14] feedback linearization controllers are designed, in [15] a robust Lyapunov based controller is designed, in [16-18] receding horizon control techniques are used in a state feedback and output feedback formulation, in [19-21] a practical control algorithm is presented, in [22] a controller is designed using an approximation of immune system dynamics and in [23], [24] optimal control is used for the drug scheduling problem against HIV.

The objective of control theoretic approaches, to HIV drug scheduling problems, is to use proposed drugs dosage as a guideline for clinical use. In this paper, we propose nonlinear control algorithms for the drug dosage scheduling problem for people infected by HIV, using a model form [8]. The control problem is stated as an output feedback stabilization problem assuming that only the CD4 cell concentration and the viral load are measured. Thus, a nonlinear observer is first designed. Then, two state feedback controllers are designed; a sliding mode controller and a receding horizon controller. For the sliding mode controller a separation principle is also proved.

The paper is organized as follows. In section 2, a dynamical model presented in [8] is analyzed and some properties are proved. In section 3 a new nonlinear observer for the non directly measureable state variable of the model is designed. In section 4 two state feedback control schemes are designed. In section 4.1 a sliding mode controller is designed and in section 4.2 a receding horizon controller is designed. In section 5 the proposed control schemes are tested via simulation and some practical forms of these schemes are proposed. In section 6 the results are summarized. This paper is largely based on an earlier work reported in [25].

2. Description and properties of the model

2.1. Description of the model

The model used [8] describes the interaction among the CD4+ T cells, the CD8 lymphocytes and the virus particles. The equations of the model are:

$$\begin{aligned}\dot{y}_1 &= p_1(x_{10} - y_1) - p_2 y_1 y_3 \\ \dot{y}_2 &= p_3(x_{20} - y_2) + p_4 y_2 y_3 \\ \dot{y}_3 &= p_5 y_1 y_3 - p_6 y_2 y_3 - u\end{aligned} \tag{1}$$

where y_1 is the CD4 population, y_2 is the CD8 population, y_3 is the viral load. The parameters x_{10} and x_{20} are the normal values of the CD4 and CD8 counts respectively and u corresponds to the dosage of the drug used in the treatment. The parameters $p_1,\dots,p_6$ are positive constants describing the interaction rates among the CD4 cells, CD8 cells and the virus particles. Identification procedures for HIV models may be found in [26], [27].

The above model describes the following known facts about the interaction of the virus particles and the immune cells CD4 and CD8 [9], [8]:

1) HIV utilizes the CD4 cells to replicate itself and high HIV load leads to CD4 cell count reduction.
2) The number of CD8 cells increases responding to the increased HIV load, and CD8 cells attack to the virus.
3) The growth rate of HIV increases proportional to the HIV and CD4 populations

2.2. Some properties of the model

For $u = 0$, the model (1) has two equilibrium points. The first one with $y_1 = x_{10}$, $y_2 = x_{20}$ and $y_3 = 0$ corresponds to the uninfected state and is unstable under the assumption $p_5 x_{10} > p_6 x_{20}$. The second one with:

$$\begin{aligned}y_1^{(e)} &= \frac{p_1 p_4 p_5 x_{10} + p_2 p_6 p_3 x_{20}}{p_5(p_2 p_3 + p_1 p_4)} \\ y_2^{(e)} &= \frac{p_1 p_4 p_5 + p_2 p_6 p_3 x_{20}}{p_6(p_2 p_3 + p_1 p_4)} \\ y_3^{(e)} &= \frac{p_1 p_4 (p_5 x_{10} - p_6 x_{20})}{p_1 p_4 p_5 x_{10} + p_2 p_6 p_3 x_{20}}\end{aligned} \tag{2}$$

is stable [10].

We will examine only physically meaningful solutions of model (1) i.e. the solutions such that y_1, y_2 and y_3 remain nonnegative and thus they have physical meaning. In the following, the more convenient form of the model is used:

$$\begin{aligned}\dot{x}_1 &= -p_1 x_1 - p_2(x_1 + x_{10})x_3 \\ \dot{x}_2 &= -p_3 x_2 + p_4(x_2 + x_{20})x_3 \\ \dot{x}_3 &= [p_5(x_1 + x_{10}) - p_6(x_2 + x_{20})]x_3 - u\end{aligned} \tag{3}$$

where $x_1 = y_1 - x_{10}$, $x_2 = y_2 - x_{20}$ and $x_3 = y_3$.

In [10] it is shown that physically meaningful solutions of model (3) belong to the set $D_1 = \{(x_1, x_2, x_3): -x_{10} < x_1 \le 0, x_2 \ge 0, x_3 \ge 0\}$. Here it is shown that physically meaningful solutions belong to a smaller, bounded domain.

Lemma 1: If $u(t)$ is such that $x_3(t) \ge 0$ for any $t \ge 0$ then
i) The sets:

$$D_2(C_1, C_2) = \left\{(x_1, x_2, x_3) \in D_1 : x_1 + \frac{p_2}{p_5}x_3 \le C_1, x_2 + \frac{p_4}{p_6}x_3 < C_2\right\} \tag{4}$$

with $C_1 > 0$, $C_1 > -(p_2 x_{20} - p_1)x_{10} / (p_6 x_{20})$ and $C_2 > C_2^*(C_1)$ for suitable function $C_2^*(C_1)$, are positively invariant.
ii) The sets:

$$D_3(C_3, A) = \{(x_1, x_2, x_3) \in D_1 : x_1 + A x_2 \ge C_3\} \tag{5}$$

with $C_3 < \min\{0, (p_1 - p_3)x_{10} / p_3\}$ and $A > \dfrac{p_2 x_{10} - p_4 C_3}{p_4 x_{20}}$, are positively invariant.

Proof:
i) Let $V_1 = x_1 + p_2 x_3 / p_5$. For C_1 satisfying the above conditions it will be shown that $\dot{V}_1 < 0$ for any $(x_1, x_2, x_3) \in D_1$ such that $V_1 = C_1$. It holds:

$$\begin{aligned}\dot{V}_1 &= -p_1 x_1 - p_2 p_6 x_{20} x_3 / p_5 - u' \\ \dot{V}_1 &= -p_1 x_1 + p_6 x_{20} x_1 - p_6 x_{20} C_1 - u' \\ \dot{V}_1 &\le -p_1 x_1 + p_6 x_{20} x_1 - p_6 x_{20} C_1\end{aligned}$$

where $u' = p_2(u + p_6 x_2 x_3)/ p_5$. The right hand side of the last inequality is linear in x_1 and thus by the conditions of the lemma $\dot{V}_1$ is negative for $-x_{10} \le x_1 \le 0$ and $x_1 + p_2 x_3 / p_5 = C_1$.
Let $V_2 = x_2 + p_4 x_3 / p_4$. It will be shown that for suitable C_2, $\dot{V}_2 < 0$ for any $(x_1, x_2, x_3) \in D_1$ such that $V_2 = C_2$. It holds:

$$\begin{aligned}\dot{V}_2 &= -p_3 x_2 + [p_5(x_1 + x_{10})x_3 - u] p_4 / p_6 \\ \dot{V}_2 &\le -p_3 x_2 + p_4 p_5 (x_1 + x_{10}) x_3 / p_6 \\ \dot{V}_2 &\le -p_3 C_2 + p_4 [p_3 + p_5(x_1 + x_{10})] x_3 / p_6 .\end{aligned}$$

The second term of the last inequality depends only on x_1 and x_3. Thus it has a maximum value on $D_2(C_1, C_2)$ depending only on C_1. Let us denote by $M(C_1)$ that value. For $C_2 > C_2^*(C_1) = M(C_1)/ p_3$ it holds $\dot{V}_2 < 0$ for any $(x_1, x_2, x_3) \in D_1$ such that $V_2 = C_2$.

ii) Let $V_3 = x_1 + A x_2$. It will be shown that $\dot{V}_3 > 0$ for $(x_1, x_2, x_3) \in D_1$ such that $V_3 = C_3$. It holds:

$$\dot{V}_3 = -p_1 x_1 - p_2(x_1 + x_{10})x_3 - Ap_3 x_2 + Ap_4(x_2 + x_{20})x_3$$
$$\dot{V}_3 = [(p_3 - p_1)x_1 - p_3 C_3] + \\ + [p_4 A x_{20} + p_4 C_3 - p_2 x_{10} - (p_4 + p_2)x_1]x_3 \ .$$
The first term of the right hand side of the last equality is positive by the inequality $C_3 < \min\{0, (p_1 - p_3)x_{10} / p_3\}$ and the second is positive by the relation $A > (p_2 x_{10} - p_4 C_3)/ p_4 x_{20}$. ◊

The previous lemma implies that for every initial condition in D_1 one may find suitable constants C_1, C_2, C_3 and A such that the solution remains in $D = D_2(C_1, C_2) \cap D_3(C_3, A)$ and $(-x_{10}, 0, x_3) \notin \overline{D}$ for every $x_3 \geq 0$. This result may be used for estimating a state variable given the other two with a single measurement, for obtaining bounds for the parameters in an identification procedure or for deriving bounds of the state variables for control use.

3. Observer design

CD8 count measurements are not always available. In this section a simple nonlinear reduced order observer is designed for the state variable x_2 of the model (3). Another observer for this model is also available [4] but the convergence rate is slow.

The observer designed, is based in the following lemma, in which an observer is designed for a special class of systems.

Lemma 2: Consider the system

$$\begin{aligned} \dot{z}_1 &= f_{11}(z_1)z_2 + f_{12}(z_1, v) \\ \dot{z}_2 &= f_{21}(z_1)z_2 + f_{22}(z_1, v) \\ y &= z_1 \end{aligned} \tag{6}$$

where y is the measured output. Assume that there is a constant K such that $f_{21}(z_1) - Kf_{11}(z_1) < -\varepsilon < 0$ for every z_1. Then an observer of the form:

$$\begin{aligned} \dot{\xi} &= f_{21}(z_1)(\xi + Kz_1) + f_{22}(z_1, v) - \\ &\quad - K(f_{11}(z_1)(\xi + Kz_1) + f_{12}(z_1, v)) \\ \hat{z}_2 &= \xi + Kz_1 \end{aligned} \tag{7}$$

may be designed such that the estimation error $e(t) = z_2(t) - \hat{z}_2(t) \to 0$ faster than $e^{-\varepsilon t}$.

Proof:
For the estimation error it holds:
$$\dot{e} = \dot{z}_2 - \dot{\hat{z}}_2 = f_{21}(z_1)z_2 + f_{22}(z_1, v) - \\ - f_{21}(z_1)(\xi + Kz_1) - f_{22}(z_1, v) + K(f_{11}(z_1)(\xi + Kz_1) + f_{12}(z_1, v)) - \\ - K(f_{11}(z_1)z_2 + f_{12}(z_1, v))$$
Thus: $\dot{e} = [f_{21}(z_1) - Kf_{11}(z_1)]e$ ◊

The above lemma may be used in order to design a reduced order observer for system (3).

Corollary 3: Consider system (3) and the reduced order observer:

$$\begin{aligned} \dot{\xi} &= (p_4 x_3 - p_3)(\xi + Kx_3) + p_4 x_{20} x_3 - \\ &\quad -K(-p_6 x_3(\xi + Kx_3) + (p_5(x_1 + x_{10}) - p_6 x_{20})x_3 - u) \\ \hat{x}_2 &= \xi + Kx_3 \end{aligned} \tag{8}$$

Let also $K < -p_4 / p_6$. Then the estimation error $e(t) = x_2(t) - \hat{x}_2(t) \to 0$ faster than $e^{-p_3 t}$

Proof:
Lemma 2 applies with:
$z_1 = x_3$, $z_2 = x_2$, $f_{11}(x_3) = -p_6 x_3$, $f_{21}(x_3) = p_4 x_3 - p_3$, $f_{22} = p_4 x_{20} x_3$, $v = [x_1 \quad u]^T$ and
$f_{12}(x_3, x_1, u) = (p_5(x_1 + x_{10}) - p_6 x_{20})x_3 - u$.
The dynamics of the estimation error is described by:
$\dot{e} = \dot{x}_2 - \dot{\hat{x}}_2 = [-p_3 + (p_6 K + p_4)x_3]e$ ◊

4. Controller design

In this section two state feedback control schemes are designed. The aim of the control schemes is to steer system (3) to the equilibrium point $(0,0,0)$ which corresponds to the uninfected state. The parameters of the model are assumed to be exactly known and that all state variables are directly measurable. In case x_2 is not directly measurable, the observer designed in the previous section will be used.

In section 4.1 a sliding mode controller is designed and a receding horizon control scheme is designed in section 4.2.

4.1. Sliding mode controller

In this section a sliding mode controller for the model (3) is designed. The system may be written in the "regular form" [28]:

$$\begin{aligned} \dot{\eta} &= f_a(\eta, \xi) \\ \dot{\xi} &= f_b(\eta, \xi) - u \end{aligned} \tag{9}$$

where $\eta = [x_1 \quad x_2]^T$ and $\xi = x_3$. A function $\phi(\eta)$ such that $\xi = \phi(\eta)$ stabilizes the origin of the η subsystem is first determined. Consider the Lyapunov function:

$$V_\eta = (x_1^2 + x_2^2)/2 \tag{10}$$

$\phi(\eta)$ will be designed such that:

$$\dot{V}_\eta \leq -(p_1 x_1^2 + p_3 x_2^2)\gamma(t) \tag{11}$$

with $\gamma(t) \in (m, 1]$ and $m > 0$. A function $\phi(\eta)$ that makes (11) hold is:

$$\phi(x_1,x_2,\gamma(t))=\begin{cases}\dfrac{\left(p_1x_1^2+p_3x_2^2\right)(1-\gamma(t))}{x_2p_4(x_2+x_{20})-x_1p_2(x_1+x_{10})} & \text{if } (x_1,x_2)\neq 0\\ 0 & \text{if } (x_1,x_2)=0\end{cases} \quad (12)$$

The sliding manifold for the state feedback scheme is:

$$s(x)=x_3-\phi(x_1,x_2,t) \quad (13)$$

In the next lemma, it will be shown that the output feedback scheme including system (3), sliding mode controller with sliding surface $s(x)=0$ and any observer satisfying some additional conditions, is asymptotically stable.

Lemma 5: Let $\hat{x}_2(t)$ be the output of an asymptotically stable observer for $x_2(t)$ such that $\hat{x}_2(t)\geq 0$. Assume also that there is a constant $\overline{M}$ such that $\left|\dot{\hat{x}}_2(t)\right|\leq \overline{M}$ (in some region that the solution belongs). If $|\dot{\gamma}(t)|\leq M$ then for every $x(0)\in D_1$, the control law:

$$u=\begin{cases}0 & \text{if } x_3\leq\phi(x_1,\hat{x}_2,\gamma(t))\\ U_{\max} & \text{if } x_3>\phi(x_1,\hat{x}_2,\gamma(t))\end{cases} \quad (14)$$

for a suitable value of $U_{\max}$, makes the origin of the composite system including system (3) and the observer, asymptotically stable with a region of attraction containing $x(0)$.

Proof:

For any initial condition $x(0)\in D_1$, the state variable x_3 remains nonnegative and thus lemma 1 applies. Therefore, there exist constants C_1,C_2,C_3,A such that the set $D=D_2(C_1,C_2)\cap D_3(C_3,A)$ is positively invariant, bounded, $x(0)\in D$ and $(-x_{10},0,x_3)\notin\overline{D}$ for any $x_3\geq 0$. One may claim that:

Claim 1: $\phi(x_1,x_2,\gamma(t))$ is continuous in D and there is a constant M_2 such that:

$$\left|\frac{d\phi(x_1,\hat{x}_2,\gamma(t))}{dt}\right|\leq M_2.$$

Claim 2: For any positive constant r, there is a time $T(r)$ such that:

$$\phi(x_1,\hat{x}_2,\gamma(t))\leq\phi(x_1,x_2,m/2)$$

for any $x\in\overline{D}-U_r$ where $U_r=\left\{x:x_1^2+x_2^2<r^2\right\}$ and $t\geq T(r)$.

Claims 1 and 2 are proved in Appendix 1.

3. At first, it will be shown that there exist a constant $U_{\max}$ and a time t_0 such that any solution of (3) with $x(0)\in D$ satisfies: $x(t)\in P(t)=\{x\in D: x_3\leq\phi(x_1,\hat{x}_2,\gamma(t))\}$ for every $t\geq t_0$. For x such that $s(\hat{x})>0$ it holds:

$$\frac{ds(\hat{x})}{dt}=p_5(x_1+x_{10})x_3-p_6(x_2+x_{20})x_3-\frac{d\phi(x_1,\hat{x}_2,\gamma(t))}{dt}-u$$

Choosing:

$U_{\max}>\max_{x\in\overline{D}}\{p_5(x_1+x_{10})x_3-p_6(x_2+x_{20})x_3\}+M_2+\varepsilon$

with $\varepsilon>0$, it holds $\dfrac{ds(\hat{x})}{dt}<-\varepsilon$ if $s(\hat{x})>0$. Thus $x(t)$ reaches $P(t)$ in finite time.

4. It will be shown that for any $r>0$, there is a time t_1 such that any solution of (3) with $x(0)\in D$ satisfies: $V_\eta(x(t))\leq r^2$ for any $t\geq t_1$. One may see that for $t\geq\max\{t_0,T(r)\}$, it holds:

$$\frac{dV_\eta(x(t))}{dt}\leq\frac{\partial V_\eta}{\partial\eta}f_a(\eta,\phi(x_1,\hat{x}_2,t))\leq-\left(p_1x_1^2+p_3x_2^2\right)\frac{m}{2}$$

for any $x\in D-U_r$. Therefore the solution $x(t)$ enters the set U_r in finite time. The set U_r is positively invariant in the x_1-x_2 plane for $t\geq\max\{t_0,T(r)\}$.

5. It will be shown that for every $\delta_1>0$ there exist a $\delta_2>0$ such that:

$\|(x_1(0),x_2(0),x_3(0),\hat{x}_2(0))\|_\infty<\delta_2$, $(x_1,x_2,x_3)\in D$ and $\hat{x}_2\geq 0$ implies $\|(x_1(t),x_2(t),x_3(t),\hat{x}_2(t))\|_\infty<\delta_1$.

Continuity of ϕ implies the existence of a positive constant r such that $\phi(x_1,x_2,\gamma(t))\leq\delta_1$ for any $x\in U_r$ and $\gamma(t)\in[m,1)$. From 4 and the proof of claim 2, one may see that there exist a positive constant δ_3 such that $|x_2-\hat{x}_2|<\delta_3$ implies $U_{\min\{r,\delta_1\}}$ is positively invariant for $x_3<\min\{\delta_1,r\}$. From stability of the observer, there exist a positive constant δ_4 such that $|x_2(0)-\hat{x}_2(0)|<\delta_4$ implies $|x_2(t)-\hat{x}_2(t)|<\delta_3$ for any $t>0$. Thus $\|(x_1(0),x_2(0),x_3(0),\hat{x}_2(0))\|_\infty<\min\left\{\delta_4,r/\sqrt{2},\delta_1\right\}$ implies $\|(x_1(t),x_2(t),x_3(t),\hat{x}_2(t))\|_\infty<\delta_1$.

This implies the stability of the origin.

6. Finally, from 4 one may see that $(x_1(t),x_2(t))\to 0$ as $t\to\infty$. Furthermore, from the continuity of ϕ and the facts

$x_2(t)\to 0$ and $\hat{x}_2\to x_2$, we conclude:

$$0 \le x_3(t) \le \phi(x_1(t), \hat{x}_2(t), \gamma(t)) \to 0 \text{ as } t \to \infty . \qquad \lozenge$$

In the next corollary it will be proved that observer (8) satisfies the conditions of Lemma (5). Thus the composite system (3), (8), with the controller (14) is asymptotically stable.

Corollary 6: For any initial condition in D_1, the controller (14), for a suitable value of $U_{\max}$, with observer (8) for $\hat{x}_2(0) \ge 0$ makes the origin asymptotically stable with a region of attraction containing $x(0)$.

Proof:
It is sufficient to show that:
i) $\hat{x}_2 \ge 0$
ii) that there exist a constant $\overline{M}$ such that $\left|\dot{\hat{x}}_2\right| \le \overline{M}$.
One may compute:
$$\dot{\hat{x}}_2 = (p_4 x_3 - p_3)\hat{x}_2 + p_4 x_{20} x_3 + K p_6 x_3 \hat{x}_2 - K p_6 x_2 x_3$$
For (i), one may see that if $\hat{x}_2(t) = 0$ then since $K < 0$, it holds:
$$\dot{\hat{x}}_2(t) = p_4 x_{20} x_3 - K p_6 x_2 x_3 \ge 0$$

For (ii), one may observe that $\hat{x}_2 \to x_2$ monotonically and thus it has a maximum value: $\hat{x}_{2m} = \hat{x}_2(0) + \max_{x \in \overline{D}} x_2$.
Thus a constant $\overline{M}$ satisfying (ii) is:

$$\overline{M} = \max_{\substack{x \in \overline{D} \\ 0 \le \hat{x}_2 \le \hat{x}_{2m}}} \left|(p_4 x_3 - p_3)\hat{x}_2 + p_4 x_{20} x_3 + K p_6 x_3 \hat{x}_2 - K p_6 x_2 x_3\right| \qquad \lozenge$$

4.2. Receding Horizon Controller

In this section a discrete time receding horizon controller for the system (3) is designed.

In discrete time receding horizon control, at each step a finite horizon open loop optimal control problem is solved and the first component of the control sequence obtained, is applied to the plant [29].

A discrete time approximate model for the system (3) is first obtained using Euler discretization:

$$\begin{aligned}
x_1(k+1) &= x_1(k) + \delta\left(-p_1 x_1(k) - p_2\left(x_1(k) + x_{10}\right)x_3(k)\right) \\
x_2(k+1) &= x_2(k) + \delta\left(-p_3 x_2(k) - p_4\left(x_2(k) + x_{20}\right)x_3(k)\right) \qquad (15) \\
x_3(k+1) &= x_3(k) + \delta\left(p_5\left(x_1(k) + x_{10}\right)x_3(k) - p_6\left(x_2(k) + x_{20}\right)x_3(k)\right)
\end{aligned}$$

where δ is the discretization time.

The cost function at step i has a quadratic form:
$$V = x_{i+N}^T Q x_{i+N} + \sum_{k=i}^{i+N-1}\left(x_k^T Q_k x_k + r_k u_k^2\right) \qquad (16)$$
where Q_k and Q are positive definite symmetric matrices, r_k positive constants and N the horizon of optimization. The cost function (16) penalizes the deviations of state variables from their nominal values and high control input values. The constraints of the state variables and control are explicitly involved in the optimization problem.

The procedure used for the receding horizon state feedback control scheme is the following:

1. At step i an optimization problem of the form:

$$\begin{aligned}
&\text{minimize } V(x_i u_i, \ldots, u_{i+N-1}) = x_{i+N}^T Q x_{i+N} + \\
&\qquad + \sum_{k=i}^{i+N-1}\left(x_k^T Q_k x_k + r_k u_k^2\right) \\
&\textit{subj. to} \quad (17) \\
&\qquad 0 \le u_k \le U_{\max}, \quad k = i, \ldots, i+N\text{-}1 \\
&\qquad x_3(k) \ge 0, \quad k = i, \ldots, i+N\text{-}1
\end{aligned} \qquad (17)$$

   is solved numerically.
2. The control action u_i is applied
3. Measurements $x(i)$ are taken
4. Continue to step $i+1$

5. Simulation results and practical forms

5.1 Simulation results

In this section the above control schemes are simulated using the parameter values from [8]: $p_1 = 0.25$, $p_2 = 5 \cdot 10^{-6}$, $p_3 = 0.25$, $p_4 = 10^{-6}$, $p_5 = 0.01$, $p_6 = 0.0045$, $x_{10} = 1000$ and $x_{20} = 550$.

At first the observer (8) is simulated and compared with an observer from [4]. The observer designed in [4] is based on the observer error linearization technique. The linear system obtained, after a transformation and an output injection, is detectable but not observable, having a not moving pole at $-p_3$. Thus for the observer designed in [4] the convergence rate is not tunable. On the other hand the reduced order observer (8) has error dynamics given by: $\dot{e} = \left[-p_3 + (p_6 K + p_4)x_3\right]e$. Thus the convergence rate may be tuned using the parameter K i.e. with a smaller K, the convergence if faster.

Figure 1 shows the simulation result for the reduced order observer in comparison with the observer presented in [4]. The observers start at time 7 (years). Reduced order observer (8) converges faster than the observer designed in [4].

In Figure 2 the simulation results for system (3) using the sliding mode controller are presented. In order to simulate the system, the discontinuity of the controller is approximated using hysteresis [30]. System has initial values $x_1(0) = x_2(0) = 0$ and $x_3(0) = 100$. Control action starts at time $t = 10$ years.

For the sliding mode controller, state variables converge to their nominal values. The speed of convergence may be adjusted by the signal $\gamma(t)$ i.e. using a bigger $\gamma(t)$, the convergence is faster. Hysteresis approximation of the sliding mode controller discontinuity is not suitable for practical use due to the very fast changes in the input signal (Figure 2b) and the need for continuous time measurements. A practical form of sliding mode controller is presented in the next section.

Simulation results using receding horizon controller are reported in Figure 3. The state variables converge to their nominal values. The speed of convergence may be tuned by the matrices Q_k and Q, the constants r_k, or the value of $U_{\max}$ i.e. bigger values for Q_k, Q or $U_{\max}$ lead to faster convergence and bigger values for r_k lead to slower convergence.

5.2 Practical forms of the above control schemes

In this section practical forms of the above control schemes are proposed. We assume that measurements are taken only at discrete times (1 week), the control action is fixed during that period and the control input is quantized and can take a value from a finite set: $\{0, u_b, 2u_b, \ldots, Nu_b\}$.

For the sliding mode controller input values in $\{0, U_{\max}\}$ may be used or input may take also some intermediate values. A practical form of the sliding mode controller that gives also intermediate values is:

$$u = u_{q1}\left(x_3\left(p_5\left(x_1 + x_{10}\right) - p_6\left(x_2 + x_{20}\right)\right) - \frac{d\phi}{dt} + \operatorname{sgn}(s)\left(u_0 + u_b/2\right)\right) \quad (18)$$

where u_0 is a small positive real and the function $u_{q1}(u)$ is given by (19).

For the receding horizon controller a simple quantizer on the form:

$$u_{q1}(u) = u_b \arg\min_{n \in N} \left|u - nu_b\right| \quad (19)$$

may be used.

The simulation results using the practical forms of the control schemes are essentially the same except the input response. Figure 4 shows the response of the receding horizon controller and Figure 5 shows the input responses for the sliding mode controller.

5.3 Robustness tests

In this section, robustness of the proposed control schemes is investigated via simulation. Controllers designed in previous sections are applied to a system in the form:

$$\begin{aligned} \dot{x}_1 &= -\bar{p}_1 x_1 - \bar{p}_2\left(x_1 + x_{10}\right)x_3 \\ \dot{x}_2 &= -\bar{p}_3 x_2 + \bar{p}_4\left(x_2 + x_{20}\right)x_3 \\ \dot{x}_3 &= \left[\bar{p}_5\left(x_1 + x_{10}\right) - \bar{p}_6\left(x_2 + x_{20}\right)\right]x_3 - u \end{aligned} \quad (20)$$

Constants $\bar{p}_1, \ldots, \bar{p}_6$ have values:

$$\bar{p}_i = \left(1 + ar_i\right)p_i \quad (21)$$

where constants r_i are random numbers chosen independently from the interval $[-1,1]$ with uniform distribution. Results from ten simulations for system (20) with controller (14) and $a = 0.25$ are presented in Figure 6. Results from ten simulations for system (20) with receding horizon controller and $a = 0.15$ are presented in Figure 7.

6. Conclusion

A nonlinear dynamic model describing the interaction among CD4 T cells, CD8 cells and HIV-1 was analyzed and the solutions of that model was proved that belong to a bounded positively invariant set. A nonlinear observer was designed for a special class of systems and applied to the dynamic model. The observer designed was compared to another observer for the same model [4] and appeared to converge faster. Then two control schemes for the model were designed. In the first control approach a sliding mode controller was designed, based on the observation that the system is in the regular form. A separation principle for sliding mode controller was also proved. In the second approach a receding horizon control scheme was designed using a quadratic cost function. Simulation tests for the control schemes designed show that controllers have a robust behavior

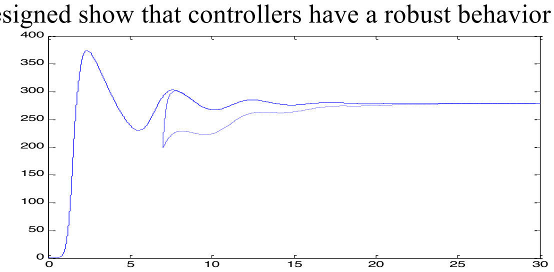

Figure 1: Simulation of the reduced order observer. The solid line is the actual x_2 state, line (-- -- --) is the reduced order observer output and line (-- . -- . --) is the output of the observer presented in [7]

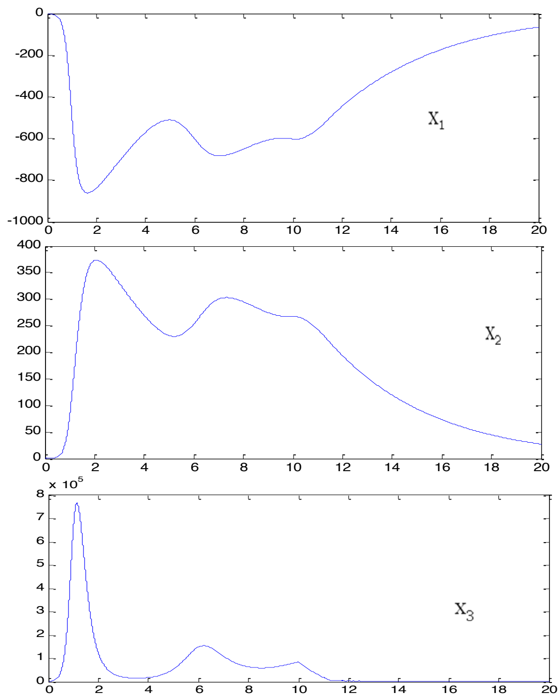

Figure 2a: Simulation of the sliding mode controller, system states. The control action starts at time 10 (years)

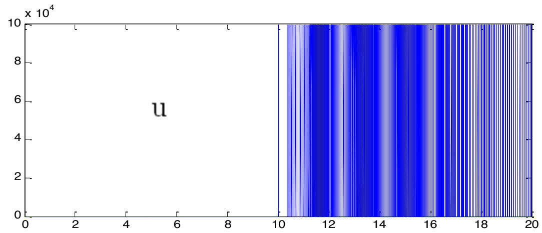

Figure 2b: Simulation of the sliding mode controller: control input. The control action starts at time 10 (years)

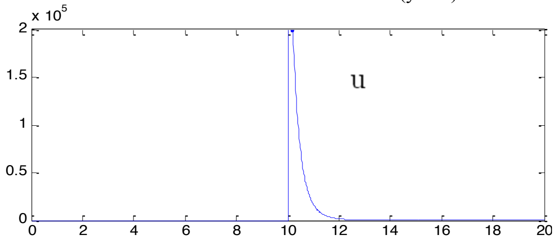

Figure 3a: Simulation of the receding horizon: control input. The control action starts at time 10 (years)

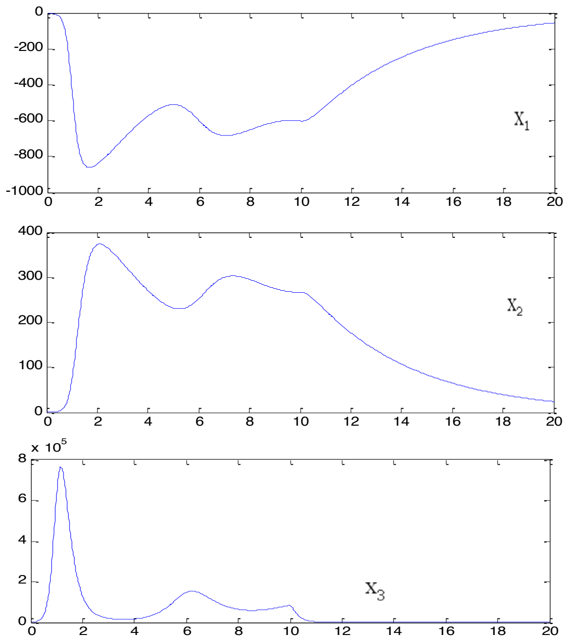

Figure 3b: Simulation of the receding horizon: system states. The control action starts at time 10 (years)

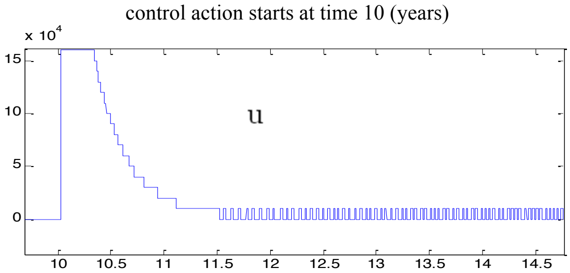

Figure 4: Control input for the receding horizon controller

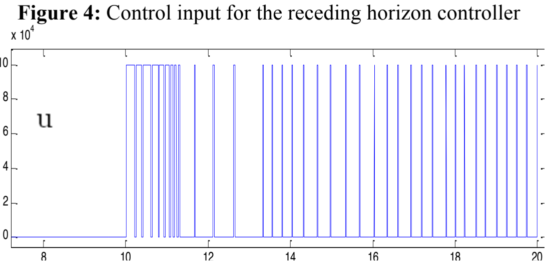

Figure 5a: Control input for sliding mode controller using only values in $\{0, U_{\max}\}$

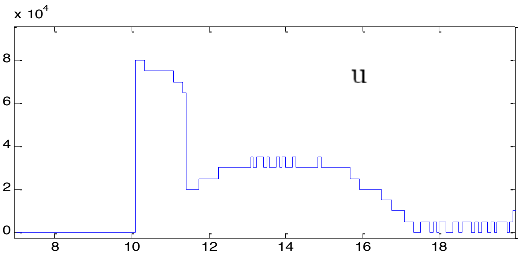

Figure 5b: Control input for the sliding mode controller using (18)

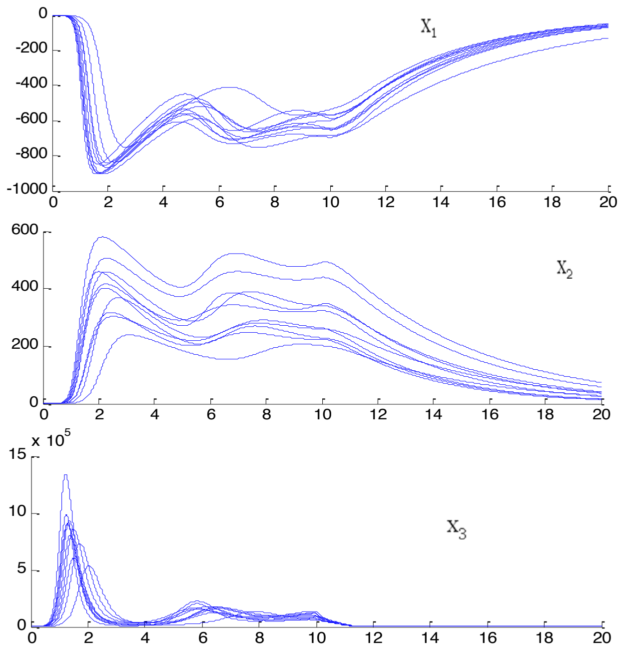

Figure 6: System response with sliding mode controller. Parameters differ at most 25% from the nominal

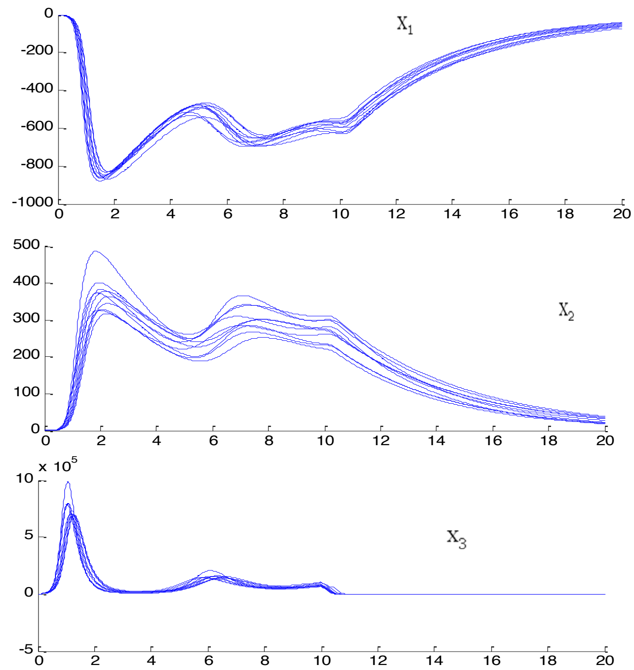

Figure 7: System response with receding horizon controller parameters differ at most 15% from the nominal

Appendix 1

Proof of claim 1:

One may see that $|d\phi(x_1,\hat{x}_2,t)/dt|$ is continuous and thus bounded in the set: $\overline{D}-U_r$. Let $M_6(r)$ be such a bound. In order to show that $|d\phi(x_1,x_2,t)/dt|$ is bounded in the set U_r, this set is divided into: $U_{1r}=\{\hat{x}\in U_r : |x_1|\le \hat{x}_2\}$ and $U_{2r}=\{\hat{x}\in U_r : \hat{x}_2\le |x_1|\}$. In U_{1r} it holds:

$$\hat{x}_2 p_4(\hat{x}_2+x_{20})-x_1 p_2(x_1+x_{10})\ge \hat{x}_2 p_4 x_{20}$$

and thus:

$$\left|\frac{d\phi(x_1,x_2,\gamma(t))}{dt}\right|\le\left|\frac{d\gamma(t)}{dt}\right|\phi+\frac{|2p_1x_1\dot{x}_1+2p_3\hat{x}_2\dot{\hat{x}}_2|}{\hat{x}_2 p_4(\hat{x}_2+x_{20})-x_1p_2(x_1+x_{10})}+\frac{|p_4(x_{20}+\hat{x}_2)\dot{\hat{x}}_2-p_2(x_{10}-2x_1)\dot{x}_1|(p_1x_1^2+p_3x_2^2)}{(\hat{x}_2p_4(\hat{x}_2+x_{20})-x_1p_2(x_1+x_{10}))^2}$$

Therefore:

$$\left|\frac{d\phi(x_1,x_2,\gamma(t))}{dt}\right|\le\frac{(p_1+p_3)\hat{x}_2^2}{p_4x_{20}\hat{x}_2}M+\frac{4\max\{p_1\bar{\dot{x}}_1,p_3\overline{M}\}\hat{x}_2}{p_4x_{20}\hat{x}_2}+M_3\frac{(p_1+p_3)\hat{x}_2^2}{(\hat{x}_2p_4x_{20})^2}$$

$$\le\frac{(p_1+p_3)}{p_4x_{20}}rM+\frac{4\max\{p_1\bar{\dot{x}}_1,p_3\overline{M}\}}{p_4x_{20}}+M_3\frac{(p_1+p_3)}{(p_4x_{20})^2}=M_4(r)$$

where: $\bar{\dot{x}}_1=\sup_{x\in U_r}\{|\dot{x}_1|\}$, and

$$M_3=\sup_{x\in U_r}\{|p_4(x_{20}+2\hat{x}_2)\dot{\hat{x}}_2-p_2(x_{10}-2x_1)\dot{x}_1|\}.$$

Similarly in U_{2r} it holds:

$$\hat{x}_2p_4(\hat{x}_2+x_{20})-x_1p_2(x_1+x_{10})\ge -x_1p_2(x_{10}-r)$$

and thus:

$$\left|\frac{d\phi(x_1,x_2,\gamma(t))}{dt}\right|\le\frac{(p_1+p_3)x_1^2}{-x_1p_2(x_{10}-r)}M+\frac{4\max\{p_1\bar{\dot{x}}_1,p_3\overline{M}\}|x_1|}{-x_1p_2(x_{10}-r)}+M_3\frac{(p_1+p_3)x_1^2}{(x_1p_2(x_{10}-r))^2}$$

$$\left|\frac{d\phi(x_1,x_2,\gamma(t))}{dt}\right|\le\frac{(p_1+p_3)r}{p_2(x_{10}-r)}M+\frac{4\max\{p_1\bar{\dot{x}}_1,p_3\overline{M}\}}{p_2(x_{10}-r)}+M_3\frac{p_1+p_3}{(p_2(x_{10}-r))^2}=M_5(r)$$

Thus a constant satisfying claim 1 is:
$M_2=\max\{M_4(r),M_5(r),M_6(r)\}$.
In the previous inequalities it was also shown that if $x\in U_r$, then

$$\phi(x_1,x_2,\gamma(t))\le\max\left\{\frac{p_1+p_3}{p_2(x_{10}-r)}r(1-m),\frac{(p_1+p_3)}{p_4x_{20}}r(1-m)\right\}$$

From this fact, one may conclude that $\phi(x_1,x_2,\gamma(t))$ is continuous at 0 and thus $\phi(x_1,x_2,\gamma(t))$ is continuous at D.

Proof of claim 2: Since $\hat{x}_2\to x_2$ it is sufficient to show that for any $r>0$, there exist an $\varepsilon>0$ such that if $|x_2-\hat{x}_2|<\varepsilon$ then $\phi(x_1,\hat{x}_2,\gamma(t))\le\phi(x_1,x_2,m/2)$ for every $x\in D-U_r$.

If $|x_2-\hat{x}_2|<\varepsilon$, for some $\varepsilon>0$ and $\hat{x}_2<x_2$, it holds:

$$\phi(x_1,\hat{x}_2,\gamma(t))\le\frac{(p_1x_1^2+p_3x_2^3)(1-\gamma(t))}{p_4(x_2+x_{20})x_2-p_2(x_1+x_{10})x_1-p_4\varepsilon(2x_2+x_{20}-\varepsilon)}$$

The function $F_1(x_1,x_2)=p_4(x_2+x_{20})x_2-p_2(x_1+x_{10})x_1$ is positive in the set $\overline{D}-U_r$. Let $\min_{x\in\overline{D}-U_r}\{F_1(x_1,x_2)\}=d_m$. One has $d_m>0$. If

$$p_4\varepsilon(2x_2+x_{20}-\varepsilon)\le\frac{\gamma(t)-m/2}{1-m/2}\qquad(22)$$

for any $x\in D-U_r$ then it holds:

$$\frac{(p_1x_1^2+p_3x_2^3)(1-\gamma(t))}{p_4(x_2+x_{20})x_2-p_2(x_1+x_{10})x_1-p_4\varepsilon(2x_2+x_{20}-\varepsilon)}\le\frac{(p_1x_1^2+p_3x_2^3)(1-m/2)}{p_4(x_2+x_{20})x_2-p_2(x_1+x_{10})x_1}$$

for any $x\in D-U_r$. Since $\gamma(t)\ge m$ and the set $D-U_r$ is bounded, a value for ε, making (22) valid, always exists. Let ε_1 be such a value.

If $|x_2-\hat{x}_2|<\varepsilon$, for some $\varepsilon>0$ and $\hat{x}_2>x_2$, it holds:

$$\phi(x_1,\hat{x}_2,\gamma(t))\le\frac{(p_1x_1^2+p_3{x_2}^2+p_3(\varepsilon^2+2x_2\varepsilon))(1-\gamma(t))}{p_4(x_2+x_{20})x_2-p_2(x_1+x_{10})x_1}.$$

The function $F_2(x_1,x_2)=p_1x_1^2+p_3x_2^2$ is positive in the set $\overline{D}-U_r$. Let $\min_{x\in\overline{D}-U_r}\{F_2(x_1,x_2)\}=n_m$. One has $n_m>0$. If

$$p_3(\varepsilon^2+2\varepsilon x_2)\le n_m\frac{m}{2-2m}\qquad(23)$$

for any $x\in D-U_r$ then it holds:

$$\frac{(p_1x_1^2+p_3{x_2}^2+p_3(\varepsilon^2+2x_2\varepsilon))(1-\gamma(t))}{p_4(x_2+x_{20})x_2-p_2(x_1+x_{10})x_1}\le\frac{(p_1x_1^2+p_3{x_2}^2)(1-m/2)}{p_4(x_2+x_{20})x_2-p_2(x_1+x_{10})x_1}$$

for any $x\in D-U_r$. Since the set $D-U_r$ is bounded, a value for ε, making (23) valid, always exists. Let ε_2 be such a value.

One may choose: $\varepsilon=\min\{\varepsilon_1,\varepsilon_2\}$. ◊

REFERENCES

[1] A. Perelson and P. Nelson “Mathematical analysis of HIV-1 Dynamics in Vivo” Siam Review vol. 41, 1999.

[2] L.M. Wein, S.A. Zenios and M.A. Nowak: “Dynamic multidrug therapies for HIV: A control theoretic approach”, Journal of theoretical biology, Elsevier 1997.

[3] Z. Bentwich “CD4 Measurements in Patients with HIV: Are They Feasible for Poor Settings?”, PLoS Medicine, vol2 no.7 2005.

[4] D.U. Campos-Delgado and E. Palacios “Nonlinear Observer for the estimation of CD8 Count Under HIV-1 infection”, Proceedings of the American Control Conference, 2007.

[5] D. Wodarz and M.A. Nowak “Mathematical models of HIV pathogenesis and treatment”, Bioessays, Wiley Periodicals, 2002.

[6] D. Wodarz “Helper-dependent vs. Helper independent CTL responses in HIV infection: Implications for Drug Therapy and Resistance”, Journal Theoretical Biology, Academic Press, 2001.

[7] H. Wu and A. A. Ding “Population HIV-1 Dynamics in Vivo: Applicable Models and Inferential Tools for Virological Data from AIDS Clinical Trials” Biometrics, 1999.

[8] M. Campello de Souza, “Modeling the dynamics of HIV-1 and CD4 and CD8 lymphocytes”, IEEE Engineering in Medicine and Biology Magazine, IEEE, vol.18, 1999.

[9] M.E. Brandt and G. Chen, “Feedback control of a biodynamical model of HIV-1”, IEEE Transactions on Biomedical Engineering vol.48, July 2001.

[10] S.S. Ge, Z. Tian and T.H.Lee “Nonlinear Control of a Dynamic model of HIV-1”, IEEE Transactions on Biomedical Engineering, March, 2005.

[11] E. Palacios, G. Espinosa-Perez and D.U. Campos-Delgado “A passivity-based approach for HIV-1 treatment scheduling” Proceedings of the American Control Conference, 2007.

[12] C.N Rautenberg and C.E. D’Attellis “Nonlinear Feedback Control of a Dynamical Model of HIV-1”, WSEAS International Conference on Electronics, Control & Signal Processing 2002.

[13] F.L Biafore and C.E.D. Attellis “Exact Linearization and Control of a HIV-1 Predator – Prey model”, Proceedings of the IEEE Engineering in Medicine and Biology, 2005.

[14] M. Barao and J.M. Lemos “Nonlinear control of HIV-1 infection with a singular perturbation model”, Biomedical Signal Processing and Control, Elsevier, 2007.

[15] J.A. Moreno, G. Espinosa-Perez and E. Palacios “A robust output-feedback treatment scheduling for HIV-1”, International IFAC Symposium on Computer Applications in Biotechnology, 2007.

[16] R. Zurakowski, M. Messina, S.E. Tuna and A.R. Teel “HIV treatment scheduling via robust nonlinear model predictive control”, Proceedings of the Asian Control Conference 2004.

[17] R. Zurakowski, A.R. Teel and D. Wodarz “Utilizing alternate target cells in treating HIV infection through scheduled treatment interruptions”, Proceedings of the American Control Conference, 2004.

[18] R. Zurakowski and A. R. Teel “A model predictive control based scheduling method for HIV therapy”, Journal of Theoretical Biology, Elsevier, 2006.

[19] H. Chang and A. Astolfi “Immune Response’s Enhancement via Controlled Drug Scheduling”, Proceedings of the 46th IEEE Conference on Decision and Control, 2007.

[20] H. Chang and A. Astolfi “Estimation of Immune States in HIV Dynamics”, Proceedings of the IEEE Conference on Decision and Control, 2008.

[21] H. Chang and A. Astolfi “Enhancement of the immune system in HIV dynamics by output feedback”, Automatica, Elsevier, 2009

[22] H. Chang and A. Astolfi “Control of HIV infection dynamics: Approximating high order dynamics by adapting reduced order model parameters”, Control Systems Magazine, IEEE, April 2005.

[23] B.M. Adams, H.T. Banks, H.D. Kwon and H.T. Tran “Dynamic multidrug therapies for HIV: Optimal and STI approaches” Mathematical Biosciences and Engineering, 2004.

[24] H. Shim, S.J. Han, C. C. Chung, S. W. Nam, and J. H. Seo “Optimal Scheduling of Drug Treatment for HIV Infection: Continuous Dose Control and Receding Horizon Control” International Journal of Control, Automation, and Systems Vol. 1, 2003.

[25] I.P. Kordonis “Applications of nonlinear control theory in AIDS models”, master’s thesis, National Technical University of Athens, 2009 (in Greek).

[26] A.M. Jeffery and X. Xia “Identifiability of HIV/AIDS models” in “Deterministic and Stochastic Models of AIDS Epidemics and HIV Infections with Intervention”, World Scientific Publishing, 2005.

[27] X. Xia and C.H. Moog “Identifiability of Nonlinear Systems with Application to HIV/AIDS Models” Transactions an Automatic control, IEEE, 2003.

[28] H.K. Khalil “Nonlinear systems”, Prentice Hall, 2002.

[29] D.Q. Mayne, J.B. Rawlings, C.V. Rao and P.O.M. Scokaert “Constrained Model Predictive Control: Stability and Optimality”, Automatica, Elsevier, 2000.

[30] V. Utkin “Sliding Modes in Control and Optimization”, Springer Verlag, 1992.