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Nonlinear and Adaptive Control of a HIV-1 Infection Model ⋆

João M. Lemos * **Miguel S. Barão** **

* *INESC-ID/IST, R. Alves Redol 9, 1000-029 Lisboa, Portugal, (e-mail: jlml@inesc-id.pt)*
** *INESC-ID/Univ. Évora, R. Alves Redol 9, 1000-029 Lisboa, Portugal, (e-mail: mjsb@ramses.inesc-id.pt)*

Abstract: This paper presents algorithms for nonlinear and adaptive control of the viral load in a HIV-1 infection model. The model considered is a reduced complexity nonlinear state-space model with two state variables, representing the plasma concentration of un-infected and infected CD4+ T-cells of the human immune system. The viral load is assumed to be proportional to the concentration of infected cells. First, a change of variables that exactly linearizes this system is obtained. For the resulting linear system the manipulated variable is obtained by state feedback. To compensate for uncertainty in the infection parameter of the model an adaptation mechanism based on a Control Lyapunov Function is designed. Since the dependency on parameters is not linear, an approximation is made using a first order Taylor expansion.

Keywords: Nonlinear Adaptive Control, HIV-1 infection, Immunology, Exact Linearization, Control Lyapunov Function.

1. INTRODUCTION

1.1 Framework

Strategies for counteracting HIV infection designed using control methods are receiving an increased attention. Detailed studies that combine modeling analysis with clinical results show that the initial infection phase may be represented using simple nonlinear state models Perelson and Nelson (1999). This fact boosted the production of an increasing number of papers where therapy strategies are derived from control principles.

A straightforward approach to the design of a controller to regulate the state of a nonlinear system consists in obtaining an approximate linear model around the equilibrium point considered using Taylor series approximations and then to design a state feedback controller that drives the state increments with respect to the equilibrium to zero. Although simple, this method has the drawback of requiring that the initial conditions are close to the equilibrium for the approximation to be valid, being difficult to establish stability results. Furthermore, if the linearized system is not controllable, it may not be possible to design adequately the state feedback. This is the case of the model of HIV-1 infection considered hereafter around the equilibrium corresponding to an healthy person. If this approach is followed, the linearization must then be performed around the equilibrium point corresponding to infection and the state feedback controller should thus drive the state away from it, with the risk of becoming unstable due to the neglected higher order terms of the model.

Opposite to this approach, feedback linearization Nijmeijer and van der Schaft (1990) aims at exactly canceling the nonlinearities using a nonlinear static feedback. This results in a transformed model that is exactly linear in a region around the equilibrium point to which a linear regulator may then be applied. In this region, that is usually larger than the one resulting from Taylor approximation methods, stability of the closed loop is ensured.

This paper proposes a strategy that combines model reduction using a simple singular perturbation approximation, feedback linearization and LQ regulation based on state feedback. Due to the wide variability of the dynamics associated to different patients the capacity of a controller to stabilize models that are different from the nominal one is quite important. Hence, we consider the inclusion of an estimator of the infection parameter.

It should be remarked that the present paper, as well as the references quoted above, forms just one step towards the application of control techniques to the design of HIV-1 infection therapy. Indeed, in the actual clinical practice, the drugs currently used for treatment of HIV-1 infection are neither continuously infused nor is the virus concentration measured in permanence. The sampling of the controllers designed is therefore required, a subject that deserves attention on its own from the point of view of systems and control.

1.2 Literature review

Examples of research papers addressing the design of HIV-1 infection therapy with control techniques include nonlinear control based on Lyapunov methods and on the use of decomposition in strict feedback form with backstepping Gee *et al.* (2005), adaptive control Cheng and Chang (2004), Optimal Control Souza *et al.* (2000) and Predictive Control Zurakowski and Teel (2006). In Brandt and Chen (2001) various methods based on time-delay feedback control are shown, via Lyapunov

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Parameter	Value	Units
d	0.02	day^{-1}
s	10	$\text{mm}^{-3}\text{day}^{-1}$
θ	1×10^{-3}	$\text{mm}^{3}\text{day}^{-1}$
μ	0.24	day^{-1}

Table 1. Model parameters.

function methods, to stabilize an HIV-1 model similar to the one considered in the present paper. In Biafore and D'Atellis (2005) a HIV-1 infection control strategy based on nonlinear geometric control (exact linearization) is described, but without any mention to adaptive control and considering a different model.

1.3 Paper contributions and organization

The contribution of this paper consists of a therapy design procedure for HIV-1 based on nonlinear control. The controller proposed combines exact linearization with an adaptation mechanism that relies on a joint control Lyapunov function for the tracking and estimation errors.

the paper is organized as follows: After this introduction that motivates the problem, reviews the main references and states the paper contribution and structure, the model used for HIV-1 infection is presented in section 2. This model has two equilibrium points that are characterized in section 3. Section 4 addresses exact linearization and section 5 describes the design of the controller for the resulting linear system. Section 6 deduces the adaptive controller and finally section 7 draws conclusions.

2. HIV-1 INFECTION MODEL

Hereafter, the model considered is the reduced complexity second order model:

$$\dot{x}_1 = s - dx_1 - (1-u)\theta x_1 x_2 \tag{1}$$

$$\dot{x}_2 = (1-u)\theta x_1 x_2 - \mu x_2 \tag{2}$$

In equation (1), s represents the production rate of healthy cells, the coefficient d the natural death of the cells and θ the infection rate coefficient. The infection rate of healthy cells is proportional to the product of healthy cells x_1 and free virus x_3. This process can be influenced by drugs (Reverse Transcriptase Inhibitors – RTI) that reduce the virus ability to infect cells. This influence is represented by the manipulated variable u, in which $u = 0$ corresponds to absence of drug and $u = 1$ to a drug efficiency in preventing infection of 100%. Actually, with the available drugs, the efficiency is below 100%, and u is constrained to the interval $[0, u_{\text{max}}]$ with $u_{max} < 1$.

Equation (2) comprises two terms that represent, respectively, the transition of healthy cells to infected cells and the death of infected cells, with μ the death coefficient.

An infected cell liberates free virus. In this reduced complexity model the virus load is assumed to be proportional to the concentration of infected cells.

Table 1 shows one possible set of model parameters, used in simulations.

The reduced nonlinear model (1, 2), may also be written as

$$\dot{x} = f(x) + g(x)u \tag{3}$$

Equilibrium point:	$\begin{bmatrix}240.0000 & 21.6667\end{bmatrix}^T$
Eigenvalues:	$-0.0208 \pm 0.0690j$
Stability:	asymptotically stable
Equilibrium point:	$\begin{bmatrix}500.0000 & 0.0000\end{bmatrix}^T$
Eigenvalues:	$-0.0200, \quad 0.2600$
Stability:	unstable

Table 2. Stability of the equilibrium points of the reduced model.

where the state vector is given by $x = [x_1\, x_2]'$ and with the vector functions f and g defined as

$$f := \begin{bmatrix} s - dx_1 - \theta x_1 x_2 \\ \theta x_1 x_2 - \mu x_2 \end{bmatrix} \tag{4}$$

$$g := \theta x_1 x_2 \begin{bmatrix} 1 \\ -1 \end{bmatrix} \tag{5}$$

3. EQUILIBRIUM POINTS

In the absence of therapy, *i. e.* when $u = 0$, model (1, 2) has as equilibrium points the solutions of the algebraic equations

$$0 = s - dx_1 - (1-u)\theta x_1 x_2 \tag{6}$$

$$0 = (1-u)\theta x_1 x_2 - \mu x_2. \tag{7}$$

with respect to the state variables x_1 and x_2. These equilibrium points are

$$x_1 = \frac{s}{d}, \quad x_2 = 0 \tag{8}$$

corresponding to an healthy person, and

$$x_1 = \frac{\mu}{\theta(1-u)}, \quad x_2 = \frac{s}{\mu} - \frac{d}{\theta(1-u)} \tag{9}$$

corresponding to an infected individual.

The local stability analysis of these equilibrium points is made by computing the eigenvalues of the Jacobian matrix $\tilde{A} = \partial f / \partial x$, given by

$$\tilde{A} = \begin{bmatrix} -d - \theta x_2 & -\theta x_2 \\ \theta x_2 & \theta x_1 - \mu \end{bmatrix}_{x = x_{eq}} \tag{10}$$

By using the model parameters of table 1, the results of table 2 are obtained.

4. EXACT LINEARIZATION

System (1, 2) is not linearizable by performing a state transformation only. However, by the combined use of the transformations

$$u = \alpha(x) + \beta(x)v \tag{11}$$

$$z = S(x) \tag{12}$$

the following linear model is obtained

$$\dot{z} = Az + Bv. \tag{13}$$

with

$$A = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} \quad B = \begin{bmatrix} 0 \\ 1 \end{bmatrix} \tag{14}$$

Figure 1 shows a block diagram of these transformations. The manipulated variable v in the transformed model is called "virtual" because it has only mathematical existence, in opposition to u, that has the physical meaning of being the drug dosage actually applied to the patient. Eq. (11) allows to compute the actual drug dose u such that between v and z there is a linear relationship to which linear control techniques may then be applied.

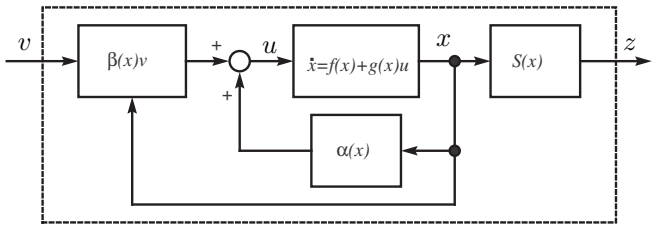

Fig. 1. Exact linearization.

Proposition 1 The transformations performing linearization are

$$\beta(x) = \frac{1}{\theta x_1 x_2(\mu - d)} \tag{15}$$

$$\alpha(x) = \frac{-ds + d^2 x_1 + \mu^2 x_2 + (d-\mu)\theta x_1 x_2}{(d-\mu)\theta x_1 x_2} \tag{16}$$

$$S(x) = \begin{bmatrix} \varphi(x) \\ s - dx_1 - \mu x_2 \end{bmatrix} \tag{17}$$

with $\varphi(x)$ given by

$$\varphi(x) = x_1 + x_2 - \frac{\mu}{\theta} - \frac{s}{\mu} + \frac{d}{\theta} \tag{18}$$

□

Proof of Proposition 1

In Nijmeijer and van der Schaft (1990) it is shown that the nonlinear system (3) with $f(x_0) = 0$ and scalar input u is feedback linearizable around the equilibrium x_0 if and only if the distributions D_i defined by

$$D_i = \text{span}\left\{g(x), \text{ad}_f g(x), \ldots, \text{ad}_f^{i-1} g(x)\right\} \tag{19}$$

verify the two following conditions:

$$\dim D_n(x_0) = n, \tag{20}$$

$$D_{n-1} \text{ is involutive around } x_0 \tag{21}$$

In relation to the model (3) with f and g given by (4) and (5), the first condition results in

$$\begin{aligned} \dim D_2(x) &= \text{rank}\,[g(x)\ \text{ad}_f g(x)] \\ &= \frac{\beta k}{c} x_2 \,\text{rank} \begin{bmatrix} x_1 & s - \mu x_1 \\ -x_1 & -s + dx_1 \end{bmatrix} \\ &= 2, \text{ for } x_1, x_2 \neq 0 \text{ and } \mu \neq d. \end{aligned} \tag{22}$$

and hence $\dim D_2(x_0) = 2$. The second condition is also verified because $D_1 = span\{g(x)\}$ is involutive since the Lie bracket $[g, g] = 0 \in D_1$. The model is therefore feedback linearizable.

Since the conditions on D_i are satisfied, there exists (Nijmeijer and van der Schaft (1990)) a function $\varphi(x)$ that verifies the following three conditions:

$$\varphi(x_0) = 0 \tag{23}$$

$$\langle \mathrm{d}\varphi, ad_f^k g\rangle(x) = 0, \quad k = 0, 1, \ldots, n-2 \tag{24}$$

$$\langle \mathrm{d}\varphi, ad_f^{n-1} g\rangle(x_0) \neq 0 \tag{25}$$

In terms of $\varphi(x)$, the linearizing transforms yielding (14) around the equilibrium state x_0 are given by Nijmeijer and van der Schaft (1990):

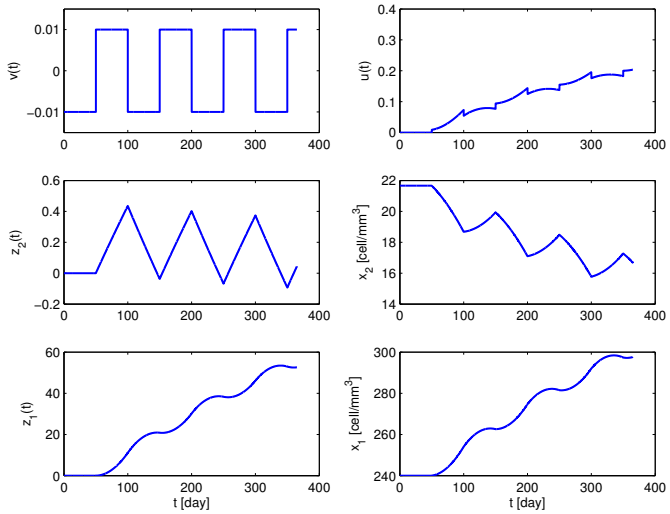

Fig. 2. Time response of the linearized system to a virtual rectangular system (virtual signal on the left, actual signal on the right).

$$\alpha(x) = -\left(L_g L_f^{n-1}\varphi(x)\right)^{-1} L_f^n \varphi(x) \tag{26}$$

$$\beta(x) = \left(L_g L_f^{n-1}\varphi(x)\right)^{-1} \tag{27}$$

$$z_i = L_f^{i-1}\varphi(x), \quad i = 1, 2, \ldots, n \tag{28}$$

The function 18 satisfies the three conditions, in particular

(1) Computing $\varphi(x)$ at the equilibrium x_0 given by point (9) yields $\varphi(x_0) = 0$;
(2) $\langle \mathrm{d}\varphi, g\rangle = \frac{\partial\varphi(x)}{\partial x} g(x) = 0$;
(3) $\langle \mathrm{d}\varphi, [f, g]\rangle = \frac{\partial\varphi(x)}{\partial x}[f, g] = \frac{\beta k}{c}(d - \mu)x_1 x_2 \neq 0$, for $x = x_0$.

Using $\varphi(x)$ as given by (18) and (26)-(28) yields the transformations (15-17).

The expression (18) for $\varphi(x)$ is obtained by noting that Condition 2 may be written as

$$\begin{bmatrix} \frac{\partial\varphi}{\partial x_1} & \frac{\partial\varphi}{\partial x_2} \end{bmatrix} \begin{bmatrix} 1 \\ -1 \end{bmatrix} \frac{\beta k}{c} x_1 x_2 = 0 \tag{29}$$

and hence implies that $\varphi(x)$ satisfies the partial differential equation

$$\frac{\partial\varphi}{\partial x_1} = \frac{\partial\varphi}{\partial x_2} \tag{30}$$

whose solution is given by any differentiable function Φ of argument $x_1 + x_2$:

$$\varphi(x_1, x_2) = \Phi(x_1 + x_2) \tag{31}$$

The simplest choice that also satisfies Condition 1 is given by (18). The expressions for α and β follow then in a straightforward way from 28.

□

With these transformations, the system in a region of state space around the equilibrium (9) is transformed exactly in the linear system (14). Figure 2 shows the response of the linearized system to a rectangular virtual input (*i. e.* the input v before the transform).

5. CONTROL WITH KNOWN PARAMETERS

The problem of designing a control law for the linearized system is addressed hereafter. The aim is to design a state feedback control law that generates the virtual manipulated variable v as a function of the transformed state z. More specifically, we want to design the vector of feedback gains $K = [k_1\, k_2]$, the equilibrium value of v (denoted $\bar{v}$) and the equilibrium $\bar{z} = [\bar{z}_1\, \bar{z}_2]^T$ of z corresponding to the a specified equilibrium of x, in the control law:

$$v = \bar{v} - K\tilde{z} \tag{32}$$

where

$$\tilde{z} := z - \bar{z} \tag{33}$$

The equilibrium value of the control variable of the linear system verifies

$$A\bar{z} + B\bar{v} = 0 \tag{34}$$

5.1 Equilibrium values

Assume that the concentration of infected cells x_2 is to be driven to a reference value r and kept there. At the equilibrium defined by $x_2 = r$ one has, by equating the derivatives to zero in (1, 2)

$$u = 1 - \frac{\mu d}{\theta(s - \mu r)} \tag{35}$$

and

$$x_1 = \frac{s - \mu r}{d} \tag{36}$$

In terms of the linearized system (that operates with transformed variables) this results in the equilibrium point $\bar{z} = S(\bar{x})$, *i. e.*:

$$\begin{bmatrix}\bar{z}_1\\ \bar{z}_2\end{bmatrix} = \begin{bmatrix}\dfrac{s-\mu r}{d} + r + \dfrac{1}{\theta}(d-\mu) - \dfrac{s}{\mu}\\ 0\end{bmatrix} = T(r) \tag{37}$$

5.2 LQ controller design

It is then possible to design a LQ controller, using the linearized dynamics, that keeps the system at the desired reference value r.

The transformation $T(r)$ allows to compute the equilibrium point in terms of the variables (z_1, z_2). The controller is designed by minimizing the quadratic cost:

$$J = \int_0^{+\infty} z^T Q_z z + \rho v^2 \mathrm{d}t \tag{38}$$

where Q_z and ρ adjust the contribution of the variables $z(t)$ and $v(t)$. Since these variables are virtual (corresponding to transformed states) it is difficult to develop heuristic choices of their values. Thus it was decided to adjust the weights Q_x for the state variables x and then compute the corresponding Q_z. Using a linear approximation, it is shown in the Appendix that

$$Q_z = \left(\frac{\partial S^{-1}}{\partial z}\right)^T Q_x \left(\frac{\partial S^{-1}}{\partial z}\right). \tag{39}$$

With the following choice of the weights

$$Q_x = \begin{bmatrix}0.01 & 0\\ 0 & 23\end{bmatrix}, \qquad \rho = 10^3 \tag{40}$$

the results shown in figures 3 and 4 are obtained. These weights are "tuning knobs" that allow the designer to adjust the relative importance of the state variables and the drug usage.

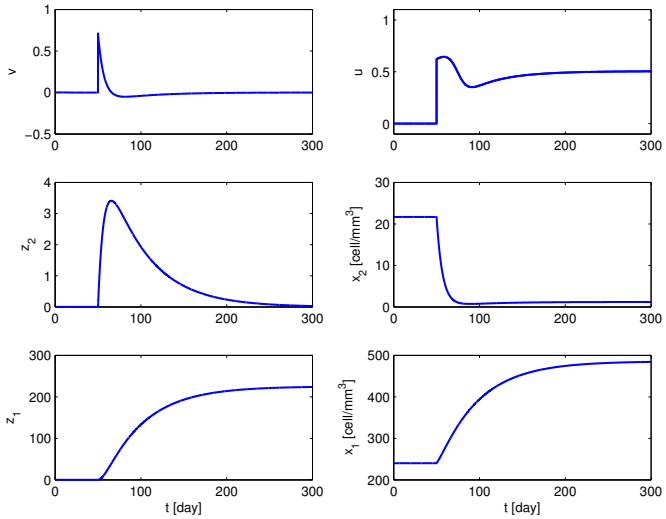

Fig. 3. Changing the reference in the number of infected cells.

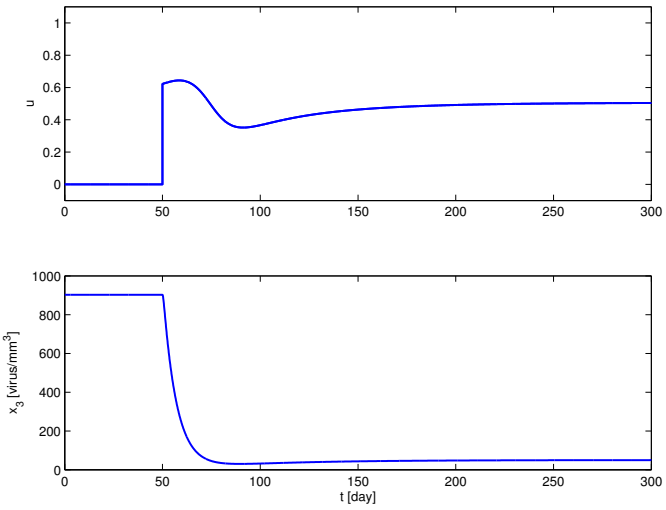

Fig. 4. Evolution of viral load.

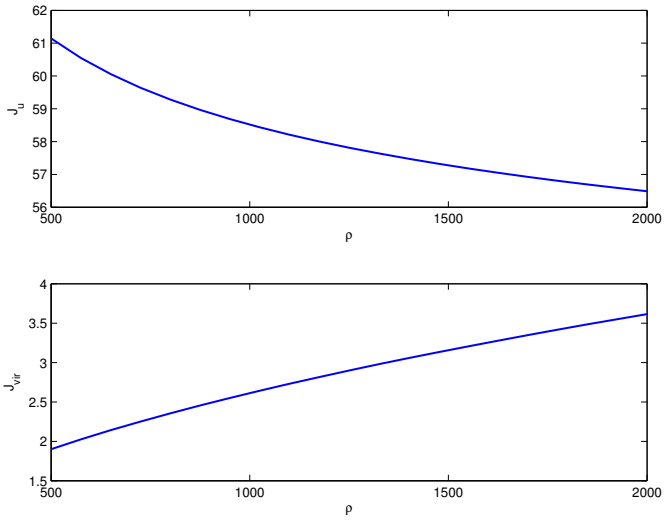

Fig. 5. Selection of the weight ρ.

Figure 3 shows in the three left graphics the variables of the linearized system (virtual input v and states z_1, z_2), and on the three graphics of the right the actual variables (input u and states x_1, x_2) with the above choice of weights. Fig. 4 shows the concentration of free virus. Its value decays fast, such as the one of infected cells, as shown in fig. 3. The specification consists in reducing the number of virus to 50 copies per mm^3 in a period of less then 50 days.

In order to provide an overall idea of the influence of ρ on control performance, fig. 5 plots

$$J_u := \int_{50}^{300} u^2(t)dt$$

and

$$J_{vir} := \lambda \int_{50}^{300} (x_3(t) - r)^2 dt \quad \lambda = 10^{-6},\ r = 50$$

as a function of ρ. Decreasing ρ leads to a smaller viral load integrated over time, but to bigger drug dose administration. The choice $\rho = 10^{-3}$ was selected as a possible compromise.

6. ADAPTIVE CONTROL

In practice model parameters are not perfectly known. A possible approach to estimate them is described hereafter and relies on a joint control Lyapunov function for both the control and estimation errors Sastry and Isidori (1989). In the work reported only the adaptation of the infection parameter θ is considered.

6.1 Error equation

Let θ^* be the (unknown) true value of parameter θ, assumed to be constant, and $\hat{\theta}$ its estimate. The estimation error $\tilde{\theta}$ verifies

$$\hat{\theta} = \theta^* + \tilde{\theta} \tag{41}$$

Differentiating (12) with respect to time and using the change of variable (11) yields

$$\dot{z} = \frac{\partial S}{\partial x}\{f(x,\theta^*) + g(x,\theta^*)[\alpha(x,\hat{\theta}) + \beta(x,\hat{\theta})v]\} \tag{42}$$

For the adaptive technique to be applied the equation error that relates the tracking error with the estimation error should be linear in $\tilde{\theta}$. For this sake, we do a first order expansion of both α and β and neglect higher order terms:

$$\alpha(x,\theta^*) \approx \alpha(x,\hat{\theta}) - \tilde{\alpha}(x,\hat{\theta})\tilde{\theta} \tag{43}$$

$$\beta(x,\theta^*) \approx \beta(x,\hat{\theta}) - \tilde{\beta}(x,\hat{\theta})\tilde{\theta} \tag{44}$$

where

$$\tilde{\alpha}(x,\hat{\theta}) = \frac{\partial \alpha}{\partial \hat{\theta}} = \frac{ds - d^2x_1 - \mu^2 x_2}{(d-\mu)x_1x_2\hat{\theta}^2} \tag{45}$$

and

$$\tilde{\beta}(x,\hat{\theta}) = \frac{\partial \beta}{\partial \hat{\theta}} = \frac{1}{\hat{\theta}^2(d-\mu)x_1x_2} \tag{46}$$

With this approximation, and using the fact that

$$\frac{\partial S}{\partial x}\{f(x,\theta^*) + g(x,\theta^*)[\alpha(x,\theta^*) + \beta(x,\theta^*)v]\} = Az + Bv \tag{47}$$

equation (42) becomes

$$\dot{z} = Az + Bv + \Psi(x,v,\theta)\tilde{\theta} \tag{48}$$

where

$$\Psi(x,v,\theta) := -\frac{\partial S}{\partial x} g(x,\hat{\theta})[\tilde{\alpha}(x,\hat{\theta}) + \tilde{\beta}(x,\hat{\theta})v] \tag{49}$$

From this equation and using (32) and (34) the error equation is written as

$$\dot{\tilde{z}} = A_k\tilde{z} + \Psi(x,v,\theta)\tilde{\theta} \tag{50}$$

Since

$$\frac{\partial S}{\partial x} = \begin{bmatrix} 1 & 1 \\ -d & -\mu \end{bmatrix} \tag{51}$$

it follows that

$$\Psi(x,v,\hat{\theta}) = \begin{bmatrix} 0 \\ 1 \end{bmatrix} \frac{v + ds - d^2x_1^2 - \mu^2 x_2}{\hat{\theta}} \tag{52}$$

6.2 Adaptation law

In order to design an adaptation mechanism to adjust θ, consider the candidate Control Lyapunov Function

$$V(\tilde{z},\tilde{\theta}) = \tilde{z}^T P\tilde{z} + \frac{1}{\gamma}\tilde{\theta}^2 \tag{53}$$

where $P = P^T$ is a positive definite matrix and $\gamma > 0$ is a scalar design parameter.

Differentiating V with respect to time and using (50) it follows that

$$\dot{V} = \tilde{z}^T(A_k^T P + PA_k)\tilde{z} + \tilde{\theta}(2\Psi^T(x,v,\hat{\theta})P\tilde{z} + \frac{2}{\gamma}\dot{\tilde{\theta}}) \tag{54}$$

Where

$$A_k := A - BK \tag{55}$$

For K such that A_k is hurwitz (as it happens, for instance, if K is designed by solving the LQ problem in section 5.1), there is $Q = Q^T$ positive definite such that

$$A_k^T P + PA_k = -Q \tag{56}$$

Using (56) and selecting $\dot{\tilde{\theta}}$ such that

$$\dot{\tilde{\theta}} = -\gamma\Psi(x,v,\hat{\theta})^P\tilde{z} \tag{57}$$

equation (54) becomes

$$\dot{V} = -\tilde{z}^T Q\tilde{z} \leq 0 \qquad \forall \tilde{z} \neq 0 \tag{58}$$

Using a standard argument based on La Salle's Invariant Set Theorem it is then concluded that $\tilde{z} \to 0$. Equation (57) implies the use of an adaptation law given by

$$\hat{\theta}(t) = -\hat{\theta}(0) + \int_0^t \gamma\Psi^T(x,v,\hat{\theta})P\tilde{z}dt \tag{59}$$

or

$$\hat{\theta}(t) = \hat{\theta}(0) + \gamma\int_0^t \frac{d^2x_1 + \mu^2x_2 - ds - v}{\hat{\theta}}(p_{12}\tilde{z}_1 + p_{22}\tilde{z}_2)dt \tag{60}$$

Figure 6 shows a result obtained using adaptive controller.

7. CONCLUSIONS

It was shown that a reduced complexity nonlinear model for the HIV-1 infection can be controlled using adaptive nonlinear control methods. The approach followed combines exact linearization, LQ control and a joint control Lyapunov function for for the tracking and estimation errors, to design the estimation law. Since this requires a linear dependence of the error equation on the estimation error, some approximations related to the linearizing transforms have to be performed.

The adaptation law considers only the tuning of the infection parameter. The same procedure may be extended to estimate the other parameters at the cost of a more cumbersome algebra.

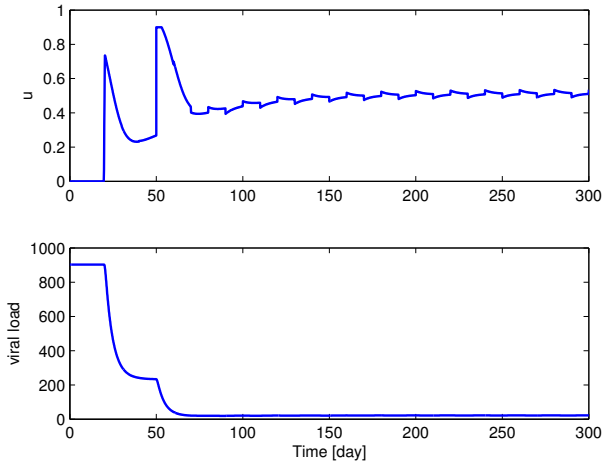

Fig. 6. Results with adaptive control.

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APPENDIX – WEIGHT SELECTION

Since $x = S^{-1}(z)$, the corresponding in z to the quadratic form in x is given by

$$(x - x_0)^T Q_x (x - x_0) = (S^{-1}(z) - S^{-1}(z_0))^T Q_x (S^{-1}(z) - \\ - S^{-1}(z_0)) \qquad (.1)$$

that is not, in general, a quadratic form in z.

Using the linear approximation

$$S^{-1}(z) \approx S^{-1}(z_0) + \frac{\partial S^{-1}}{\partial z}|_{z_0}(z - z_0) \qquad (.2)$$

and replacing (.2) in (.1), it follows that

$$(x - x_0)^T Q_x (x - x_0) \approx \\ \approx (z - z_0)^T \left(\frac{\partial S^{-1}}{\partial z}\right)^T Q_x \left(\frac{\partial S^{-1}}{\partial z}\right)(z - z_0) \qquad (.3)$$

and hence (39) follows.