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CONTROL DESIGN OF AN HIV-1 MODEL

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ABSTRACT. In this paper, we formulate a dynamic mathematical model that describes the interaction of the immune system with the human immunodeficiency virus (HIV), combined with nonlinear continuous feedback control. The detailed computations of two linearizing inputs is presented. It results in the design of a first fully linearizable system and a second partially linearizable one. The proposed controllers have the ability to drive the system close to the healthy equilibrium state. Numerical simulations demonstrate their effectiveness by maintaining virus concentration in very low levels and healthy cells in satisfactory levels.

1. INTRODUCTION

Since the human immunodeficiency virus (HIV), the virus that causes acquired immune deficiency syndrome (AIDS), was first identified in the United States more than 35 years ago, expanded treatment options have brought down death rates, increased patient adherence, improved the quality of life for patients and paved the way for future research focused on preventing the disease.

Nowadays, there are 52 medicines and vaccines for HIV currently in development, including additional combination treatments, more effective therapies and preventative vaccines [26]. Among the 52 medicines in development for HIV, there are 32 antiretrovirals and antivirals, 16 vaccines and 4 cell therapies including a potential first-in-class medicine intended to prevent HIV from attaching to new cells and breaking through the cell membrane [26].

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In this frame, mathematical models attempt to describe viral replication dynamics and virus-specific immune responses of HIV-AIDS infection. Most of them are proposed in an abstract sense, involving nonlinear ordinary differential equations [15, 19]. They suggest different possibilities in which the body interacts with the pathogen, the most basic of these models typically include three of the key dynamic compartments: uninfected target cells, infected cells and virus. We refer the reader to [1, 20, 25] for an extensive survey on the collection of mathematical models used to analyze HIV infection.

If the range of model parameters for a population is such that dramatically different outcomes are predicted for different individuals, bifurcation values for different parameters could suggest target interventions for continued successful treatment. In [22], Lyapunov-Schmidt reduction method is used to investigate topological bifurcation when varying the force of infection parameter. In [27] a study on the global stability and Hopf bifurcation of an HIV-1 infection model with saturation incidence is proposed and in [28] the global properties and bifurcation analysis of an HIV-1 infection model with two target cells is proposed.

On the other hand, many control strategies have been used in literature to design epidemic control programs [6, 23]. Various objective criteria are adopted and produce valuable theoretical results. One can find a good summary of the different methods of optimal control that may be applied to disease models in [13] and for HIV in [8]. In [4], authors describe a continuous differential equation model of the HIV-1 interaction with the body and could use external feedback stabilizing controls. A technique to control virus concentration for HIV-1 infection model obtained from actual patients data is introduced in [2], the strategy is based on Linear quadratic regulator (LQR). Interesting work was done in [14] on the optimal control of HIV chemotherapy. In [21], an application of Pontryaguine maximum principle to compute the optimal control under quadratic cost for an HIV-1 within host model was performed. A realistic dosage regimen was designed in [17] which drives the immunological system close to the healthy equilibrium state.

In this work, a three dimensional nonlinear HIV-1 within host model is considered, two controls representing possible treatments are incorporated. We then develop a feedback linearization for this controlled model. The aim is to cancel existing nonlinearities by algebraically transforming the nonlinear model into an equivalent system of a linear form. That way, linear control techniques can be applied.

In this frame, according to dynamic feedback linearization theory, two cases may occur, the system can be fully feedback linearized or only partially feedback linearized depending on the value of its relative degree. In the latter case, the total dynamics of the system can be divided into an external controlled part and an internal unobserved uncontrolled part.

The inputs considered in our model give rise to both cases. We then construct an appropriate coordinate transformation for each case that is chosen to be a diffeomorphism. After this, simulations are performed to illustrate the control action.

This paper is organized as follows: in section 2, a description of the considered mathematical model is given, as well as the incorporation of two different controls representing possible treatments. In section 3, the detailed linearization, analyze and control feedback design are presented for both adopted controls and in section 4, numerical simulations are given to highlight the pertinence of the obtained results. Conclusion and perspective are given in section 5, whereas some recalls and detailed calculs are given in the Annex.

2. MODEL DESCRIPTION AND PROBLEM STATEMENT

Once the infection by HIV occurs, the virus gets attached to a $CD4^+$ T-cell and gets into its interior, then changes its RNA to DNA. This occurs thanks to Reverse Transcriptase enzyme which is furnished by the virus itself [15]. This new DNA gets inserted into the host cell DNA. It is then considered by the $CD4^+$ host cell as a normal set of genes, that is why the fouled cell produces thousands of copies of the virus different Proteins. After a very complex process, Protease enzyme helps those proteins gathering together to form complete virus, that are released by the mother cell [15].

Although the mechanism for T-cells proliferation is largely unknown, most models in HIV-1 literature exhibit a constant source term that represents the number of $CD4^+$ T-cells population in the thymus, that is decreased by their natural death, so in those models, healthy cells dynamics (with no interaction with virus or infected cells) are governed by an equation of the form: $\dot{S} = \delta - \alpha S$ [19]. A logistic term to this equation is added in [20] to represent mitosis multiply when stimulated by antigen or mitogen, which resulted in an equation of the form: $\dot{S} = \delta - \alpha S + bS(1 - \frac{S}{K})$. In [25], authors had taken into account infected cells concentration as well in the logistic term, which gave the equation: $\dot{S} = \delta - \alpha S + bS(1 - \frac{S+I}{K})$.

Based on the 3-Dimensional model considered by A. Perelson in [20], we consider the following system, where healthy cells evolve according to a simple logistic growth, neglecting source term and infected cells concentration:

$$(S) \quad \begin{cases} \dot{S}(t) = bS(t) \left(1 - \frac{S(t)}{K}\right) - \beta S(t)V(t) \\ \dot{I}(t) = -cI(t) + \beta S(t)V(t) \\ \dot{V}(t) = -dV(t) + rcI(t) \\ S(0) = S_0, I(0) = I_0, V(0) = V_0 \end{cases}$$

Where $S(\cdot)$ denotes susceptible exposed (not yet infected) $CD4^+$ T-cells concentration at time t , $t \in [0, T]$ $T > 0$; $I(\cdot)$ denotes infected $CD4^+$ T-cells

density and $V(\cdot)$ represents circulating free virus quantity in blood at the same time.

b is the healthy cells reproduction rate, K is the system's carrying capacity, β is a constant rate at which a healthy cell meets a free virus and becomes infected, also called the force of infection; c , d are the clearance rates of infected cells and virus respectively; r is the number of infective virus released by an infected cell over its life span.

Our model has a biological sense if its solution is positive at every moment t , we thus consider the domain of definition of (S) as the positive cone:

TABLE 1. Model (S) parameters and initial conditions.

Parameter	Significance	Value	Unit	Reference
b	Healthy cells reproduction rate	10	mm^3/day	[8]
K	Carrying capacity of the system	10^3	$/\text{mm}^3$	estimated
c	Death rate of infected cells	0.24	$/\text{day}$	[8]
β	Force of infection	2.4×10^{-5}	mm^3/day	[8]
d	Clearance rate of virus	2.4	$/\text{day}$	[15]
r	New infective virus	3000	$/\text{day}$	[15]
S_0	Healthy cells initial condition	1000	$/\text{mm}^3$	[15]
I_0	Infected cells initial condition	10	$/\text{mm}^3$	[15]
V_0	Virus initial condition	100	$/\text{mm}^3$	[15]

According to [21], model (S) has three possible equilibriums:

1/ The trivial equilibrium $E_0 = (0, 0, 0)$. It corresponds to the extinction of all kinds of cells (healthy, infected, and virus).

2/ The healthy equilibrium $E_1 = (K, 0, 0)$. It corresponds to a healthy body with no infection.

3/ A third positive equilibrium that exists if (and only if) $\frac{r\beta K}{d} > 1$, and is given by $E^* = (S^*, I^*, V^*)$ where:

$$S^* = \frac{d}{r\beta}, \quad I^* = \frac{db}{cr\beta} \left(1 - \frac{d}{r\beta K}\right), \quad V^* = \frac{b}{\beta} \left(1 - \frac{d}{r\beta K}\right).$$

We call this point the "chronic equilibrium", it represents the coexistence of healthy and infected cells as well as free virus in blood.

Now, to suggest treatment strategies, we will incorporate the action of two inputs $u_i(\cdot)$, $i = 1, 2$ to our model (S).

The first control aims to boost the immune system. A treatment by Interleukin 2 (IL-2) is then the perfect candidate [23], recall that IL-2 is a naturally-occurring cytokine that can also be made artificially and a real hope with regard to clinical trials, that shown its ability to enhance the immune system at different disease stages, particularly restore defective Natural

Killers¹ [9]. So it is applied on the logistic term in system (S) to increase the parameter b . One gets the first controlled model:

$$(S_1) \quad \begin{cases} \dot{S}(t) = bS(t) \left(1 - \frac{S(t)}{K}\right) (1 + u_1(t)) - \beta S(t)V(t) \\ \dot{I}(t) = -cI(t) + \beta S(t)V(t) \\ \dot{V}(t) = rcI(t) - dV(t) \\ S(0) = S_0, I(0) = I_0, V(0) = V_0 \end{cases}$$

The second control is employed to compromise viral entry into the host cell, which is the first step of infection. It is applied on the term βSV in system (S) to reduce the parameter β . It could be an entry inhibitor or another type of treatment like the infusion of autologous CD4⁺ T cells in which the CCR5 gene was rendered permanently dysfunctional² as proved in [16, 24]. It could also be the regular use of microbicide gel³ that can block infection by the AIDS virus as showed in [7]. CXCL4 protein that directly binds to the virus and prevents HIV from entering human host cell may also be prescribed, see [3] for more details. It could be also the use of a compound of cannabis, known to slow down the disease in advance states of AIDS as demonstrated in [5].

Applying this second control, one gets the following system:

$$(S_2) \quad \begin{cases} \dot{S}(t) = bS(t) \left(1 - \frac{S(t)}{K}\right) - \beta S(t)V(t)(1 - u_2(t)) \\ \dot{I}(t) = -cI(t) + \beta S(t)V(t)(1 - u_2(t)) \\ \dot{V}(t) = rcI(t) - dV(t) \\ S(0) = S_0, I(0) = I_0, V(0) = V_0 \end{cases}$$

Our aim is to compute a linearizing input, using sweetble poles placement to linearize models ($S_{1,2}$), then a controller design will guarantee the decrease of viral load by at least 90% of its value within 2-8 weeks of treatment. That way, healthy CD4⁺ T-cells count will significantly increase according to [6].

3. CONTROL DESIGN ANALYSIS

In [17], authors considered a basic HIV model where healthy cells dynamics are represented by a source term decreased by the conversion to infected cells. They incorporated two inputs and demonstrated (based on real clinical data) that this modified system may be approximated by a single input one. The resulting control aimed to reduce the number of free virus circulating in the blood and was therefore applied in the third equation. In what follows, we

¹Natural Killer Cells are a type of cytotoxic lymphocyte critical to the innate immune system, that provide rapid responses to virally infected cells.

²CCR5 is the major coreceptor for human immunodeficiency virus.

³Still in experimentation for human use, gave interesting results on simians.

investigate the case of the first control noted u_1 (as a $CD4^+$ T-cells booster), then the case of the second control noted u_2 (as an entry inhibitor). Remark that our model is slightly different from the one in [17], since it involves a logistic function.

As the control design requires a preliminary and a mandatory test of accessibility of the system, let us first analyze this property for both controlled models $(S_{1,2})$.

3.1. *Analyzing accessibility of systems $(S_{1,2})$.* Put $x = (S, I, V)$ and:

$$f(x) = \begin{pmatrix} bS(1 - \frac{S}{K}) - \beta SV \\ -cI + \beta SV \\ rcI - dV \end{pmatrix}; g_1(x) = \begin{pmatrix} bS(1 - \frac{S}{K}) \\ 0 \\ 0 \end{pmatrix}; g_2(x) = \begin{pmatrix} \beta SV \\ -\beta SV \\ 0 \end{pmatrix}; h(x) = V.$$

The choice of V as an output is justified by the fact that in HIV infection, a practical data one can measure to evaluate the disease progression is the viral load.

So, one has:

$$[f, g_1] = b\beta SV \begin{pmatrix} \frac{S}{K} \\ \frac{S}{K} - 1 \\ 0 \end{pmatrix}$$

and

$$[f, g_2] = \beta SV \begin{pmatrix} b\frac{S}{K} + \frac{rcI}{V} - d \\ -b(1 - \frac{S}{K}) + \frac{rcI}{V} + 2\beta V + d - c \\ rc \end{pmatrix}$$

So,

$$\mathcal{C}_1 = \begin{pmatrix} bS(1 - \frac{S}{K}) - \beta SV & bS(1 - \frac{S}{K}) & (b\beta SV)\frac{S}{K} \\ -cI + \beta SV & 0 & (b\beta SV)(\frac{S}{K} - 1) \\ rcI - dV & 0 & 0 \end{pmatrix}$$

and

$$\mathcal{C}_2 = \begin{pmatrix} bS(1 - \frac{S}{K}) - \beta SV & (\beta SV) & (\beta SV)(b\frac{S}{K} + \frac{rcI}{V} - d) \\ -cI + \beta SV & -(\beta SV) & (\beta SV)[-b(1 - \frac{S}{K}) + \frac{rcI}{V} + 2\beta V + d - c] \\ rcI - dV & 0 & (\beta SV)rc \end{pmatrix}$$

Since the dynamics as well as all the parameters of model (Sc) are nonzero and $S \neq K$ according to [21], then $\mathcal{C}_{1,2}$ are both of rank 3. One concludes that the models $(S_{1,2})$ are both accessible in D .

3.2. *Control design analysis of model (S_1)*. Consider the SISO (Single Input, Single Output) system (S_1), where only the control $u_1(\cdot)$, that corresponds to the injection of IL-2 to boost the immune system is incorporated.

Detailed calculation of model's (S_1) relative degree is presented in the annex section.

In this case, one gets $r = 3$, thus, this system is fully linearizable by considering the following variables change:

$$(3.2) \quad Z = \begin{pmatrix} Z_1 \\ Z_2 \\ Z_3 \end{pmatrix} = \begin{pmatrix} h(x) \\ L_f h(x) \\ L_f^2 h(x) \end{pmatrix}$$

and the control:

$$(3.3) \quad u_1(t) = \frac{v - L_f^3(h(x))}{L_{g_1}(L_f^2 h(x))}$$

Where:

$$L_f^3 h(x) = rc\beta S \left[b \left(1 - \frac{S}{K} \right) V - \beta V^2 - (c + d)V + rcI - dV \right] + rcI [c(c + d) + d^2] - d^3 V.$$

In (3.3), v is a feedback control of the following form:

$$v = C_1 Z_1 + C_2 Z_2 + C_3 Z_3 \quad , \text{ where } C_1, C_2, C_3 \in \mathbb{R}$$

System (S_1) with (3.3) is equivalent to the following linear form:

$$(3.4) \quad \begin{pmatrix} \dot{Z}_1 \\ \dot{Z}_2 \\ \dot{Z}_3 \end{pmatrix} = \begin{pmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ C_1 & C_2 & C_3 \end{pmatrix} \begin{pmatrix} Z_1 \\ Z_2 \\ Z_3 \end{pmatrix}$$

According to Routh-Hurwitz criteria [10], the necessary and sufficient conditions that constants C_1, C_2 and C_3 should verify to obtain all eigenvalues with negative real parts are:

$$(3.5) \quad \begin{cases} C_1, C_2 \text{ and } C_3 < 0 \\ C_2 C_3 > (-C_1) \end{cases}$$

Finely, the system (S_1) is fully linearizable, controllable and can be stabilized by any control v provided that constants $C_i, i = 1, 2, 3$ satisfy conditions (3.5).

3.3. *Control design analysis of model (S_2)*. Now, consider the SISO system (S_2), where only control $u_2(\cdot)$ that corresponds to an entry inhibitor, is incorporated.

Once again, the calculation of its relative degree is fully presented in the annex section.

One has $r = 2$. This means that the system (S_2) is partially linearizable.

Thus, the first two components of the needed variables change are:

$$(3.6) \quad \begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix} = \begin{pmatrix} h(x) \\ L_f h(x) \end{pmatrix}$$

To complete the coordinate change, let's choose φ such that:

$$(3.7) \quad L_{g_2} \varphi(x) = 0$$

Take:

$$(3.8) \quad \varphi(x) = S + I - K.$$

to get the following coordinate change:

$$(3.9) \quad Z = \begin{pmatrix} Z_1 \\ Z_2 \\ Z_3 \end{pmatrix} = \begin{pmatrix} V \\ rcI - dV \\ S + I - K \end{pmatrix}$$

It is easy to check that this coordinate change is a diffeomorphism.

Now, consider the following input:

$$(3.10) \quad u_2(t) = \frac{v - L_f^2(h(x))}{L_{g_2} L_f h(x)}$$

$$(3.11) \quad \text{where } v = C_1 Z_1 + C_2 Z_2, \quad C_1, C_2 \in \mathbb{R}$$

and

$$L_f^2 h(x) = rc(\beta S V - (c + d)I) + d^2 V$$

That way, system (S_2) with (3.10) is equivalent to the following form:

$$(3.12) \quad \begin{cases} \dot{Z}_1 = Z_2 \\ \dot{Z}_2 = v \\ \dot{Z}_3 = q_3(Z) \end{cases}$$

Where:

$$q_3(Z) = b \left(Z_3 + K - \frac{Z_2 - dZ_1}{rc} \right) \left(1 - \frac{Z_3 + K - \frac{Z_2 - dZ_1}{rc}}{K} \right).$$

$$(3.13) \quad \begin{pmatrix} \dot{Z}_1 \\ \dot{Z}_2 \end{pmatrix} = \begin{pmatrix} 0 & 1 \\ C_1 & C_2 \end{pmatrix} \begin{pmatrix} Z_1 \\ Z_2 \end{pmatrix}$$

Using the Routh-Hurwitz criteria again, constants C_1, C_2 should be negative to ensure the stability of 3.13.

On the other hand, one has:

$$\dot{\varphi} = \dot{S} + \dot{I} = bS \left(1 - \frac{S}{K} \right) - cI$$

PROOF. Then,

$$\left(\dot{S} + \dot{I} \right) + c(S + I - K) = bS \left(1 - \frac{S}{K} \right) - cI + c(S + I - K)$$

Which gives:

$$\left(\dot{S} + \dot{I} \right) + c(S + I) = (c + b)S - \frac{b}{K}S^2 - cK$$

Or equivalently:

$$\dot{\varphi} = \left[(c + b)S - \frac{b}{K}S^2 - cK \right] - c\varphi$$

One sees that:

$$\dot{\varphi} \Big|_{(S=K, I=0, V=0)} = -c\varphi$$

So this dynamics is asymptotically stable and drives the system near the healthy equilibrium point $(K, 0, 0)$. \square

4. NUMERICAL SIMULATIONS

4.1. *The uncontrolled model.* We begin by simulating the uncontrolled system (S) to display its behavior using parameters and initial conditions of table 1:

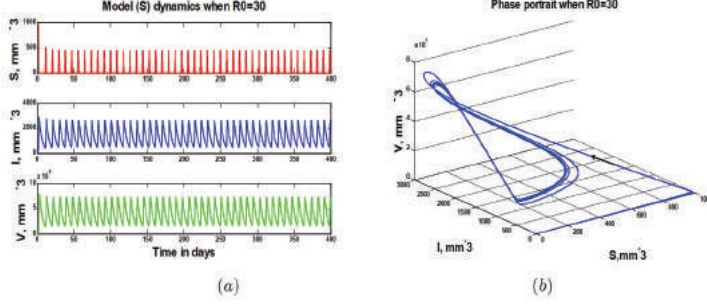


FIGURE 1

- (a) The uncontrolled Model (S) global dynamics.
 (b) The corresponding phase portrait.

We see stable oscillations in the dynamics of healthy and unfected cells as well as virus (Figure 1 (a)), which gives rise to a periodic solution contained in a stable cycle (Figure 1 (b)). The outcome is that, in this situation, it is impossible to reach the healthy equilibrium state of the model without intervention.

4.2. *The controlled model.* Since any intervention is most likely to happen when the CD4⁺ T-cells count is below 200mm⁻³, (350 or even 500mm⁻³, depending on the country's HIV treatment policy), initial conditions are considered now as $S_0 = 180$, $I_0 = 750$, $V_0 = 1e6$ [26] and pole placement constants are $C_1 = -0.0028$, $C_2 = -0.045$ [estimated].¹ We demonstrated in section (3) that the system (S_1) is fully linearizable. Simulation of its implementation (3.3-3.4) gives:

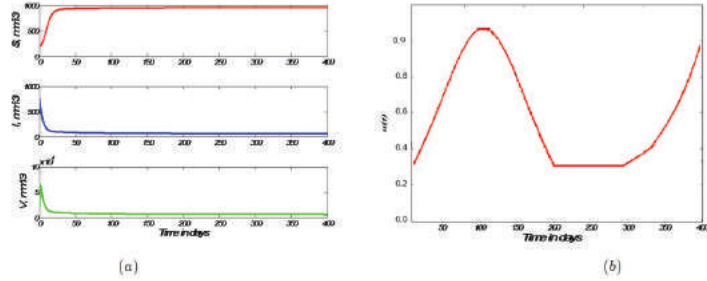


FIGURE 2

- (a) Simulation of the partial linearization of (S_1).
 (b) The corresponding control.

Using this control seems to be the best way to control the overall infection in this case, healthy cells get stabilized on high level and infected cells as well as viruses pass to undetectable levels after a short period of treatment (approximatively 20 days of continuous treatment). It is to be mentioned that control u_1 passes to its minimal value after almost 200 days of treatment, and stays there for a while. After this, we remark a high rise in the dosage of the immune system booster to maintain low levels of infected and virus concentrations. 2/ We now propose to simulate the partial linearization of system (S_2) given in (3.10-3.12).

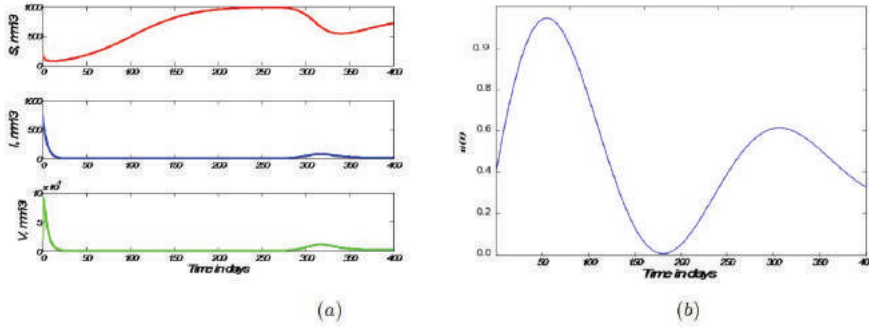


FIGURE 3

- (a) Simulation of the partial linearization of (S_2) .
- (b) The corresponding control.

After suitable pole placement, simulation shows that the viral load as well as the number of infected cells are reduced significantly after almost 30 days of treatment. This means that in only one month, the entry inhibitor control law designed was successful to bring the model near the healthy equilibrium point. We see also a significant drop in the value of the needed control after approximatively 180 days of continuous treatment, which is not negligible since this remedee may be cytotoxique. Unfortunately, this drop doesn't last long and we remark a rise again in the control law so that it maintains the infected cells and virus concentrations in low levels.

5. DISCUSSION AND PERSPECTIVES

In this paper we have formulated a dynamic model with compartments including healthy cells, infected cells, and virus that is subject to two treatments as control inputs, Interleukin2 and some entry inhibitor. The uncontrolled model possesses a locally asymptotically stable steady state and a chronic unstable one. We then applied techniques and ideas from control theory to derive

continuous therapy protocols. In the treatment of diseases, factors such as duration of therapy, the amount of prescribed medication, intervals for drugs and treatment costs can form parts of the systems control. Considering that the control models made in most cases lead to complex nonlinearities, possibly with high dimensions, solving them with the help of classical methods or other numerical methods is very difficult.

When the treatment efficacy varies from no medication (0) to full medication (1), a major advantage of "target tracking" approach, (the control u is proportional to the viral load V) is that once the virus is controlled to low levels, the drug dosage can be reduced proportionately. Under such circumstances, side effects of the therapy will also be reduced.

The issue with this control approach is relating it to real drug posology. Although several studies were performed in this area, they are not ready to be applied yet in real life. The reason is that they do not provide a discrete-time drug posology, but rather a continuous-time optimal control stated in terms of abstract mathematical parameters, hardly interpreted by clinicians.

Knowing that drugs are most commonly prescribed to be taken on a fixed dose, fixed-time interval basis, the potential success of this approach is the periodic modification of the antiretroviral treatment regimen similar in some ways to the infusion pump control of insulin levels in the juvenile diabetics.

Perhaps in time, this will lead to the development of a similar automated device for this purpose.

In future work, a different approach based on hybrid controller is to be considered and the approach used in this study will be extended to more complex HIV-1 models.

6. ANNEX

6.1. *Accessibility of nonlinear dynamical systems.* Consider the nonlinear system defined by:

$$(6.14) \quad \dot{x} = f(x) + g(x)u$$

Where $x \in \mathbb{R}^n$, is the state of the system, $u \in \mathbb{R}^m$, is the input to the model, f and g , are analytic functions of appropriate dimensions.

Remember that Lie brackets between two functions f and g is noted by $[f, g]$ and is given by:

$$[f, g] = \nabla g \cdot f - \nabla f \cdot g$$

THEOREM 6.1. [11]

If the matrix \mathbb{C} defined by:

$$\mathbb{C} = (f, g, [f, g])$$

is of rank n then the system (6.14) is accessible.

6.2. Relative degree.

DEFINITION 6.2.

The system (6.14) is said to have a relative degree r if:

$$(6.15) \quad \begin{cases} L_g L_f^k h(x) = 0 & \text{for all } k < r - 1 \\ L_g L_f^{r-1} h(x) \neq 0 \end{cases}$$

Where $L_f h(x) = (\nabla h(x))^T \cdot f(x)$ is the Lie derivative of h in the direction of f .

In fact, r represents the number of times we have to differentiate the output y to have an explicit dependence on the input u .

Remember that if the system (6.14) admits a relative degree that is equal to r , then $r \leq n$.

- When $r < n$: consider the variables change defined by:

$$\begin{cases} \Phi_1(x) = h(x) \\ \Phi_2(x) = L_f h(x) \\ \vdots \\ \Phi_r(x) = L_f^{r-1} h(x) \end{cases}.$$

According to [11], there exists $(n - r)$ functions $\Phi_j(x)$, $r + 1 \leq j \leq n$, such that $\forall x \in D, \text{Jac}(\Phi(x)) \neq 0$.

In this case, the first r components of the system can be rewritten in the new coordinates $Z_i = \Phi_i(x)$, $i = 1, \dots, n$ as:

$$\begin{cases} \dot{Z}_1 = Z_2 \\ \vdots \\ \dot{Z}_{r-1} = Z_r \\ \dot{Z}_r = L_f^r h(x(t)) + (L_g L_f^{r-1} h(x(t))) u(t) \end{cases}$$

and as $x(t) = \Phi^{-1}(Z(t))$, putting:

$$\begin{cases} a(Z) = L_g L_f^{r-1} h(\Phi^{-1}(Z)) \\ b(Z) = L_f^r h(\Phi^{-1}(Z)) \end{cases}$$

then

$$\dot{Z}_r = b(Z) + a(Z)u(t)$$

In addition, according to [11], it is possible to choose the components $\Phi_j(x)$, $j = r + 1, \dots, n$ such that:

$$L_g \Phi_j(x) = 0, \forall x \in D, j = r + 1, \dots, n$$

then,

$$\dot{Z}_j = q_j(Z(t)) \text{ where } q_j(Z(t)) = L_f \Phi_j(\Phi^{-1}(Z)), \quad j = r+1, \dots, n$$

In this case, the system (6.14) is equivalent to:

$$\begin{cases} \dot{Z}_1 = Z_2 \\ \vdots \\ \dot{Z}_{r-1} = Z_r \\ \dot{Z}_r = b(Z) + a(Z)u(t) \\ \dot{Z}_{r+1} = q_{r+1}(Z) \\ \vdots \\ \dot{Z}_n = q_n(Z) \end{cases}$$

and considering

$$u(t) = \frac{v - b(Z)}{a(Z)} \text{ (knowing that } a(Z) \neq 0),$$

one gets the partial linearization:

$$\begin{cases} \dot{Z}_1 = Z_2 \\ \vdots \\ \dot{Z}_{r-1} = Z_r \\ \dot{Z}_r = v \\ \dot{Z}_{r+1} = q_{r+1}(Z) \\ \vdots \\ \dot{Z}_n = q_n(Z) \end{cases}$$

- When $r = n$, the same methodology applies but without the need of functions $\Phi_j(\cdot)$, $j = r+1, \dots, n$. We then get a fully linear and controllable system, see [11] or [12] for further development.

6.2.1. *The relative degree of the system (S₁).* Consider the first control applied in the model (S1), one has:

$$L_{g_1} h(x) = \begin{pmatrix} 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} bS \left(1 - \frac{S}{K}\right) \\ 0 \\ 0 \end{pmatrix} = 0$$

and

$$\begin{aligned}
L_f h(x) &= \begin{pmatrix} 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} bS \left(1 - \frac{S}{K}\right) - \beta SV \\ -cI + \beta SV \\ rcI - dV \end{pmatrix} \\
&= rcI - dV
\end{aligned}$$

Which gives:

$$L_{g_1}(L_f h(x)) = \begin{pmatrix} 0 & rc & -d \end{pmatrix} \begin{pmatrix} bS \left(1 - \frac{S}{K}\right) \\ 0 \\ 0 \end{pmatrix} = 0$$

Then:

$$\begin{aligned}
L_f^2 h(x) &= L_f(L_f h(x)) \\
&= \begin{pmatrix} 0 & rc & -d \end{pmatrix} \begin{pmatrix} bS \left(1 - \frac{S}{K}\right) - \beta SV \\ -cI + \beta SV \\ rcI - dV \end{pmatrix} \\
&= rc(\beta SV - (c + d)I) + d^2 V
\end{aligned}$$

Gives :

$$\begin{aligned}
L_{g_1}(L_f^2 h(x)) &= \begin{pmatrix} rc\beta V & -rc(c + d) & rc\beta S + d^2 \end{pmatrix} \begin{pmatrix} bS \left(1 - \frac{S}{K}\right) \\ 0 \\ 0 \end{pmatrix} \\
&= rc\beta V bS \left(1 - \frac{S}{K}\right) \\
&\neq 0 \text{ (because } S \neq K \text{ according to [21])}.
\end{aligned}$$

So, one has:

$$\begin{cases} L_{g_1} h(x) = 0 \\ L_{g_1}(L_f h(x)) = 0 \\ L_{g_1}(L_f^2 h(x)) = rc\beta V bS \left(1 - \frac{S}{K}\right) \neq 0 \end{cases}$$

This means that $r = 3$.

And,

$$\begin{aligned}
L_f^3 h(x) &= L_f (L_f^2 h(x)) \\
&= \begin{pmatrix} rc\beta V & -rc(c+d) & rc\beta S + d^2 \end{pmatrix} \begin{pmatrix} bS(1 - \frac{S}{K}) - \beta SV \\ -cI + \beta SV \\ rcI - dV \end{pmatrix} \\
&= rc\beta S \left[b \left(1 - \frac{S}{K} \right) V - \beta V^2 - (c+d)V + rcI - dV \right] + rcI [c(c+d) + d^2] - d^3 V
\end{aligned}$$

6.2.2. *The relative degree of the system (S₂).* Consider the second control applied in the model (S₂), one has:

$$\begin{aligned}
L_{g_2} h(x) &= \begin{pmatrix} 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} \beta SV \\ -\beta SV \\ 0 \end{pmatrix} = 0 \\
L_f h(x) &= \begin{pmatrix} 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} bS(1 - \frac{S}{K}) - \beta SV \\ -cI + \beta SV \\ rcI - dV \end{pmatrix} \\
&= rcI - dV
\end{aligned}$$

This gives:

$$\begin{aligned}
L_{g_2} (L_f h(x)) &= \begin{pmatrix} 0 & rc & -d \end{pmatrix} \begin{pmatrix} \beta SV \\ -\beta SV \\ 0 \end{pmatrix} \\
&= -rc\beta SV \\
&\neq 0
\end{aligned}$$

Yields:

$$\begin{cases} L_{g_2} h(x) = 0 \\ L_{g_2} (L_f h(x)) = -rc\beta SV \neq 0 \end{cases}$$

Since the dynamics S and V are nonzero [21], as well as all the parameters of model (Sc), then $r = 2$.

And,

$$\begin{aligned}
L_f^2 h(x) &= \begin{pmatrix} 0 & rc & -d \end{pmatrix} \begin{pmatrix} bS(1 - \frac{S}{K}) - \beta SV \\ -cI + \beta SV \\ rcI - dV \end{pmatrix} \\
&= rc(\beta SV - (c+d)I) + d^2 V
\end{aligned}$$

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