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Bang-Bang Control Applied on an HIV-1 within host Model

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ABSTRACT

Local controllability analysis of an HIV infection model on which three controls are effective is investigated, the optimal control policy to minimize the number of infected cells, the number of free virus and maximize the number of healthy cells for each control separately, then for all controls applied at once is formulated and solved as an optimal bang-bang control problem (command all or nothing). Numerical examples are given to illustrate the obtained results.

1. Introduction

Treatment of patients infected by the Human Immunodeficiency Virus (HIV) is of great concern nowadays, aiming to find the optimal way for administering the cure.

Different chemotherapies are being tested, most widely using drugs as the reverse transcriptase inhibitors, integrase inhibitors or protease inhibitors, but clinical trials based on other forms of treatments are being performed, as the use of bee venom [3], antibodies [nature], the infusion of autologous $CD4^+$ T-cells in which the CCR5 gene was rendered permanently dysfunctional, (CCR5 is the major co receptor for human immunodeficiency virus) [4], injection of the Interleukin2 [8, 9], and so on.

HIV is an RNA virus, when it infects a human immune $CD4^+$ T-cell, its RNA is transcribed into DNA. Reverse transcriptase inhibitors interfere in this process by halting. the duplication of virus, consequently reducing the apoptosis phenomenon of the infected cells, integrase inhibitors can compromise the viral entry into the host cell which can seriously reduce the infection, on the other side the protease inhibitors interfere in the process of protein assembly of new viruses, which leads in the creation of non infectious

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ones, easily cleared by immune cells, that helps in increasing clearance rate of virus.

Lot of data is available on the HIV-1 infection treatment, we know for example that many problems arise from the use of most chemotherapies with multiple and harmful side effects or ineffectiveness of treatment after a certain time due to the capability of the virus to mutate and become resistant, see [14] for example. For us, it is crucial to know if the application of multiple drugs is the best way of treatment, or if there is another way that can avoid or at least minimize side effects, while maintaining viral load under a specific threshold.

Motivated by this question, we have considered a system of Ordinary Differential Equations that describes the interaction of the immune system with the HIV-1, we have introduced treatments as three inputs to the model, we first study local controllability of the system for each control, then for all controls together, further, we consider objective functions to 1/ minimize infected cells, 2/ minimize free viruses in the blood, 3/ maximize healthy cells for each input separately, then for all inputs together at the same time, we derive the optimum strategy using the Pontryagin Maximum Principle, finally, numerical simulations are used to compare all cases.

In this paper we analyze the following system of Ordinary Differential Equations that models a cell-to-cell spread of HIV-1 infection in tissue culture based on the 3-Dimensional model considered by A. Perelson in [11], nevertheless, here, we consider the evolution of healthy cells as having a simple logistic growth, so our model is given by the following autonomous system :

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

Where $S(\cdot)$ denotes the concentration of susceptible exposed (not yet infected) $CD4^+$ T-cells at time $t \in \Omega = [0, T]$; $I(\cdot)$ denotes the concentration of infectious $CD4^+$ T-cells and $V(\cdot)$ represents the concentration of free viruses at the same time. Put $x = (S, I, V)^T$ the vector of state variables.

b is the reproductive rate of healthy cells, K is the carrying capacity of the system, β is a constant rate at which a healthy cell meet a virus and becomes infected, also called the capturing rate, c, d are the clearance rates of infected cells and virus respectively ; r is the number of viruses released by an infected cell over its lifespan, sometimes called the conversion factor.

Initial conditions are fixed, we suppose $S_0 \leq K$ to fit reality, and all parameters of the system (S) are assumed to be strictly positive and are summarized in the following table :

Table 1 – Model's (S) parameters description.

Parameters	Significance	Value	Unit	References
b	Healthy cells reproduction rate	10	mm^3/day	[12]
K	Carrying capacity of the system	10^3	/ mm^3	Estimated
c	Death rate of infected cells	0.24	/ day	[12]
β	Rate of infection	2.4×10^{-5}	mm^3/day	[12]
d	Clearance rate of virions	2.4	/day	[13]
r	Number of virus released by an infected cell	3000	/day	[13]

2. Previous results

Proposition 1 [1]
The system (S) has three equilibriums :
– The origin,
– The infected-free (healthy) equilibrium, that we denote by $E_1 = (K, 0, 0)$,
– The chronic equilibrium, that we denote by $E^* = (S^*, I^*, V^*)$ where :

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

This equilibrium only exists when the parameter $R_0 = \frac{r\beta K}{d}$ is greater than 1.
Proposition 2 [1]
– The positive octant is positively invariant by system (S), and all solutions of (S) are bounded.
– Local stability :
a) The origin is a saddle point
b) E_1 is locally asymptotically stable if $R_0 < 1$, locally stable but not asymptotically if $R_0 = 1$ and unstable if $R_0 > 1$.
c) E^* when it exists ($R_0 > 1$) is locally asymptotically stable if and only if $R > R_0 > 1$, where $R = \frac{2b(c+d)}{-\left[(c+d)^2+cd\right]+\sqrt{\left[(c+d)^2+cd\right]^2+4bcd(c+d)}}$.
– Global stability :
a) The healthy equilibrium $E_1 = (K, 0, 0)$ is Globally Asymptotically Stable if and only if $R_0 \leq 1$
b) When $R_0 > 1$ suppose the derivative of the logistic term in (S) is strictly negative for $S \in [0, K]$, then the chronic equilibrium point E^* is Globally Asymptotically Stable with respect to solutions not initiated on the S-axis.

3. Problem statement

We propose to control the model representing the HIV evolution with three inputs, one at each step, using controls $u_i(\cdot)$, $i = 1, 2, 3$, then apply all these controls at once.

a) The first one is applied on the virus directly to increase its clearance rate, it could be an antiretroviral drug like the so called Protease inhibitor (Pi) that has a direct effect of increasing the viral clearance, (see [10]), or it could be recent treatments like the use of nanoparticles carrying a toxin found in bee venom that are capable of destroying HIV particles while leaving neighboring cells intact, see [3], or some antibodies used to surround the virus in macrophage and keep it therein [2], or it could represent the association of all these treatments at the same time.

So, when therapy effects of the first control are taken into consideration, model reads as follows :

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

Where $\overline{d} = (1+\zeta_{Pi})d$, and ζ_{Pi} denotes the effectiveness of the administrated therapy in increasing natural death rate of virus, thus ζ_{Pi} may be considered as independent control input say u_1 which can be function of time t, one obtains then the first controlled system :

$$\dot{x}(t) = F_1(x(t),\, u_1(t)) \Leftrightarrow \begin{cases} \dot{S}\,(t) = bS(t)(1 - \frac{S(t)}{K}) - \beta S(t)V(t) \\ \dot{I}\,(t) = -cI(t) + \beta S(t)V(t) \\ \dot{V}\,(t) = -dV(t)(1 + u_1(t)) + rcI(t) \\ S(0) = S_0,\ I(0) = I_0,\ V(0) = V_0 \end{cases}$$

Characteristics of a sweetble function $u_1\,(\cdot)$ are to be defined further in the text.

b) The second control is employed to compromise the viral entry into the host cell, which is the first step of infection, so it will be applied on the term βSV in system (S), it could be the Integrase inhibitor or any entry inhibitor, it could be another type of treatment like the infusion of autologous $CD4^+$ T cells in which the CCR5 gene was rendered permanently dysfunctional[1] (see [4]), or it could be the regular use of microbicide gel that can block infection by the AIDS virus[2], as explained by the research in [5], it could be also the use of the CXCL4 protein, because its mechanism and its composition is totally different compared to all other proteins already known that regulate the movement of immune cells. CXCL4 protein directly binds to the virus, and is able to prevent HIV from entering human host cell [6], finely it could be the use of a compound of cannabis known to slow down the disease in advance states of AIDS [7].

Now model reads as follows :

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

[1]CCR5 is the major co receptor for human immunodeficiency virus

[2]in experimentation for the human use, gave interesting results on simians

Where $\bar{\beta} = (1 - \zeta_{Ii})\beta$, ζ_{Ii} denotes the effectiveness of the therapy in decreasing the penetration of the virus in the CD4$^+$ cells and can be considered as an independent control, which leads us to our second controlled system

$$\dot{x}(t) = F_2(x(t),\, u_2(t)) \Leftrightarrow \begin{cases} \dot{S}(t) = bS(t)(1 - \frac{S(t)}{K}) - \beta S(t)V(t)(1 - u_2(t)) \\ \dot{I}(t) = -cI(t) + \beta S(t)V(t)(1 - u_2(t)) \\ \dot{V}(t) = -dV(t) + rcI(t) \\ S(0) = S_0,\, I(0) = I_0,\, V(0) = V_0 \end{cases}$$

c) The third control represents a manner to reduce the apoptosis of infected cells population, this will have as consequence to reduce the new born viruses, so, one wants to keep an infected cell alive as long as possible so that it doesn't release virions therein, it could be a treatment by the Reverse Transcriptase inhibitors, so it will be applied on the term $-cI$ in the system (S).

$$\begin{cases} \dot{S}(t) = bS(t)(1 - \frac{S(t)}{K}) - \beta S(t)V(t) \\ \dot{I}(t) = -\bar{c}I(t) + \beta S(t)V(t) \\ \dot{V}(t) = -dV(t) + r\bar{c}I(t) \\ S(0) = S_0,\, I(0) = I_0,\, V(0) = V_0 \end{cases}$$

Where $\bar{c} = (1 - \zeta_{RTI})c$, and ζ_{RTI} measures the effect of therapy in reducing the natural death rate of infected cells, that way one obtains the third controlled system

$$\dot{x}(t) = F_3(x(t),\, u_3(t)) \Leftrightarrow \begin{cases} \dot{S}(t) = bS(t)(1 - \frac{S(t)}{K}) - \beta S(t)V(t) \\ \dot{I}(t) = -cI(t)(1 - u_3(t)) + \beta S(t)V(t) \\ \dot{V}(t) = -dV(t) + rcI(t)(1 - u_3(t)) \\ S(0) = S_0,\, I(0) = I_0,\, V(0) = V_0 \end{cases}$$

d) When all controls applied at once, one has :

$$\dot{x}(t) = F(x(t),\, u_i(t)); i = 1,\, 2,\, 3 \Leftrightarrow \begin{cases} \dot{S}(t) = bS(t)(1 - \frac{S(t)}{K}) - \beta S(t)V(t)(1 - u_2(t)) \\ \dot{I}(t) = -cI(t)(1 - u_3(t)) + \beta S(t)V(t)(1 - u_2(t)) \\ \dot{V}(t) = -dV(t)(1 + u_1(t)) + rcI(t)(1 - u_3(t)) \\ S(0) = S_0,\, I(0) = I_0,\, V(0) = V_0 \end{cases}$$

Our goal is to study the model response to each of those controls separately, then see what happens when all of them are applied at once.

In fact, we have incorporated time dependent drug efficacies using controls $u_i(\cdot)$, $i = 1, 2, 3$. Note that setting $u_i(\cdot) = 0$ or $u_i(\cdot) = 1$, $i = 1, 2, 3$ in (S) would give either a non disease model or an uncontrolled model (i.e dynamics of the disease without treatment). Note also that values of $u_i > 1$, for $i = 2, 3$ correspond to treatment with a cytotoxic[3]

[3]Cytotoxicity is the quality of being toxic to cells. Examples of toxic agents are a chemical substance, an immune cell or some types of venom

drug, which is not the case of u_i, indeed this control is supposed to affect only virus particles, without having any effects on healthy or even infected cells, that is why its value is bounded by a constant L that might be larger than 1.

In view of this, consider the set :

$$U = \left\{ \begin{array}{l} u_i(t) \text{ is Lebesgue measurable } i = \overline{1,\,3}; a \leq u_1(t) \leq L, (L > 1)\ , \\ \text{and } 0 < a \leq u_i(t) \leq b < 1, \text{ for } i = 2,\,3,\, t \in [0,\,T] \end{array} \right\}$$

As the control admissible set.

4. Local controllability

Let's start with a study of local controllability of systems (S_i) , $i = \overline{1,\,3}$ and (S_c) at all equilibrium points :

Proposition 3 All systems are uncontrollable around the origin and the infection-free equilibrium, for any measurable bounded controls $u_i \in U$, $i = \overline{1,\,3}$.

Proof

Put :

$$A_1 = \frac{\partial F_1}{\partial x} = \begin{pmatrix} b(1-\frac{2S}{K}) - \beta V & 0 & -\beta S \\ \beta V & -c & \beta S \\ 0 & rc & -d(1+u_1) \end{pmatrix},\ B_1 = \frac{\partial F_1}{\partial u_1} = \begin{pmatrix} 0 \\ 0 \\ -dV \end{pmatrix}$$

$$A_2 = \frac{\partial F_2}{\partial x} = \begin{pmatrix} b(1-\frac{2S}{K}) - \beta V(1-u_2) & 0 & -\beta S(1-u_2) \\ \beta V(1-u_2) & -c & \beta S(1-u_2) \\ 0 & rc & -d \end{pmatrix},\ B_2 = \frac{\partial F_2}{\partial u_2} = \begin{pmatrix} \beta SV \\ -\beta SV \\ 0 \end{pmatrix}$$

$$A_3 = \frac{\partial F_3}{\partial x} = \begin{pmatrix} b(1-\frac{2S}{K}) - \beta V & 0 & -\beta S \\ \beta V & -c(1-u_3) & \beta S \\ 0 & rc(1-u_3) & -d \end{pmatrix},\ B_3 = \frac{\partial F_3}{\partial u_3} = \begin{pmatrix} 0 \\ cI \\ -rcI \end{pmatrix}$$

And

$$A_c = \frac{\partial F}{\partial x} = \begin{pmatrix} b(1-\frac{2S}{K}) - \beta V(1-u_2) & 0 & -\beta S(1-u_2) \\ \beta V(1-u_2) & -c(1-u_3) & \beta S(1-u_2) \\ 0 & rc(1-u_3) & -d(1+u_1) \end{pmatrix},$$

$$B_c = \frac{\partial F}{\partial u_i} = \begin{pmatrix} 0 & \beta SV & 0 \\ 0 & -\beta SV & cI \\ -dV & 0 & -rcI \end{pmatrix},\ i = 1,\,2,\,3$$

With the simple remark that $B_{1,2,3,c}|_{(0,0,0)} = B_{1,2,3,c}|_{(K,0,0)} = 0$, and using the Kalman criterion for local controllability [15], one concludes the result.

We now consider that $R_0 > 1$ and discuss the controllability around the chronic equilibrium E^*, in all systems :

Proposition 4 When $R_0 > 1$ all four systems $(S_1), (S_2), (S_3), (S_c)$ are locally controllable around E^*. If and only if R_0 is different from the values $\frac{2d}{d+c}$ and $\frac{2b}{b+c}$.

Proof

1) Case of system (S_1)

To simplify calculus put :

$$\begin{cases} X = b(1 - \frac{2S}{K}) \\ Y = \beta V \\ Z = \beta S \\ T = d(1 + u_1) \end{cases},$$

That way :

$$A_1 = \begin{pmatrix} X - Y & 0 & -Z \\ Y & -c & Z \\ 0 & rc & -T \end{pmatrix}$$

In this case, the Kalman matrix $\Lambda_1 = \begin{pmatrix} B_1 & A_1B_1 & A_1^2B_1 \end{pmatrix}$ is given by :

$$\Lambda_1 = -dV \begin{pmatrix} 0 & -Z & -Z(X - Y) + ZT \\ 0 & Z & -YZ - cZ - TZ \\ 1 & -T & rcZ + T^2 \end{pmatrix}$$

And

$$\det \Lambda_1 = -dVZ^2 \begin{vmatrix} -1 & -(X - Y) + T \\ 1 & -Y - c - T \end{vmatrix}$$

$$\det \Lambda_1 = -dVZ^2 [X + c]$$

$\det \Lambda_1$ vanishes for the quantity $X = -c$

Replacing in $X = b(1 - \frac{2S}{K})$ by S^* the first chronic equilibrium coordinate, one obtains :

If $R_0 \neq \frac{2b}{b+c}$ then $\det \Lambda_1 \neq 0$ and $rg\Lambda_1 = 3$ so, the system is locally controllable around the chronic equilibrium for any measurable bounded control $u_1 \in U$.

2) Case of system (S_2)

Here, to facilitate calculus, put :

$$\begin{cases} X = b(1 - \frac{2S}{K}) \\ Y = \beta V(1 - u_2) \\ Z = \beta S(1 - u_2) \end{cases},$$

That way :

$$A_2 = \begin{pmatrix} X-Y & 0 & -Z \\ Y & -c & Z \\ 0 & rc & -d \end{pmatrix}$$

In this case, the Kalman matrix $\Lambda_2 = \begin{pmatrix} B_2 & A_2B_2 & A_2^2B_2 \end{pmatrix}$ is

$$\Lambda_2 = \beta SV \begin{pmatrix} 1 & X-Y & (X-Y)^2 + rcZ \\ -1 & Y+c & Y(X-Y-c) - c(c+rZ) \\ 0 & -rc & rc(Y+c+d) \end{pmatrix}$$

And

$$\begin{aligned} \det \Lambda_2 = \; & rc\beta SV \left[(Y+c)(Y+c+d) + Y(X-Y-c) - c(c+rZ) + \right. \\ & \left. (X-Y)(Y+c+d) + (X-Y)^2 + rcZ\right] \end{aligned}$$

$$\det \Lambda_2 = rc\beta SV \left[(Y+c+d)(X+c) + Y(X-Y-c) - c^2 + (X-Y)^2\right]$$

This finely yields :

$$\det \Lambda_2 = rc\beta SV \left[X^2 + (c+d)X + dc\right]$$

So, $\det \Lambda_2$ vanishes for two values of X : $-c$ and $-d$.

Recall that $X = b\left(1 - \frac{2S}{K}\right)$, replacing by the chronic equibrium coordinates gives us two values of R_0 for which vanishes :

$$R_0 = \frac{2b}{b+c} \text{ and } R_0 = \frac{2d}{d+c}$$

So, if (and only if) $R_0 \neq \frac{2b}{b+c}$ and $R_0 \neq \frac{2d}{d+c}$ then $rg\Lambda_2 = 3$, hence the system is locally controllable around the chronic equilibrium for any measurable bounded control u_2.

3) Case of system (S_3)

To facilitate calculus, let's put :

$$\begin{cases} X = b(1 - \frac{2S}{K}) \\ Y = \beta V \\ Z = \beta S \\ \alpha = c(1-u_3) \end{cases} .,$$

A_3 reads as :

$$A_3 = \begin{pmatrix} X-Y & 0 & -Z \\ Y & -\alpha & Z \\ 0 & r\alpha & -d \end{pmatrix}$$

Here : $\Lambda_3 = \begin{pmatrix} B_3 & A_3B_3 & A_3^2B_3 \end{pmatrix}$
One gets :

$$\Lambda_3 = cI \begin{pmatrix} 0 & rZ & rZ(-\alpha + X - Y - d) \\ 1 & -\alpha - rZ & \alpha^2 + r\alpha Z + rZ(Y + \alpha + d) \\ -r & r(\alpha + d) & -r\left[\alpha^2 + d\alpha + (rZ\alpha + d^2)\right] \end{pmatrix}$$

And

$$\det \Lambda_3 = cr^2 IZ \begin{vmatrix} 0 & 1 & -\alpha + X - Y - d \\ 1 & -\alpha - rZ & \alpha^2 + r\alpha Z + rZ(Y + \alpha + d) \\ -1 & \alpha + d & -\left[\alpha^2 + d\alpha + (rZ\alpha + d^2)\right] \end{vmatrix}$$

Basic calculus yields :

$$\det \Lambda_3 = cr^2 IZ \left[X\left(d - rZ\right) - Yd\right]$$

When replacing by the chronic equilibrium coordinates, one gets that $(d - rZ) = 0$ so :

$$\det \Lambda_3 = -\frac{b^2}{\beta} d^3 \left(1 - \frac{1}{R_0}\right)^2$$

In this case, the system (S_3) is locally controllable around the chronic equilibrium for any measurable bounded control u_3.
4) Case of system (S_c)
Recall that

$$B_c = \begin{pmatrix} 0 & \beta SV & 0 \\ 0 & -\beta SV & cI \\ -dV & 0 & -rcI \end{pmatrix}$$

In this case,

$$\det B_c = -dV(c\beta SVI) \neq 0$$

So the Kalman matrix $\Lambda = \begin{pmatrix} B_c & A_cB_c & A_c^2B_c \end{pmatrix}$ is of $rank = 3$. This means that the system (S_c) is also locally controllable around the chronic equilibrium for all measurable bounded controls u_i, $i = 1, 2, 3$.

In view of those results, all our systems (S_i), $i = 1, 2, 3, c$, are locally controllable around E^* if and only if R_0 is different from the two values in the set : $\left\{\frac{2d}{d+c}, \frac{2b}{b+c}\right\}$.

5. Optimal control

– Case of system (S_1)

We want to minimize the number of infected cells in the body, so consider the cost function :

$$J_I\left[u_1\right] = \min_{u_1 \in U} \int_0^T I(t)dt.$$

Using the Pontryaguin Maximum Principle (see [15]) to compute the optimal control one has the Hamiltonian of the system (S_1) as follows :

$$\begin{aligned} H(t,\, x,\, \lambda,\, u_1) = \quad & -I(t) + \lambda_1(t)\left(bS(t)(1-\tfrac{S(t)}{K}) - \beta S(t)V(t)\right) + \\ & \lambda_2(t)\left(-cI(t) + \beta S(t)V(t)\right) + \lambda_3(t)\left(-dV(t)(1+u_1(t)) + rcI(t)\right) \end{aligned}$$

And the corresponding adjoint equations :

$$\begin{cases} \dot{\lambda}_1(t) = -\frac{\partial H}{\partial S} = -\lambda_1(t)\left[b(1-\frac{2S(t)}{K}) - \beta V(t)\right] - \lambda_2(t)\beta V(t) \\ \dot{\lambda}_2(t) = -\frac{\partial H}{\partial I} = 1 + c\lambda_2(t) - rc\lambda_3(t) \\ \dot{\lambda}_3(t) = -\frac{\partial H}{\partial V} = \beta S(t)\lambda_1(t) - \beta S(t)\lambda_2(t) + d(1+u_1(t))\lambda_3(t) \\ \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0 \text{ are the transversality conditions} \end{cases}$$

The control u_1^* is optimal if it verifies the maximum principle :

$$H(t,\, x,\, \lambda,\, u_1^*) = \max_{u_1 \in U} H(t,\, x,\, \lambda,\, u_1).$$

The Hamiltonian being linear in the control, the optimal policy will be a combination between bang-bang control and singular control.

The Pontryaguin Maximum Principle leads to :

$$-dV(t)\lambda_3(t)u_1^*(t) = \max_{u_1 \in U} -dV(t)\lambda_3(t)u_1(t)$$

Put $\varphi\left(t\right) = -dV\left(t\right)\lambda_3\left(t\right)$ the switch function; recall that moments of switch are the zeros of function φ.

We get to the characterization of our optimal bang-bang control :

$$u_1^*(t) = \begin{cases} u_{\min} \text{ if } \phi(t) < 0 \\ u_{\max} \text{ if } \phi(t) > 0 \\ \text{undefined if } \phi(t) = 0 \end{cases}$$

d and V being always strictly positive, one has :

$$u_1^*(t) = \begin{cases} a \text{ if } \lambda_3(t) > 0 \\ L \text{ if } \lambda_3(t) < 0 \\ \text{undefined if } \lambda_3(t) = 0 \end{cases}$$

Taking a look in the derivative of φ, and considering that $\varphi(T) = \lambda_3(T) = 0$ one concludes that $\frac{\partial \varphi}{\partial t}$ vanishes for at most one $t^* \in \mathring{\Omega}$ and hence φ changes its sign at most once on Ω. So there is no singular control and the optimal control reduces to the bang-bang one.

Using the same method, one obtains the bang-bang optimal control for minimizing the level of free viruses in the blood using the cost function : $J_V[u_1] = \min_{u_1 \in U} \int_0^T V(t)dt$, and maximizing healthy cells using the cost function : $J_V[u_1] = \min_{u_1 \in U} \int_0^T V(t)dt$ in (S_1) the expression of the optimal control is unchanged, only expressions of the associated Hamiltonians and corresponding adjoint systems change, we omit them here for convenience.

– Case of system (S_2) and (S_3)

For the remaining systems, by the same way, we derive the expressions of the optimal bang-bang controls, summarized in what follows :

$$u_2^*(t) = \begin{cases} a \text{ if } \lambda_2(t) - \lambda_1(t) < 0 \\ b \text{ if } \lambda_2(t) - \lambda_1(t) > 0 \\ \text{undefined if } \lambda_2(t) - \lambda_1(t) = 0 \end{cases}$$

Here, we can use the fact that $\frac{\partial^2 H}{\partial u_2^2} = 0$ (the Hamiltonian being linear in the control) to conclude that there is no singular control.

$$u_3^*(t) = \begin{cases} a \text{ if } r\lambda_3(t) - \lambda_2(t) < 0 \\ b \text{ if } r\lambda_3(t) - \lambda_2(t) > 0 \\ \text{undefined if } r\lambda_3(t) - \lambda_2(t) = 0 \end{cases}$$

Again, one obtains the same expressions of u_2^*, and u_3^* when minimizing the level of free viruses and maximizing healthy cells in (S_2), and (S_3) respectively, notice that expressions of Hamiltonians and adjoint systems change depending on the associate case, we omit them here to avoid repetition.

– Case of system (S_c)

The Hamiltonian associated with system (S_c) is :

$$\begin{aligned} H(t, X, \lambda, u_c) = \; & L(t) + \lambda_1(t)\left[bS(t)\left(1 - \tfrac{S(t)}{K}\right) - \beta S(t)V(t)(1 - u_2(t))\right] \\ & + \lambda_2(t)\left[-cI(t)(1 - u_3(t)) + \beta S(t)V(t)(1 - u_2(t))\right] \\ & + \lambda_3(t)\left[rcI(t)(1 - u_3(t) - dV(t)(1 + u_1(t))\right] \end{aligned}$$

Where $L(t)$ represents the objective functional to optimize, i.e :

$$L(t) = \begin{cases} -I(t) \text{ when minimizing the infected cells population} \\ -V(t) \text{ when minimizing the virus particles number} \\ S(t) \text{ when maximizing the healthy cells population} \end{cases}$$

The associated adjoint system when minimizing infected cells population is :

$$(S'_{Ic}) \begin{cases} \dot{\lambda}_1(t) = -\frac{\partial H}{\partial S} = \left[\beta V(t)(1-u_2(t)) - b\left(1-\frac{2S(t)}{K}\right)\right]\lambda_1(t) - \\ \qquad [\beta V(t)(1-u_2(t))]\,\lambda_2(t) \\ \dot{\lambda}_2(t) = -\frac{\partial H}{\partial I} = [c(1-u_3(t))]\,\lambda_2(t) - [rc(1-u_3(t))]\,\lambda_3(t) + 1 \\ \dot{\lambda}_3(t) = -\frac{\partial H}{\partial V} = [\beta S(t)(1-u_2(t))]\,\lambda_1(t) - [\beta S(t)(1-u_2(t))]\,\lambda_2(t) + \\ \qquad [d(1+u_1(t))]\,\lambda_3(t) \\ \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0 \text{ are the transversality conditions} \end{cases}$$

Whereas when minimizing the virus particles number, the associated adjoint system is :

$$(S'_{Vc}) \begin{cases} \dot{\lambda}_1(t) = -\frac{\partial H}{\partial S} = \left[\beta V(1-u_2(t)) - b\left(1-\frac{2S(t)}{K}\right)\right]\lambda_1(t) - \\ \qquad [\beta V(t)(1-u_2(t))]\,\lambda_2(t) \\ \dot{\lambda}_2(t) = -\frac{\partial H}{\partial I} = [c(1-u_3(t))]\,\lambda_2(t) - [rc(1-u_3(t))]\,\lambda_3(t) \\ \dot{\lambda}_3(t) = -\frac{\partial H}{\partial V} = [\beta S(t)(1-u_2(t))]\,\lambda_1(t) - [\beta S(t)(1-u_2(t))]\,\lambda_2(t) + \\ \qquad [d(1+u_1(t))]\,\lambda_3(t) + 1 \\ \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0 \text{ are the transversality conditions} \end{cases}$$

And, when maximizing the healthy cells populations, one gets :

$$(S'_{Sc}) \begin{cases} \dot{\lambda}_1(t) = -\frac{\partial H}{\partial S} = \left[\beta V(1-u_2(t)) - b\left(1-\frac{2S(t)}{K}\right)\right]\lambda_1(t) - \\ \qquad [\beta V(t)(1-u_2(t))]\,\lambda_2(t) - 1 \\ \dot{\lambda}_2(t) = -\frac{\partial H}{\partial I} = [c(1-u_3(t))]\,\lambda_2(t) - [rc(1-u_3(t))]\,\lambda_3(t) \\ \dot{\lambda}_3(t) = -\frac{\partial H}{\partial V} = [\beta S(t)(1-u_2(t))]\,\lambda_1(t) - [\beta S(t)(1-u_2(t))]\,\lambda_2(t) + \\ \qquad [d(1+u_1(t))]\,\lambda_3(t) \\ \lambda_1(T) = \lambda_2(T) = \lambda_3(T) = 0 \text{ are the transversality conditions} \end{cases}$$

By the Pontryagin Maximum Principle to compute the optimal control, one gets :

$$u_1^*(t) = \begin{cases} a \text{ if } \lambda_3(t) > 0 \\ L \text{ if } \lambda_3(t) < 0 \\ \text{undefined if } \lambda_3(t) = 0 \end{cases}$$

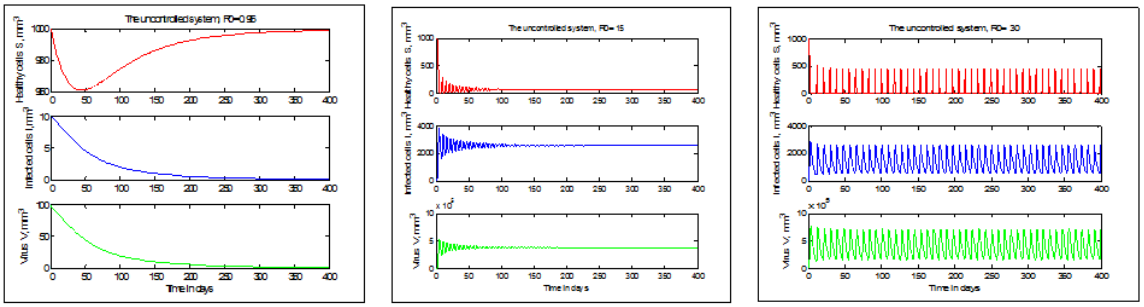
$$u_2^*(t) = \begin{cases} a \text{ if } \lambda_2(t) - \lambda_1(t) < 0 \\ b \text{ if } \lambda_2(t) - \lambda_1(t) > 0 \\ \text{undefined if } \lambda_2(t) - \lambda_1(t) = 0 \end{cases}$$

$$u_3^*(t) = \begin{cases} a \text{ if } r\lambda_3(t) - \lambda_2(t) < 0 \\ b \text{ if } r\lambda_3(t) - \lambda_2(t) > 0 \\ \text{undefined if } r\lambda_3(t) - \lambda_2(t) = 0 \end{cases}$$

6. Numerical simulations

6.1. The uncontrolled system

We begin by simulate the system without any control input to visualize its behavior, and we distinguish three cases depending on the parameter R_0, as resumed in propositions 1, initial conditions are considered as $S_0 = 1000$, $I_0 = 10$, $V_0 = 100$ [estimated], $T = 400$:



(a) (b) (c)

Fig. 1 – The uncontrolled system (S).

Fig. 1 shows :

- In (a) the dynamics of healthy and infected cells, as well as free virus in the uncontrolled model (S) with $R_0 = 0.96 < 1$, one sees clearly that the infection dies out. Here the parameters chosen were : $d = 5$, $c = 0.24$, $\beta = 0.000024$, $b = 0.03$, $r = 200$, $K = 1000$.
- In (b), global stability when using the parameters $d = 5$, $c = 0.24$, $\beta = 0.000024$, $b = 0.03$, $r = 1500$, $K = 1000$ to get $1 < (R_0 = 15) < (R = 15.90)$
- In (c) a periodic solution when using parameters of table 1 in the uncontrolled model (S) ; here : $(R_0 = 30) > (R = 15.90) > 1$.

6.2. The controlled system

Now, we discuss the numerical solutions of the optimality system and the corresponding optimal controls, and give interpretations for various cases.

Figures are obtained by solving the optimality system consisting of 6 ODEs from the state and the corresponding adjoint equations. An iterative method is used for solving the optimality system. We start by solving the state equations with a guess for the control over the simulated time using a forward (because of initial state conditions) fourth order Runge-Kutta scheme, followed by a backward (because of the final adjoint conditions) implicit Euler scheme for the adjoint equations and using the current iteration solution of the state equations. Then the controls are updated from the characterization (1). This process is repeated and iterations are stopped if the values of unknowns at the previous iteration are very close to the ones at present iteration.

Parameters of table 1 were used, Initial conditions are considered as $S_0 = 1000$, $I_0 = 10$, $V_0 = 100$ [estimated], $T = 50$, final adjoint variables are zero in all cases, parameters used were : $a = 0.01$ and $b = 0.9$, $L = 5$ [estimated] in all cases.

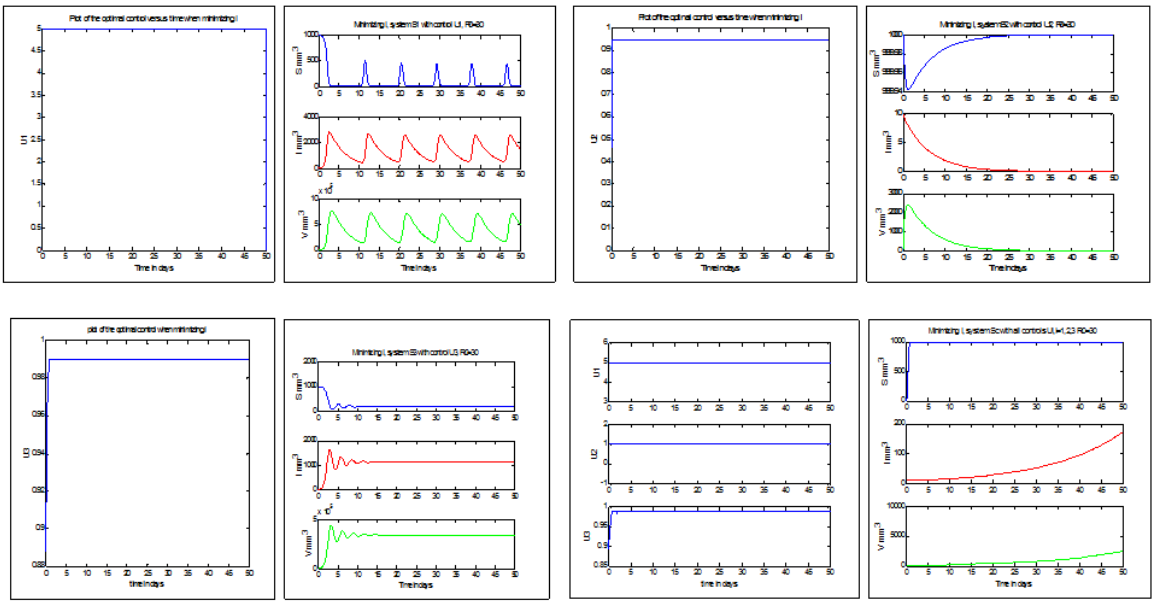


Fig. 2 – The controlled system (S_i) when minimizing infected cells population, $i = 1, 2, 3, c$.

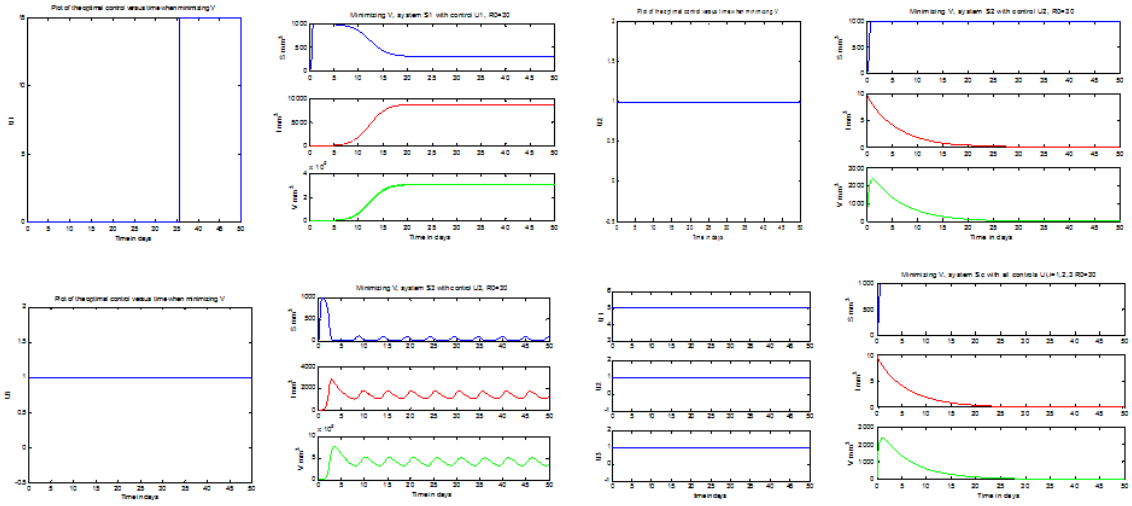


Fig. 3 – The controlled system (S_i) when minimizing virus population, $i = 1, 2, 3, c$.

Fig. 2. shows on the left hand side the plot of optimal controls $u_i, i = \overline{1,3}$, as function of time, and on the right hand side the corresponding densities of healthy and infected cells as well as free viruses circulating in the blood in the associated controlled system when minimizing the infected cells population (When u_i is active, then $u_j = 0$ for $j \neq i$, $i, j = \overline{1,3}$).

Despite the fact that the first control is always in its maximal value, and reduces efficiently the number of infected cells, it is not very effective on the overall infection ; this

might be due to the fact that the number of new born viruses still is much greater than the modified clearance rate.

On the other hand, the second control, which is also always in its maximum value, is very effective and has an instantaneous effect in turning over the viruses as well as infected cells, and driving the healthy cells to the top value.

The third control is in its maximal value, and is very effective in reducing the number of infected cells as wanted, after this, healthy cells gets stabilized in a low level and viruses in a relatively high level, that is why this control is considered not to be very effective.

When all controls are applied together, infection is well controlled, certainly thanks to the second control more than any other one.

Figure 3 shows on the left hand side the plot of optimal controls $u_i, i = \overline{1,3}$, as function of time, and on the right hand side the corresponding densities of healthy and infected cells as well as free viruses circulating in the blood in the associated controlled system when minimizing the virus population (When u_i is active, then $u_j = 0$ for $j \neq i, i, j = \overline{1,3}$)

The first control is on its minimal value until day 35 when it jumps to its maximal value. It is quite effective in reducing the number of free viruses that stabilizes around $3 \times 10^5 mm^3$ the overall infection, wherever, is derived to a point where healthy cells get stabilized in a quite low level and infected cells as well as viruses get stabilized in a high level.

Once again, control u_2 is very effective, but control u_3 here gives very bad results in comparison with the "minimizing infected cells" case, because oscillations occur driving healthy cells to a minimal threshold and infected as well as viruses to a higher level, the increase of infected cells can be a consequence of the cellular division also, not only a direct effect on infection ; that is why u_3 can be considered as "not very effective".

Finely, using all controls together is very effective.

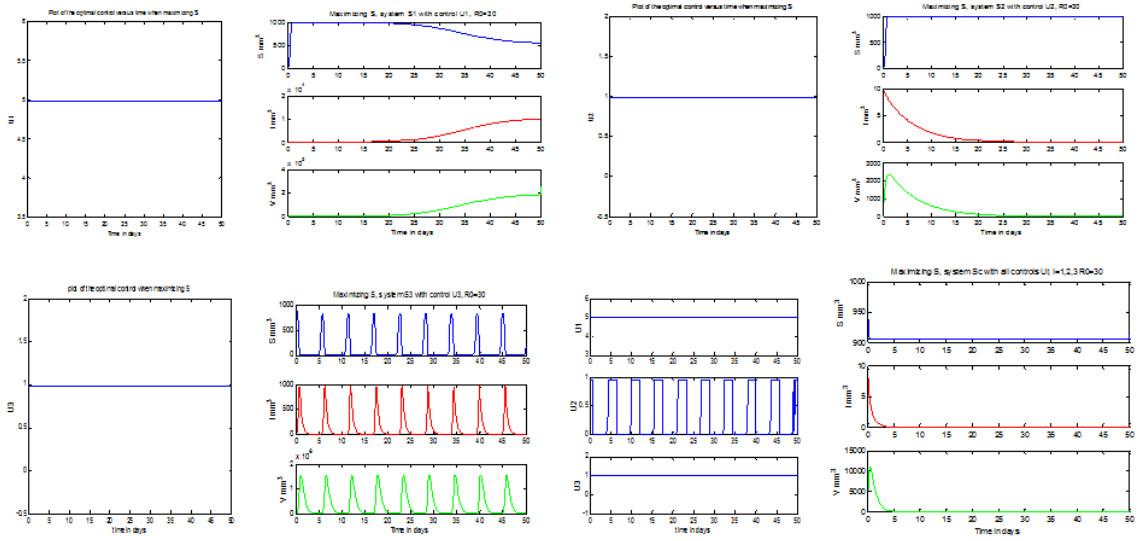


Fig. 4 – The controlled system (S_i) when maximizing healthy cells population, $i = 1, 2, 3, c$.

Figure 4 shows on the left hand side the plot of optimal controls $u_i, i = \overline{1,3}$ as function of time, and on the right hand side the corresponding densities of healthy and infected cells as well as free viruses circulating in the blood in the associated controlled system when maximizing healthy cells population (When u_i is active, then $u_j = 0$ for $j \neq i$, $i, j = \overline{1,3}$)

When maximizing healthy cells, control u_1 works pretty well and keeps the infection away until day 30, where one can notice a decline in healthy cells population and an instantaneous increase in infected cells and virus population driving the infection to move forward.

Control u_2 is very effective as usual, but control u_3 seems to be absolutely not effective, even if the number of infected cells and free virus are reduced, the oscillations occur which precludes that the infection is not controlled.

When all controls are effective, the infection is once again well controlled.

7. Conclusion

A mathematical model that deals with the spread of infection by the Human Immunodeficiency Virus of type one (HIV-1) in vivo in which the evolution of healthy cells has a logistic growth was considered, local controllability was studied and the optimal bang-bang policy using the Pontryagin Maximum Principle was performed to achieve three goals : firstly to minimize the number of infected cells into the body, secondly to minimize the number of free virus particles circulating in the blood and finely, to maximize the number of healthy $CD4^+$ T-cells. This was done using three decoupled controls. After this, those controls were applied at once on the system. Numerical simulations were given to compare all cases.

Our comparative study on the controls is of great importance, knowing that adherence to the "Highly Active Antiretroviral Therapy" (HAART) is a significant problem, many patients have troubles with the dosing requirement, in addition, side effects of such therapies can be severe ; a regimen that could reduce dosage requirements or the drugs taken while maintaining control over viral plasma levels might not only increase patient adherence but also the overall health of the patient by reducing side effects.

According to these simulations, it comes that u_2, the control applied to compromise the viral entry to the cell is the "best" way to 1/minimize infected cells population, 2/ maximize healthy cells population, and even 3/ minimize free circulating virus ; it is now a real question for scientists to know if the use of other controls really decreases the overall infection in a significant manner, or if it only increases treatment resistance and side effects. Balance between the use of different treatments and clinical situation of the concerned infected being has to be found.

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