A Scalable Engineering Combination Therapies for Evolutionary Dynamic of Macrophages

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Abstract The study of human immunodeficiency virus (HIV) has been the subject of massive scientific research in recent years. Some works have focused on the evolution of the virus mutations developed against the immune system or the combination design therapy. But most of these models are too complex to analyze in details and to design an optimal combination therapy. The main objective of this paper is to analyse the stability and optimal control of a HIV combination therapy nonlinear model, which takes into account the mutations and latent cells. We use a $\mathcal{L}_1$ controller that stabilize the evolutionary dynamics of HIV disease. Because of the positive nature of the system, this problem can be solved with a scalable iterative algorithm that finds the best medication.Therefore, following recent work of V. Jonsson and R. Murray we introduce a similar algorithm to solve the combination therapy design problem. We obtain efficient results for this nonlinear model and thereby show that optimal control theory can be applied on more complex and realistic models.

Keywords HIV infection · Stability · Combination of therapies · Optimal control

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1 Introduction

The Human Immunodeficiency virus (HIV) is still one of the main public health problem across the world, with more than 1 million deaths in 2018, and 379 million people living with HIV. It has been progressively understood that mutations and latent cells are the main factors that complicate the treatment of people infected with HIV. Recently, several mathematical models have been proposed, some describe the interactions between viruses and the immune system or antiretroviral therapy, in order to understand the evolution of mutations during the infection of the body by the HIV virus [1–5]. HIV mutations make ineffective the anti-HIV monotherapy, this phenomenon has received considerable attention in the biology and biomedical communities. The resistance of HIV to a monotherapy has led to use a combination of therapies to combat the progression of the disease, especially against mutations. An effective combination of therapies can stop the evolution of mutations, but it can not cure the disease. In addition, a combination of therapies can cause very harmful side effects (neurological disorders, acute diarrhea, metabolic disorders) if the dose is exceeded, therefore it is necessary to optimize the combination therapy to find the best dose possible. In this context, optimal control techniques have allowed a better understanding on the application of the therapy [6–9]. It is also necessary for people infected with HIV to take antiretroviral therapies for life, because if they stop the treatment the disease may be reactivated because of the existence of latent cells, such as macrophages. Latently infected cells are classically defined as cells that contain integrated HIV DNA and are transcriptionally silent, but upon activation are capable of producing infectious virus. Macrophages play a crucial role in innate and adaptative immunity in response to microorganisms. They are an important cellular target during HIV-1 infection and the infected cells are considered as a long-term active reservoir, which play an important role in the final stages of the infection, the AIDS phase.

In recent years, enormous progress has been made in the mathematical modeling of the evolution of HIV and the application of combination therapies [1, 6–8, 10–12]. However, interactions between viruses and the immune system are poorly understood, as they are very complicated to be modeled. The models of mutations are complicated to analyze, both theoretically and numerically because of the number of equations and parameters they present [1, 4]. In addition, most existing models are not able to reproduce the three stages of infection (initial acute infection, a long asymptomatic period and AIDS phase) through numerical simulation, but they just reproduce the first two. Recently, in 2007 Hadjiandreou and al have proposed the first HIV ODE model time invariant parameters that can represent the clinical course of HIV. The model proposed by Hadjiandreou and al was very sensitive to the variation of parameters, it is in this sense that Esteban A. Hernandez-Vargas and Richard H. Middleton [13] have studied a simplified model of Hadjiandreou and al. Their model besides being robust to the variation of the parameters can also reproduce the three stages of the evolution of HIV.

The main objective of this paper is the study of the macrophages model proposed by Esteban A. Hernandez-Vargas and Richard H. Middleton and more precisely the stability analysis of the proposed model. Then we add the mutations and the combination therapies, which are modeled as a Hill function. Finally we apply the optimal control techniques to our nonlinear model, which take in account the mutations, CD4+ T cell, macrophages and the combination therapies. We use a $\mathcal{L}_1$ controllers that stabilize the evolutionary dynamics of HIV disease. Because of the positive nature of the system, this problem can be solved with a scalable iterative algorithm that finds the best medication.Therefore, following recent work of V. Jonsson and R. Murray [10–12] we introduce a similar algorithm to solve the combination therapy design problem. The model proposed by V. Jonsson and R. Murray besides being simple, is linear and just takes into account the evolution of mutations. Despite the complexity of our nonlinear model, with the theory of optimal control we obtain efficient and realistic results.

2 Mathematical Models

In this part we present the mathematical model proposed in [14] and study the behavior of the model around its equilibrium points.This model has five state variables: uninfected $CD4+T$ cells (T), infected $CD4+T$ cells (T^*), uninfected macrophages (M), infected macrophages (M^*) and viral load (V). In this model, we assumed that the $CD4+T$ cells and macrophages, that are the main targets of the virus are produced respectively by the thymus at a constant rate S_T and S_M and both can die respectively at the rate δ_T and δ_M. $CD4+T$ cells become $CD4+T$ cells infected at a speed $k_T T V$ and the macrophages at a speed $k_M M V$. Infected $CD4+T$ cells and infected macrophages, respectively, have the following mortality rates δ_{T^*} and δ_{M^*} and the viral load is produced at the rates $P_T T^*$ and $P_M M^*$ by the infected CD4+ T cells and infected macrophages and the rate of degradation of the virus is δ_V. So we get the following system of differential equations:

$$\begin{cases} \dot{T} &= s_T - k_T T V - \delta_T T, \\ \dot{T^*} &= k_T T V - \delta_{T^*} T^*, \\ \dot{M} &= s_M - k_M M V - \delta_M M, \\ \dot{M}^* &= k_M M V - \delta_{M^*} M^*, \\ \dot{V} &= p_T T^* + p_M M^* - \delta_V V. \end{cases} \tag{2.1}$$

The values $\frac{1}{\delta_T}$, $\frac{1}{\delta_{T^*}}$, $\frac{1}{\delta_M}$, $\frac{1}{\delta_{M^*}}$ and $\frac{1}{\delta_V}$ represent, respectively, the lifespan of uninfected $CD4+T$ cells, infected $CD4+T$ cells, uninfected macrophages, infected macrophages and the virus.

2.1 Stability Analysis of the System

The model (2.1) was proposed and studied by Esteban A. Hernandez-Vargas in [14]. In the analysis of the stability of the model we will use a different approach, which will be based on the basic reproductive ratio of the epidemic noted R_0 (see Definition 2.1). We will carry out a detailed study on the stability of the system around its equilibrium points.

2.1.1 Existence of the Equilibrium Points

To determine the equilibrium points we must solve the following equation:

$$\begin{cases} \dot{T} &= 0 \\ \dot{T^*} &= 0 \\ \dot{M} &= 0 \\ \dot{M^*} &= 0 \\ \dot{V} &= 0 \end{cases} \Longleftrightarrow \begin{cases} s_T - k_T T V - \delta_T T &= 0 \\ k_T T V - \delta_{T^*} T^* &= 0 \\ s_M - k_M M V - \delta_M M &= 0 \\ k_T M V - \delta_{M^*} M^* &= 0 \\ p_T T^* + p_M M^* - \delta_V V &= 0 \end{cases}$$

after calculation, we obtain the following results:

$$T = \frac{s_T}{k_T V + \delta_T}, \quad T^* = \frac{k_T s_T}{\delta_{T^*}} \frac{V}{k_T V + \delta_T},$$

$$M = \frac{s_M}{k_M V + \delta_T}, \quad M^* = \frac{k_M s_M}{\delta_{M^*}} \frac{V}{k_M V + \delta_M}.$$

where V is the solution of the polynomial

$$\frac{p_T k_T s_T}{\delta_{T^*}} \frac{V}{k_T V + \delta_T} + \frac{p_M k_M s_M}{\delta_{M^*}} \frac{V}{k_M V + \delta_M} - \delta_V V = 0,$$

this equation is in the form

$$aV^3 + bV^2 + cV = 0$$

and admits three solutions

$$V_0 = 0, \quad V_1 = \frac{-b + \sqrt{b^2 - 4ac}}{2a}, \quad V_2 = \frac{-b - \sqrt{b^2 - 4ac}}{2a},$$

where

$a = \delta_{T^*} \delta_{M^*} \delta_V k_T k_M$,
$b = \delta_{T^*} \delta_{M^*} \delta_V (k_M \delta_T + k_T \delta_M) - p_T k_T s_T k_M \delta_{M^*} - p_M k_M s_M k_T \delta_{T^*}$,
$c = \delta_{T^*} \delta_{M^*} \delta_V \delta_T \delta_M - p_T k_T s_T \delta_M \delta_{M^*} - p_M k_M s_M \delta_{T^*} \delta_T$.

In conclusion the system (2.1) admits three equilibrium points that we will note $X_0 = (T_0, T_0^*, M_0, M_0^*, V_0)$, $X_1 = (T_1, T_1^*, M_1, M_1^*, V_1)$ and $X_2 = (T_2, T_2^*, M_2, M_2^*, V_2)$.

Remark X_0 represents the equilibrium point without infection and it exists when $V_0 = 0$, in other words, when the viral load is zero. We have

$$T_0(t) = \frac{s_T}{\delta_T} + \lambda_T \exp(-\delta_T t), \quad M_0(t) = \frac{s_M}{\delta_M} + \lambda_M \exp(-\delta_M t),$$

$$T_0^* = 0, \qquad M_0^* = 0.$$

So when $V_0 = 0$, $\lim_{t\to\infty} T_0(t) = \frac{s_T}{\delta_T}$ and $\lim_{t\to\infty} M_0(t) = \frac{s_M}{\delta_M}$.

The equilibrium points X_1 and X_2 exist if and only if we have respectively $V_1 > 0$ and $V_2 > 0$, because we can not have a negative viral load for biological reasons.

Definition 2.1 The basic reproductive ratio of the epidemic noted R_0 is the total amount of healthy cells that an infected $CD4 + T$ cell and an infected macrophage cell can infect during HIV evolution.

In our model an infected CD4 + T cell that has a life expectancy $\frac{1}{\delta_{T^*}}$ produces $k_T p_T$ virions, which have a life expectancy $\frac{1}{\delta_V}$ will infect some of the s_T healthy cells, which have a lifetime of $\frac{1}{\delta_T}$. So, an infected $CD4 + T$ cell can infect $R_1 = \frac{p_T k_T s_T}{\delta_{T^*}\delta_T\delta_V}$ healthy cells and an infected macrophage, by analogy can infect $R_2 = \frac{p_M k_M s_M}{\delta_{M^*}\delta_M\delta_V}$. Finally, the basic reproductive ratio of the epidemic,

$$R_0 = R_1 + R_2 = \frac{p_T k_T s_T}{\delta_{T^*}\delta_T\delta_V} + \frac{p_M k_M s_M}{\delta_{M^*}\delta_M\delta_V}.$$

Proposition 2.2 *If there is an infection* $(V > 0)$*, the system* (2.1) *has a single equilibrium point and this point exists if and only if* $c < 0$ *so, if and only if*

$$R_0 = \frac{p_T k_T s_T}{\delta_{T^*}\delta_T\delta_V} + \frac{p_M k_M s_M}{\delta_{M^*}\delta_M\delta_V} > 1.$$

Proof We assume there is infection $(V > 0)$ and that $c < 0$, it is clear that $-b + \sqrt{b^2 - 4ac} > 0$ and $-b - \sqrt{b^2 - 4ac} < 0$ whatever the value taken by b, because $a > 0$. So only the point X_1 exists $(V_1 > 0)$.

If $c > 0$ we have,

$$R_0 = \frac{p_T k_T s_T}{\delta_{T^*}\delta_T\delta_V} + \frac{p_M k_M s_M}{\delta_{M^*}\delta_M\delta_V} < 1.$$

If b takes positive values, then we get $V_1 < 0$ and $V_2 < 0$, so neither X_1 nor X_2 exists.

If $b < 0$, from the expression of b noted above the following condition is obtained

$$\frac{p_T k_T s_T}{\delta_{T^*}\delta_T\delta_V}\frac{k_M}{k_M + k_T\frac{\delta_M}{\delta_T}} + \frac{p_M k_M s_M}{\delta_{M^*}\delta_M\delta_V}\frac{k_T}{k_T + k_M\frac{\delta_T}{\delta_M}} > 1.$$

This result is in contradiction with the fact $c > 0$, because we have $R_0 < 1$.

Now let's suppose that $c = 0$, it means that $R_0 = 1$, so we have $\frac{p_T k_T s_T}{\delta_{T^*}\delta_T\delta_V} < 1$ and $\frac{p_M k_M s_M}{\delta_{M^*}\delta_M\delta_V} < 1$. We obtain from the equation $aV^3 + bV^2 + cV = 0$, $V = \frac{-b}{a}$,

$$\begin{aligned} V = -\frac{b}{a} &= \frac{p_T k_T s_T k_M \delta_{M^*}}{\delta_{T^*}\delta_{M^*}\delta_V k_M k_T} + \frac{p_M k_M s_M k_T \delta_{T^*}}{\delta_{T^*}\delta_{M^*}\delta_V k_M k_T} - \frac{\delta_{T^*}\delta_{M^*}\delta_V(k_M\delta_T + k_T\delta_M)}{\delta_{T^*}\delta_{M^*}\delta_V k_M k_T} \\ &= \frac{p_T k_T s_T}{\delta_{T^*}\delta_T\delta_V} \times \frac{\delta_T}{k_T} + \frac{p_M k_M s_M}{\delta_{M^*}\delta_M\delta_V} \times \frac{\delta_M}{k_M} - \frac{\delta_T}{k_T} - \frac{\delta_M}{k_M} \\ &\leq \frac{\delta_T}{k_T} + \frac{\delta_M}{k_M} - \frac{\delta_T}{k_T} - \frac{\delta_M}{k_M} \\ &\leq 0. \end{aligned}$$

Remark If $R_0 = \frac{p_T k_T s_T}{\delta_{T^*}\delta_T\delta_V} + \frac{p_M k_M s_M}{\delta_{M^*}\delta_M\delta_V} \leq 1$, it means that $c \geq 0$, b is necessarily nonnegative ($b \geq 0$) and there is not infection.

Finally, if there is an infection ($V > 0$) only the equilibrium point X_1 define by $V_1 = \frac{-b+\sqrt{b^2-4ac}}{2a}$, such as $c < 0$, that exists. □

2.1.2 Stability of Equilibrium Points

We will study the stability of the uninfected equilibrium point $X_0 = (T_0, T_0^*, M_0, M_0^*, V_0)$ and the infected equilibrium point $X_1 = (T_1, T_1^*, M_1, M_1^*, V_1)$, where

$$T_0 = \frac{s_T}{\delta_T}, \quad T_0^* = 0, \quad M_0 = \frac{s_M}{\delta_M}, \quad M_0^* = 0, \quad V_0 = 0,$$

$$T_1 = \frac{s_T}{k_{T_1}V_1 + \delta_T}, \quad T_1^* = \frac{k_T s_T}{\delta_{T^*}}\frac{V_1}{k_T V_1 + \delta_T},$$

$$M_1 = \frac{s_M}{k_M V_1 + \delta_T}, \quad M_1^* = \frac{k_M s_M}{\delta_{M^*}}\frac{V_1}{k_M V_1 + \delta_M}.$$

We start with the first equilibrium point X_0.

Proposition 2.3 *The compact set*
$\Gamma = \{(T, T^*, M, M^*, V) \in \mathbb{R}^5 : 0 \leq T + T^* \leq \frac{s_T}{\delta_T}$,
$0 \leq M + M^* \leq \frac{s_M}{\delta_M}$, $V \leq K$, $K > 0\}$ *is a positive invariant set for the system* (2.1).

Proof Let Φ_t be the flow of the system (2.1), the compact set Γ is a positive invariant set for the system (2.1) if $\forall\ Y = (y_1, y_2, y_3, y_4, y_5) \in \Gamma$, we have $\Phi_t(Y) \in \Gamma$ for $\forall\ t > 0$. So we have,

$$\begin{cases} \dot{y_1} = s_T - k_T y_1 y_5 - \delta_T y_1, \\ \dot{y_2} = k_T y_1 y_5 - \delta_{T^*} y_2, \\ \dot{y_3} = s_M - k_M y_3 y_5 - \delta_M y_3, \\ \dot{y_4} = k_M y_3 y_5 - \delta_{M^*} y_4, \\ \dot{y_4} = p_T y_2 + p_M y_4 - \delta_V y_5. \end{cases}$$

$\dot{y_1} + \dot{y_2} = s_T - \delta_T y_1 - \delta_{T^*} y_2 \leq s_T - \delta_T(y_1 + y_2)$, because the mortality rate of infected cells is higher than the mortality rate of uninfected cells ($\delta_{T^*} > \delta_T$), so if we pose $Y_1 = y_1 + y_2$ we get $\dot{Y_1} \leq s_T - \delta_T Y_1$, Finally we find $Y_1 \leq \frac{s_T}{\delta_T} + (Y_1(0) - \frac{s_T}{\delta_T}) exp(-\delta_T t)$, we can assume that when $t = 0$, the number of infected CD4 + T cells is negligible and the concentration of uninfected CD4 + T cells is less than s_T/δ_T. So we get, $Y_1(0) < \frac{s_T}{\delta_T}$ and $Y_1 = y_1 + y_2 \leq \frac{s_T}{\delta_T}$. By analogy, we also have $Y_2 = y_3 + y_4 \leq \frac{s_M}{\delta_M}$, since the viral load is bounded, so there exists a real $K > 0$ such that $y_5 \leq K$. We conclude that $\Phi_t(Y) \in \Gamma$, hence Γ is a positive invariant set for the system (2.1). □

Theorem 2.4 *The uninfected equilibrium point X_0 is globally asymptotically stable in Γ if $R_0 \leq 1$ and is unstable if $R_0 > 1$.*

Proof Before proving the theorem (2.4) let us recall the Lyapunov–Lasalle theorem.

Theorem 2.5 *Let $\Omega \subset D \subset \mathcal{R}^n$ be a compact positively invariant set with respect to the system dynamics* (1). *Let $V : D \longrightarrow \mathcal{R}^n$ be a continuously differentiable function such that $\dot{V}(x(t)) \leq 0$ in Ω. Let $E \subset \Omega$ be the set of all points in Ω where $\dot{V}(x) = 0$. Let $H \subset E$ be the largest invariant set in E. Then every solution starting in Ω approaches M as $t \longrightarrow \infty$.*

Let's put

$$F(T, T^*, M, M^*, V) = \frac{p_T}{\delta_T^*} T^* + \frac{p_M}{\delta_M^*} M^* + V,$$

$F(T, T^*, M, M^*, V)$ is a Lyapunov function for the nonlinear system (2.1) and we have $\dot{F} = [\frac{p_T k_T T}{\delta_{T^*} \delta_V} + \frac{p_M k_M M}{\delta_{M^*} \delta_V} - 1]\delta_V V$, since $T \leq \frac{s_T}{\delta_T}$ and $M \leq \frac{s_M}{\delta_M}$, then we get $\dot{F} \leq [\frac{p_T k_T s_T}{\delta_{T^*} \delta_T \delta_V} + \frac{p_M k_M s_M}{\delta_{M^*} \delta_M \delta_V} - 1]\delta_V V$. It is obvious that if $R_0 \leq 1$ we obtain $\dot{F} \leq 0$. Now we suppose that H is the set of solutions of the system where $\dot{F} = 0$, we can see that all paths in Γ approach the largest positively invariant subset of the

set H thanks to the Lyapunov–Lasalle Theorem. So, when $V = 0$ we have on the boundary of Γ,

$$T(t) = \frac{s_T}{\delta_T} + \lambda_T \exp(-\delta_T t), \quad M(t) = \frac{s_M}{\delta_M} + \lambda_M \exp(-\delta_M t),$$

$$\lim_{t\to\infty} T(t) = \frac{s_T}{\delta_T}, \quad \lim_{t\to\infty} M(t) = \frac{s_M}{\delta_M}.$$

$$T^* = 0, \qquad M^* = 0.$$

Hence all solution paths in Γ converge asymptotically towards the uninfected equilibrium point X_0.

To demonstrate the instability of the uninfected equilibrium point, we must calculate the Jacobian matrix of the system (2.1). This Jacobian Matrix evaluated to the point X_0 is defined as follows

$$J(X_0) = \begin{pmatrix} -\delta_T & 0 & 0 & 0 & -k_T T_0 \\ 0 & -\delta_T^* & 0 & 0 & k_T T_0 \\ 0 & 0 & -\delta_M & 0 & -k_M M_0 \\ 0 & 0 & 0 & -\delta_M^* & k_M M_0 \\ 0 & p_T & 0 & p_M & -\delta_V \end{pmatrix}.$$

Let $P_{J(X_0)}(x) = det(J(X_0) - xI_5)$ be the characteristic polynomial of $J(X_0)$. After calculation we get

$$P_{J(X_0)}(x) = -(\delta_T + x)(\delta_M + x)A(x)$$

where $A(x)$ is in the following form

$$A(x) = x^3 + \alpha x^2 + \beta x + \gamma,$$

$\alpha = \delta_T^* + \delta_M^* + \delta_V$,
$\beta = \delta_T^*\delta_M^* + \delta_T^*\delta_V + \delta_M^*\delta_V - \frac{p_T k_T s_T}{\delta_T} - \frac{p_M k_M s_M}{\delta_M}$,
$\gamma = \delta_T^*\delta_M^*\delta_V - \frac{p_T k_T s_T \delta_M^*}{\delta_T} - \frac{p_M k_M s_M \delta_T^*}{\delta_M}$.

Finally, the uninfected equilibrium point X_0 is asymptotically stable if and only if all the roots of the polynomial $P_{J(X_0)}(x)$ have a real negative part and that is possible if the Routh–Hurwitz stability criterion is satisfied for the polynomial $A(x)$. The roots of $A(x)$ have a negative real part if and only if we have $\alpha > 0$, $\gamma > 0$ and $\alpha\beta - \gamma > 0$, we can remark that $\gamma > 0 \Longleftrightarrow R_0 < 1$.

Hence if $R_0 > 1$ the uninfected equilibrium point X_0 is unstable. □

Theorem 2.6 *The infected equilibrium point X_1 exists if $R_0 > 1$ and when it exists, it is unstable.*

Proof The characteristic polynomial

$$P_{J(X_1)}(x) = det(J(X_1) - xI_5)$$

of the Jacobian matrix $J(X)$ evaluated to the infected steady state X_1 is in the following forms,

$P_{J(X_1)}(x) = H_0(x) + H_1(x) + H_2(x)$,
$P_{J(X_1)}(x) = x^5 + Ax^4 + Bx^3 + Cx^2 + Dx + E$,
$H_0(x) = -(\delta_T^* + x)(k_M V_1 + \delta_M + x)(k_T V_1 + \delta_T + x) \times$
$(\delta_M^* + x)(\delta_V + x)$,
$H_1(x) = p_M k_M M_1(\delta_T^* + x)(\delta_M + x)(k_T V_1 + \delta_T + x)$,
$H_2(x) = p_T k_T T_1(\delta_M^* + x)(\delta_T + x)(k_M V_1 + \delta_M + x)$.

A necessary condition of the Routh–Hurwitz stability criterion is satisfied if $A > 0$, $B > 0$, $C > 0$, $D > 0$ and $E > 0$. From the expression of $H_0(x)$ we can easily calculate

$$A = -(\delta_T^* + \delta_M^* + \delta_V + \delta_T + \delta_M + k_T V_1 + k_M V_1),$$

A is negative because all the parameters values are assumed positive and also $V_1 > 0$.This proves the instability of the infected steady state X_1, when $R_0 > 1$. □

Numerical analysis of this model has been well studied by A. Hernandez-Vargas and Richard H. Middleton in [13]. They have shown the ability of this model to reproduce the clinical data of HIV evolution and the impact of macrophages on exploding viral load in the last phase of infection. They also prove that this model is not sensitive to a variation of the parameters. However, this model does not significantly reproduce the last phase for viral load. So, to have the three stage of the evolution of HIV, they add the proliferation of CD4 + T cells and macrophage cells in model (2.1), modeled as a kinetic function of Michaelis–Menten.

2.2 Mutations and Therapy

In this part, we will add the mutations and the combination of therapies to the model (2.1). Despite the fact that the model (2.1) describes the evolution of HIV fairly well, it remains too simplified. Because it does not take into account the mutations of the virus. These mutations are due either to the reaction of the immune system or to reaction against therapy.

2.2.1 Model of Mutations

Uninfected $CD4+T$ cells (T) and uninfected macrophages (M) are still considered and we add the cell proliferation terms using Michaelis–Menten kinetics in the

following form $\frac{\rho_T V}{C_T+V}$ and $\frac{\rho_M V}{C_M+V}$ respectively for uninfected $CD4+T$ cells and uninfected macrophages. We introduce the mutations as follows: Uninfected $CD4+T$ cells and uninfected macrophages can be infected by all different viral strains. It is assumed that a strain i is obtained during the replication of this same strain with a probability q_{ii}, or it is obtained from the mutation of the strain j with a probability q_{ij}. Thus, a viral strain i can infect CD4 + T and macrophages respectively at rates k_T and k_M. The bilinear terms in the equations of infected CD4 + T cells and infected macrophages become $k_T T \sum_{j=1}^{n} q_{ij} V_j$ and $k_M M \sum_{j=1}^{n} q_{ij} V_j$. We will note a $CD4+T$ cell infected by the strain i (T_i^*), macrophages infected by i (M_i^*) and V_i represents the density of the viral strain i. We obtain the following modified systems, no cells proliferation model with mutations

$$\begin{cases} \dot{T} &= s_T - k_T T V - \delta_T T, \\ \dot{T_i^*} &= k_T T \sum_{j=1}^{n} q_{ji} V_j - \delta_{T^*} T_i^*, \\ \dot{M} &= s_M - k_M M V - \delta_M M, \\ \dot{M_i^*} &= k_M M \sum_{j=1}^{n} q_{ji} V_j - \delta_{M^*} M_i^*, \\ \dot{V_i} &= p_T T_i^* + p_M M_i^* - \delta_V V_i. \end{cases} \tag{2.2}$$

and cells proliferation model with mutations

$$\begin{cases} \dot{T} &= s_T + \frac{\rho_T V}{C_T+V} T - k_T T V - \delta_T T, \\ \dot{T_i^*} &= k_T T \sum_{j=1}^{n} q_{ji} V_j - \delta_{T^*} T_i^*, \\ \dot{M} &= s_M + \frac{\rho_M V}{C_M+V} M - k_M M V - \delta_M M, \\ \dot{M_i^*} &= k_M M \sum_{j=1}^{n} q_{ji} V_j - \delta_{M^*} M_i^*, \\ \dot{V_i} &= p_T T_i^* + p_M M_i^* - \delta_V V_i. \end{cases} \tag{2.3}$$

These systems contain $(3n + 2)$ equations, where n is the number of strains. But if we pose $T^* = \sum_{i=1}^{n} T_i^*$, $M^* = \sum_{i=1}^{n} T_i^*$ and $V = \sum_{i=1}^{n} V_i$ in the system (2.2) we go back to the system (2.1). A theoretical analysis of the evolution of the mutation system (2.3) is very complex. However the numerical analysis will also allow us to understand the evolution of this system, in particular the evolution of the total viral load and CD4+ T cells.

2.2.2 Numerical Analysis of the Mutation Model

We will use the values of the parameters used in [14] for the numerical analysis of the model of mutations. For the initial conditions, it will be assumed that all strains are born with the same concentration $V_i(0) = 10^{-3}$ copies/ml, $CD4+T$ cells in the initial state are equal to 1000 cells/mm^3, uninfected macrophages are equal to 150 cells/mm^3 and infected $CD4+T$ cells and infected macrophages are assumed equal to zero.

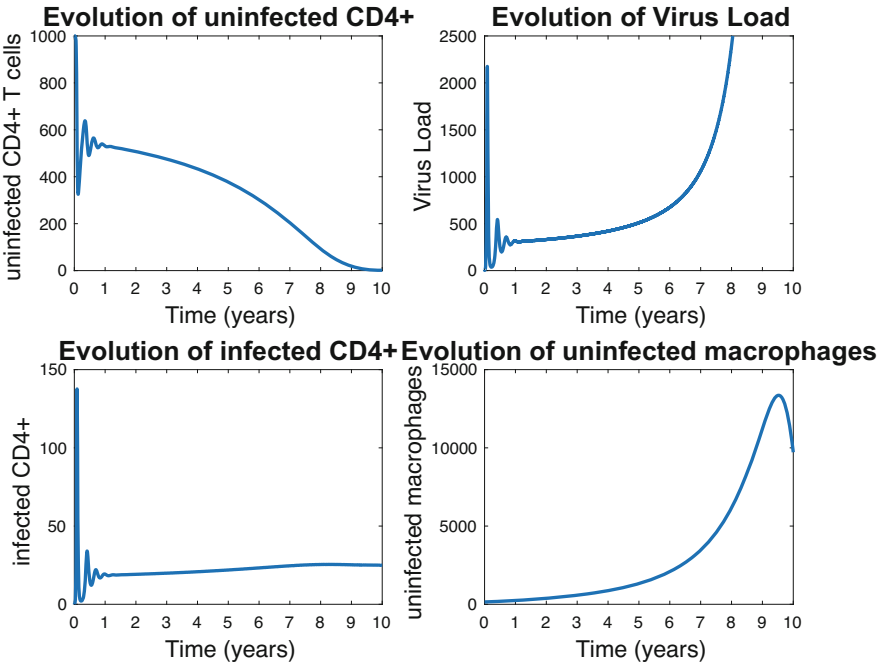

Fig. 1 Evolution of uninfected (T) and total infected CD4 + T cells T^*, uninfected macrophages M and the total viral load V of the nonlinear system (2.3)

The uninfected $CD4 + T$ cells, in the presence of strains, tend more rapidly to 200 cells/mm^3 in the mutation model than the simplified model presented in [13]. Mutations accelerate the appearance of the last phase of HIV infection, which is AIDS. Figure 1 shows the three phases of HIV evolution, initial acute infection, a long asymptomatic period and AIDS phase. We can observe the long life of macrophages in the evolution of uninfected macrophages. Modeling the proliferation of CD4 + cells and macrophage cells as a form Michaelis–Menten kinetics allows the system (2.3) to have a certain level of robustness in relation to the variation of the parameters s_T, s_M, k_T, k_M, δ_T, δ_M, δ_{T^*}, δ_{M^*} and δ_V [14]. An increase in parameter values ρ_T and ρ_M leads to a rapid decrease in CD4 + cells below 200 cells/mm^3 and enables to reach more quickly the last phase of HIV infection. We can notice in Fig. 4 the system (2.3) is more sensitive to the variation of the parameter ρ_M than to the parameter ρ_T (Figs. 2 and 3).

In the Fig. 4, we checked the changes that the viral load suffered if we increase the values of the parameters ρ_T and ρ_M from 1 to 4%. The mutation system is not sensitive to the variation of the parameter ρ_T all the time, on the other hand a slight variation of the value of ρ_M leads to an explosion of viral load more quickly. But it can be noted that the system (2.3) is robust to the variation of ρ_M for the first 6 years as can be seen in Fig. 4.

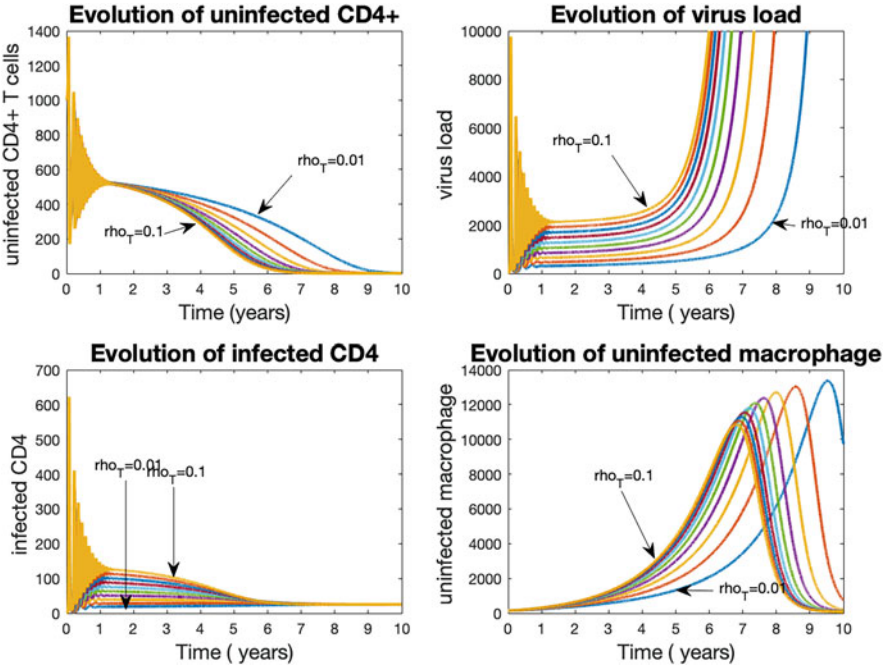

Fig. 2 Evolution of uninfected (T) and infected CD4 + T cells T^*, uninfected macrophages M and the total viral load V for $\rho_T = 0.01, 0.02, \ldots 0.1$

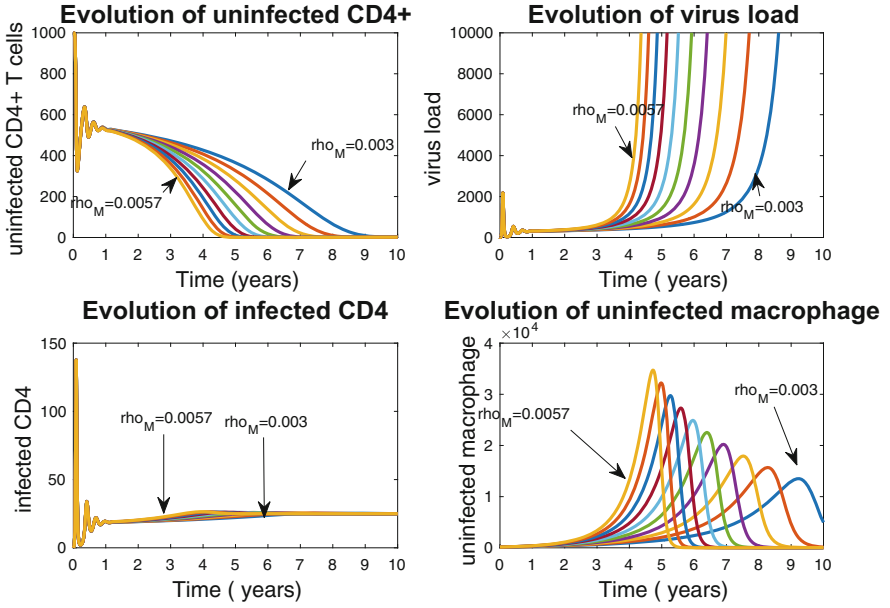

Fig. 3 Evolution of uninfected (T) and infected CD4 + T cells T^*, uninfected macrophages M and the total viral load V for a variation of ρ_M of 10, 20, 30, 40, 50, 60, 70, 80 and 90%

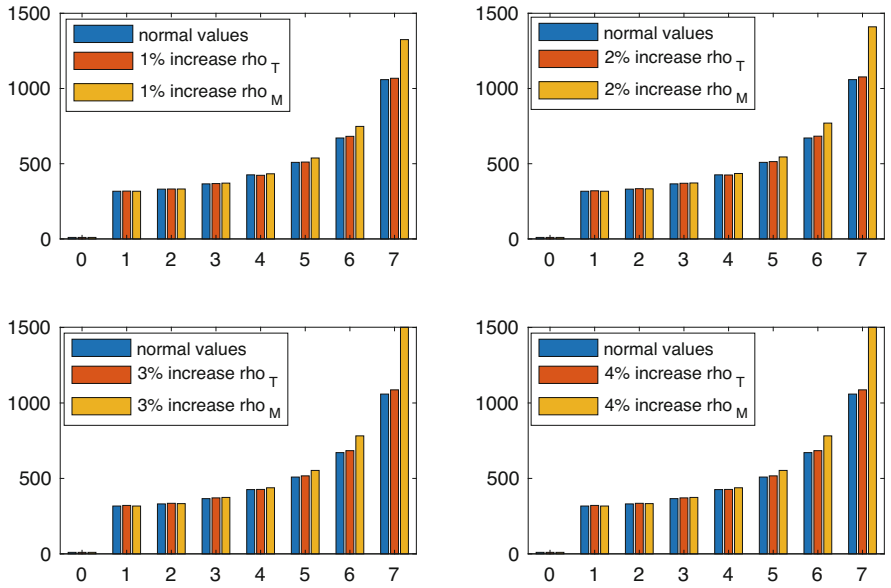

Fig. 4 The variation of the parameters ρ_T and ρ_M for the verification of the robustness of the system (2.2) in the viral load

In the following, we assume the uninfected $CD4 + T$ cells and the uninfected macrophages are constants. Indeed, for a short period of time, the number of healthy T cells and macrophages remain mainly constant so they are the same as the initial condition because uninfected $CD4 + T$ cells and uninfected macrophages decrease really slowly during the latency period [13, 14]. So, the system (2.2) and (2.3) become the following linear system

$$\begin{cases} \dot{T}_i^* &= k_T T \sum_{j=1}^n q_{ji} V_j - \delta_{T^*} T_i^*, \\ \dot{M}_i^* &= k_M M \sum_{j=1}^n q_{ji} V_j - \delta_{M^*} M_i^*, \\ \dot{V}_i &= p_T T_i^* + p_M M_i^* - \delta_V V_i. \end{cases} \tag{2.4}$$

2.2.3 Combination of Therapies

In this part, we add the therapy to the model (2.4). We assumed that the combination of therapies is modeled as a Hill function in the following form [10, 11],

$$\psi_{ik}(\ell_k) = f(K_{ik}) = \frac{\ell_k^n}{\ell_k^n + K_{ik}^n}$$

$f(K_{ik})$ is a function of K_{ik}, which is the association constant for the virus/antibody binding reaction $\ell_j + V_i \longrightarrow \ell_j V_i$, for each neutralization reaction representing the rate at which a neutralizing macromolecule ℓ_k (assumed to remain at constant concentrations) neutralizes mutant i. To obtain a linear pharmacodynamics it will be assumed that $n = 1$ and $K_{ik} >> \ell_k$, so we have

$$\psi_{ik}(\ell_k) = f(K_{ik}) = \frac{\ell_k}{K_{ik}}.$$

The Hill equation has been used in pharmacology to model nonlinear drug dose-responses, such as the concentration dependent effects of drugs on cell viability or virus neutralization. We notice that the Hill function is a biological analog to actuator saturation, in that there is a law of diminishing returns in terms of the effect of ever increasing drug concentrations on the system [15]. We obtain the model of the following combination of therapies,

$$\begin{cases} \dot{T}_i^* &= k_T T \sum_{j=1}^n q_{ji} V_j - \delta_{T^*} T_i^*, \\ \dot{M}_i^* &= k_M M \sum_{j=1}^n q_{ji} V_j - \delta_{M^*} M_i^*, \\ \dot{V}_i &= p_T T_i^* + p_M M_i^* - \delta_V V_i - \sum_{k=1}^m \frac{\ell_k}{K_{ik}} V_i. \end{cases} \tag{2.5}$$

Therapy is added to the strain equation, because it acts on the different viruses present in the system and m represents the different therapies possible to combine. This linear system (2.5) can be rewritten as following

$$\dot{X} = \begin{pmatrix} -\delta_{T^*} I_n & 0_{n\times n} & k_T T Q \\ 0_{n\times n} & -\delta_{M^*} I_n & k_M M Q \\ p_T I_n & p_M I_n & -\delta_V I_n - \psi L \end{pmatrix} X, \tag{2.6}$$

where $X = (T_1^*, T_2^*, \dots T_n^*, M_1^*, M_2^* \dots M_n^*, V_1, V_2, \dots V_n)$, $Q = [q_{ji}]_{1\le i,j\le n}$, $0_{n\times n}$ is the null matrix of order $n \times n$, I_n is the identity matrix of size n and $\psi L = diag(\sum_{k=1}^m \frac{l_k}{K_{ik}})_{n\times n}$.

3 Optimal Control

In what follows we will apply the optimal control techniques used by V. Jonsson and R. Murray [10–12], using the theory of positive systems [16, 17], on our model of the combination of therapies, especially on the system (2.6). V. Jonsson and R. Murray, in their work to design treatment protocols to prevent mutations escape from monotherapy. They worked on three articles, in the first article they developed a suboptimal algorithm for the systematic design of feedback strategies to stabilize the evolutionary dynamics of a generic disease model, such as HIV and cancer, using an $\mathcal{H}_\infty$ approach. The lack of scalability of their $\mathcal{H}_\infty$ algorithm led them to publish a

second article, in which they propose a scalable solution to the combination therapy problem by reformulating it as a second order cone program (SOCP). In the first and second article they supposed that the effect of drugs is linear, in the third they modeled the effect of drugs as a piecewise linear function and they developed a new algorithm to find a suboptimal controller. However, the model they used is too simple and does not represent well the evolution of HIV infection, because their model only takes into account the concentration of mutations. Thus, Eloise Ganhy and Cassandra de Cock de Rameyen in their master thesis under the supervision of Raphael M. Jungers [18], introduced a new model of mutations that takes into account $CD4 + T$ cells and they applied the control techniques used in [10, 11]. Their model represents better HIV infection than the model proposed by V. Jonsson and R. Murray and they obtained good results except on the gain of closed-loop system, which takes very large values, despite a low dosage of drugs. In addition, their model represents only the first two phases of HIV infection and does not present the last phase, the AIDS phase. Their model converges towards the latent phase, despite the presence of mutations and $CD4 + T$ cells. In this part we will recall all the theory that will be needed in the design of algorithms and the resolution of our optimal control problems.

The set of nonnegative real numbers is denoted by $\mathbb{R}_+$. The inequality $X > 0$, $(X \geq 0)$ means that all elements of the matrix or vector X are positive (nonnegative). $X \succ 0$ means that X is a symmetric and positive definite matrix. The matrix X is $Hurwitz$ if all eigenvalues have negative real part and the matrix X is $Metzler$ if all off-diagonal elements are nonnegative. We define $\mathbf{1}_n$ as being the vector of all ones of dimension n.

Definition 3.1 ([17])

1. Given matrices $A \in \mathbb{R}^{n\times n}$, $B \in \mathbb{R}^{n\times n_u}$, $C \in \mathbb{R}^{n_z\times n}$ and $D \in \mathbb{R}^{n_z\times n_u}$, a Linear Time Invariant dynamical system (LTI) can be described as

$$\begin{cases} \dot{x}(t) = Ax(t) + Bu(t) \\ z(t) = Cx(t) + Du(t) \end{cases} \tag{3.1}$$

   where $x(t)$ is the state, $u(t)$ is the input and $z(t)$ is the output. The transfer matrix of system (3.1) is given by:

$$G(s) = C(sI - A)^{-1}B + D,$$

   $G(s)$ is defined in the resolvent of the matrix A and the corresponding impulse response is $g(t) = Ce^{At}B\theta(t) + D\delta(t)$, where $\theta(t)$ is the Heaviside step function and $\delta(t)$ the Dirac delta function.
2. The maximum norm of vector $x \in \mathbb{R}^n$ is given by

$$\|x\|_\infty = max\left(|x_1|, |x_2|, \ldots, |x_n|\right).$$

3. The induced matrix norm for $M \in \mathbb{R}^{r\times m}$ is given by

$$\|M\|_{p-ind} = \sup_{w\in\mathbb{R}^m\setminus\{0\}} \frac{|Mw|_p}{|w|_p}$$

where $|w|_p = (|w_1|^p + |w_2|^p + \ldots + |w_m|^p)$. If M has nonnegative entries, we have $\|M\|_{\infty-ind} < \gamma$ if and only if $M\mathbf{1}_n < \gamma\mathbf{1}_n$.

4. The p norm of an element w of some Lebesgue space $\mathcal{L}^p[0,\infty)$ is given by

$$\|w\|_p = \left(\sum_k \int_0^\infty |w_k|^p dt\right)^{\frac{1}{p}}.$$

5. For a $r \times m$ matrix transfer function $G(s) = C(sI - A)^{-1}B + D$, the induced norm of the corresponding impulse response $g(t) = Ce^{At}B\theta(t) + D\delta(t)$ is

$$\|g\|_{p-ind} = \sup_w \frac{\|g * w\|_p}{\|w\|_p}$$

for $w \in \mathcal{L}_m^p[0,\infty)$ and $g * w \in \mathcal{L}_p^r[0,\infty)$ the convolution of g and w.

Theorem 3.2 ([16]) *The LTI system defined in (3.1) is internally positive if and only if*

(1) A is Metzler
(2) $B, C, D \geq 0$.

Theorem 3.3 ([16, 17]) *Let $g(t) = Ce^{At}B\theta(t) + D\delta(t)$ where $Ce^{At}B \geq 0$ for $t \geq 0$ and $D \geq 0$ while A is Hurwitz. Then $\|g\|_{p-ind} = \|G(0)\|_{p-ind}$ for $p = 1, 2$ or ∞.*

Theorem 3.4 ([16, 17]) *Let $g(t) = Ce^{At}B\theta(t) + D\delta(t)$, then the following statements are equivalent:*

(1) A Hurwitz and $\|g\|_{\infty-ind} < \gamma$.
(2) $\exists\xi \in \mathbb{R}_+^n \setminus \{0\}$ such that

$$\begin{pmatrix} A & B \\ C & D \end{pmatrix}\begin{pmatrix} \xi \\ \mathbf{1}_n \end{pmatrix} < \begin{pmatrix} 0 \\ \gamma\mathbf{1}_n \end{pmatrix}. \tag{3.2}$$

Moreover, if ξ satisfies (8), then $-\xi < x(t) < \xi$ for all solution to the equation $\dot{x} = Ax + Bw$ with $x(0) = 0$ and $\|w\|_\infty \leq 1$.

Consider the following linear time-invariant generalized plant:

$$\begin{cases} \dot{x} = Ax + Bw + Eu \\ z = Cx + Dw + Gu \\ y = Fx + Hw \end{cases} \tag{3.3}$$

where x is the state, z the regulated output, w the disturbance, u the control input and y the measured output. The closed-loop system can be described as

$$\begin{cases} \dot{x} = (A + ELF)x + (B + ELH)w \\ z = (C + GLF)x + (D + GLH)w \end{cases} \tag{3.4}$$

L is defined as being the static controller such that $u = Ly$. We denote the closed-loop transfer matrix from w to z by T_{zw}. We have $T_{zw}(s) = (C + GLF)[sI - (A + ELF)]^{-1}(B + ELH) + (D + GLH)$, $\forall\, s \in \mathbb{C}\backslash\{spec(A + ELF)\}$, where $spec(A + ELF)$ is the set of eigenvalues of the matrix A + ELF.

Definition 3.5 Given a scalar $\gamma > 0$, a controller is said to be a $\mathcal{L}_1$ controller if the following conditions hold:

(1) $(A + ELF)$ is asymptotically stable.
(2) $\|T_{zw}\|_{\infty-ind} = \sup_{0<\|w\|_\infty<\infty} \frac{\|z\|_\infty}{\|w\|_\infty} < \gamma$.

Theorem 3.6 ([16, 17]) *Let $\mathcal{D}$ be the set of $m \times m$ diagonal matrices with entries in* [0, 1]. *We consider the system described by (3.4). Suppose that $A+ELF$ is Metzler and $C + GLF \geq 0$, $B + ELH \geq 0$, $D + GLH \geq 0\ \forall\ L \in \mathcal{D}$. Let $g_L(t)$ be the impulse response of $(C + GLF)[sI - (A + ELF)]^{-1}(B + ELH) + (D + GLH)$. If $F, H \geq 0$ then the following two conditions are equivalent:*

(1) There exists $L \in \mathcal{D}$ with $A + ELF$ Hurwitz and $\|g_L\|_{\infty-ind} < \gamma$.
(2) There exists $\xi \in \mathbb{R}^n_+$, $\mu \in \mathbb{R}^m_+$ with

$$\begin{aligned} &A\xi + B\mathbf{1}_n + E\mu < 0 \\ &C\xi + D\mathbf{1}_n + G\mu < \gamma\mathbf{1}_n \\ &F\xi + H\mathbf{1}_n \geq \mu \end{aligned} \tag{3.5}$$

Moreover, if ξ, μ satisfy (3.5.2), then (3.5.1) holds for every L with $\mu = L(F\xi + H\mathbf{1}_n)$.

Remark If the diagonal elements of $\mathcal{D}$ are restricted to $\mathbb{R}_+$ instead of [0, 1], then the condition $F\xi + H\mathbf{1}_n \geq \mu$ is replaced by $F\xi + H\mathbf{1}_n \geq 0$.

3.1 Algorithm and Numerical Results

We will apply the optimal control tools seen previously on our linearized model (2.6), which can be rewritten as a generalized plant with a controller L:

$$\begin{cases} \dot{x} = (A + EL_1F)x + Bw \\ z = Cx \end{cases} \tag{3.6}$$

where

$$A = \begin{bmatrix} -\delta_{T^*} I_n & 0_{n\times n} & k_T T Q \\ 0_{n\times n} & -\delta_{M^*} I_n & k_M M Q \\ p_T I_n & p_M I_n & -\delta_V I_n \end{bmatrix}, \quad E = \begin{pmatrix} \mathbf{0}_{n\times n} \\ \mathbf{0}_{n\times n} \\ -\mathbf{I}_n \end{pmatrix},$$

$L_1 = \Psi L$, $F = \begin{pmatrix} \mathbf{0}_{n\times n} & \mathbf{0}_{n\times n} & \mathbf{I}_n \end{pmatrix}$, $B = \mathbf{I}_{3n}$, $C = \begin{bmatrix} \mathbf{0}_n^T & \mathbf{0}_n^T & \mathbf{1}_n^T \\ \mathbf{0}_{mn\times n} & \mathbf{0}_{mn\times n} & L \end{bmatrix}$, $w \in \mathbb{R}_+^{3n}$ an arbitrary positive disturbance and
$x = (T_1^*, T_2^*, \ldots T_n^*, M_1^*, M_2^* \ldots M_n^*, V_1, V_2, \ldots V_n)^T$.

Lemma 3.7 *System (3.6) is internally positive.*

Proof We can easily notice that the matrix $A + EL_1F$ is $Metzler$ and $B, C \geq 0$ and if we refer to the Theorem 3.2 we conclude that the system (3.6) is internally positive. □

Based on the work done by V. Jonsson and R. Murray [10, 11], we will define our optimal control problem according to a scalable $\mathcal{L}_1$ controller solution.

Problem Let G to be the closed-loop transfer function of the system (3.6), the control task for a scalable solution $\mathcal{L}_1$ is to find a controller $L_1 = \Psi(I \otimes \ell)$ that leads to a stable G satisfying $\|G\|_{\infty-ind} < \gamma$, for some robustness level $\gamma > 0$.

3.1.1 Initial Problem

Exploiting the internal positivity of the system (3.6) we can formulate an iterative algorithm slightly different from the one presented by V. Jonsson and R. Murray for finding effective antibody concentrations, but which always yields a stabilizing controller.

Proposition 3.8 *There exists $\epsilon > 0$ such that the solution to the convex program:*

$$\begin{aligned} \min_{\ell \in \mathbb{R}_+^m} \quad & \|\ell\|_\infty \\ s.t. \quad & (A + EL_1F)_d + \epsilon I \prec 0 \\ & L_1 = \Psi(I \otimes \ell) \end{aligned} \tag{3.7}$$

is a stabilizing controller for system (12)*, where* $(A + EL_1F)_d$ *is a diagonal matrix comprised of the diagonal elements of* $A + EL_1F$.

Proof Let $A + EL_1F = (A + EL_1F)_d + (A + EL_1F)_{ij}$, where $(A + EL_1F)_d$ is the diagonal elements of the matrix $A + EL_1F$ and $(A + EL_1F)_{ij}$ are the elements off-diagonal of the matrix $A + EL_1F$, so the matrix $M = (A + EL_1F)_{ij} \in \mathbb{R}^{3n\times 3n}$, with $(A + EL_1F)_{ij} > 0$ if $i \neq j$ and $(A + EL_1F)_{ij} = 0$ if $i = j$. By the Perron Frobenius theorem, there exists $r > 0$ such that the spectral radius $\rho(M) = r \leq max_i \sum(A + EL_1F)_{ij}$. Let $\epsilon = max_i \sum(A + EL_1F)_{ij}$ and $M = \epsilon I - (\epsilon I - M)$. We note that $-(\epsilon I - M) \prec 0$. So we have the closed loop dynamics $A + EL_1F = (A + EL_1F)_d + \epsilon I - (\epsilon I - M) \prec (A + EL_1F)_d + \epsilon I \prec 0$, yielding the desired stability. □

3.1.2 A Suboptimal $\mathcal{L}_1$ Controller

The system (3.6) must satisfy the conditions of Theorem 3.6 to keep its stability and have a certain level of robustness γ.

The matrix $A + EL_1F$ is Metzler, because we have

$$A + EL_1F = \begin{pmatrix} -\delta_{T^*} I_n & 0_n & k_T TQ \\ 0_n & -\delta_{M^*} I_n & k_M MQ \\ p_T I_n & p_M I_n & -\delta_V I_n - \psi L \end{pmatrix},$$

$L_1 \in \mathcal{D}$ is a positive diagonal matrix and B, C and $F \geq 0$. Stability and robustness are achieved for our model if there exist $\xi \in \mathbb{R}^{3n}_+$, $\mu \in \mathbb{R}^{3n}_+$ such as

$$\begin{aligned} &A\xi + B\mathbf{1}_n + E\mu < 0 \\ &C\xi + D\mathbf{1}_n + G\mu < \gamma \mathbf{1}_n \\ &F\xi + H\mathbf{1}_n \geq \mu \end{aligned}$$

which can be rewritten as

$$\begin{aligned} &(A + EL_1F)\xi + \mathbf{1}_{3n} < 0 \\ &C\xi < \gamma \mathbf{1}_{mn+1} \\ &F\xi \geq 0 \end{aligned}$$

because we assume that $\mathcal{D} \in \mathbb{R}_+$, therefore the condition $F\xi + H\mathbf{1}_n \geq \mu$ is replaced by $F\xi + H\mathbf{1}_n \geq 0$. We have $\mu = L(F\xi + H\mathbf{1}_n)$, since $D = 0$, $G = 0$ and $H = 0$, we have $\mu = LF\xi$ and $F\xi \geq 0$. Even more, minimizing the term $C\xi$ is simply minimizing the term CV where V is the virus population, this is justified by the fact that if ξ satisfies Theorem 3.4, then $-\xi < x(t) < \xi$ for all solutions to the equation $\dot{x} = Ax + Bw$ with $x(0) = 0$ and $\|w\|_\infty \leq 1$.

In conclusion, for any given value of the regularizers $\lambda_1 \in \mathbb{R}_+ \setminus \{0\}$ and $\lambda_2 \in \mathbb{R}_+ \setminus \{0\}$, we can find by solving the following non-convex program in order to

compute the antibody:

$$\begin{aligned} \min_{\xi \in \mathbb{R}_+^{3n}, \ell \in \mathbb{R}_+^m} \quad & \|C\xi\|_\infty + \lambda_1 \|\ell\|_1 + \lambda_2 \|\ell\|_2 \\ \text{s.t.} \quad & (A + EL_1F)\xi + \mathbf{1}_{3n} < 0 \\ & \|C\xi\|_\infty < \gamma \\ & L_1 = \Psi(I \otimes \ell) \\ & \xi \geq 0. \end{aligned}$$

The antibody concentrations ℓ that yield an optimal $\infty - induced$ closed loop norm.

This problem is bilinear because of the product $L_1 x$ and there are no known convex reformulations of this problem. As is standard for bilinear problems, we propose to search for a solution by alternatively considering one variable constant and optimizing on the other. This allows us to state the following iterative algorithm, based on the two following convex programs:

Program 1

$$\begin{aligned} \min_{\xi \in \mathbb{R}_+^{3n}, \gamma \in \mathbb{R}_+} \quad & \gamma \\ \text{s.t.} \quad & (A + EL_1F)\xi + \mathbf{1}_{3n} \leq 0 \\ & \|C\xi\|_\infty \leq \gamma \\ & L_1 = \Psi(I \otimes \ell) \\ & \xi \geq 0. \end{aligned}$$

The output of this program is a value of $\xi \in \mathbb{R}_+^{3n}$ and γ, when the value of ℓ is fixed. It will be noted $P1_{\ell'}$ when ℓ is fixed to ℓ'.

Program 2

$$\begin{aligned} \min_{\gamma \in \mathbb{R}_+, \ell \in \mathbb{R}_+^m} \quad & \|C\xi\|_\infty + \lambda_1 \|\ell\|_1 + \lambda_2 \|\ell\|_2 \\ \text{s.t.} \quad & (A + EL_1F)\xi + \mathbf{1}_{3n} \leq 0 \\ & \|C\xi\|_\infty \leq \gamma \\ & L_1 = \Psi(I \otimes \ell) \\ & \xi \geq 0. \end{aligned}$$

The output of this program is a value of $\ell \in \mathbb{R}_+^m$, and γ when the value of ξ is fixed. It will be noted $P2_{\xi', \lambda_1, \lambda_2}$ when ξ is fixed to ξ'.

Algorithm 1 $\mathcal{L}_1$ Algorithm

1) **Set** $\epsilon > 0$.
Initialisation
2) **Solve** for initial stabilizing controller ℓ':
Solve (3.7) to obtain a controller ℓ_0.
Set $(\xi', \gamma) = P1_{\ell'}$.
Set $(\ell', \gamma) = P2_{\xi',0,0}$.
3) Find $(\lambda_1', \lambda_2', \ell)$ that minimize γ:
while $\gamma' - \gamma > \epsilon$ **do**
i) **Set** $(\xi', \gamma) = P1_{\ell'}$.
ii) **Set**$(\ell', \gamma) = P2_{\xi',\lambda_1,\lambda_2}$.
iii) **Set** $\gamma' = \gamma$.

3.1.3 Implementation and Results

The initial problem and Program 1 are linear and can be solved by the function (linprog.m) in matlab using an interior-point method, we choose to use CVX modeling system for a performance in time and the Program 2 is a second order cone program. we have implemented our programs with the CVX toolbox combined with the SDPT3 solver. CVX is a software package that runs in Matlab. It transforms Matlab into a modeling language to solve a disciplined convex programs (DCP). A disciplined convex programs describe objective and constraints using expressions formed from a set of basic conventions (linear, affine, convex, concave functions), a restricted set of operations or rules (that preserve convexity). CVX supports a number of standard problem types, including linear programs (LP) and quadratic programs (QP), second-order cone programs (SOCP), and semidefinite programs (SDP) [19].

The algorithm implemented in SDPT3 is a primal-dual path-following algorithm. At each iteration, we first compute a predictor search direction aimed at decreasing the duality gap as much as possible. After that, the algorithm generates a Mehrotra-type corrector step with the intention of keeping the iterates close to the central path. However, we do not impose any neighborhood restrictions on our iterates. Initial iterates need not be feasible the algorithm tries to achieve feasibility and optimality of its iterates simultaneously. It should be noted that in our implementation, the user has the option to use a primal-dual path-following algorithm that does not use corrector steps [20].

We applied the algorithm on the linearized system and then we will compare the behavior of the nonlinear systems of mutations (2.2) and (2.3), and the linearized system of mutations (2.4).

Our linearized system of mutations is stable, if and only if the matrix $(A+EL_1F)$ is Hurwitz, in other words, if and only if all real part of the eigenvalues of the matrix $(A + EL_1F)$ are negative. By construction, the matrix $(A + EL_1F)$ is Metzler, all elements in the off-diagonal of this matrix are nonnegative and we have for some $\epsilon > 0$, $A+EL_1F \prec (A+EL_1F)_d+\epsilon I$. By Proposition (3.8), $(A+EL_1F)_d+\epsilon I \prec$

0, then we have necessarily $A + EL_1F \prec 0$ that conclude the stability of the matrix $(A + EL_1F)$.

3.1.4 Parameters for the Implementation in Matlab

A main goal of our experiments is to compare the results obtained from the combination of therapies applied to our model to the results obtained by V. Jonsson and R. Murray [10, 11]. Thus, we take the same efficiency of the association constant $K_{ij} = \frac{3IC50_{ij}}{3r_i + ln(2) - IC50_{ij}}$ to calculate the matrix Ψ, where (IC50) is the half maximal inhibitory antibody concentration and these values are shown in [11]. The Q matrix is used to compute the matrix A, and $q = \frac{1}{n_a}u(1-u)^k = 1.443.10^{-6}$ (where $u = 3 \times 10^{-5}$ mutations/nucleotide base pair/replication cycle is the mutation rate for HIV reverse transcriptase, $k \simeq 3000$ is the size of the genome in residues and $n_a = 19$ is the number of amino acids that can be mutated to), is the probability that one specific amino acid mutates in another one [10]. Units of concentrations are respectively $copies/ml$, $cells/mm^3$, $\mu g/ml$ for the virus, cells and the drug dose and time is measured in days. Since the first line represents the mutation of the wild type, only one mutation is needed and $\alpha = 1-(n-1)q$. For the rest of the mutants, two mutations in a row are required hence the q^2 and $\beta = 1 - q - (n-1)q^2$,

$$Q = \begin{pmatrix} \alpha & q & \cdots & \cdots & q \\ q & \beta & q^2 & \cdots & q^2 \\ \vdots & q^2 & \beta & \ddots & \vdots \\ \vdots & \vdots & \ddots & \ddots & q^2 \\ q & q^2 & \cdots & q^2 & \beta \end{pmatrix}.$$

For initial conditions, it is assumed that an HIV-infected person starts taking therapy at the beginning of the latency phase, because HIV is detected in people infected after the first phase of infection, which is described by a strong immune system reaction against the virus. So, we will assume that the Initial conditions for our model coincide with the infected equilibrium point X_2 (see Sect. 2). In other words, we assume that all infected CD4 + T cells, infected macrophages and viral strains have respectively the same concentration at the equilibrium point X_2 and their sum is equal to the infectious equilibrium. The endemic equilibrium point depends on the parameter values. Thus, the values of the parameters are taken as we reach a concentration of CD4 + T cells which is approximately equal to 200 cells/mm^3.

In the application of the therapy, we will take into account five drugs and eighteen mutations and we will observe the concentration of drugs obtained according to the application of regularizers.

3.1.5 Experimental Results

After implementation in matlab we have the following results:

1. Solving the initial problem with $\epsilon = 0.1$, we obtain a concentration of drugs $\ell = (0.1811.10^{-8}, 0.1808.10^{-8}, 0.1748.10^{-8}, 0.1817.10^{-8}, 0.1810.10^{-8})$ μg/ml, which can stabilize our linearized and non-linearized system (2.3) for eighteen mutations (It can be noted that this quantity is very small compared to the quantity which stabilizes the model proposed in [10, 11]). More precisely this quantity of drug makes the viral load go to zero in a few weeks for our linearized model and stabilize the nonlinear system (2.2) to a small amount of concentration of the viral load and cell concentration remain at the initial conditions. We can see that in the Fig. 5 for the linearized system and Fig. 6 for the nonlinear system (2.2). These drugs can only control the system (2.3) for some period of time before the virus load explode and CD4+T cells go progressively to zeros, as one can observe in Fig. 7
2. We solve our algorithm combined with program1 and 2 without regularizations, $\lambda_1 = \lambda_2 = 0$, and no condition on the sum of the drugs ℓ for eighteen mutations.

   We get $\ell = (7.4481, 7.4481, 7.4287, 7.4481, 7.4481)$ μg/ml, this concentration of drug is very high and can stop the evolution of mutations more quickly compared to the initial concentration. The drug concentration obtained without a regulator can eliminate the mutations of the linearized and non-linearized system

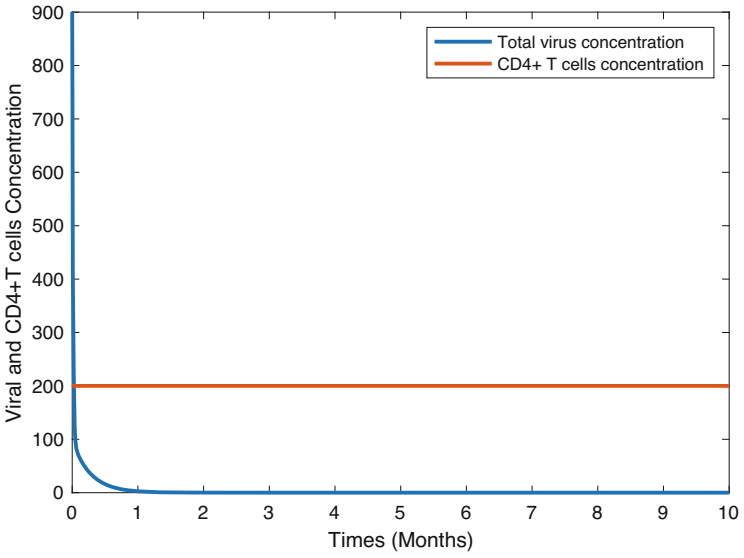

Fig. 5 Concentration of the total viral load and CD4+ T Cells for the linearized system for the concentration of drugs $\ell = (0.1811.10^{-8}, 0.1808.10^{-8}, 0.1748.10^{-8}, 0.1817.10^{-8}, 0.1810.10^{-8})$ μg/ml, without noise

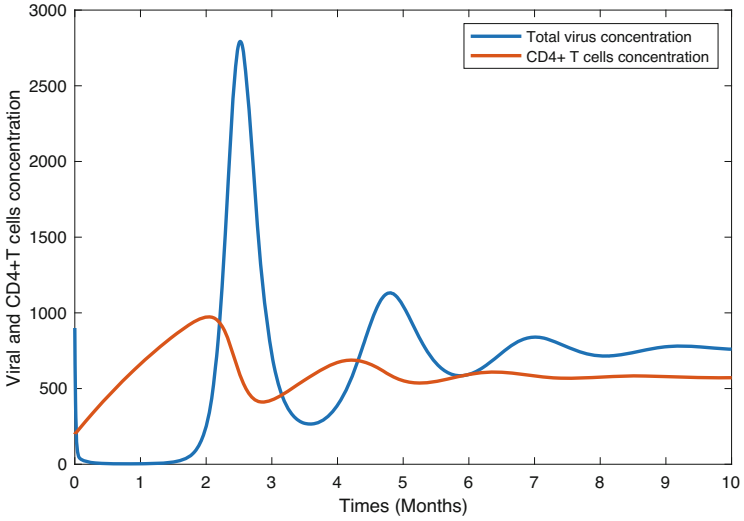

Fig. 6 Concentration of the total viral load and CD4+ T Cells for the nonlinear system (2) for the concentration of drugs $\ell = (0.1811.10^{-8}, 0.1808.10^{-8}, 0.1748.10^{-8}, 0.1817.10^{-8}, 0.1810.10^{-8})$

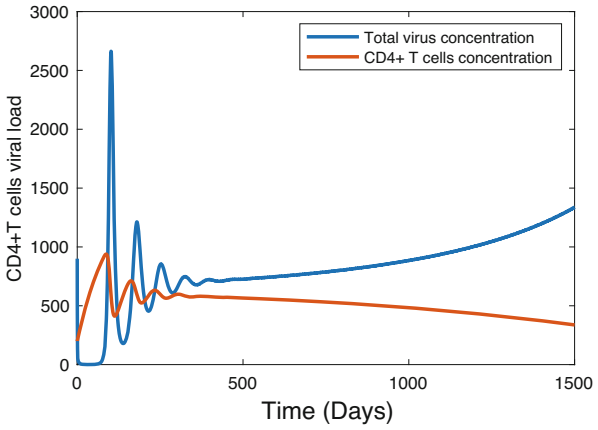

Fig. 7 Concentration of the total viral load and CD4+ T Cells for the nonlinear system (3) for the concentration of drugs $\ell = (0.1811.10^{-8}, 0.1808.10^{-8}, 0.1748.10^{-8}, 0.1817.10^{-8}, 0.1810.10^{-8})$

in a few days. However, in terms of the application of combination therapies such a concentration of drugs is not applicable in an HIV-infected person, because the side effects can be fatal. For this concentration, we found a some level of robustness $\gamma = 73.5431$ of the linearized system.

3. L_1 and L_2 regularizations: $\lambda_1 = \lambda_2 = 0.5$, our suboptimal algorithm gives the following results: $\ell = (0, 0, 4.2309, 3.7649, 0)$ and $\gamma = 155.3237$. For the regularizers $\lambda_1 = \lambda_2 = 0.5$, the concentration of combination of drugs obtained is sparse and is small compared to the drugs obtained with no regularizations, but it can still eliminate the mutations of the linearized and both nonlinear systems. With this concentration, the linearized system is more sensitive to noise than without regularizers.
4. L_1 regularization: $\lambda_1 = 0.5$ and $\lambda_2 = 0$, we obtain the following drugs concentration $\ell = (0, 0, 4.2309, 3.7649, 0)$ and $\gamma = 155.3237$. These results are the same results obtained with the combined L_1 and L_2 regularizations.
5. L_2 regularization: $\lambda_1 = 0$ and $\lambda_2 = 0.5$, we obtain the following results: $\ell = (15.9292, 15.9292, 14.4098, 15.9292, 15.9292)$ and $\gamma = 73.5601$. The drugs concentration obtained with the L_2 regulator is greater than the concentration obtained with the combined L_1 and L_2 regularizations, on the other hand, they have almost the same value of γ. This means that the linearized system has the same level of robustness for the concentration of drugs obtained in both cases, with the regularization L_2 and no regularizations (Fig. 8).

The concentration of combination of drugs obtained in each case is large, to get small drug concentrations, we add an additional constraint on the sum of drugs in the algorithm ($\sum_j \ell_j \leq 1$) to force it to find another local minimum (Fig. 9).

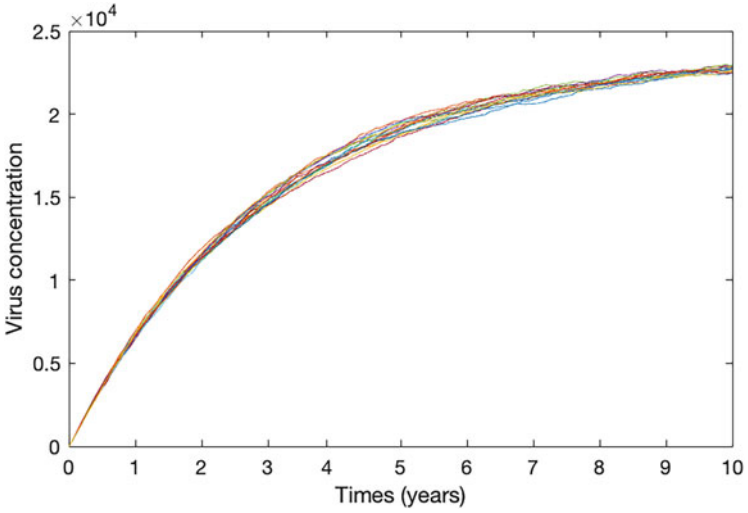

Fig. 8 Evolution of each strain viral for the linearized system for the concentration of drugs $\ell = (0.1811.10^{-8}, 0.1808.10^{-8}, 0.1748.10^{-8}, 0.1817.10^{-8}, 0.1810.10^{-8})$ with a disturbance w, whose values are taken in a uniform distribution between 0 and 1. For this concentration of drugs, the linear system is sensitive to the noise

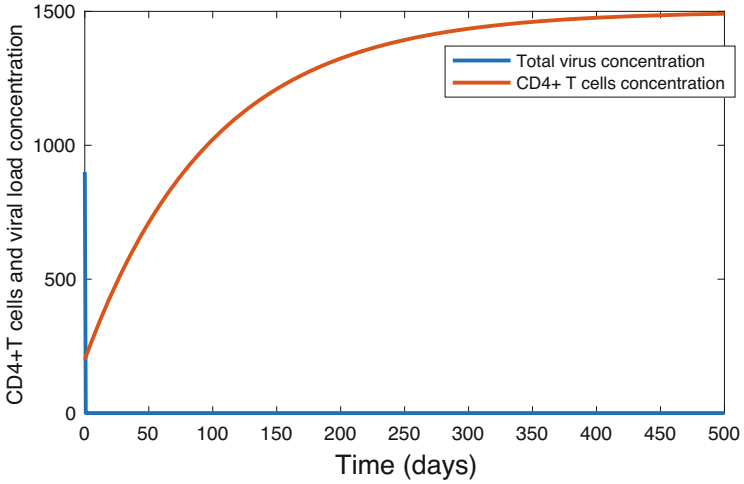

Fig. 9 Evolution of the concentration of the total virus (blue) and (red) the concentration of CD4+T cells the concentration of drugs $\ell = (0, 0, 4.2309, 3.7649, 0)$. With this concentration of drugs in the nonlinear system (2.3) the concentration of the virus go the zero and the CD4+T cells come back at the initial condition

1. No regularizations, $\lambda_1 = \lambda_2 = 0$ we obtain $\ell = (0, 0, 0.8180, 0.1820, 0)$ and $\gamma = 1662$.
2. L_1 and L_2 regularizations: $\lambda_1 = \lambda_2 = 0.5$, $\ell = (0, 0, 0.6894, 0.1669, 0)$ and $\gamma = 1862$.
3. L_1 regularization: $\lambda_1 = 0.5$, $\lambda_2 = 0$, $\ell = (0, 0, 0.6894, 0.1669, 0)$ and $\gamma = 1862$.
4. L_2 regularization: $\lambda_2 = 0.5$, $\lambda_1 = 0$, $\ell = (0.0517, 0.0401, 0.6832, 0.1240, 0.0517)$ and $\gamma = 1905$.

We observe that we have a smaller quantity of drugs but on the other hand we have a bigger γ. For these amounts of drugs the linearized system is more sensitive to the noise and it can be noted that in all the previous cases the concentration of the drugs can stabilize the evolution of the mutations for all the linearized and non-linearized systems (Fig. 10).

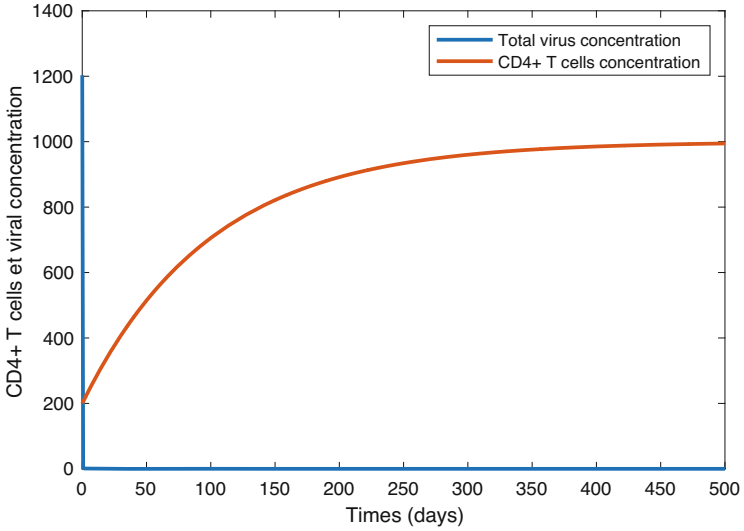

Fig. 10 Evolution of the concentration of the total virus (blue) and (red) the concentration of CD4+T cells the concentration of drugs $\ell = (0, 0, 0.6894, 0.1669, 0)$. We can remark that with this concentration of drugs in the nonlinear system (2.2) the concentration of the virus go the zero and the CD4+T cells come back at the initial condition

4 Conclusion and Perspectives

In this work, we have pushed further the system-theoretic analysis of the HIV evolution in the human body. We started with the model presented by Esteban A. Hernandez-Vargas, which is one of the models that better represents the evolution of HIV, we studied stability of the system according to the values of the basic reproduction rate R_0. We then added mutations and therapy to the above model, and we used optimal control techniques for positive systems in order to propose a slighty different scalable iterative algorithm that finds the best combination of drugs and that can minimize the induced $\mathcal{L}_1$ norm. We obtained satisfying results but our solution was more sensitive to noise than results obtained by Vanessa Jonsson and al. We observe that, with a small value of drug doses, the linearized version and system (2.2) and (2.3) behave differently. The nonlinear system converges to a nonzero equilibrium while the linearized reaches zero. With no regularization and no condition on the sum of drugs we obtained high drug concentrations and strong robustness to disturbances compared to the results obtained by applying regularizations. However, the concentration of drugs obtained in both conditions can eliminate the viral load, and in the nonlinear system CD4+T cells come back to the initial condition.

We believe that our new model is interesting because control techniques give efficient results and this model considers a more realistic HIV dynamics (Fig. 11).

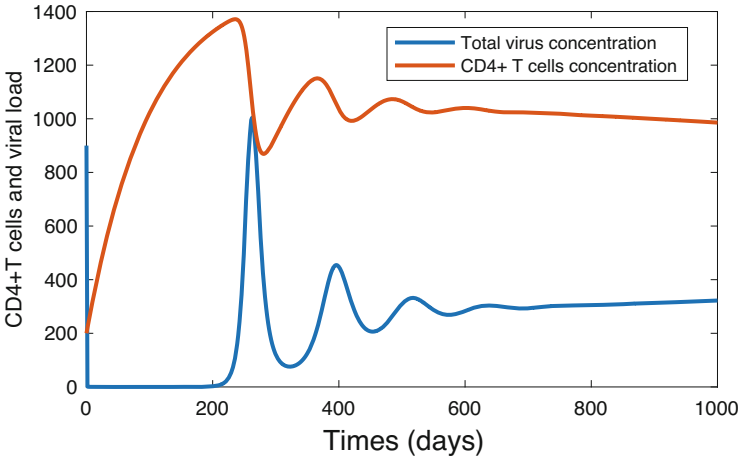

Fig. 11 Evolution of the concentration of the total virus (blue) and (red) the concentration of CD4+T cells the concentration of drugs $\ell = (0, 0, 0.6894, 0.1669, 0)$. We can remark that with this concentration of drugs in the nonlinear system (2.3) the concentration of the virus go a nonzero equilibrium and the CD4+T cells come back at the initial condition

This work was an initial attempt at making use of nonlinear optimal control techniques in an involved model taking into account mutations and therapy. Yet, our models do not take into account the response of the immune system, it would be interesting to add the response of the immune system in our models of mutations. In addition, the doses of drugs are assumed to be constant but in reality this is not possible, this assumption could be adjusted by considering a drug dose that varies over time.

References

1. M.A. Nowak, R.M. May, Mathematical biology of hiv infections: antigenic variation and diversity threshold. Math. Biosci. **106**, 1–21 (1991)
2. A.S. Perelson, *Modelling Viral and Immune System Dynamics*. Macmillan Magazines Ltd, London, 2002
3. S. Bonhoeffer, M.A. Nowak, Mutation and the evolution of virulence. Roy. Soc. **258**(1352), 133–140 (1994)
4. D. Wodarz, M.A. Nowak, The effect of different immune responses on the evolution of virulent cxcr4-tropic HIV. Proc Biol Sci. **265**(1411), 2149–2158 (1998)
5. R.F. Stengel, Mutation and control of the human immunodeficiency virus, in *Presented at the 13th Yale Workshop on Adaptive and Learning Systems, Yale University, New Haven, CT May 2005* (2005)
6. N.K. Dhingra, M. Colombino, M.R. Jovanović, On the convexity of a class of structured optimal control problems for positive systems, in *2016 European Control Conference*, June 29–July 1 2016 (2016)

7. M. Colombino, N.K. Dhingra, M.R. Jovanović, R.S. Smith, Convex reformulation of a robust optimal control problem for a class of positive systems, in *2016 IEEE 55th Conference on Decision and Control (CDC) ARIA Resort & Casino* (2016), pp. 5263–5268
8. N.K. Dhingra, M. Colombino, M.R. Jovanović, Structured decentralized control of positive systems with applications to combination drug therapy and leader selection in directed networks. National Science Foundation Under Awards ECCS-1739210 and CNS-1544887 (2018)
9. M. Colombino, N.K. Dhingra, M.R. Jovanovi, A. Rantzer, R.S. Smith, On the optimal control problem for a class of monotone bilinear systems, in *22nd International Symposium on Mathematical Theory of Networks and Systems, July 11–15 2016* (2016), pp. 411–413
10. V. Jonsson, N. Matni, R.M. Murray, Reverse engineering combination therapies for evolutionary dynamics of disease: an $\mathcal{H}_\infty$ approach, in *52nd IEEE Conference on Decision and Control* (2013), pp. 2060–2065
11. V. Jonsson, A. Rantzer, R.M. Murray, A scalable formulation for engineering combination therapies for evolutionary dynamics of disease, in *American Control Conference (ACC)* (2014), pp. 2771–2778
12. V. Jonsson, N. Matni, R.M. Murray, Synthesizing combination therapies for evolutionary dynamics of disease for nonlinear pharmacodynamics, in *53rd IEEE Conference on Decision and Control* (2014), pp. 2352–2358
13. E.A. Hernandez-Vargas, R.H. Middleton, Modeling the three stages in hiv infection. J. Theor. Biol. **320**, 33–40 (2013)
14. E.A. Hernandez Vargas, *A Control Theoretic Approach to Mitigate Viral Escape in HIV* (Hamilton Institute National University of Ireland, Maynooth, 2011)
15. V. Jonsson, Robust control of evolutionary dynamics. Ph.D Thesis, California Institute of Technology (2016)
16. A. Rantzer, Scalable control of positive systems. Eur. J. Control **24**, 72–80 (2015)
17. A. Rantzer, Distributed control of positive systems. Automatic Control LTH, Lund University (2014)
18. E. Ganhy, C. de Cock de Rameyen, Optimal control techniques applied to hiv combination therapy. Master's Thesis, Université Catholique de Louvain (2014–2015)
19. M.C. Grant, S.P. Boyd, *The CVX Users' Guide* (2018)
20. R.H. Tütüncü, K.C. Toh, M.J. Todd, a matlab software package for semidefinite-quadratic-linear programming, version 3.0. Pittsburgh, PA 15213, USA (2001)