Analysis and Optimal Control of an HIV Model with Immune Response

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Abstract

An HIV model incorporating immune response is considered. The basic reproduction number is exhibited. The global stability of the virus free equilibrium is proved and the stability of the endemic equilibrium in a special case is studied. Optimal control is applied to our model to maximize the healthy cells and minimize the cost of treatments.

1 Introduction

The human immunodeficiency virus (HIV) is the pathogen responsible for one of the world's killer disease, AIDS. The pathogen targets the immune response and then the infected person can be exposed to many opportunist diseases. The mathematical framework has been considered to model the dynamic of parasite within a host, in general and HIV in particular [1, 2, 7, 8, 14, 17, 18, 25, 29, 30, 32, 34, 35, 36, 41, 45, 46] and the references

therein. A review has been done in [6].

Let us give a quick description of the dynamics of HIV within the host. When HIV invades the body, it targets the $CD4^+$ T-cells where the RNA of the virus is converted into DNA; thus, when they begin to multiply to fight this pathogen, they produce more of the virus. $CD4^+$ T-cells are responsible for signal Cytotoxic T Lymphocyte cells (CTL) -other immune cells- that an invader is to be fought. The immune response cells respond to this message and set out to eliminate infection by killing infected cells; they act by lysing infected cells, causing them to explod, thus CTL remove infected cells from the system at constant rates, but they do not directly target free virus. Over the time, HIV is able to deplete the population of $CD4^+$ T-cells, causing that CTL cells are never deployed. $CD4^+$ T-cells in a healthy person is $1000mm^{-3}$, when the cell count reaches $200mm^{-3}$ or below in a HIV-patient, then the person is classified as having AIDS [8, 16] .

The simplest and most popular model for a virus within host is [5, 33, 36]:

$$\begin{cases} \dot{T} = \sigma - \beta TV - \mu T \\ \dot{T}^* = \beta TV - \delta T^* \\ \dot{V} = \eta T^* - cV \end{cases} \tag{1}$$

where T and T^* are respectively the concentration of healthy and infected cells. The variable V represents the load of virions. Many models derived from (1) have been mathematically studied in the literature [9, 12, 14, 22, 23, 43]. However this model does not take into account to immune response, which is a key phenomenon within the dynamics of HIV in the host. Nowak and Bangham have considered the immune response in [31].

The model is:

$$\begin{cases} \dot{T} = \sigma - \beta TV - \mu T \\ \dot{T}^* = \beta TV - \delta T^* - \gamma T^* M \\ \dot{M} = \alpha T^* M - \delta M \\ \dot{V} = \eta T^* - cV \end{cases} \tag{2}$$

The model of Nowak and Bangham is 4-dimensionnal. and studying its stability is difficult. Liu [24] proved the local asymptotic stability of equilibria by using a semisymbolic method. Liu proved also that a Hopf birfucation might occur under some conditions, as pointed out by Nowak and Bangham themselves for a 5-dimensional model proposed in the same paper. Murase et al. [28] have used Liu's technique to prove the local stability of the interior equilibrium of Nowak and Bangham's model by incorporating the absorption term, i.e: $-\beta TV$ virions lost by the infection process in the dynamic of virions. In Murase et al.'s model they consider that the immune response react on virions and not on infected cells. The global stability of equilibira of Nowak and Bangham's model has been done by Souza in [40].

Yet in Nowak and Bangham's model, the immune response decay goes to zero in the absence of infected cells T^*. However, even though small, immune response is expected during the infection [1]. In this paper, the model we consider is based on (2), but divide the immune response into two compartments where M and M^* denote the inactivated and activated immune response respectively. In this model the immune response never dies out. We prove the global stability of the virus free equilibrium (VFE) and prove there is a unique endemic equilibria. We prove also its global stability of a special case.

Optimal control has been applied to HIV models in order to find out conditions that would maximize the size of healthy cells and minimize the cost of treatment [44, 17, 16, 8]. Re-

searches have suggested that treatment strategies must incorporate the action of Reverse Transcriptase (RT) inhibitors and Protease Inhibitors (PI) [1], which lead to a therapy based on drug cocktails of three or four medicaments taken in combination; indeed, the fact that HIV replicates rapidly (producing 10^{10} viral particles per day) shows that HIV is evolving so rapidly that treatment with a single drug was not effective [1, 36].

RT inhibitors based therapy inhibit reverse transcription by being incorporated into the newly synthesized viral DNA and prevent its further elongation or directly by binding to the enzyme and interfering with its function. On the other hand, PI based therapy cause infected cells to produce non-infectious virions. Virions created prior drug treatment remain infectious [36].

The aim of this paper is then double: the stability analysis and the optimal control formation which are in the literature. The paper is organized as follows: In the section 2 we analyze the model without treatment where the stability of equilibria is done. The section 3 is dedicated to the optimal control formulation. Numerical simulations are done in the last section.

2 Analysis of the Model

2.1 The model

We divide the population as follows: T and T^* describe respectively the concentration of healthy CD^+T-cells and infected cells. M and M^* are respectively unactivated and activated immune response and V is the concentration of virions. Hence the model has

the form:

$$\begin{cases} \dot{T} = \sigma - \beta TV - \mu T \\ \dot{T}^* = \beta TV - \gamma T^* M^* - \delta T^* \\ \dot{M} = \lambda - \psi T^* M - \rho M \\ \dot{M}^* = \alpha T^* M^* - \rho M^* + \psi T^* M \\ \dot{V} = \eta T^* - cV \end{cases} \tag{3}$$

In this model, σ is the constant recruitment of healthy cells from the thymus and bone marrow. A healthy cell becomes infected through contact with a HIV virion V with rate β. The parameter δ is the natural death rate of healthy CD^+T-cells. The activated immune response M^* kills infected cells by quantity $\gamma T^* M^*$. These killed infected cells produce $\alpha T^* M^*$ activated immune cells. It is biologically meaningful to consider $\gamma \geq \alpha$. This assumption means the immune cell kills more than it replicates itself by this process.The inactivated immune response is produced at constant rate λ. The infected cells stimulate the inactivated immune cells at rate ψ. Hence $\psi T^* M$ inactivated immune cells become activated. The natural death rate of both inactivated and activated immune cells is noted by ρ. The virion are produced by infected cells at rate ηT^*. This virions' production is usually proportional to the number of dead infected cells δT^*. That is why some authors (cite authors) consider the term $N\delta T^*$ as a virion's production quantity. In this model we neglect, as [25, 31, 36] the loss of virion during the infection $-\beta TV$ is neglected .

The positive orthant $\mathbb{R}^5_+$ is positively invariant for the system (3). The dynamic of healthy cells is:

$$\dot{T} = \sigma - \beta TV - \mu T \leq \sigma - \mu T$$

Hence, we have

$$\limsup_{t \to +\infty} T \leq \frac{\sigma}{\mu}$$

Similarly, $\limsup_{t\to+\infty} C \leq \frac{\sigma+\lambda}{\varepsilon}$ where $C = T + T^* + M + M^*$ and $\varepsilon = \max\{\mu, \delta, \rho\}$. Hence, the set

$$\Omega = \left\{(C, V) \in \mathbb{R}^5_+ | T \leq \frac{\sigma}{\mu}; T + T^* + M + M^* \leq \frac{\sigma+\lambda}{\varepsilon}; V \leq \frac{\eta(\sigma+\lambda)}{c\varepsilon}\right\}$$

is a compact attracting positively invariant for the system (3) since $\gamma - \alpha \geq 0$. Hence, all solutions of (3) with positive initial conditions remain positive and bounded.

2.2 Equilibria and basic reproduction number

The virus free equilibrium of (3) is given by:

$$(T_0, 0, M_0, 0, 0) = \left(\frac{\sigma}{\mu}, 0, \frac{\lambda}{\rho}, 0, 0\right)$$

and it belongs always in Ω.

The basic reproduction number ([10, 42])

$$\mathcal{R}_0 = \frac{\eta}{\delta}\frac{\beta T_0}{c}$$

denotes the number of secondary cases produced by an infected cell during its lifespan into a susceptible population. An infected cell produce $\eta\delta^{-1}$ virions during its lifespan. These virions infect during their lifespan $\eta\delta^{-1}c^{-1}\beta T_0$ on the whole healthy population. This dimensionless parameter is a key concept in mathematical epidemiology or immunology. In fact, it determines whether the disease/virus dies out or persists.

When $\mathcal{R}_0 > 1$, the infection becomes chronic. In this case, the equilibria are solutions of

the system:

$$\begin{cases} \sigma - \beta\bar{T}\bar{V} - \mu\bar{T} = 0 \\ \beta\bar{T}\bar{V} - \gamma\bar{T}^*\bar{M}^* - \delta\bar{T}^* = 0 \\ \lambda - \psi\bar{T}^*\bar{M} - \rho\bar{M} = 0 \\ \alpha\bar{T}^*\bar{M}^* - \rho\bar{M}^* + \psi\bar{T}^*\bar{M} = 0 \\ \eta\bar{T}^* - c\bar{V} = 0 \end{cases} \tag{4}$$

We show that (4) supports a single "endemic" state. The endemic relations are given by:

$$\overline{T} = \frac{\sigma c}{\beta\eta\bar{T}^* + \mu}, \quad \overline{V} = \frac{\eta}{c}\bar{T}^*, \quad \overline{M} = \frac{\lambda}{\psi\bar{T}^* + \rho}, \quad \overline{M}^* = \frac{\psi\lambda\bar{T}^*}{(\psi\bar{T}^* + \rho)(\rho - \alpha\bar{T}^*)} \quad [*]$$

The term $\rho - \alpha\bar{T}^* \neq 0$ because otherwise, the fourth equation of (4) leads to $\psi\bar{T}^*\bar{M} = 0$ and then we reach the virus free equilibrium.

By using endemic relations $[*]$ and expressing all by $\bar{T}^*$, $\bar{T}^*$ is/are the positive root(s) of the equation:

$$A\xi^3 + B\xi^2 + C\xi + D = 0 \quad (\spadesuit)$$

where:

$$\begin{aligned} A &= \beta\eta\psi\alpha\delta \\ B &= -\beta\eta\sigma\alpha\psi - \beta\eta\gamma\psi\lambda - \beta\eta\delta\rho(\psi - \alpha) + c\mu\psi\alpha\delta \\ C &= (\psi - \alpha)\beta\eta\sigma\rho - c\mu\gamma\psi\lambda - c\mu\delta\rho(\psi - \alpha) - \beta\eta\delta\rho^2 \\ D &= \beta\eta\sigma\rho^2 - c\mu\delta\rho^2 = c\mu\delta\rho^2(\mathcal{R}_0 - 1) \end{aligned}$$

Since $D > 0$, the equation (♠) has at least one negative root. We will apply the Descartes' rule of signs to determine the number of positive real zeros of (♠). According to the Descartes' rule of signs, there is no positive real root of (♠) if B and C are both positive. Let us prove this case is not possible if $\mathcal{R}_0 > 1$.

Lemma 1. *If B and C are defined as above and $\mathcal{R}_0 > 1$ then $BC < 0$.*

Proof.

$$\begin{aligned} B &= -\beta\eta\sigma\alpha\psi - \beta\eta\gamma\psi\lambda - \beta\eta\delta\rho(\psi - \alpha) + c\mu\psi\alpha\delta \\ &< -\beta\eta\sigma\alpha\psi - \beta\eta\gamma\psi\lambda + \beta\eta\delta\rho(\alpha - \psi) + \beta\eta\sigma\psi\alpha \quad \text{because} \quad \mathcal{R}_0 > 1 \\ &= -\beta\eta\gamma\psi\lambda + \beta\eta\delta\rho(\alpha - \psi) \\ &< 0 \quad \text{if} \quad (\alpha - \psi) < 0. \end{aligned}$$

If $(\alpha - \psi) > 0$, let's show that $C < 0$.

$$\begin{aligned} C &= (\psi - \alpha)\beta\eta\sigma\rho - c\mu\gamma\psi\lambda - c\mu\delta\rho(\psi - \alpha) - \beta\eta\delta\rho^2 \\ &= -(\alpha - \psi)\beta\eta\sigma\rho - c\mu\gamma\psi\lambda - c\mu\delta\rho(\psi - \alpha) - \beta\eta\delta\rho^2 \\ &< -(\alpha - \psi)c\mu\delta\rho - c\mu\gamma\psi\lambda - c\mu\delta\rho(\psi - \alpha) - \beta\eta\delta\rho^2 \quad \text{because} \quad \mathcal{R}_0 > 1 \\ &= -c\mu\gamma\psi\lambda - \beta\eta\delta\rho^2 \\ &< 0. \end{aligned}$$

Hence, in any case, B and C cannot be both positive. □

Let us assume the worst case where there are two positive roots and let set $\bar{T}_1^*$ and $\bar{T}_2^*$ the two positive roots of (♠). Without lose of generality let's suppose that $\bar{T}_1^* < \bar{T}_2^*$. By the endemic relations defined above:

• There are two corresponding endemic equilibria if and only if both $\bar{T}_1^*$ and $\bar{T}_2^*$ satisfy :

$$\rho - \alpha \bar{T}_1^* > 0 \quad \text{and} \quad \rho - \alpha \bar{T}_2^* > 0 \quad (\text{conditions to get} \quad \bar{M}^* > 0)$$

or

$$0 < \bar{T}_1^* < \bar{T}_2^* < \frac{\rho}{\alpha} \quad (\star)$$

• There's no corresponding endemic equilibrium if and only if both $\bar{T}_1^*$ and $\bar{T}_2^*$ satisfy :

$$\frac{\rho}{\alpha} < \bar{T}_1^* < \bar{T}_2^* \quad (\star\star)$$

• There's only corresponding endemic equilibrium if and only if both $\bar{T}_1^*$ and $\bar{T}_2^*$ satisfy :

$$0 < \bar{T}_1^* < \frac{\rho}{\alpha} < \bar{T}_2^* \quad (\star\star\star)$$

Let us consider the function:

$$f(\xi) = A\xi^3 + B\xi^2 + C\xi + D$$

Since $D > 0$, $\bar{T}_1^*$ and $\bar{T}_2^*$ are the two positive roots, the curve of $f(\xi)$ looks like:

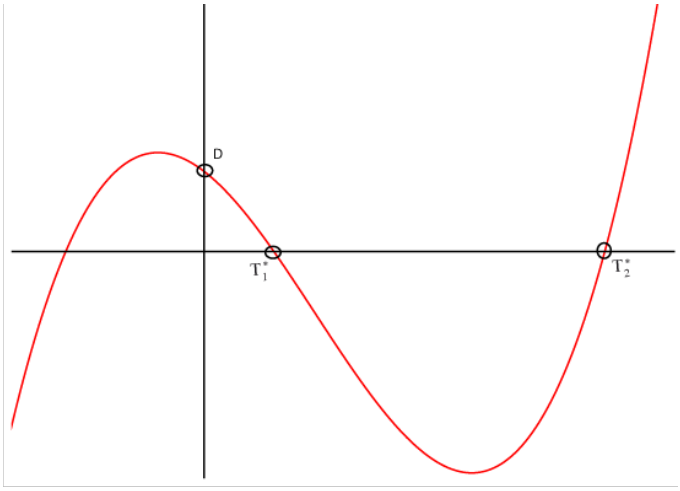

Figure 1: The shape of f

According to this curve, to satisfy the two first above conditions $(\star)$ and $(\star\star)$, we must

have $f(\frac{\rho}{\alpha}) > 0$.

And to have $(\star\star\star)$: $0 < \bar{T}_1^* < \frac{\rho}{\alpha} < \bar{T}_2^*$, which leads to the uniqueness of the endemic equilibrium, we must have $f(\frac{\rho}{\alpha}) < 0$.

$$\begin{aligned} A\frac{\rho^3}{\alpha^3} &= \beta\eta\psi\alpha\delta\frac{\rho^3}{\alpha^3} \\ &= \beta\eta\psi\delta\frac{\rho^3}{\alpha^2} \end{aligned} \tag{5}$$

$$\begin{aligned} B\frac{\rho^2}{\alpha^2} &= \Big[-\beta\eta\sigma\alpha\psi - \beta\eta\gamma\psi\Lambda + \beta\eta\delta\rho(\alpha-\psi) + c\mu\delta\psi\alpha\Big]\frac{\rho^2}{\alpha^2} \\ &= \Big[\alpha\psi(c\mu\delta - \beta\eta\sigma) - \beta\eta\gamma\psi\lambda + \beta\eta\delta\rho(\alpha-\psi)\Big]\frac{\rho^2}{\alpha^2} \\ &= \psi(c\mu\delta - \beta\eta\sigma)\frac{\rho^2}{\alpha} - \beta\eta\gamma\psi\lambda\frac{\rho^2}{\alpha^2} + \beta\eta\delta(\alpha-\psi)\frac{\rho^3}{\alpha^2} \end{aligned} \tag{6}$$

$$\begin{aligned} C\frac{\rho}{\alpha} &= \Big[(\psi-\alpha)\beta\eta\sigma\rho - c\mu\gamma\psi\lambda - c\mu\delta\rho(\psi-\alpha) - \beta\eta\delta\rho^2\Big]\frac{\rho}{\alpha} \\ &= (\psi-\alpha)\beta\eta\sigma\frac{\rho^2}{\alpha} - c\mu\gamma\psi\lambda\frac{\rho}{\alpha} - c\mu\delta(\psi-\alpha)\frac{\rho^2}{\alpha} - \beta\eta\delta\frac{\rho^3}{\alpha} \end{aligned} \tag{7}$$

Hence, we have:

$$\begin{aligned} f(\frac{\rho}{\alpha}) &= A\frac{\rho^3}{\alpha^3} + B\frac{\rho^2}{\alpha^2} + C\frac{\rho}{\alpha} + D \\ &= -\beta\eta\gamma\psi\lambda\frac{\rho^2}{\alpha^2} - c\mu\gamma\psi\lambda\frac{\rho}{\alpha} \\ &< 0 \end{aligned}$$

Hence, we have proven the proposition

Proposition 1. *If $\mathcal{R}_0 > 1$, there exists a unique endemic equilibrium of the system (3).*

2.3 Stability of equilibria

Theorem 1. *The virus free equilibrium is globally asymptotically stable if $\mathcal{R}_0 < 1$.*

Proof. Let us consider the Lyapunov function

$$\mathcal{L} = T^* + \frac{\delta}{\eta} V$$

The derivative along trajectories of (3) is:

$$\begin{aligned}
\dot{\mathcal{L}} &= \dot{T}^* + \frac{\delta}{\eta}\dot{V} \\
&= \beta T V - \gamma T^* M^* - \delta T^* + \frac{\delta}{\eta}\left(\eta T^* - cV\right) \\
&= \frac{\delta c}{\eta}\left(\frac{\beta\eta}{\delta c} T - 1\right) V - \gamma T^* M^* \\
&= \frac{\delta c}{\eta}\left(\frac{\mathcal{R}_0}{T_0} T - 1\right) V - \gamma T^* M^* \\
&\leq \frac{\delta c}{\eta}(\mathcal{R}_0 - 1) V \\
&\leq 0
\end{aligned}$$

If $\dot{\mathcal{L}} = 0$ then $\left(\frac{\beta\eta}{\delta c} T - 1\right) V = 0$ and $T^* M^* = 0$. Hence, the largest invariant set included in $\{\dot{\mathcal{L}} = 0\}$ is reduced to the virus free equilibrium. Thus by LaSalle's invariance principle [19, 20], the VFE is globally asymptotically stable. □

We proved above that the system (3) has a unique endemic equilibrium if $\mathcal{R}_0 > 1$. However we do not have its explicit expression. Since (3) is a highly nonlinear 5-dimensional system, establishing the local stability by using Routh-Hurwitz criterion becomes almost impossible. Numerical simulations suggest that this unique endemic equilibrium seems to be asymptotically stable (see Fig 2). We study analytically a particular cases of model (3).

A Special Case: We consider that the proliferation of activated immune response M^* comes only from the process of killing infected cells. This means we neglect the activation of inactivated immune response by stimulation of infected cells, i.e. the term $\psi T^* M$.

In this case, Model (3) becomes:

$$\begin{cases} \dot{T} = \sigma - \beta TV - \mu T \\ \dot{T}^* = \beta TV - \gamma T^* M^* - \delta T^* \\ \dot{M} = \lambda - \psi T^* M - \rho M \\ \dot{M}^* = \alpha T^* M^* - \rho M^* \\ \dot{V} = \eta T^* - cV \end{cases} \tag{8}$$

and Model (8) has three equilibria: The VFE E_0, the activated immune free equilibria E_1 and another interior equilibria E_2. We will study only on the interior equilibrium E_2 when it exists. In this case we can also easily get an explicit expression of this equilibrium. As in [2, 14, 21, 40], we establish the global stability of E_2 using the same kind of Lyapunov function.

Proposition 2. *If $\mathcal{R}_0 > 1$ and E_2 exists then E_2 is globally asymptotically stable.*

Proof. Let us consider the Lyapunov function:

$$\mathcal{L} = (T - \bar{T}\log T) + (T^* - \bar{T}^* \log T^*) + \frac{\beta \bar{T}}{c}(V - \bar{V}\log V) + \frac{\gamma}{\alpha}(M^* - \bar{M}^* \log M^*) + K$$

where

$$K = (\bar{T} - \bar{T}\log \bar{T}) + (\bar{T}^* - \bar{T}^* \log \bar{T}^*) + \frac{\beta \bar{T}}{c}(\bar{V} - \bar{V}\log \bar{V}) + \frac{\gamma}{\alpha}(\bar{M}^* - \bar{M}^* \log \bar{M}^*)$$

The derivative of $\mathcal{L}$ along the trajectories of (3) is given by:

$$\begin{aligned}
\dot{\mathcal{L}} &= \left(1-\frac{\bar{T}}{T}\right)\dot{T}+\left(1-\frac{\bar{T}^*}{T^*}\right)\dot{T^*}+\frac{\beta\bar{T}}{c}\left(1-\frac{\bar{V}}{V}\right)\dot{V}+\frac{\gamma}{\alpha}\left(1-\frac{\bar{M}}{M}\right)\dot{M}\\
&= \mu\bar{T}\left(2-\frac{\bar{T}}{T}-\frac{T}{\bar{T}}\right)+\beta\bar{T}\bar{V}\left(3-\frac{\bar{T}}{T}-\frac{T^*}{\bar{T}^*}\frac{\bar{V}}{V}-\frac{\bar{T}^*}{T^*}\frac{T}{\bar{T}}\frac{V}{\bar{V}}\right)-\gamma T^*M^*-\delta T^*+\gamma\bar{T}^*M^*-\gamma\bar{T}^*\bar{M}^*\\
&\quad +\beta\bar{T}\bar{V}\frac{T^*}{\bar{T}^*}+\frac{\gamma}{\alpha}\left(\alpha T^*M^*-\rho M^*-\alpha T^*\bar{M}^*+\rho\bar{M}^*\right)\\
&= C_1+C_2-\gamma T^*M^*-\delta T^*+\gamma\bar{T}^*M^*-\gamma\bar{T}^*\bar{M}^*+\beta\bar{T}\bar{V}\frac{T^*}{\bar{T}^*}+\frac{\gamma}{\alpha}\left(\alpha T^*M^*-\rho M^*-\alpha T^*\bar{M}^*+\rho\bar{M}^*\right)\\
&= C_1+C_2-\gamma T^*M^*-\delta T^*+\gamma\bar{T}^*M^*-\gamma\bar{T}^*\bar{M}^*+\beta\bar{T}\bar{V}\frac{T^*}{\bar{T}^*}\\
&\quad +\frac{\gamma}{\alpha}\left(\alpha T^*M^*-\rho M^*-\frac{\bar{M}^*}{M^*}(\alpha T^*M^*-\rho M^*)\right)\\
&= C_1+C_2-\gamma T^*M^*-\delta T^*+\gamma\bar{T}^*M^*-\gamma\bar{T}^*\bar{M}^*+\beta\bar{T}\bar{V}\frac{T^*}{\bar{T}^*}\\
&\quad +\frac{\gamma}{\alpha}\left(\alpha T^*M^*-\rho M^*-\alpha T^*\bar{M}^*+\rho\bar{M}^*\right)\\
&= C_1+C_2-\gamma T^*M^*-\delta T^*+\gamma\bar{T}^*M^*-\gamma\bar{T}^*\bar{M}^*+\beta\bar{T}\bar{V}\frac{T^*}{\bar{T}^*}\\
&\quad +\gamma T^*M^*-\rho\frac{\gamma}{\alpha}M^*-\gamma T^*\bar{M}^*+\rho\frac{\gamma}{\alpha}\bar{M}^*\\
&= C_1+C_2-\delta T^*+\beta\bar{T}\bar{V}\frac{T^*}{\bar{T}^*}-\gamma T^*\bar{M}^*\\
&= \mu\bar{T}\left(2-\frac{\bar{T}}{T}-\frac{T}{\bar{T}}\right)+\beta\bar{T}\bar{V}\left(3-\frac{\bar{T}}{T}-\frac{T^*}{\bar{T}^*}\frac{\bar{V}}{V}-\frac{\bar{T}^*}{T^*}\frac{T}{\bar{T}}\frac{V}{\bar{V}}\right)\\
&\leq 0
\end{aligned}$$

$\{\dot{V}=0\}=\{(T,T^*,V,M,M^*)\ \mid\ T=\bar{T},\ \ T^*=\bar{T}^*,\ \ V=\bar{V}\}$. Hence the invariant subset of $\{\dot{V}=0\}$ included in Ω is reduced to the E_2. By the LaSalle's invariance principle, the equilibrium E_2 is globally asymptotically stable. □

3 Optimal Control Formulation

The main purpose of formulating an optimal control problem is to determine optimal control functions u_1 and u_2 that maximize the uninfected CD4+ T-cell count and minimize the cost of treatment. With this idea in mind, let us consider the following functional

$$J(u_1, u_2) = \int_0^\tau \left(T - \frac{\alpha_1}{2}u_1^2 - \frac{\alpha_2}{2}u_2^2\right) dt$$

The goal is to obtain a pair $(\widetilde{u}_2, \widetilde{u}_1) \in \Gamma$ such that $J(\widetilde{u}_1, \widetilde{u}_2) \geq J(u_1, u_2)$, for all $(u_1, u_2) \in \Gamma$, where,

$$\Gamma = \left\{(u_1, u_2) | (u_1, u_2) \in L^2([0, \tau]), 0 \leq u_1, u_2 \leq 1\right\}$$

In other words, we want to maximize the functional J over Γ subject to the dynamical system,

$$\begin{cases} \dot{T} = \sigma - \beta(1-u_1)TV - \mu T \\ \dot{T}^* = \beta(1-u_1)TV - \gamma T^* M^* - \delta T^* \\ \dot{M} = \Lambda - \psi T^* M - \rho M \\ \dot{M}^* = \alpha T^* M^* - \rho M^* + \psi T^* M \\ \dot{V} = \eta(1-u_2)T^* - cV \\ \dot{W} = \eta u_2 T^* - cW \end{cases} \tag{9}$$

Notice that for the rest of the paper, we use Λ instead of λ to avoid any confusion with the adjoint system. We define the Hamiltoninan function given by,

$$\begin{aligned} \mathcal{H}(\cdot) \quad &= T - \tfrac{\alpha_1}{2}u^2 - \tfrac{\alpha_2}{2}v^2 + \lambda_1(\sigma - \beta(1-u_1)TV - \mu T) + \lambda_2(\beta(1-u_1)TV - \gamma T^* M^* - \delta T^*) \\ &+ \lambda_3(\Lambda - \psi T^* M - \rho M) + \lambda_4(\alpha T^* M^* - \rho M^* + \psi T^* M) + \lambda_5(\eta(1-u_2)T^* - cV) \\ &+ \lambda_6(\eta u_2 T^* - cW) + z_1 u_1 + z_2(1-u_1) + z_3(u_2) + z_4(1-u_2) \end{aligned}$$

Where $z_i \geq 0$ for $i = 1, \ldots, 4$ and,

$$z_1 u_1 = 0, \;\; z_2(1-u_1) = 0, \;\; z_3(u_2) = 0, \;\; z_4(1-u_2) = 0 \tag{10}$$

To determine the optimality conditions, it is necessary to solve the first order condition $\frac{\partial H}{\partial u_1} = 0$ and $\frac{\partial H}{\partial u_2} = 0$ to obtain,

$$u_1 = \frac{\beta TV(\lambda_1 - \lambda_2) - z_1 + z_2}{\alpha_1} \quad \text{and} \quad u_2 = \frac{\eta T^*(\lambda_6 - \lambda_5) - z_3 + z_4}{\alpha_2}$$

The next step is to use the penalty functions z_i and (10) to determine the optimal expressions for $\widetilde{u_1}$ and $\widetilde{u_2}$ to finally have,

$$\widetilde{u}_1 = \begin{cases} 0 & \frac{\beta TV(\lambda_1-\lambda_2)}{\alpha_1} \leq 0 \\ \frac{\beta TV(\lambda_1-\lambda_2)}{\alpha_1} & 0 < \frac{\beta TV(\lambda_1-\lambda_2)}{\alpha_1} < 1 \\ 1 & \frac{\beta TV(\lambda_1-\lambda_2)}{\alpha_1} \geq 1 \end{cases}$$

$$\widetilde{u}_2 = \begin{cases} 0 & \frac{\eta T^*(\lambda_6-\lambda_5)}{\alpha_2} \leq 0 \\ \frac{\eta T^*(\lambda_6-\lambda_5)}{\alpha_2} & 0 < \frac{\eta T^*(\lambda_6-\lambda_5)}{\alpha_2} < 1 \\ 1 & \frac{\eta T^*(\lambda_6-\lambda_5)}{\alpha_2} \geq 1 \end{cases}$$

However, a better way to express this functions is,

$$\widetilde{u}_1 = \max\left(0, \min\left(\frac{\beta TV(\lambda_1 - \lambda_2)}{\alpha_1}, 1\right)\right) \quad \text{and} \quad \widetilde{u}_2 = \max\left(0, \min\left(\frac{\eta T^*(\lambda_6 - \lambda_5)}{\alpha_2}, 1\right)\right)$$

Now, it is necessary to determine the adjoint equations for this problem to be solved. Pontryagin's Maximum Principle [38] establishes the adjoint equations are given by,

$$\frac{d\lambda_1}{dt} = -\frac{\partial H}{\partial T} \qquad \frac{d\lambda_2}{dt} = -\frac{\partial H}{\partial T^*} \qquad \frac{d\lambda_3}{dt} = -\frac{\partial H}{\partial M}$$
$$\frac{d\lambda_4}{dt} = -\frac{\partial H}{\partial M^*} \qquad \frac{d\lambda_5}{dt} = -\frac{\partial H}{\partial V} \qquad \frac{d\lambda_6}{dt} = -\frac{\partial H}{\partial W}$$

By doing so we get the following adjoint system of equations

$$\begin{cases} \frac{d\lambda_1}{dt} = -(1 - \lambda_1\beta(1-u_1)V + \lambda_2\beta(1-u_1)V - \mu\lambda_1) \\ \frac{d\lambda_2}{dt} = -(-\lambda_2\gamma M^* - \lambda_2\delta + \lambda_3\psi M + \lambda_4\alpha M + \lambda_4\psi M + \lambda_5\eta(1-u_2) + \lambda_6\eta u_2) \\ \frac{d\lambda_3}{dt} = -(\lambda_3\psi T^* - \lambda_3\rho + \lambda_4\psi T^*) \\ \frac{d\lambda_4}{dt} = -(-\lambda_2\gamma T^* + \lambda_4\alpha T^* - \lambda_4\rho) \\ \frac{d\lambda_5}{dt} = -(-\lambda_1\beta(1-u_1)T + \lambda_2\beta(1-u_1)T - \lambda_5 c) \\ \frac{d\lambda_6}{dt} = c\lambda_6 \end{cases} \tag{11}$$

subject to the transversality condition $\lambda_i(\tau) = 0$, for $i = 1, \ldots, 6$.

4 Numerical simulations

4.1 Model without Control

Figures (2) and (**??**) show the behavior of a patient in his initial stage of infection. The initial conditions considered were $T_0 = 1000$; $T_0^* = 0$, $M_0 = 0$, $M_0^* = 1$, $V_0 = 10$, and the parameters were $\sigma = 15$, $\beta = 0.000024$, $\mu = 0.02$, $\eta = 500$, $c = 2.4$, $\delta = 0.26$, $\Lambda = 0.1$, $\psi = 0.01$, $\rho = 0.05$ and $\alpha = 0.005$. In figure (2) it is considered $\gamma = 0.01$ and in figure (**??**) $\gamma = 1$. It is easy to see how a bigger γ has a bigger impact on reducing the effects of infection, leading to higher levels in the uninfected $CD4^+$ T-cell counts.

In both cases of the value of $\mathcal{R}_0 = 14.42$ and $T^* = 9.84$ in the figure (2) and $T^* = 4.19$ in the figure (**??**).

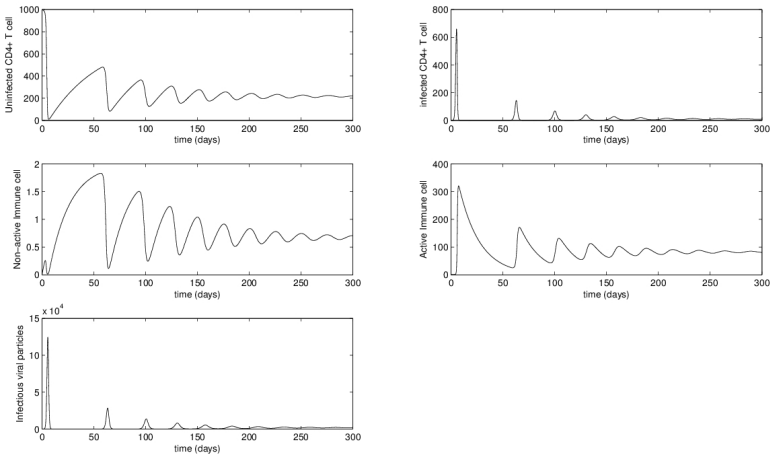

Figure 2: Graph without control

4.2 Model with Constant Control

Figure (3) exibits the behavior of the HIV dynamics considering different constant values for the control u_1 and with $u_2 = 0$ (only RTI control). The values of the initial condition and parameters are as before with $\gamma = 1$. In figure (4) is almost the same situation with $u_1 = 0$ and different constant values for u_2 (only PI control).

It is easy to see that the principal difference between both treatment is the appearance of the non-infectious viral particles because the application of PI treatment in figure (4) but this apparently do not have a big impact on cellular or viral levels compared to corresponding in figure (3). Both graphs show how increasing the effectiveness of control has a positive effect on uninfected CD4+ T-cells and a negative effect on viral loads, as expected.

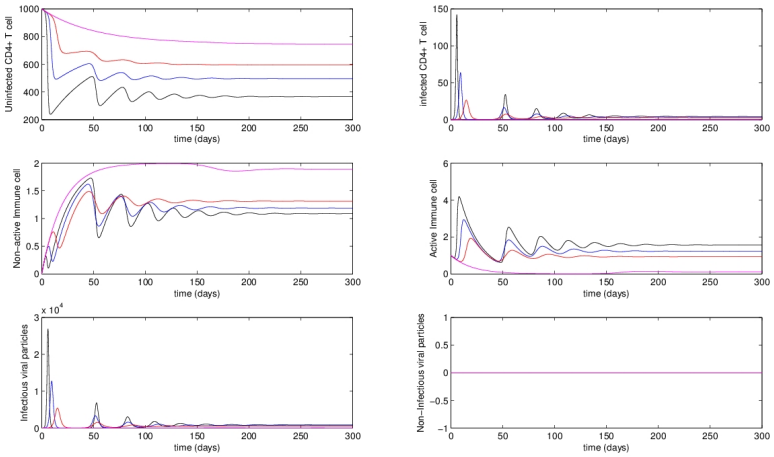

Figure 3: Graph with no control (black), control at $u_1 = 0.4$ (blue), $u_1 = 0.6$ (red) and $u_1 = 0.9$ (magenta). For the set of parameters we have $u_c = 0.931$.

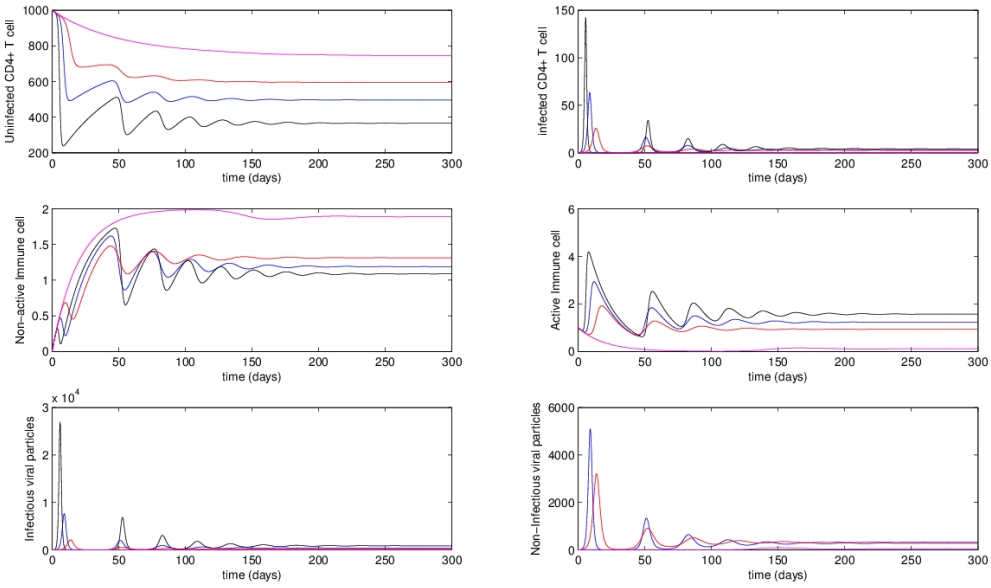

Figure 4: Graph with no control (black), control at $u_2 = 0.4$ (blue), $u_2 = 0.6$ (red) and $u_2 = 0.9$ (magenta). For the set of parameters we have $u_c = 0.931$.

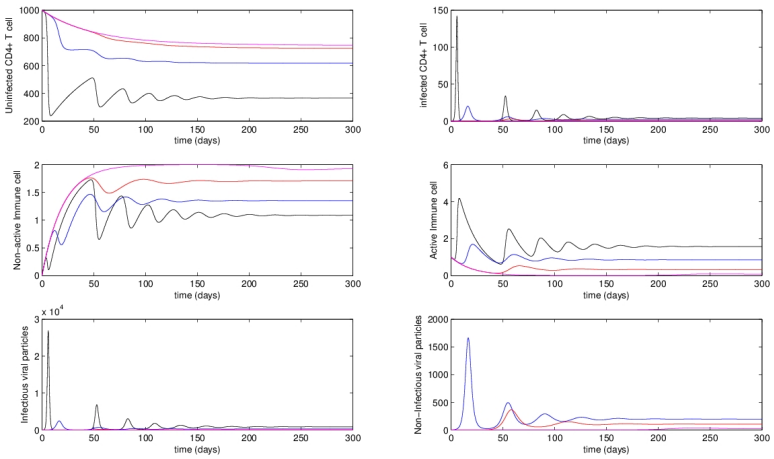

Figure 5: Graph with no control (black), control at $u_1 = u_2 = 0.4$ (blue), $u_1 = u_2 = 0.6$ (red) and $u_1 = u_2 = 0.7$ (magenta). For the set of parameters we have $u_c = 0.931$.

Figure (5) show the scenario with both control strategies and the same parameters as above. It is possible to see how lower levels on each control are needed to increase the uninfected cell count.

Figure (6) show the dynamic of the system (9) in both cases: without control and optimal controls.

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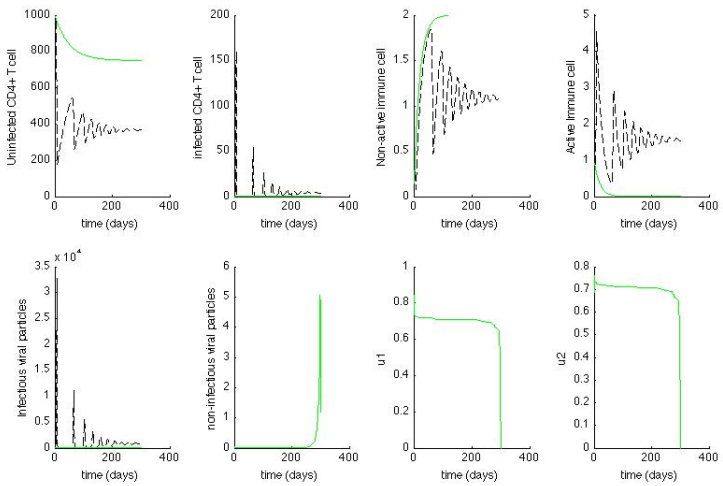

Figure 6: Graph with optimal control (green) using weight constants $\alpha_1 = \alpha_2 = 1$ and without control (black).

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