OPTIMAL CONTROL OF AN HIV MODEL WITH A TRILINEAR ANTIBODY GROWTH FUNCTION

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Abstract. We propose and study a new mathematical model of the human immunodeficiency virus (HIV). The main novelty is to consider that the antibody growth depends not only on the virus and on the antibodies concentration but also on the uninfected cells concentration. The model consists of five nonlinear differential equations describing the evolution of the uninfected cells, the infected ones, the free viruses, and the adaptive immunity. The adaptive immune response is represented by the cytotoxic T-lymphocytes (CTL) cells and the antibodies with the growth function supposed to be trilinear. The model includes two kinds of treatments. The objective of the first one is to reduce the number of infected cells, while the aim of the second is to block free viruses. Firstly, the positivity and the boundedness of solutions are established. After that, the local stability of the disease free steady state and the infection steady states are characterized. Next, an optimal control problem is posed and investigated. Finally, numerical simulations are performed in order to show the behavior of solutions and the effectiveness of the two incorporated treatments via an efficient optimal control strategy.

1. Introduction. Human immunodeficiency virus (HIV) remains a worldwide health problem that can cause the well known acquired immunodeficiency syndrome (AIDS). Once it invades the body, HIV virus begins to destruct the vast majority of CD4+ T cells, often referred to as “helper” cells. These cells can be considered the command centers of the immune system [4]. The immune system is represented by the cytotoxic T lymphocytes (CTLs) and antibodies respond to their message by attacking and killing the infected cells and HIV virus. In the last decades, many mathematical models have been developed to better describe and understand the dynamics of the HIV disease, e.g., [8, 14, 17, 25, 26]. An HIV model with adaptive immune response, two saturated rates, and therapy, is studied in [2], showing that the goal of immunity response is controlling the load of HIV viruses. Mathematical models of HIV and tuberculosis coinfection have been carried out in [7, 23, 24]. Models of HIV infection...
using optimization techniques and optimal control in the study of HIV have been investigated in [20, 21, 27]. Recently, the same problem was tackled by introducing the HIV virus dynamics into the system of equations in view of its importance in the infection [1]. Here, we continue the investigation of such kind of problems by introducing antibodies immune response. Similar models can be found in [15]. Wodarz wrote an entire monograph reviewing different models for CD8 cells [30]. In 2013, De Boer and Perelson have reviewed the existing literature on T-cell models [6]. For previous HIV modeling studies using optimal control theory to determine optimal treatment protocols, we refer the reader to [1, 7, 20, 21, 22, 24, 27] and references therein. Finally, it should be mentioned that there is abundant data on viral and T cell kinetics during HIV and simian immune deficiency (SIV) infection and the effects of therapy. For an example of an experimental study that quantifies the effects of therapy, see, e.g., [5], where data on SIV and CTL cell kinetics during primary monkey infection is provided. For similar compartmental models in different contexts see [11, 13]. The main novelty here is to consider that the antibody growth depends not only on the virus and on the antibodies concentration but also on the uninfected cells concentration. That was never investigated before, from a mathematical point of view, but it is very important since the role of the immune response to HIV infection has been recently recognized by the medical literature to be of a great value. Indeed, it is now well known that the CTL immune response grows depending on the infected cells. This growth also depends on the number of CTL cells themselves. Moreover, the antibody immune response grows depending on the virus proliferation and this growth also depends on the number of viruses. Because the growth of the immune system cells depends on the number of healthy target cells CD4+ T cells, hence the trilinear term to describe the growth of the immune responses [4, 29, 31]. The goal of HIV virus is to destruct CD4+ T cells, often named “messengers” or the command centers of the immune system. Once the virus invades the body, these cells give a signal to the immune system. The immune system is represented by CTL and antibodies that respond to this message and set out to eliminate the infection by killing infected cells and free virus. To include into the model the antibodies participation in controlling the infection is thus essential. The mathematical model we propose is the following one:

\[
\begin{align*}
\frac{dx}{dt} &= \lambda - dx - \beta xv, \\
\frac{dy}{dt} &= \beta xv - ay - pyz, \\
\frac{dv}{dt} &= aNy - \mu v - qw, \\
\frac{dz}{dt} &= cxyz - hz, \\
\frac{dw}{dt} &= gxvw - aw,
\end{align*}
\]

with given initial conditions

\[
x(0) = x_0, \quad y(0) = y_0, \quad v(0) = v_0, \quad z(0) = z_0, \quad w(0) = w_0.
\]

In this model, \(x(t), y(t), v(t), z(t),\) and \(w(t)\) denote the concentrations of uninfected cells, infected cells, HIV virus, CTL cells, and antibodies at time \(t\), respectively. The healthy CD4+ T cells \((x)\) grow at a rate \(\lambda\), die at a rate \(d\), and become infected by the virus at a rate \(\beta xv\). Infected cells \((y)\), die at a rate \(a\) and are killed by the
CTLs response at a rate $p$. Free virus $(v)$ is produced by the infected cells at a rate $aN$, die at a rate $\mu$, and decay in the presence of antibodies at a rate $q$, where $N$ is the number of free virus produced by each actively infected cell during its life time. CTLs $(z)$ expand, in response to viral antigen derived from infected cells, at a rate $c$ and decay in the absence of antigenic stimulation at a rate $h$. Finally, antibodies $(w)$ develop in response to free virus at a rate $g$ and decay at a rate $\alpha$. It is worthy to note that all the model rates are assumed to be nonnegative.

The paper is organized as follows. Section 2 is devoted to the existence, positivity, and boundedness of solutions. The analysis of the model is carried out in Section 3. In Section 4, an HIV optimal control problem is posed and solved. Then, in Section 5, the results are illustrated through numerical simulations. We finish with Section 6 of conclusions.

2. Well-posedness of solutions. For problems dealing with cell population evolution, the cell densities should remain non-negative and bounded. In this section, we establish the positivity and boundedness of solutions of the model (1). First of all, for biological reasons, the parameters $x_0$, $y_0$, $v_0$, $z_0$, and $w_0$, must be larger than or equal to zero. Hence, we have the following result.

Proposition 1. The solutions of the problem (1) exist. Moreover, they are bounded and nonnegative for all $t > 0$.

Proof. First, we show that the nonnegative orthant $\mathbb{R}^5_+ = \{(x, y, v, z, w) \in \mathbb{R}^5 : x \geq 0, y \geq 0, v \geq 0, z \geq 0 \text{ and } w \geq 0\}$ is positively invariant. Indeed, for $(x(t), y(t), v(t), z(t), w(t)) \in \mathbb{R}^5_+$, we have: $\dot{x} |_{x=0} = \lambda \geq 0$, $\dot{y} |_{y=0} = \beta xv \geq 0$, $\dot{v} |_{v=0} = aN y \geq 0$, $\dot{z} |_{z=0} = 0 \geq 0$, and $\dot{w} |_{w=0} = 0 \geq 0$. Therefore, all solutions initiating in $\mathbb{R}^5_+$ are positive. Next, we prove that these solutions remain bounded. Remark that, by adding the two first equations in (1), we have $\dot{x}_1 = \lambda - dx - ay - pyz$, thus

$$x_1(t) \leq x_1(0)e^{-\delta t} + \frac{\lambda}{\delta}(1 - e^{-\delta t}),$$

where $x_1(t) = x(t) + y(t)$ and $\delta = \min(d; a)$. Since $0 \leq e^{-\delta t} \leq 1$ and $1 - e^{-\delta t} \leq 1$, we deduce that $x_1(t) \leq x_1(0) + \frac{\lambda}{\delta}$. Therefore, $x$ and $y$ are bounded. From the equation $\dot{v} = aNy - \mu v - qvw$, we have

$$v(t) \leq v(0)e^{-\mu t} + aN \int_0^t y(\xi)e^{(\xi-t)\mu}d\xi.$$

Then,

$$v(t) \leq v(0) + \frac{aN}{\mu} \|y\|_\infty (1 - e^{-\mu t}).$$

Since $1 - e^{-\mu t} \leq 1$, we have $v(t) \leq v(0) + \frac{aN}{\mu} \|y\|_\infty$. Thus, $v$ is bounded. Now, we prove the boundedness of $z$. From the fourth equation of (1), we have

$$\dot{z}(t) + hz(t) = cz(t)y(t)z(t).$$

Moreover, from the second equation of (1), it follows that

$$\dot{z}(t) + hz(t) = \sum_{p} x(t) \left(\beta z(t)v(t) - ay(t) - \dot{y}(t)\right).$$
By integrating over time, we have
\[ z(t) = z(0)e^{-ht} + \int_0^t \frac{c}{p} x(s) (\beta x(s) v(s) - ay(s) - \dot{y}(s)) e^{h(s-t)} ds. \]

From the boundedness of \(x, y,\) and \(v,\) and by using integration by parts, it follows the boundedness of \(z.\) The two equations \(\dot{v}(t) = aNy(t) - \mu v(t) - qv(t)w(t)\) and \(\dot{w}(t) = gx(t)v(t)w(t) - \alpha w(t)\) imply
\[
\dot{w}(t) + \alpha w(t) = gx(t)v(t)w(t) = \frac{g}{q} x(t) (aNy(t) - \dot{v}(t) - \mu v(t)) .
\]

Then,
\[
w(t) = w(0)e^{-\alpha t} + \int_0^t \frac{g}{q} x(s) (aNy(s) - \mu v(s) - \dot{v}(s)) e^{\alpha(s-t)} ds .
\]

From the boundedness of \(x, y,\) and \(v,\) and by integration by parts, it follows the boundedness of \(w.\)

3. Analysis of the model. In this section, we show that there exists a disease-free equilibrium point and four infection equilibrium points. Moreover, we study the stability of these equilibrium points.

3.1. Stability of the disease-free equilibrium. System (1) has an infection-free equilibrium \(E_f = \left( \lambda d, 0, 0, 0, 0 \right),\) corresponding to the maximal level of healthy CD4\(^+\) T-cells. In this case, the disease cannot invade the cell population. By a simple calculation [28], the basic reproduction number of (1) is given by
\[ R_0 = \frac{\lambda N \beta d}{\mu}. \]

At any arbitrary point, the Jacobian matrix of the system (1) is given by
\[
J = \begin{pmatrix}
-d - \beta v & 0 & -\beta x & 0 & 0 \\
\beta v & -a - pz & \beta x & -py & 0 \\
0 & aN & -\mu - qw & 0 & -qv \\
cyz & cxz & 0 & cyx - h & 0 \\
gvw & 0 & gxw & 0 & gxv - \alpha
\end{pmatrix}.
\]

Proposition 2.

1. The disease-free equilibrium, \(E_f,\) is locally asymptotically stable for \(R_0 < 1.\)
2. The disease-free equilibrium, \(E_f,\) is unstable for \(R_0 > 1.\)

Proof. At the disease-free equilibrium, \(E_f,\) the Jacobian matrix is given as follows:
\[
J_{E_f} = \begin{pmatrix}
-d & 0 & -\beta \lambda & 0 & 0 \\
0 & -a & \beta \lambda & 0 & 0 \\
0 & aN & -\mu & 0 & 0 \\
0 & 0 & 0 & -h & 0 \\
0 & 0 & 0 & 0 & -\alpha
\end{pmatrix}.
\]

The characteristic polynomial of \(J_{E_f}\) is
\[ P_{E_f}(\xi) = (\xi + d)(\xi + \alpha)(\xi + h)[\xi^2 + (a + \mu)\xi + a\mu(1 - R_0)] \]
and the eigenvalues of the matrix \( J_E \) are
\[
\begin{align*}
\xi_1 &= -d, \\
\xi_2 &= -\alpha, \\
\xi_3 &= -h, \\
\xi_4 &= \frac{-(a+\mu) - \sqrt{(a+\mu)^2 - 4a\mu(1-R_0)}}{2}, \\
\xi_5 &= \frac{-(a+\mu) + \sqrt{(a+\mu)^2 - 4a\mu(1-R_0)}}{2}.
\end{align*}
\]
It is clear that \( \xi_1, \xi_2, \xi_3 \) and \( \xi_4 \) are negative. Moreover, \( \xi_5 \) is negative when \( R_0 < 1 \), which means that \( E_f \) is locally asymptotically stable.

3.2. Infection steady states. We now focus on the existence and stability of the infection steady states. All these steady states exist when the basic reproduction number exceeds the unity and the disease invasion is always possible. In fact, it is easily verified that the system (1) has four of them:
\[
\begin{align*}
E_1 &= \left( \frac{\mu}{\beta N}, \frac{d\mu(1-R_0) - d(1-R_0)}{\beta}, 0, 0 \right), \\
E_2 &= \left( \frac{\lambda g - \alpha \beta}{d\mu}, \frac{\alpha \beta}{\lambda g - \alpha \beta}, \frac{a\alpha d}{p(R_{CTL} - 1)}, 0, 0 \right), \\
E_3 &= \left( \frac{\lambda g - \alpha \beta}{d\mu}, \frac{\alpha \beta}{\lambda g - \alpha \beta}, \frac{a\alpha d}{p(R_{CTL} - 1)}, 0, 0 \right), \\
E_4 &= \left( \frac{\lambda g - \alpha \beta}{d\mu}, \frac{\alpha \beta}{\lambda g - \alpha \beta}, \frac{a\alpha d}{p(R_{CTL,W} - 1)}, 0, 0 \right).
\end{align*}
\]
Here the endemic equilibrium point \( E_1 \) represents the equilibrium case in the absence of the adaptive immune response (CTLs and antibody responses). The endemic equilibria points \( E_2 \) and \( E_3 \) represent the equilibrium case in the presence of only one kind of the adaptive immune response, antibody response and CTL response, respectively, while the last endemic equilibrium point \( E_4 \) represents the equilibrium case of chronic HIV infection with the presence of both kinds of adaptive immune response, CTLs and antibody. In order to study the local stability of the points \( E_1, E_2, E_3 \) and \( E_4 \), we first define the following numbers:
\[
R_{CTL} = \frac{N\beta}{\mu} \left( \frac{\lambda g - \alpha \beta}{d\mu} \right),
\]
where \( R_{CTL} \) represents the reproduction number in presence of CTL immune response,
\[
R_W = \frac{N\beta(\lambda g - \alpha \beta)}{\mu d\mu},
\]
where \( R_W \) represents the reproduction number in presence of antibody immune response,
\[
R_{1,CTL,W} = \frac{a\alpha d}{\alpha \mu c} \quad \text{and} \quad R_{2,CTL,W} = \frac{\alpha \beta c(\lambda g - \alpha \beta)}{a\mu c},
\]
where \( R_{1,CTL,W} \) and \( R_{2,CTL,W} \) represent the reproduction number in presence of antibody immune response and CTL immune response, respectively. For the first point \( E_1 \), we have the following result.

**Proposition 3.** 1. If \( R_0 < 1 \), then the point \( E_1 \) does not exist.
2. If \( R_0 = 1 \), then \( E_1 = E_f \).
3. If \( R_0 > 1 \), then \( E_1 \) is locally asymptotically stable for \( R^W < 1 \) and \( R^{CTL} < 1 \). However, it is unstable for \( R^W > 1 \) or \( R^{CTL} > 1 \).

Proof. Let \( \lambda \mu c - aN\beta h > 0 \). It is easy to see that if \( R_0 < 1 \), then the point \( E_1 \) does not exist and if \( R_0 = 1 \), then the two points \( E_1 \) and \( E_f \) coincide. If \( R_0 > 1 \), then the Jacobian matrix at \( E_1 \) is given by

\[
J_{E_1} = \begin{pmatrix}
-d - \beta v_1 & 0 & -\beta x_1 & 0 & 0 \\
\beta v_1 & -a & \beta x_1 & -p y_1 & 0 \\
0 & aN & -\mu & 0 & -q v_1 \\
0 & 0 & 0 & cx_1 y_1 - h & 0 \\
0 & 0 & 0 & 0 & gx_1 v_1 - \alpha
\end{pmatrix}.
\]

Its characteristic equation is

\[(cx_1 y_1 - h - \xi)(gx_1 v_1 - \alpha - \xi)(\xi^3 + A_1 \xi^2 + B_1 \xi + C_1) = 0,
\]

where
\[
A_1 = a + \mu + dR_0, \\
B_1 = ad + \mu dR_0 + ad(R_0 - 1), \\
C_1 = ad\mu(R_0 - 1).
\]

Direct calculations lead to
\[
 gx_1 v_1 - \alpha = D_1(R^W - 1) \text{ and } cx_1 y_1 - h = D_2(R^{CTL} - 1)
\]

with
\[
D_1 = \frac{dg\mu}{N\beta^2} \text{ and } D_2 = \frac{dc\mu^2}{aN^2\beta^2}.
\]

The sign of the eigenvalue \( D_1(R^W - 1) \) is negative if \( R^W < 1 \), zero if \( R^W = 1 \), and positive if \( R^W > 1 \). The sign of the eigenvalue \( D_2(R^{CTL} - 1) \) is negative if \( R^{CTL} < 1 \), zero if \( R^{CTL} = 1 \), and positive if \( R^{CTL} > 1 \). On the other hand, we have \( A_1 > 0 \) and \( A_1B_1 - C_1 > 0 \) (as \( R_0 > 1 \)). From the Routh–Hurwitz theorem [10], the other eigenvalues of the above matrix have negative real parts. Consequently, \( E_1 \) is unstable when \( R^W > 1 \) or \( R^{CTL} > 1 \) and locally asymptotically stable when \( R_0 > 1 \), \( R^W < 1 \), and \( R^{CTL} < 1 \).

For the second endemic-equilibrium point \( E_2 \), we have the following result.

**Proposition 4.**
1. If \( R^{CTL} < 1 \), then the point \( E_2 \) does not exists and \( E_2 = E_1 \) when \( R^{CTL} = 1 \).
2. If \( R^{CTL} > 1 \) and \( R^{CTL,W}_1 \leq 1 \), then \( E_2 \) is locally asymptotically stable.
3. If \( R^{CTL} > 1 \) and \( R^{CTL,W}_1 > 1 \), then \( E_2 \) is unstable.

Proof. Let \( \lambda \mu c - aN\beta h > 0 \). If \( R^{CTL} < 1 \), then the point \( E_2 \) does not exists and \( E_2 = E_1 \) when \( R^{CTL} = 1 \). We assume that \( R^{CTL} > 1 \). The Jacobian matrix of \( E_2 \) is given as follows:

\[
J_{E_2} = \begin{pmatrix}
-d - \beta v_2 & 0 & -\beta x_2 & 0 & 0 \\
\beta v_2 & -a - p z_2 & \beta x_2 & -p y_2 & 0 \\
0 & aN & -\mu & 0 & -q v_2 \\
c y_2 z_2 & c x_2 z_2 & 0 & cx_2 y_2 - h & 0 \\
0 & 0 & 0 & 0 & gx_2 v_2 - \alpha
\end{pmatrix}.
\]

The characteristic equation of the system (1) at the point \( E_2 \) is given by

\[(gx_2 v_2 - 1 - \xi)(\xi^4 + A_2 \xi^3 + B_2 \xi^2 + C_2 \xi + D_2) = 0,
\]
Proof.

It is clear that when \( E \) then \( J \) the characteristic equation associated with the above matrix have negative real part when \( \langle CTL \rangle > 1 \), and positive if \( \langle CTL \rangle < 1 \).

On the other hand, from the Routh–Hurwitz theorem, the other eigenvalues of the above matrix have negative real parts when \( \langle CTL \rangle > 1 \). Consequently, \( E_2 \) is unstable when \( \langle CTL \rangle > 1 \) and \( \langle CTL \rangle > 1 \) and locally asymptotically stable when \( \langle CTL \rangle > 1 \) and \( \langle CTL \rangle < 1 \).

For the third endemic-equilibrium point \( E_3 \), the following result holds.

**Proposition 5.**

1. If \( R^W < 1 \), then the point \( E_3 \) does not exist and \( E_3 = E_1 \) when \( R^W = 1 \).
2. If \( R^W > 1 \), then \( E_3 \) is locally asymptotically stable for \( \langle CTL \rangle < 1 \) and unstable if \( \langle CTL \rangle > 1 \).

**Proof.** It is clear that when \( R^W < 1 \) the point \( E_3 \) does not exist and, if \( R^W = 1 \), then \( E_3 = E_1 \). We assume that \( R^W > 1 \). The Jacobian matrix of the system at point \( E_3 \) is given by

\[
J_{E_3} = \begin{pmatrix}
-d - \beta v_3 & 0 & -\beta x_3 & 0 & 0 \\
\beta v_3 & -a & \beta x_3 & -p_y & 0 \\
0 & aN & -\mu - qw_3 & 0 & -qv_3 \\
0 & 0 & 0 & cx_3 y_3 - h & 0 \\
gx_3 w_3 & 0 & gx_3 w_3 & 0 & gx_3 v_3 - \alpha
\end{pmatrix}.
\]

The characteristic equation associated with \( J_{E_3} \) is given by

\[(cx_3 y_3 - h - \xi)(\xi^4 + A_3 \xi^3 + B_3 \xi^2 + C_3 \xi + D_3) = 0,
\]

where

\[
A_3 = a + d + \mu + \beta v_3 + qw_3,
B_3 = (d + \beta v_3)(a + \mu) + a\mu + (d + a + \alpha + \beta v_3)qw_3 - aN\beta x_3,
C_3 = a\mu(d + \beta v_3) + (ad + ad + a\alpha + a\beta v_3)qw_3 - aNd\beta x_3,
D_3 = ad\alpha qw_3.
\]

Here \( cx_3 y_3 - h \) is an eigenvalue of \( J_{E_3} \). By assuming \( cx_3 y_3 - h = h \left( \langle CTL \rangle - 1 \right) \), we deduce that the sign of this eigenvalue is negative when \( \langle CTL \rangle < 1 \), zero when \( \langle CTL \rangle = 1 \), and positive for \( \langle CTL \rangle > 1 \). On the other hand, from the Routh–Hurwitz theorem, the other eigenvalues of the above matrix have negative real parts when \( R^W > 1 \). Consequently, \( E_3 \) is unstable when \( \langle CTL \rangle > 1 \) and locally asymptotically stable when \( R^W > 1 \) and \( \langle CTL \rangle < 1 \).

For the last endemic-equilibrium point \( E_4 \), we prove the following result.
Proposition 6.

1. If $R_{CTL,W}^3 < 1$ or $R_{CTL,W}^4 < 1$, then the point $E_4$ does not exists. Moreover, $E_4 = E_3$ when $R_{CTL,W}^4 = 1$ and $E_4 = E_2$ when $R_{CTL,W}^3 = 1$.

2. If $R_{CTL,W}^3 > 1$ and $R_{CTL,W}^4 > 1$, then $E_4$ is locally asymptotically stable.

Proof. It is clear that when $R_{CTL,W}^3 < 1$ or $R_{CTL,W}^4 < 1$ the point $E_4$ does not exists and, if $R_{CTL,W}^4 = 1$, then $E_4 = E_3$ and $E_4 = E_2$ when $R_{CTL,W}^3 = 1$. We assume that $R_{CTL,W}^3 > 1$ and $R_{CTL,W}^4 > 1$. The Jacobian matrix of the system at the point $E_4$ is given by

$$J_{E_4} = \begin{pmatrix}
-d - \beta v_4 & 0 & -\beta x_4 & 0 & 0 \\
\beta v_4 & -a - pz_4 & \beta x_4 & -p y_4 & 0 \\
0 & aN & -\mu - qw_4 & 0 & -q v_4 \\
c y_4 z_4 & c x_4 z_4 & 0 & c x_4 y_4 - h & 0 \\
g y_4 w_4 & 0 & g x_4 w_4 & 0 & g x_4 v_4 - \alpha \\
\end{pmatrix}.$$  (3)

The characteristic equation associated with $J_{E_4}$ is given by

$$\xi^5 + A_4 \xi^4 + B_4 \xi^3 + C_4 \xi^2 + D_4 \xi + E_4 = 0,$$

where

$$A_4 = a + d + \mu + \beta v_4 + pz_4 + qw_4,$$

$$B_4 = (d + \beta v_4)(a + \mu) + a\mu + pz_4(d + h + \mu + \beta v_4 + qw_4) + qw_4(d + a + \alpha + \beta v_4) - aN\beta x_4,$$

$$C_4 = a\mu(d + \beta v_4) + pz_4(dh + d\mu + \mu h + \mu \beta v_4 + h\beta v_4) + qw_4(a + d + a\alpha + a\beta v_4) + pq z_4 w_4(d + a + h + \beta v_4) - aN\beta dx_4,$$

$$D_4 = adqw_4 + pz_4(d\mu + dh + \mu h + \mu \beta v_4 - aN\beta hy_4) + pq z_4 w_4(d\alpha + a\beta v_4 + h\alpha),$$

$$E_4 = ahd(pq z_4 w_4 + aN\beta v_4 - aN\beta x_4).$$

From the Routh–Hurwitz theorem applied to the fifth order polynomial, the eigenvalues of the Jacobian matrix (3) have negative real parts since we have $A_4 > 0$, $A_4 B_4 > C_4$, $A_4 B_4 C_4 > A_4^2 D_4$, and $A_4 B_4 C_4 D_4 > A_4 B_4^2 E_4 + A_4^2 D_4^2$. Consequently, we obtain the asymptotic local stability of the endemic point $E_4$.

4. Optimal control. In this section, we study an optimal control problem by introducing drug therapy into the model (1) and assuming that treatment reduces the viral replication. Our purpose is to find a treatment strategy $u(t)$ that maximizes the number of CD4$^+$ T-cells as well as the number of CTL and antibody immune response, keeping the cost, measured in terms of chemotherapy strength and a combination of duration and intensity, as low as possible.
4.1. The optimization problem. To apply optimal control theory, we suggest the following control system with two control variables:

\[
\begin{aligned}
\frac{dx(t)}{dt} &= \lambda - dx(t) - \beta(1 - u_1(t))x(t)v(t), \\
\frac{dy(t)}{dt} &= \beta(1 - u_1(t))x(t)v(t) - ay(t) - py(t)z(t), \\
\frac{dv(t)}{dt} &= aN(1 - u_2(t))y(t) - \mu v(t) - qv(t)w(t), \\
\frac{dz(t)}{dt} &= cx(t)y(t)z(t) - hz(t), \\
\frac{dw(t)}{dt} &= gx(t)v(t)w(t) - \alpha w(t).
\end{aligned}
\]

Here, \(u_1\) represents the efficiency of drug therapy in blocking new infection, so that infection rate in the presence of drug is \((1 - u_1)\); while \(u_2\) stands for the efficiency of drug therapy in inhibiting viral production, such that the virion production rate under therapy is \((1 - u_2)\). Our optimization problem consists to maximize the following objective functional:

\[
J(u_1, u_2) = \int_0^{t_f} \left\{ x(t) + z(t) + w(t) - \left[ \frac{A_1}{2} u_1^2(t) + \frac{A_2}{2} u_2^2(t) \right] \right\} dt,
\]

where \(t_f\) is the time period of treatment and the positive constants \(A_1\) and \(A_2\) stand for the costs of the introduced treatment. The two control functions, \(u_1\) and \(u_2\), are assumed to be bounded and Lebesgue integrable. We look for \(u_1^*\) and \(u_2^*\) such that

\[
J(u_1^*, u_2^*) = \max \left\{ J(u_1, u_2) : (u_1, u_2) \in U \right\},
\]

where \(U\) is the control set defined by

\[
U = \{(u_1(\cdot), u_2(\cdot)) : u_i(\cdot) \text{ is measurable, } 0 \leq u_i(t) \leq 1, t \in [0, t_f], i = 1, 2\}.
\]

Note that it is natural to maximize the number of CTL and immune response in the optimal control problem. Indeed, it has been noted clinically that individuals who maintain a high level of CTLs remain healthy longer. Therefore, we wish to maximize the number of CTL so as to ensure that if viral load does rebound, the immune system will be able to handle it. The best drug treatments should establish this result, while keeping adverse effects to a minimum.

4.2. Existence of an optimal control pair. The existence of the optimal control pair can be directly obtained using the results in [9, 12]. More precisely, we have the following theorem.

**Theorem 4.1.** There exists an optimal control pair \((u_1^*, u_2^*) \in U\) solution of (4)–(6).

**Proof.** To use the existence result in [9], we first need to check the following properties:

- \((P_1)\) the set of controls and corresponding state variables is nonempty;
- \((P_2)\) the control set \(U\) is convex and closed;
- \((P_3)\) the right-hand side of the state system is bounded by a linear function in the state and control variables;
- \((P_4)\) the integrand of the objective functional is concave on \(U\);
By applying Pontryagin’s minimum principle \( \lambda \)

\[
L(x, z, w, u_1, u_2) = x + z + w - \left( \frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2 \right)
\]

of the objective functional (5) satisfies

\[
L(x, z, w, u_1, u_2) \leq c_2 - c_1 (|u_1|^2 + |u_2|^2)^{\frac{3}{2}}.
\]

Using the result in [12], we obtain existence of solutions of system (4), which gives condition \((P_1)\). The control set is convex and closed by definition, which gives condition \((P_2)\). Since our state system is bilinear in \( u_1 \) and \( u_2 \), the right-hand side of system (4) satisfies condition \((P_3)\), using the boundedness of solutions. Note that the integrand of our objective functional is concave. Also, we have the last needed condition:

\[
L(x, z, w, u_1, u_2) \leq c_2 - c_1 (|u_1|^2 + |u_2|^2),
\]

where \(c_2\) depends on the upper bound on \(x\), and \(c_1 > 0\) since \(A_1 > 0\), \(A_2 > 0\). We conclude that there exists an optimal control pair \((u_1^*, u_2^*) \in U\) such that 

\[
J(u_1^*, u_2^*) = \max_{(u_1, u_2) \in U} J(u_1, u_2).
\]

\[\square\]

Theorem 4.1 does not provide a uniqueness result for the optimal control problem. The uniqueness of the optimal controls is obtained in terms of the unique solution of the optimality system.

### 4.3. The optimality system

Pontryagin’s minimum principle provides necessary optimality conditions for such optimal control problem [19]. This principle transforms (4), (5) and (6) into a problem of minimizing an Hamiltonian, \(H\), pointwisely with respect to \( u_1 \) and \( u_2 \), where

\[
H(t, x, y, z, w, u_1, u_2, \lambda) = \frac{A_1}{2}u_1^2 + \frac{A_2}{2}u_2^2 - x - z - w + \sum_{i=0}^{5} \lambda_i f_i
\]

with

\[
\begin{align*}
    f_1 &= \lambda - dx - \beta(1 - u_1)xv, \\
    f_2 &= \beta(1 - u_1)xv - ay - pyz, \\
    f_3 &= \alpha N(1 - u_2)y - \mu v - qvw, \\
    f_4 &= cxyz - hz, \\
    f_5 &= gxyz - aw.
\end{align*}
\]

By applying Pontryagin’s minimum principle [19], we obtain the following result.

**Theorem 4.2.** Given optimal controls \( u_1^*, u_2^* \), and solutions \( x^*, y^*, v^*, z^* \), and \( w^* \) of the corresponding state system (4), there exists adjoint variables \( \lambda_1, \lambda_2, \lambda_3, \lambda_4, \) and \( \lambda_5 \) satisfying the equations

\[
\begin{align*}
    \lambda_1'(t) &= 1 + \lambda_1(t) [d + (1 - u_1^*(t)) \beta v^*(t)] - \lambda_2(t) (1 - u_1^*(t)) \beta v^*(t) - \lambda_4(t) cy^*(t) z^*(t) - \lambda_3(t) gw^*(t) w^*(t), \\
    \lambda_2'(t) &= \lambda_2(t) (a + pz^*(t)) - \lambda_3(t) (1 - u_2^*(t)) aN - \lambda_4(t) cx^*(t) z^*(t), \\
    \lambda_3'(t) &= \lambda_3(t) (1 - u_1^*(t)) \beta x^*(t) - \lambda_2(t) (1 - u_1^*(t)) \beta v^*(t) + \lambda_5(t) (\mu + qw^*(t)) - \lambda_5(t) (a + qz^*(t)) w^*(t), \\
    \lambda_4'(t) &= 1 + \lambda_2(t) py^*(t) + \lambda_4(t) [h - cx^*(t) y^*(t)], \\
    \lambda_5'(t) &= 1 + \lambda_3(t) qw^*(t) + \lambda_5(t) [a - gx^*(t) v^*(t)] + \lambda_5(t) (\mu + qw^*(t)).
\end{align*}
\]

(7)
with the transversality conditions

$$\lambda_i(t_f) = 0, \quad i = 1, \ldots, 5. \quad (8)$$

Moreover, the optimal control is given by

$$u_1^*(t) = \min \left(1, \max \left(0, \frac{\beta}{A_1} \left(\lambda_2(t) - \lambda_1(t)x^*(t)v^*(t)\right)\right)\right),$$

$$u_2^*(t) = \min \left(1, \max \left(0, \frac{1}{A_2} \lambda_3(t)Ny^*(t)\right)\right). \quad (9)$$

Proof. The proof of positivity and boundedness of solutions is similar to the one of Proposition 1. It is enough to use the fact that $u_i(\cdot) \in U, i = 1, 2$, which means that $\|u_i(\cdot)\|_{L^\infty} \leq 1$. For the rest of the proof, we remark that the adjoint equations and transversality conditions are obtained by using the Pontryagin minimum principle of [19], from which

$$\begin{align*}
\lambda_1'(t) &= -\frac{\partial H}{\partial x}, \quad \lambda_1(t_f) = 0, \\
\lambda_2'(t) &= -\frac{\partial H}{\partial y}, \quad \lambda_2(t_f) = 0, \\
\lambda_3'(t) &= -\frac{\partial H}{\partial v}, \quad \lambda_3(t_f) = 0, \\
\lambda_4'(t) &= -\frac{\partial H}{\partial z}, \quad \lambda_4(t_f) = 0, \\
\lambda_5'(t) &= -\frac{\partial H}{\partial w}, \quad \lambda_5(t_f) = 0.
\end{align*}$$

From the optimality conditions

$$\frac{\partial H}{\partial u_1} = 0 \quad \text{and} \quad \frac{\partial H}{\partial u_2} = 0,$$

that is,

$$A_1u_1(t) + \lambda_1(t)\beta x^*(t)v^*(t) - \lambda_2(t)\beta x^*(t)v^*(t) = 0,$$

$$A_2u_2(t) - aNy^*(t)\lambda_3(t) = 0,$$

and taking into account the bounds in $U$ for the two controls, one obtains $u_1^*$ and $u_2^*$ in the form (9).

The optimality system consists of the state system (4) coupled with the adjoint equations (7), the initial conditions (2), transversality conditions (8), and the characterization of optimal controls (9). Precisely, if we substitute the expressions of $u_1^*$
and $u_1^*$ in (4), then we obtain the following optimality system:

$$
\begin{align*}
\frac{dx^*(t)}{dt} &= \lambda - dx^*(t) - \beta (1 - u_1^*(t)) x^*(t) v^*(t), \\
\frac{dy^*(t)}{dt} &= \beta (1 - u_1^*(t)) x^*(t) v^*(t) - ay^*(t) - py^*(t) z^*(t), \\
\frac{dv^*(t)}{dt} &= aN (1 - u_2^*(t)) y^*(t) - \mu v^*(t) - qv^*(t) w^*(t), \\
\frac{dz^*(t)}{dt} &= cx^*(t) y^*(t) z^*(t) - h z^*(t), \\
\frac{dw^*(t)}{dt} &= gx^*(t) v^*(t) w^*(t) - \alpha w^*(t), \\
\frac{d\lambda_1(t)}{dt} &= 1 + \lambda_1(t) \left[ d + (1 - u_1^*(t)) \beta v^*(t) \right] - \lambda_2(t) (1 - u_1^*(t)) \beta v^*(t) \\
&- \lambda_4(t) c y^*(t) z^*(t) - \lambda_5(t) g v^*(t) w^*(t), \\
\frac{d\lambda_2(t)}{dt} &= \lambda_2(t) (a + pz^*(t)) - \lambda_3(t) (1 - u_2^*(t)) aN - \lambda_4(t) c x^*(t) z^*(t), \\
\frac{d\lambda_3(t)}{dt} &= \lambda_1(t) (1 - u_1^*(t)) \beta x^*(t) - \lambda_2(t) (1 - u_1^*(t)) \beta x^*(t) \\
&+ \lambda_3(t) (\mu + qw^*(t)) - \lambda_5(t) g x^*(t) w^*(t), \\
\frac{d\lambda_4(t)}{dt} &= 1 + \lambda_2(t) py^*(t) + \lambda_4(t) [h - c x^*(t) y^*(t)], \\
\frac{d\lambda_5(t)}{dt} &= 1 + \lambda_3(t) g v^*(t) + \lambda_5(t) [a - g x^*(t) v^*(t)], \\

u_1^* &= \min \left( 1, \max \left( 0, \frac{\beta}{A_1} \left[ (\lambda_2(t) - \lambda_1(t)) x^*(t) v^*(t) \right] \right) \right), \\

u_2^* &= \min \left( 1, \max \left( 0, \frac{1}{A_2} \lambda_3(t) a N y^*(t) \right) \right), \\
\lambda_i(t_f) &= 0, \quad i = 1, \ldots, 5.
\end{align*}
$$

5. Numerical simulations. In order to solve the optimality system (10), we use a numerical scheme based on forward and backward finite difference approximations. Precisely, we implemented Algorithm 1.

For our numerical simulations, we have chosen the following parameters (see Table 1): $\lambda = 1$, $d = 0.1$, $\beta = 0.00025$, $p = 0.01$, $a = 0.2$, $c = 0.03$, $N = 2000$, $\mu = 2.4$, $h = 0.2$, $g = 0.00013$, $\alpha = 0.12$, $q = 0.01$, $A_1 = 250$, $A_2 = 2500$. These parameters show the stability of the last endemic point $E_4$ with all non-zero system components. The initial value of each system component is given as follows: $x_0 = 5,$
Algorithm 1 Numerical algorithm for the optimal control problem (4)–(6).

Step 1:

\[ x(0) = x_0, \quad y(0) = y_0, \quad v(0) = v_0, \quad z(0) = z_0, \quad w(0) = w_0, \quad u_1(0) = 0, \]
\[ u_2(0) = 0, \quad \lambda_1(t_f) = 0, \quad \lambda_2(t_f) = 0, \quad \lambda_3(t_f) = 0, \quad \lambda_4(t_f) = 0, \quad \lambda_5(t_f) = 0. \]

Step 2:
for \( i = 0, \ldots, n - 1 \), do:

\[ x_{i+1} = x_i + h[\lambda - dx_i - \beta(1 - u_1^i)x_iv_i], \]
\[ y_{i+1} = y_i + h[\beta(1 - u_1^i)x_i - \mu y_i - py_iz_i], \]
\[ v_{i+1} = v_i + h[\alpha N(1 - u_2^i)y_i - \mu v_i - qv_iw_i], \]
\[ z_{i+1} = z_i + h[\lambda x_i y_i z_i - h z_i], \]
\[ w_{i+1} = w_i + h[g x_i v_i w_i - \alpha w_i], \]
\[ \lambda_1^{n-i-1} = \lambda_1^{n-i} - h[1 + \lambda_1^{n-i}(d + (1 - u_1^i)\beta v_i + 1)] \]
\[ - \lambda_2^{n-i}(1 - u_1^i)\beta v_i + 1 - \lambda_2^{n-i}e v_i z_i + 1 - \lambda_5^{n-i}g v_i w_i + 1, \]
\[ \lambda_2^{n-i-1} = \lambda_2^{n-i} - h[\lambda_1^{n-i}(a + p z_i + 1)] \]
\[ - \lambda_3^{n-i}(a N(1 - u_2^i)) - \lambda_4^{n-i}c x_i z_i + 1], \]
\[ \lambda_3^{n-i-1} = \lambda_3^{n-i} - h[\lambda_1^{n-i}(1 - u_1^i)\beta x_i + 1 - \lambda_2^{n-i}(1 - u_1^i)\beta x_i + 1] \]
\[ + \lambda_3^{n-i}(\mu + q v_i + 1) - \lambda_5^{n-i}g x_i + 1 w_i + 1], \]
\[ \lambda_4^{n-i-1} = \lambda_4^{n-i} - h[1 + \lambda_2^{n-i}p x_i + 1 + \lambda_4^{n-i}(h - c x_i + 1 y_i + 1)], \]
\[ \lambda_5^{n-i-1} = \lambda_5^{n-i} - h[1 + \lambda_3^{n-i}q v_i + 1 + \lambda_5^{n-i}e x_i + 1 y_i + 1] + \lambda_5^{n-i}(\alpha + g x_i + 1 w_i + 1)], \]
\[ R_1^{i+1} = (\beta/A_1)(\lambda_2^{n-i} e v_i - m_1 x_i - m_1 - \lambda_1^{n-i} e v_i x_i + m_1), \]
\[ R_2^{i+1} = (1/A_2)\lambda_3^{n-i+1}a N y_i + 1, \]
\[ u_1^{i+1} = \min(1, \max(R_1^{i+1}, 0)), \]
\[ u_2^{i+1} = \min(1, \max(R_2^{i+1}, 0)). \]

end for.

Step 3:
for \( i = 1, \ldots, n \), write:

\[ x^*(t_i) = x_i, \quad y^*(t_i) = y_i, \quad v^*(t_i) = v_i, \quad z^*(t_i) = z_i, \quad w^*(t_i) = w_i, \]
\[ u_1^*(t_i) = u_1^i, \quad u_2^*(t_i) = u_2^i. \]

end for.

\[ y_0 = 1, \quad v_0 = 1, \quad z_0 = 2, \quad \text{and} \quad w_0 = 1. \] In Fig. 1, it can be clearly seen that, after introducing therapy, the uninfected cells population grows significantly compared with those without control.
### Table 1. Parameters, their symbols and meaning, and default values used in HIV literature.

| Parameters | Meaning | Value | References |
|------------|---------|-------|------------|
| \( \lambda \) | source rate of CD4+ T cells | 1–10 cells \( \mu l^{-1} \) days\(^{-1} \) | [4] |
| \( d \) | decay rate of healthy cells | 0.007–0.1 days\(^{-1} \) | [4] |
| \( \beta \) | rate at which CD4+ T cells become infected | 0.00025–0.5 \( \mu l \) virion\(^{-1} \) days\(^{-1} \) | [4] |
| \( a \) | death rate of infected CD4+ T cells, not by CTL | 0.2–0.3 days\(^{-1} \) | [4] |
| \( \mu \) | clearance rate of virus | 2.06–3.81 days\(^{-1} \) | [18] |
| \( N \) | number of virions produced by infected CD4+ T-cells | 6.25–23599.9 virion\(^{-1} \) | [3, 29] |
| \( p \) | clearance rate of infection | \( 1–4.048 \times 10^{-4} \) ml virion days\(^{-1} \) | [3, 16] |
| \( c \) | activation rate of CTL cells | 0.0051–3.912 days\(^{-1} \) | [3] |
| \( h \) | death rate of CTL cells | 0.004–8.087 days\(^{-1} \) | [3] |
| \( q \) | Neutralization rate of virions | 0.12 days\(^{-1} \) | Assumed |
| \( g \) | activation rate of antibodies | 0.00013 days\(^{-1} \) | Assumed |
| \( \alpha \) | death rate of antibodies | 0.12 days\(^{-1} \) | Assumed |

Figure 1. The evolution of the uninfected cells during time.

Figure 2 shows that, with control, the number of infected cells are significantly reduced after few weeks of therapy. Nevertheless, without control, this number remains much higher.

Figure 2. The evolution of the infected cells during time.
Figure 3 shows that, with control, the viral load decreases towards a very low level after the first days of therapy, whereas, without control, it remains much higher. This indicates the impact of the administrated therapy in controlling viral replication.

\[\text{Figure 3. The evolution of the HIV virus during time.}\]

Figures 4 and 5 show the adaptive immune response as function of time. The adaptive immunity is clearly affected by the control. Their curves converge towards zero with control, whereas, without any control, it converges towards 66.2721 for CTL cells and converge towards 48.888 for antibodies immune response.

\[\text{Figure 4. The evolution of the CTL cells during time.}\]

\[\text{Figure 5. The evolution of the antibodies during time.}\]
We note that all the curves (without control) of previous figures converge towards the endemic point with coordinates $(7.6923, 0.8666, 120.66, 48.888)$. This result is in good agreement with the result of Proposition 6, since with our chosen parameters we have $R_0 = 2.0833 > 1$, $R_{CTL,W}^1 = 1.2037 > 1$, and $R_{CTL,W}^2 = 1.3313 > 1$. The behavior of the two treatments during time is given in Fig. 6. The curves present the drug administration schedule during the time of treatment. This figure shows that we should give more importance to the first drug (RTIs) than to the second one (PIs).

![Figure 6. The behaviour of the two optimal controls.](image)

6. **Conclusion.** In this work, we proposed and studied a mathematical model describing the human immunodeficiency virus with adaptive immune response and a trilinear antibody growth function. The main novelty in the model is to consider that the antibody growth depends not only on the virus and on the antibodies concentration but also on the uninfected cells concentration, which is supported by recent medical discoveries. After proposing the new mathematical model, positivity and boundedness of solutions were established. Then, local stability of the disease free steady state and the infection steady states was investigated. Next, an optimal control problem was proposed and studied. Two types of treatments were incorporated into the model: the purpose of the first consists to block the viral proliferation, while the role of the second one is to prevent new infections. Finally, numerical simulations were performed, confirming the stability of the free and endemic equilibria and illustrating the effectiveness of the two incorporated treatments via optimal control.

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