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Mathematical analysis of HIV model with two saturated rates, CTL and antibody responses

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Abstract. The mathematical model of the Human Immunodeficiency Virus (HIV) pathogenesis with Cytotoxic T Lymphocytes (CTL) and antibody responses is presented in this paper. The model includes the cure of infected cells and two saturated rates describing viral infection and CTL proliferation. The positivity and boundedness of solutions for nonnegative initial data are proved which is consistent with the biological studies. The disease free steady state is locally asymptotically stable when the basic reproduction number is less than unity ($R_0 < 1$). The existence of four infection steady states when $R_0 > 1$ is established. The local stability of these infection steady states depend on the basic reproduction number R_0, the CTL immune response reproduction number D_0^Z and the antibody immune response reproduction number D_0^W. Numerical simulations are performed to show the behavior of solutions and the effectiveness of CTL and antibody responses in controlling HIV replication, this can improve the quality of patient care.

Keywords: HIV infection, viral dynamics, antibody response modelling

1 Introduction

Human Immunodeficiency Virus (HIV) is known as a pathogen causing the Acquired Immunodeficiency Syndrome (AIDS), which is the end-stage of the infection. After that the immune system fails to play its role[1, 2]. In the last decades, many mathematical models describing HIV dynamics were developed[3–8]. For example, the model describing the interaction between the HIV viruses, CD4$^+$ T cells and the Cytotoxic T Lymphocytes taking into account two saturated rates describing viral infection and Cytotoxic T Lymphocytes (CTL) proliferation is studied in [8]. The authors show how the cellular immune response can control the load of the HIV viruses. In this paper, we extend the latter work by incorporating the antibody response into the model and study its role in the dynamics and stability of the derived model. Recently, many works have highlighted the role of antibodies in controlling viral replication and then improving the patient life quality[9–12]. The dynamics of HIV infection with CTL and antibody responses that we consider is given by the following nonlinear system of differential equations:

$$\begin{cases} \frac{dT}{dt} = s - dT - \frac{\beta VT}{1+aV} + \rho I, \\ \frac{dI}{dt} = \frac{\beta VT}{1+aV} - (\delta + \rho)I - pIZ, \\ \frac{dV}{dt} = N\delta I - \mu V - qVW, \\ \frac{dW}{dt} = gVW - hW, \\ \frac{dZ}{dt} = \frac{cIZ}{1+\alpha I} - bZ. \end{cases} \tag{1}$$

With the initial conditions $T(0) = T_0$, $I(0) = I_0$, $V(0) = V_0$, $Z(0) = Z_0$ and $W(0) = W_0$.

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In this model, T, I, V, Z and W denote the concentration of uninfected cells, infected cells, free virus, CTL cells and antibodies, respectively. Susceptible host cells CD4$^+$ T cells are produced at a rate s, die at a rate dT and become infected by virus at a rate $\frac{\beta VT}{1+aV}$. Infected cells die at a rate δI and are killed by the CTL response at a rate pIZ. Free virus is produced by infected cells at a rate $N\delta I$ and decays in the presence of antibodies at a rate $\mu V + qVW$. CTLs expand in response to viral antigen derived from infected cells at a rate $\frac{cIZ}{1+\alpha I}$ and decay in the absence of antigenic stimulation at a rate bZ. Finally, antibodies develop in response to free virus at a rate gVW and decay at a rate hW.

Note that this model (1), includes a cure rate ρ of the infected cells to the susceptible host cells due to the noncytolytic processes[13, 14]. The model contains also two saturated rate, the first is the saturated mass action[15, 16] which describe better the rate of viral infection while the second is the saturated function describing CTL proliferation when it is reduced by the presence of immune impairment effects caused by HIV infection[17].

2 Positivity and boundedness of solutions

For the problems deal with cell population evolution, the cell densities should remain non-negative and bounded. In this section, we will establish the positivity and boundedness of solutions of the model (1). First of all, for biological reasons, the parameters T_0, I_0, V_0, W_0 and Z_0 must be larger than or equal to 0. Hence, we have the following result:

Proposition 1 *The solutions of the problem (1) exist. Moreover, they are bounded, nonnegative and verify:*

i) $T_1(t) \leq T_1(0) + \frac{s}{\delta_1}$,
ii) $V(t) \leq V(0) + \frac{N\delta}{\mu} \|I\|_\infty$,
iii) $W(t) \leq W(0) + \frac{g}{q}[\max(1; 2 - \frac{\mu}{h})V(0) + (\frac{N\delta}{\mu} + \frac{N\delta}{h}) \|I\|_\infty]$,
iv) $Z(t) \leq Z(0) + \frac{c}{p}[\max(1; 2 - \frac{d}{b})T(0) + I(0) + \max(\frac{s}{b}; \frac{s}{d}) + \max(0; 1 - \frac{\delta}{b}) \|I\|_\infty]$,

where $T_1(t) = T(t) + I(t)$ *and* $\delta_1 = \min(d; \delta)$.

Proof. First, we will show the nonnegative orthant $\mathbb{R}^5_+ = \{(T, I, V, W, Z) \in \mathbb{R}^5 : T \geq 0, I \geq 0, V \geq 0, W \geq 0 \text{ and } Z \geq 0\}$ is a positively invariant region. Indeed, for $(T(t), I(t), V(t), W(t), Z(t)) \in \mathbb{R}^5_+$ we have: $\dot{T} \mid_{T=0} = s + \rho I \geq 0$, $\dot{I} \mid_{I=0} = \frac{\beta VT}{1+aV} \geq 0$, $\dot{V} \mid_{V=0} = N\delta I \geq 0$, $\dot{W} \mid_{W=0} = 0 \geq 0$ and $\dot{Z} \mid_{Z=0} = 0 \geq 0$. Therefore, all solutions initiating in $\mathbb{R}^5_+$ are positive. Also, we will prove that these solutions are bounded. First, by adding the first and second equation in (1), we have $\dot{T_1} = s - dT - \delta I - pIZ$, thus

$$T_1(t) \leq T_1(0)e^{-\delta_1 t} + \frac{s}{\delta_1}(1 - e^{-\delta_1 t})$$

since $0 \leq e^{-\delta_1 t} \leq 1$ and $1 - e^{-\delta_1 t} \leq 1$, we deduce (i).

From the equation $\dot{V} = N\delta I - \mu V - qVW$, we have

$$V(t) \leq V(0)e^{-\mu t} + N\delta \int_0^t I(\xi)e^{(\xi - t)\mu} d\xi$$

then,

$$V(t) \leq V(0) + \frac{N\delta}{\mu} \|I\|_\infty (1 - e^{-\mu t})$$

Since $1 - e^{-\mu t} \leq 1$, we have (ii).

The two equations $\dot{V} = N\delta I - \mu V - qVW$ and $\dot{W} = gVW - hW$ imply

$$\dot{W} + hW = gVW = \frac{g}{q}\left(N\delta I - (\dot{V} + \mu V)\right)$$

then,

$$W(t) = W_0 e^{-ht} + \frac{g}{q}\left\{\int_0^t [N\delta I(\xi) + (h-\mu)V(s)]e^{h(\xi-t)}d\xi - V(t) + V(0)e^{-ht}\right\}.$$

If $h - \mu \leq 0$, then we have

$$W(t) \leq W_0 + \frac{g}{q}\left\{\frac{N\delta}{h}\left\|I\right\|_\infty + V(0)\right\},$$

else, we will have

$$W(t) \leq W_0 + \frac{g}{q}\left\{(\frac{N\delta}{h} + \frac{N\delta}{\mu})\left\|I\right\|_\infty + (2 - \frac{\mu}{h})V(0)\right\}.$$

From the two last inequalities, we deduce (iii).

Finally, from the equation $\dot{Z} = \frac{cIZ}{1+\alpha I} - bZ$ we have

$$\dot{Z} + bZ \leq cIZ.$$

Since $cIZ = \frac{c}{p}[s - (\dot{T} + dT) - (\dot{I} + \delta I)]$, we get

$$Z(t) \leq [\frac{c}{p}(T(0) + I(0) - \frac{s}{b}) + Z(0)]e^{-bt} + \frac{c}{p}\{\frac{s}{b} + \int_0^t [(b-d)T(\xi) + (b-\delta)I(\xi)]e^{b(\xi-t)}d\xi - T(t) - I(t)\}.$$

Following the same reasoning as in the previous cases for each sign of the $(b-d)$ and $(b-\delta)$, we will deduce (iv).

3 Analysis of the model

This section is devoted to the stability analysis of the disease-free equilibrium and the endemic equilibrium points. Also, we will give numerical simulations for each case.

3.1 Stability of the disease-free equilibrium

System (1) has an infection-free equilibrium $E_f = (\frac{s}{d}, 0, 0, 0, 0)$, corresponding to the maximal level of healthy CD4$^+$ T-cells. By a simple calculation, the basic reproduction number of ((1)) is given by

$$R_0 = \frac{\beta N \delta s}{d\mu(\delta + \rho)}. \tag{2}$$

At any arbitrary point, the Jacobian matrix of the system ((1)), is given by

$$J = \begin{pmatrix} -d - \frac{\beta V}{1+aV} & \rho & -\frac{\beta T}{(1+aV)^2} & 0 & 0 \\ \frac{\beta V}{1+aV} & -(\delta+\rho) - pZ & \frac{\beta T}{(1+aV)^2} & 0 & -pI \\ 0 & N\delta & -\mu - qW & -qV & 0 \\ 0 & 0 & gW & gV - h & 0 \\ 0 & \frac{cZ}{(1+\alpha I)^2} & 0 & 0 & \frac{cI}{1+\alpha I} - b \end{pmatrix} \tag{3}$$

Proposition 2 *The two following assertions hold:*

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:

$$J_{E_f} = \begin{pmatrix} -d & \rho & -\frac{\beta s}{d} & 0 & 0 \\ 0 & -(\delta+\rho) & \frac{\beta s}{d} & 0 & 0 \\ 0 & N\delta & -\mu & 0 & 0 \\ 0 & 0 & 0 & -h & 0 \\ 0 & 0 & 0 & 0 & -b \end{pmatrix} \tag{4}$$

The characteristic polynomial of J_{E_f} is

$$P_{E_f}(\xi) = (\xi + d)(\xi + b)(\xi + h)[\xi^2 + (\delta + \rho + \mu)\xi + (\delta + \rho)\mu(1 - R_0)],$$

then the eigenvalues of the matrix J_{E_f} are

$$\xi_1 = -d, \xi_2 = -b, \xi_3 = -h,$$
$$\xi_4 = \frac{-(\delta + \rho + \mu) - \sqrt{(\delta + \rho + \mu)^2 - 4(\delta + \rho)\mu(1 - R_0)}}{2},$$
$$\xi_5 = \frac{-(\delta + \rho + \mu) + \sqrt{(\delta + \rho + \mu)^2 - 4(\delta + \rho)\mu(1 - R_0)}}{2},$$

it is clear that ξ_1, ξ_2, ξ_3 and ξ_4 are negative. Moreover, ξ_5 is negative when $R_0 < 1$, which mean that E_f is locally asymptotically stable.

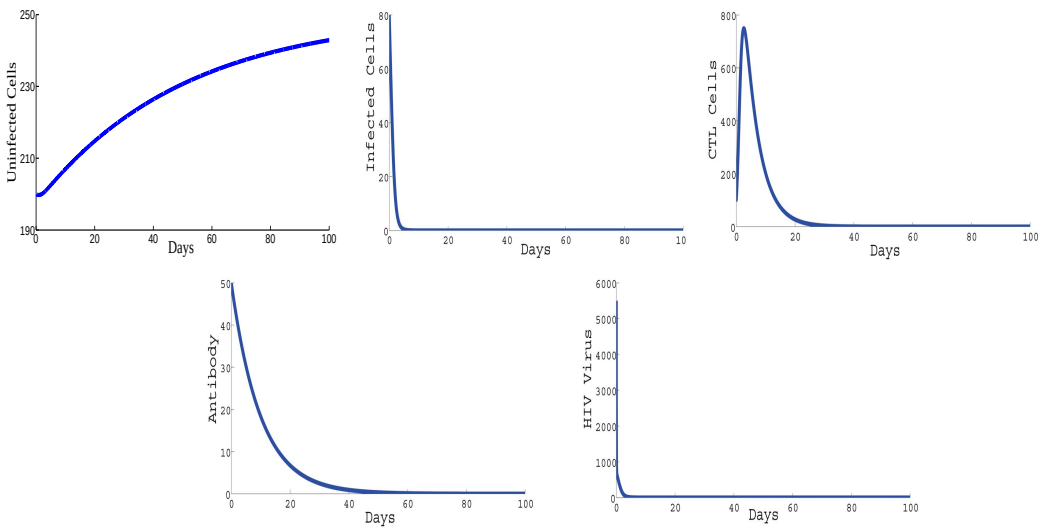

Fig. 1: Behavior of the infection during the time for $s = 5$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 500$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.5$, $g = 10^{-11}$ and $h = 0.1$, which correspond to the stability of the free-equilibrium E_f.

3.2 Infection steady states

In this subsection, attention is focused on the stability of the infection steady states. Indeed, it is easy see that the system (1) has four of them: $E_1 = (T_1, I_1, V_1, 0, 0)$, where

$$T_1 = \frac{s}{d}[\frac{aNs + \mu}{aNs + \mu R_0}], I_1 = \frac{s}{\delta}[\frac{\mu(R_0 - 1)}{aNs + \mu R_0}], V_1 = \frac{Ns(R_0 - 1)}{aNs + \mu R_0}, E_2 = (T_2, I_2, V_2, W_2, 0),$$

where

$$T_2 = \frac{(\rho + \delta)(g + ah)s}{d(\rho + \delta)(g + ah) + \beta\delta h}, I_2 = \frac{\beta hs}{d(\rho + \delta)(g + ah) + \beta\delta h},$$
$$V_2 = \frac{h}{g}, W_2 = \frac{\mu}{q}[\frac{N\delta\beta gs}{\mu[d(\rho + \delta)(g + ah) + \beta\delta h]} - 1],$$

$E_3 = (T_3, I_3, V_3, 0, Z_3)$, where

$$I_3 = \frac{b}{c-\alpha b}, T_3 = \frac{(aN\delta\rho)I_3^2 + (aNs\delta + \mu\rho)I_3 + \mu s}{N\delta(ad+\beta)I_3 + \mu d},$$
$$V_3 = \frac{N\delta I_3}{\mu}, Z_3 = \frac{-N\delta[ad\rho + \delta(ad+\beta)]I_3 + (\beta Ns\delta - d\mu(\rho+\delta))}{p(N\delta(ad+\beta)I_3 + \mu d)},$$

and $E_4 = (T_4, I_4, V_4, W_4, Z_4)$, where

$$I_4 = \frac{b}{c-\alpha b}, V_4 = \frac{h}{g}, T_4 = \frac{(s+\rho I_4)(1+aV_4)}{d(1+aV_4)+\beta V_4},$$
$$W_4 = \frac{1}{q}(\frac{N\delta I_4}{V_4} - 1), Z_4 = \frac{1}{p}(\frac{s}{I_4} - \frac{dT_4}{I_4} - \delta).$$

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:

$$D_0^W = \frac{gNs}{h\mu},\ \widetilde{D_0^W} = D_0^W \frac{\mu R_0}{(aNs + \mu R_0)},\ H_0^W = \frac{1}{\frac{1}{R_0} + \frac{1}{\widetilde{D_0^W}}},$$

$$D_0^Z = \frac{cs}{b\delta},\ \widetilde{D_0^Z} = D_0^Z \frac{\mu R_0}{(aNs + \mu R_0) + \alpha\mu(R_0 - 1)},\ H_0^Z = \frac{1}{\frac{1}{R_0} + \frac{1}{\widetilde{D_0^Z}}}$$

and

$$H_0^{W,Z} = \frac{D_0^Z R_0}{D_0^W(1 + \frac{ah}{g}) + R_0(1 + \frac{\alpha s^2}{\delta})},$$

where D_0^Z represents the CTL immune response reproduction number, D_0^W represents the antibody immune response reproduction number, H_0^W is the half harmonic mean of R_0 and $\widetilde{D_0^W}$ and H_0^Z is the half harmonic mean of R_0 and $\widetilde{D_0^Z}$.

Theorem 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 $H_0^W < 1$, and $H_0^Z < 1$; however it is unstable for $H_0^W > 1$ or $H_0^Z > 1$.

Proof. It easy to see that if $R_0 < 1$, then the point E_1 does not exist and if $R_0 = 1$ the two points E_1 and E_f coincide. If $R_0 > 1$, the Jacobian matrix at E_1 is given by

$$J_{E_1} = \begin{pmatrix} -d - \frac{\beta V_1}{1+aV_1} & \rho & -\frac{\beta T_1}{(1+aV_1)^2} & 0 & 0 \\ \frac{\beta V_1}{1+aV_1} & -(\delta+\rho) & \frac{\beta T_1}{(1+aV_1)^2} & 0 & -pI_1 \\ 0 & N\delta & -\mu & -qV_1 & 0 \\ 0 & 0 & 0 & gV_1 - h & 0 \\ 0 & 0 & 0 & 0 & \frac{cI_1}{1+\alpha I_1} - b \end{pmatrix}$$

then, its characteristic equation is

$$(\xi + h - gV_1)(\xi + b - \frac{cI_1}{1+\alpha I_1})(\xi^3 + a_1\xi^2 + a_2\xi + a_3) = 0,$$

where

$$a_1 = d + \delta + \mu + \rho + \frac{\beta V_1}{1+aV_1},$$
$$a_2 = (\delta+\mu+\rho)d + (\mu+\delta)\frac{\beta V_1}{1+aV_1} + \mu(\delta+\rho) - \frac{N\delta\beta T_1}{(1+aV_1)^2},$$
$$a_3 = \mu d(\delta+\rho) + \frac{\mu\delta\beta V_1}{1+aV_1} - \frac{N\delta\beta T_1 d}{(1+aV_1)^2}.$$

Simple calculation leads to $gV_1 - h = \frac{h\widetilde{D_0^W}(H_0^W - 1)}{H_0^W}$ and $\frac{cI_1}{1+\alpha I_1} - b = \frac{b\widetilde{D_0^Z}(H_0^Z - 1)}{H_0^Z}$. They are two eigenvalues of J_{E_1}. The sign of the eigenvalue $\frac{h\widetilde{D_0^W}(H_0^W - 1)}{H_0^W}$ is negative if $H_0^W < 1$, zero if $H_0^W = 1$ and positive if $H_0^W > 1$. The sign of the eigenvalue $\frac{b\widetilde{D_0^Z}(H_0^Z - 1)}{H_0^Z}$ is negative if $H_0^Z < 1$, zero if $H_0^Z = 1$ and positive if $H_0^Z > 1$. On the other hand, we have $a_1 > 0$ and $a_1 a_2 - a_3 > 0$ (as $R_0 > 1$). From the Routh-Hurwitz Theorem[18], the other eigenvalues of the above matrix have negative real parts. Consequently, E_1 is unstable when $H_0^W > 1$ or $H_0^Z > 1$ and locally asymptotically stable when $R_0 > 1$, $H_0^W < 1$ and $H_0^Z < 1$.

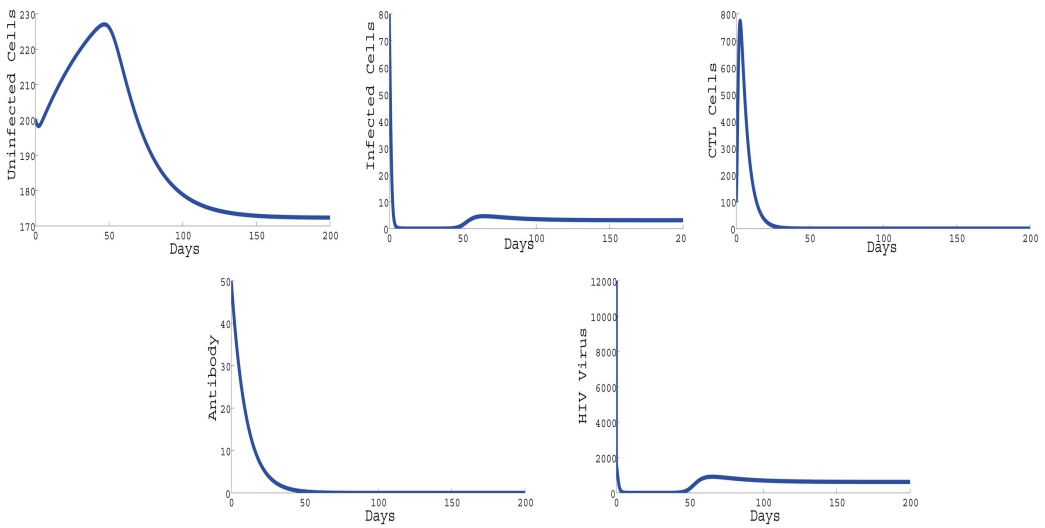

Fig. 2: Behavior of the infection during the time for $s = 5$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.5$, $g = 10^{-11}$ and $h = 0.1$, which correspond to the stability of the endemic-equilibrium point E_1.

For the second endemic-equilibrium point E_2, we have the following result:

Theorem 4. *1. If $H_0^W < 1$, then the point E_2 does not exist.*
2. If $H_0^W = 1$ then $E_2 = E_1$.
3. If $H_0^W > 1$ then E_2 is locally asymptotically stable for $H_0^{W,Z} < 1$ and unstable for $H_0^{W,Z} > 1$.

Proof. We notice that the condition $H_0^W > 1$ is equivalent to $V_2 < V_1$. It easy to verify that the point E_2 does not exist if $H_0^W < 1$; moreover, we have $E_2 = E_1$ when $H_0^W = 1$. Now, we assume that $H_0^W > 1$, the Jacobian matrix at E_2 is

$$J_{E_3} = \begin{pmatrix} -d - \frac{\beta V_2}{1+aV_2} & \rho & -\frac{\beta T_2}{(1+aV_2)^2} & 0 & 0 \\ \frac{\beta V_2}{1+aV_2} & -\rho - \delta & \frac{\beta T_2}{(1+aV_2)^2} & 0 & -pI_2 \\ 0 & N\delta & -\mu - qW_2 & -\frac{qh}{g} & 0 \\ 0 & 0 & gW_2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{cI_2}{1+\alpha I_2} - b \end{pmatrix}$$

The characteristic equation associated with J_{E_2} is given by

$$(\frac{cI_2}{1+\alpha I_2} - b - \xi)(\xi^4 + b_1\xi^3 + b_2\xi^2 + b_3\xi + b_4) = 0, \tag{5}$$

where

$$b_1 = \delta + d + \mu + +\rho + qW_2 + A_1,$$
$$b_2 = (\mu + qW_2)(d + A_1 + \rho) + \delta(d + A_1) + d\rho + qW_2(h + \delta) - N\delta A_2 + \mu\delta,$$
$$b_3 = (\mu + qW_2)(\delta A_1 + d\rho) + qhW_2(\delta + d + A_1 + \rho) - Nd\delta A_2 + \mu\delta d + qW_2\delta d,$$
$$b_4 = qhW_2(\delta d + \delta A_1 + d\rho),$$

here $A_1 = \frac{\beta V_2}{1+aV_2}$ and $A_2 = \frac{\beta T_2}{(1+aV_2)^2}$. Since $\frac{cI_2}{1+\alpha I_2} - b$ is an eigenvalue of J_{E_2}, by assuming $\frac{cI_2}{1+\alpha I_2} - b = (H_0^{W,Z} - 1)$, we deduce that the sign of this eigenvalue is negative when $H_0^{W,Z} < 1$, zero when $H_0^{W,Z} = 1$ and positive for $H_0^{W,Z} > 1$.

On the other hand, from the Routh-Hurwitz Theorem applied to the fourth order polynomial in the characteristic equation, the other eigenvalues of the above matrix have negative real parts when $H_0^{W,Z} < 1$ (since $b_1b_2 > b_3$ and $b_1b_2b_3 > b_3^4 + b_1^2b_4$). Consequently, E_2 is unstable when $H_0^W > 1$ and $H_0^{W,Z} > 1$ and locally asymptotically stable when $H_0^W > 1$ and $H_0^{W,Z} < 1$.

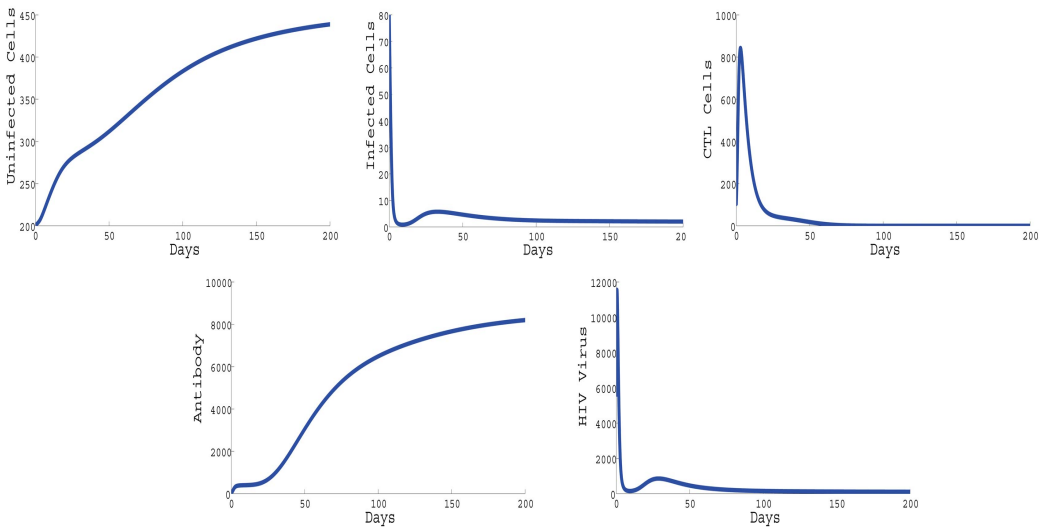

Fig. 3: Behavior of the infection during the time for $s = 10$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.001$, $g = 10^{-4}$ and $h = 0.01$, which correspond to the stability of the endemic-equilibrium E_2.

For the third endemic-equilibrium point E_3, we have the following result:

Theorem 5. *1. If $\alpha > \frac{c}{b}$ or $H_0^Z < 1$, then the point E_3 does not exist and $E_3 = E_2$ when $H_0^Z = 1$.*
2. If $\alpha < \frac{c}{b}$, $H_0^Z > 1$ and $D_0^W < (1 - \frac{\alpha b}{c})D_0^Z$, then E_3 is locally asymptotically stable.
3. If $\alpha < \frac{c}{b}$, $H_0^Z > 1$ and $D_0^W > (1 - \frac{\alpha b}{c})D_0^Z$, then E_3 is unstable.

Proof. We notice that the condition $\alpha < \frac{c}{b}$ and $H_0^Z > 1$ is equivalent to $I_3 < I_1$. It easy to very that the point E_3 does not exists if $H_0^Z < 1$ or $\alpha > \frac{c}{b}$. Moreover, we have $E_3 = E_1$ for $H_0^Z = 1$. We assume now that $\alpha < \frac{c}{b}$ and $H_0^Z > 1$; the Jacobian matrix at E_3 is

$$J_{E_3} = \begin{pmatrix} -d - \frac{\beta V_3}{1+aV_3} & \rho & -\frac{\beta T_3}{(1+aV_3)^2} & 0 & 0 \\ \frac{\beta V_3}{1+aV_3} & -\rho - \delta - pZ_3 & \frac{\beta T_3}{(1+aV_3)^2} & 0 & -pI_3 \\ 0 & N\delta & -\mu & -qV_3 & 0 \\ 0 & 0 & 0 & gV_3 - h & 0 \\ 0 & \frac{cZ_3}{(1+\alpha I_3)^2} & 0 & 0 & \frac{cI_3}{1+\alpha I_3} - b \end{pmatrix}$$

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

$$(\xi - gV_3 + h)(\xi^4 + c_1\xi^3 + c_2\xi^2 + c_3\xi + c_4) = 0, \tag{6}$$

where

$$\begin{aligned}
c_1 =& -cI_3B_3 + \rho + d + B_1 + \delta + pZ_3 + \mu + b,\\
c_2 =& cB_3I_3(-d - \rho - \mu - \delta - pZ_3 - B_1 + pZ_3B_3) + \mu(pZ_3 + \rho + b + d + B_1 + \delta)\\
&+ b(d + B_1 + \rho + pZ_3 + \delta) + (pZ_3 + \delta)B_1 - N\delta B_2 + d\delta + dpZ_3 + d\rho,\\
c_3 =& (cZ_3B_3^2pI_3 + (-\delta cI_3 - \mu cI_3 - pZ_3cI_3)B_3 + \delta\mu + pZ_3b + \mu b + pZ_3\mu + \delta b)B_1 +\\
&(N\delta cI_3B_3 - N\delta b - dN\delta)B_2 + (cZ_3pI_3\mu + dcZ_3pI_3)B_3^2 +\\
&(-\delta\mu cI_3 - dpZ_3cI_3 - d\delta cI_3 - d\mu cI_3 - \rho\mu cI_3 - d\rho cI_3 - pZ\mu cI_3)B_3 +\\
&pZ_3\mu b + \delta\mu b + d\delta b + d\mu b + d\rho b + dpZ_3b + d\delta\mu + \rho\mu b + dpZ_3\mu + d\rho\mu,\\
c_4 =& (cZ_3B_3^2pI_3\mu + (-pZ_3\mu cI_3 - \delta\mu cI_3)B_3 + \delta\mu b + pZ_3\mu b)B_1 +\\
&(-dN\delta b + dN\delta cI_3B_3)B_2 + dcZ_3B_3^2pI_3\mu +\\
&(-d\rho\mu cI_3 - d\delta\mu cI_3 - dpZ_3\mu cI_3)B_3 + dpZ_3\mu b + d\delta\mu b + d\rho\mu b,
\end{aligned}$$

here $B_1 = \frac{\beta V_3}{1+aV_3}$, $B_2 = \frac{\beta T_3}{(1+aV_3)^2}$ and $B_3 = (1+\alpha I_3)^{-1}$. It is clear that $gV_3 - h = h\frac{(D_0^W - (1-\frac{\alpha b}{c})D_0^Z)}{(1-\frac{\alpha b}{c})D_0^Z}$ is an eigenvalue of J_{E_3}. The sign of this eigenvalue is negative if $D_0^W < (1-\frac{\alpha b}{c})D_0^Z$, zero if $D_0^W = (1-\frac{\alpha b}{c})D_0^Z$ and positive if $D_0^W > (1-\frac{\alpha b}{c})D_0^Z$.

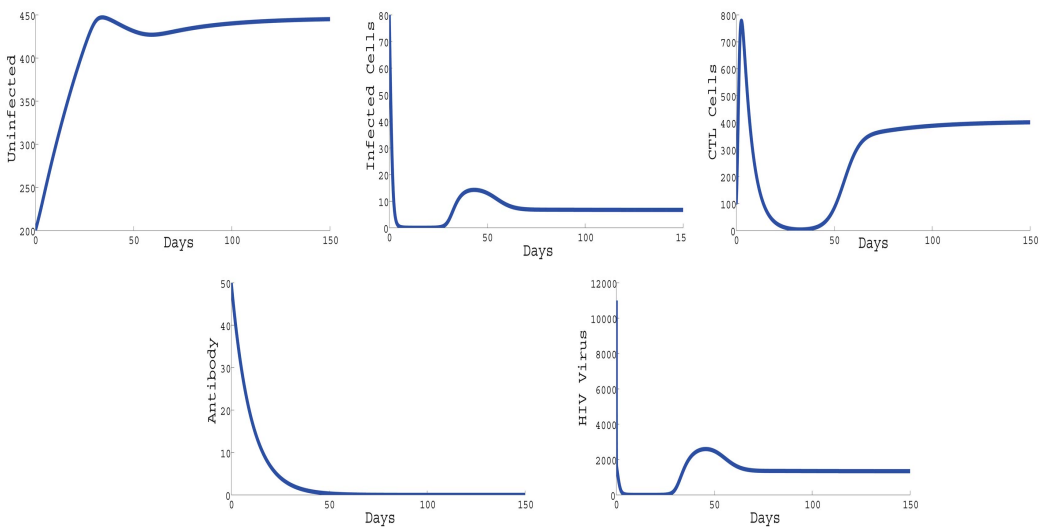

Fig. 4: Behavior of the infection during the time for $s = 15$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.5$, $g = 10^{-11}$ and $h = 0.1$, which correspond to the stability of the endemic-equilibrium E_3.

Again by Routh-Hurwitz stability criterion, the other eigenvalues of the above matrix have negative real parts when $H_0^Z > 1$. We conclude that E_3 is unstable when $H_0^Z > 1$ and $D_0^W > (1-\frac{\alpha b}{c})D_0^Z$ and locally asymptotically stable when $D_0^W < (1-\frac{\alpha b}{c})D_0^Z$ and $H_0^Z > 1$.

Using the same reasoning as for the previous theorems, we finally have the following result concerning the last endemic-equilibrium point E_4:

Theorem 6. *1. If $\alpha > \frac{c}{b}$ or $D_0^W < (1-\frac{\alpha b}{c})D_0^Z$ or $H_0^{W,Z} < 1$, then the point E_4 does not exist. Moreover $E_4 = E_2$ when $H_0^{W,Z} = 1$ and $E_4 = E_3$ when $D_0^W = D_0^Z$*

2. If $\alpha < \frac{c}{b}$, $D_0^W > (1 - \frac{\alpha b}{c}) D_0^Z$ *and* $H_0^{W,Z} > 1$, *then* E_4 *is locally asymptotically stable.*

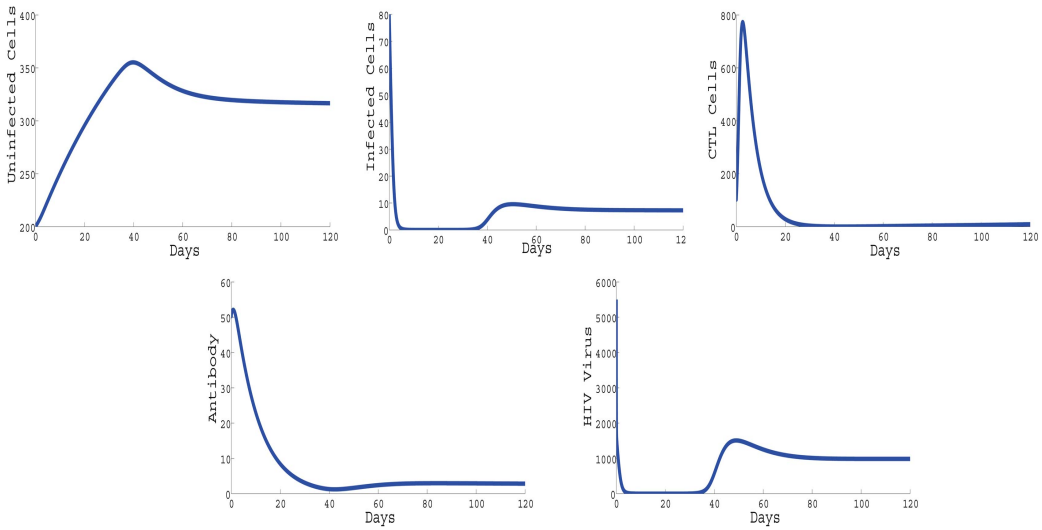

Fig. 5: Behavior of the infection during the time for $s = 10$, $\beta = 0.000024$, $d = 0.02$, $\delta = 0.5$, $p = 0.001$, $N = 1200$, $\mu = 3$, $\rho = 0.01$, $a = 0.001$, $\alpha = 0.001$, $c = 0.03$, $b = 0.2$, $q = 0.5$, $g = 10^{-4}$ and $h = 0.1$, which correspond to the stability of the endemic-equilibrium E_4.

4 Numerical simulations

For our numerical simulations, we have used the Euler finite-difference scheme method in order to discretize the five equations. The parameters of the simulations are inspired from [8, 19, 20], while the other new three parameters to the problem (1); q, g and h is chosen adequately since they may vary with various types of antibodies[21]. Also, we will take into account the initial conditions approaching the clinical data values for HIV infected individuals during symptomatic phase[22]. Fig. 1 shows the evolution of the infection during the 100 first days for the free-equilibrium case. It is interesting to point out that with antibody response the uninfected cells tend quickly to its equilibrium comparing with the previous model without this response[8]. Also, we remark that the antibody response reduce CTL generation. Fig. 2 shows the behavior of the infection for the case of the endemic-equilibrium E_1; in the presence of the antibodies an increase of uninfected cells during the first days is observed, also the plot of cellular immunity indicate that the antibody response reduce the maximum of CTL cells. Figs. 3 and 4 show the behavior of the disease in the absence CTLs and antibody response, respectively. The plots show that antibodies reduce more viral replication than CTLs. Also, the level of the uninfected cells is greater with antibodies than with CTLs. Finally, Fig. 5 shows the behavior of the disease in the presence of all the variables acting in the model. The figure show the persistence of HIV virus; also, we observe that the two immunities systems may control better the infection than only with one immunity type.

5 Conclusion

In this paper, we have studied the model of the Human Immunodeficiency Virus (HIV) dynamics in the presence of the adaptive immune response which is represented by the cytotoxic T lymphocytes (CTL) cells and the antibodies. The model includes two saturated rates in order to better describe the viral infection and the CTL proliferation. The positiveness and the boundedness of solutions are proved; which is consistent with biological studies. Also, we have studied the stability of both disease-free equilibrium and endemic

equilibria. The disease free steady state is locally asymptotically stable when the basic reproduction number is less than unity ($R_0 < 1$). The existence of four infection steady states when $R_0 > 1$ is established. The local stability of these infection steady states depend on the basic reproduction number R_0, the CTL immune response reproduction number D_0^Z and the antibody immune response reproduction number D_0^W. Numerical simulations are performed in order to show the behavior of infection during the days of observation. It was shown that in the presence of antibody response, the infection dies out much faster compared with the previous model without this response. In addition, the results of this work confirm that the humoral immunity may control viral replication and reduce the infection, this improves the quality of patient's life.

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