Modeling the cytotoxic immune response effects on human immunodeficiency virus

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Abstract

The immune system is responsible for the body defense against strange organisms. This type of control is performed by molecules and cells in an organized way. The proposed model consists in a system of ordinary deferential equations intended to resemble the interaction between HIV and the immune response when considering cytotoxic cells. Standard local stability analysis at the virus free equilibrium is carried out to determine the theoretical conditions that avoid infection. Simulations were run to obtain results for particular immunological conditions and also to describe the dynamics of the system when facing infection states.

Key words

Immune System, HIV, Cytotoxic Response, Dynamic System.

1. Introduction

UNAIDS, in its Global Report (2013), estimates that 35.3 million people were living with HIV by 2012. These figures show an increase compared to previous reports, and the report itself suggests that this is due to a major access to antiretroviral therapy. On the other hand, there were 2.3 million new infections globally; this represents a reduction of 33%. Also, AIDS related deaths are declining from 2.3 million people in 2005 to 1.6 million in 2012. The estimated cost of the treatment and care programs for of HIV and AIDS patients is measured in billions of dollars. This scenario motivates scientific research aimed at unders-

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tanding the mechanisms responsible for HIV transmission, treatment and control [1].

Although recent developments of antiviral treatment and the increasing access to such treatment have significantly reduced mortality and morbidity of HIV infected patients, the control of high viral replication continuous to be a major research challenge. It is known that treatment is unlikely to eradicate HIV in the short or mid term, and uncontrolled therapy interruptions lead to rebounds in viral replication. Therefore, there is increasing interest in developing vaccination strategies that make use of joint antiviral treatment, allowing long-term immune control of viral replication [2].

Antigen presenting cells are the first in fighting HIV once infection starts. These cells phagocytize and process viral particles, marking them on their surface to be recognized by CD4 T cells, which are then activated, (these cells specialize in identifying viral particles). Subsequently, the cells deploy adequate immune responses: humoral immune response or cytotoxic immune response. Simultaneously, the same CD4 T cells may become infected by the virus and initiate their replication process; in particular, when an activated T cell is infected, it loses the ability to deploy the appropriate immune response to cope with the infection [3-6].

This response activation occurs through the production of cytokines, which promote the proliferation of other specific cells of the immune system. In the case of humoral immune response, B lymphocytes are activated and produce neutralizing antibodies that bind to infected CD4 T cells, "marking" them, and "making them to be recognizable." As the cellular immune response is activated, cytotoxic cells proliferation occurs, especially regarding CD8 T cells in initial phases of infection,

and Natural Killer cells at later stages. These two types of cell have cytotoxic properties and are primarily responsible for eliminating the infected cells by stimulating CD4 T cells to "kill themselves" (i.e. apoptosis), thus inhibiting viral replication [4, 6].

Consistent with foregoing content, the relationship between the virus, the activation of CD4 T cells and the cellular immune response, appears to be decisive in the future evolution of the infection, because if active CD4 T cells concentration is low, cellular immune responses is not be deployed effectively and the body does not have the necessary tools to control the infection.

In order to gain a better understanding of this type of problems, the need arises to model the situation described above and study the behavior of the cytotoxic immune response over time together with the effects of the relationship with resting and helper CD4 T cells and HIV on the evolution of infection. Additional information on HIV dynamics and mathematical models is provided in [3-12].

2. Model description

Let $T = T(t)$ be the average number of resting CD4 T cells at time , t, $V = V(t)$ the average concentration of HIV at time t. Now suppose that the average number of helper CD4 T cells is $T^h = T^h(t)$ and the average number of cytotoxic cells, which are *active* against HIV, is represented by $R = R(t)$. Finally, let $T* = T*(t)$ be the average number of infected CD4 T cells that actively replicate the virus.

T resting cells are considered to increase at a constant rate σ and die by infection-unrelated reasons at a an average of μT. If a popu-

lation of resting T cells is infected with a probability β at time t, then an average number of new infected cells βTV are produced. On the other hand, some cells become active to recognize viral particles with probability ϕ; then we have ϕT as the average number of new helper cells at time t. It is assumed that helper cells die at an average of μT^h.

Helper T^h cells are also susceptible to become infected with probability ψ, so $\psi T^h V$ represents the average number of helper cells that become infected at time t. It is assumed that cytotoxic cells grow at an average of $\alpha T^h V$ in response to infection, and die at a rate ρ, so the average number of cytotoxic cells that die is ρR. The infected cells T^* die by the action of cytotoxic cells (apoptosis) at an average of $\gamma R T^*$ and make cellular lysis with probability δ; so δT^* is the average number of destruction of infected cells at time t. When the cells die by lysis, viral particles are released at a rate η, then, there

is an average of $\eta \delta T^*$ new viral particles and cV virus clearance. The corresponding differential equations are as follows:

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

$$T^h = \phi TV - \psi T^h V - \mu T^h$$

$$\dot{T}^* = \beta TV + \psi T^h V - \gamma R T^* - \delta T^*$$

$$\dot{R} = \alpha T^h V - \rho R$$

$$\dot{V} = \eta \delta T^* - cV \qquad (1)$$

Parameter and state definitions can be found in Table 1. System (1) is not likely to be solvable using analytical techniques. In the following sections, attention is paid to the study of the *basic reproduction number* R_0 and its influence on the virus-free equilibrium. This will bring analytical conditions to avoid infection.

Table 1. Parameter definitions and baseline values used in numerical simulations

Parameter definition		Value	Ref.
T	Average number of resting CD4 T cells	1000	-
T^h	Average number of helper CD4 T cells	0	-
T^*	Average number of infected CD4 T cells	0	-
R	Average number of cytotoxic cells	0	-
V	Average concentration of HIV	1×10^{-3}	-
σ	Constant source term for CD4 T cells	$10 \frac{cells}{mm^3}$	[6, 9, 11]
φ	Activation rate of resting CD4 T cells	$[0, 4 \times 10^{(-4)}]cells/(mm^3)$	-
β	Infection rate of resting T cells	$2.4 \times 10^{-5} \frac{cells}{mm^3}$	[6, 9, 11]

Parameter definition		Value	Ref.
ψ	Infection rate of helper T cells	$5 \times 10^{-4} \ \dfrac{cells}{mm^3}$	ad hoc
α	Rate cytotoxic cell activation	$\left[0, 2.8 \times 10^{-4}\right]\dfrac{cells}{mm^3}$	-
δ	Death rate of infected T cells by lysis	$0.26\dfrac{cells}{mm^3}$	[6, 9, 11]
μ	Death rate of resting and helper CD4 T cells	$0.01\dfrac{cells}{mm^3}$	[11]
γ	Infected cells death rate by cytotoxic action	$\left[0, 4 \times 10^{-3}\right]\dfrac{cells}{mm^3}$	-
ρ	Death rate of cytotoxic cells	$0.01\dfrac{cells}{mm^3}$	ad hoc
η	Viral production	1000	[6, 9, 11]
c	Virus clearance rate.	2.4	[6, 9, 11]

Source: own elaboration

2.1 Equilibriums and R_0

System (1) has two constant solutions given by $E_0 = \left(\frac{\sigma}{\mu}, 0,0,0,0\right)$, which corresponds to the virus free equilibrium, or absence of infection, and $E_1 = \left(\bar{T}_1, \bar{T}^h_1, \bar{T}^*_{11}, \bar{R}_1, \bar{V}_1\right)$, which corresponds to the infection state, with:

$$\bar{T}_1 = \frac{\phi\bar{T}_1\bar{V}_1}{\psi\bar{V}_1 + \mu} \ , \quad \bar{T}^h_1 = \frac{\phi\sigma\bar{V}_1}{\left(\psi\bar{V}_1 + \mu\right)\left[(\phi+\beta)\bar{V}_1 + \mu\right]}$$

$$\bar{T}^*_1 = \bar{V}_1\left(\beta\bar{T}_1 + \psi \ \bar{T}^h_1\right) \quad \bar{R}_1 = \frac{\phi\bar{T}^h_1\bar{V}_1}{\rho} \quad (2)$$

Where $\bar{V}_1$ is a non-negative root of the quadratic polynomial $p(V) = V^2 + A_1V + A_2$, where:

$$A_1 = \frac{c\left[\gamma\alpha\phi\sigma + \delta\rho\psi\left(\phi+\beta\right)\right]}{\delta\rho\left[\mu\psi c + \left(1-R_1\right)\left(\beta+\phi\right)\right]}$$

$$A_2 = \frac{\rho\mu\delta\left[c\mu + \eta\sigma\beta\right]}{\delta\rho\left[\mu\psi c + \left(1-R_1\right)\left(\beta+\phi\right)\right]} \quad (3)$$

With $R_1 = \frac{\eta\phi\sigma}{c\mu}$.

Now the following proposition and lemma ensures for the model: existence of infection state and the basic reproduction number.

Proposition 1. if $A_1 < 0$ *and* $A_2 < 0$, *then system (1) has an infection steady state* E_1, *and*

it is not possible for system (1) to have two different infection steady states.

Proof. *Routh-Hurtwiz criteria states that the necessary conditions for $p(V)$ to have two negative real part roots are $A_1 > 0$ and $A_2 > 0$; a sufficient condition for this to occur is when $R_1 < 1$, and therefore, the equilibrium would be E_0.*

Routh-Hurwitz criteria can also be used to study the case of two positive real part roots. Indeed, If $p(-V)$ has two negative real part roots, then $p(V)$ will have two positive real part roots. In this case, $p(-V) = V^2 - A_1 V + A_2$. Considering the definition of A_1 and A_2 above, it is obvious that both coefficients in $p(-V)$ have different signs, and the Routh-Hurwitz condition states that there is no two negative roots, and then, $p(V)$ has no two positive roots simultaneously.

To ensure the existence of infection states, the existence of at least one positive real root of $p(V)$ that occurs on the root should be guaranteed, namely $\bar{V}_1 = \frac{1}{2}\left[-A_1 + \sqrt{A_1^2 - 4A_2}\right]$ under the sufficient, but not necessary conditions $A_1 < 0$ and $A_2 < 0$. Indeed, in that case it will be $\sqrt{A_1^2 + 4(-A_2)} > 0$ and since $-A_1 > 0$, then $-A_1 + \sqrt{A_1^2 - 4A_2} > 0$. This proves that $\bar{V}_1 > 0$, at least when $A_1 < 0$ and $A_2 < 0$. ∎

The existence of E_0 is then more likely than in the previous proposition, and that is made explicit in the simulations. The importance of Proposition 1 is that it ensures the existence of E_1 and so guarantees that the model accepts infection to thrive into the body.

The following lemma shows the *basic reproduction number*, namely a threshold quantity that determines the *number of secondary infected cells produced by an infected cell from an initial viral load*. Additional information on the basic reproduction number can be found in [12].

Lemma. *The basic reproduction number of system (1) is given by $R_0 = \frac{\eta\beta\sigma}{c\mu}$.*

Proof. *The basic reproduction number, R_0, is defined as the spectral radius of the Next Generation Matrix [13]. To find such a number, consider the states that are responsible for transmission T^* and V, and with their corresponding equations define vectors*

$$f = \begin{bmatrix} \beta TV + \psi T^h V - \gamma RT^* \\ 0 \end{bmatrix} \quad and \quad v = \begin{bmatrix} -\delta T^* \\ \eta\delta T^* - cV \end{bmatrix} \quad (4)$$

The next generation matrix is then defined as $M = FV$, where $F = -Df$, and $V = (Dv)^{-1}$; here, Df and Dv denote the Jacobian matrix of f and v, respectively. Then, by substituting E_0,

$$M = \begin{bmatrix} \dfrac{\eta\beta\sigma}{c\mu} & 0 \\ 0 & 0 \end{bmatrix} \quad (5)$$

Thus, $R_0 = \dfrac{\eta\beta\sigma}{c\mu}$, as the lemma states ∎

This quantity, R_0, is broadly used in epidemiology, as a measure of how fast the infection will colonize an entirely susceptible population or whether, on the contrary, it will disappear in a short time. This is the rationale behind analyzing E_0 in the next subsection.

2.2 Local stability analysis of E_0

Proposition 2. *If $R_0 < 1$, then the virus free equilibrium E_0 is local and asymptotically stable.*

Proof. *The Jacobian matrix of system (1) in E_0 has the characteristic equation, [14]:*

$$(x + \mu)^2 (x + \rho)\left[x^2 + (c + \delta)x - c\delta(R_0 - 1)\right] = 0$$

$$(6)$$

Three eigenvalues are $x_1 = -\mu, x_2 = -\mu, x_3 = -\rho$. To analyze the other two, consider that the Routh-Hurwitz criterion establishes that both solutions of the quadratic factor have negative real part if the coefficients are positive; in this case, it means $R_0 < 1$.

The result above indicates that when $R_0 < 1$, the infection is not deployed in the body and the initial viral load tends to be eliminated in a short time.

3. Simulation

Model simulation is made using the parameters shown in Table 1. Variations are made over some parameters to see their impact on the system. Such parameters were selected to take an approximate representative value due to the lack of information in the bibliography. Twenty random values are generated for each parameter, using a uniform distribution over a given interval, to illustrate how the change in values affects system evolution.

In Figure 1, the parameter that varies is α, which represents the *activation rate of the cytotoxic cells*. It can be seen that, for infected cells and viral load, all values of α lead to the same initial outbreak; however, the second outbreak of infection is moving forward as increases. Also, increasing has the effect of increasing the average number of both resting and helper T cells, but with higher amplitude in the oscillations.

In Figure 2, the parameter to be varied is γ, which represents the *death rate of infected cells by cytotoxic action*. The highest γ represents the largest number of resting and helper CD4 T cells, but these curves are characterized by oscillations with increasing amplitude. It is important to consider that, as in the simulation for α, infection outbreaks move forward as γ increases; in fact, both parameters have a similar effect on the resulting dynamics.

Figure 1. Variation of α is made over the interval $\left[0, 2.8 \times 10^{-5}\right]$. Aditionally, $\gamma = 1 \times 10^{-3}$ and $\phi = 1 \times 10^{-5}$.
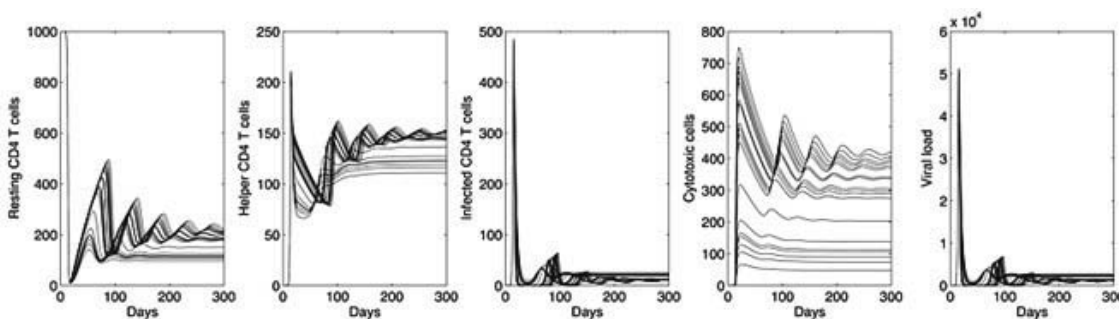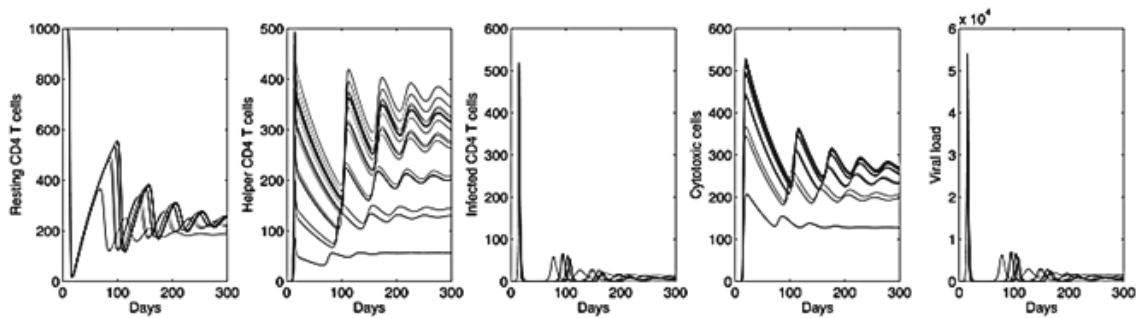

Soruce: own elaboration

Figure 2. Variation of γ is made over the interval $[0,0.004]$. Aditionally, $\alpha = 1.4 \times 10^{-4}$, and $\phi = 1 \times 10^{-5}$
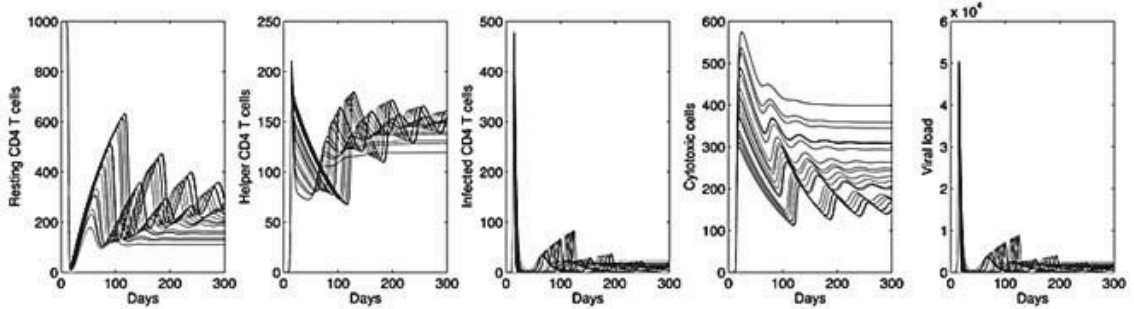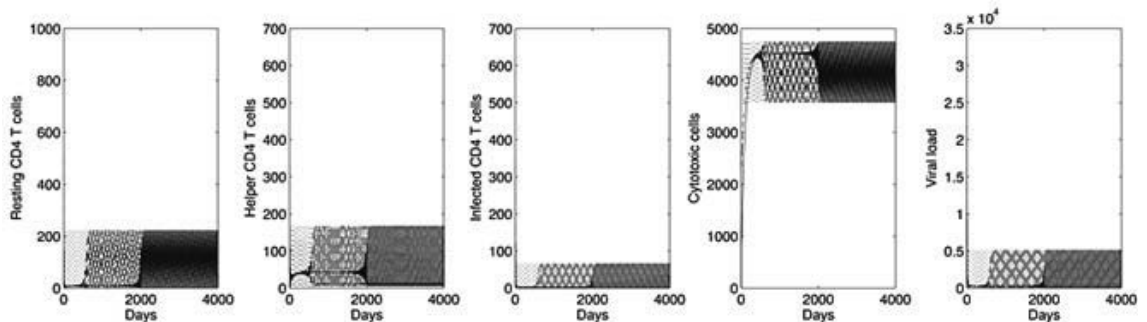

Soruce:

Figure 3. Variation of is made over the interval $\left[0, 4 \times 10^{-5}\right]$. Aditionally, $\alpha = 1.4 \times 10^{-4}$, $\gamma = 2 \times 10^{-3}$

Soruce:

Figure 4. This special case is obtained with the values $\beta = 2.4 \times 10^{-4}$, $\phi = 5 \times 10^{-3}$ $\gamma = 1 \times 10^{-3}$ and $\alpha = 5 \times 10^{-3}$. Correspond to three different initial conditions drawn $T_0 = 1000$ (dotted line), $T_0 = 500$ (dashed line) and $T_0 = 100$ (solid line), the other states are $T_0^h = 0; T_0^* = 0; R_0 = 0$ and $V_0 = 0.001$

Source: own elaboration

Figure 3, shows the variation of parameter ϕ, where it can be seen that the parameter has a significant impact on the dynamics of helper CD4 T cells, which exhibit an important increase as ϕ increases. Also, the secondary outbreaks of infection presented in viral load and infected cells are reduced when compared to Figures 1 and 2.

Finally, as a result of extensive simulations for every parameter, Figure 4 shows a special situation obtained with a change in some parameters, as specified in the figure. This suggests the way dynamics may lead to a cycle after some time depending on the initial conditions. It is beyond the aim of this paper to study and clarify the specific conditions for this situation to occur, and so these issues are left for future work.

4. Conclusions

It has been shown that under special immunological conditions ($R_0 < 1$), it is possible that the infection does not thrive in the body. This situation might be related to the cases of individuals who did not become infected after a situation of risk, and so could be considered when designing a vaccine or any other kind of prophylaxis (such as the use of antiretroviral gel). This will allow people to have their immune system at safe states before falling into risk.

Variations of α and γ allow observing that increasing the activation of cytotoxic response, or its effectiveness to destroy infected cells, increases the time between infection outbreaks; however, this also causes wide oscillations in T cells dynamics, which could affect the patient's health condition. Furthermore, it is obvious that the cytotoxic response, together with a strong activation rate of resting CD4 T cells (variation of ϕ), is effective in reducing infection levels and therefore should not be neglected in the construction of antiretroviral therapy protocols.

Further study is necessary to evaluate the effect of the cytotoxic response along with antiretroviral therapy, and also to determine optimal control strategies to ensure the strengthening of the immune system.

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