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STUDY OF A FRACTIONAL-ORDER MODEL FOR HIV INFECTION OF CD4^+ T-CELLS WITH TREATMENT

A. J. FERRARI, E. A. SANTILLAN MARCUS

Abstract. In view of the problem of human immunodeficiency virus (HIV) infection of CD4^+ T-cells, further considering the effect caused by treatment therapy on the infected patient, an analytical model with fractional differential equations for susceptible cells density, infected cells density and virus density is presented in order to test how infection develops. Existence and uniqueness of the model solution are explicitly proved and its positive invariance and stability are studied.

1. Introduction

HIV is a virus, a microorganism that does not have the capacity to replicate itself. To do so it must penetrate certain types of cells. HIV has the peculiarity of invading the body's defense cells, CD4^+ T-lymphocytes, progressively destroying them if left untreated. In this way, the immune system is weakened and the body is unable to defend itself, so the infected person can develop opportunistic diseases [3, 5, 21]. Antiretroviral therapy (ART) consists of the use of drugs to prevent the virus from reproducing. Nowadays, ARTs last a lifetime and use combinations of three or more drugs. Although ART reduces the progression of infection by causing viral load to become undetectable and restores the defenses, antiretrovirals may have undesirable side effects (like any other drug) [5, 21]. It is for this reason that one of the main objectives of this work is to find out how effective a drug should be so that ART can be carried out only with this drug, instead of needing the combination of several of them, thus achieving a simpler treatment and less exposure to possible side effects caused by the medication. A fractional-order model of HIV infection presented in [5] will be analyzed in this work along with the immune system cells, the CD4^+ T-lymphocytes. In [5] existence and uniqueness of the solution of the problem are stated, and non-negativity of the solution is proved. An explicit proof of existence and uniqueness of the solution will be shown here, plus its positive invariance. Furthermore, stability of the solution will be studied to obtain results about the efficacy of the drug in order to achieve an undetectable level of virus density. The paper is organized as follows: the model is presented in section 2,

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some basic definitions of fractional derivatives are shown in section 3, existence and uniqueness of the model solution is proved in section 4, its positive invariance is demonstrated in section 5, stability of the model is studied in section 6 and finally conclusions are presented in section 7.

2. Model description

This work is based on the models presented by Arafa, Rida, Khalil [5] and Srivastava, Banerjee and Chandra [21] in which the presence of a reverse transcriptase (RT) inhibitor is considered, as it is the most recurrent in treatments. At first, three variables could be considered in the model: virus density, infected $CD4^+$ T-cells, and uninfected $CD4^+$ T-cells. However, there is a phase in the cycle of the virus called eclipse phase prior to reverse transcription during which no virus is being produced [21]. Therefore, there are considered two subsets within the set of infected $CD4^+$ T-cells: those that are latently infected (in eclipse phase) and those productively infected (producing virus). Thus, the variables considered in the model are: T: density of susceptible $CD4^+$ T-cells; I: density of infected $CD4^+$ T-cells before reverse transcription (pre-RT class); V: density of infected $CD4^+$ T-cells in which reverse transcription is completed (post-RT class) and so are capable of producing virus; L: virus density. In addition, the following positive parameters have been considered: s: inflows rate of $CD4^+$ T-cells; k: interaction infection rate of $CD4^+$ T-cells; μ: natural death rate of $CD4^+$ T-cells; η: efficacy of RT inhibitor ($0 < \eta < 1$); ϵ: transition rate of pre-RT class infected $CD4^+$ T-cells to post-RT class; b: reverting rate of infected cells to uninfected class due to non-completion of reverse transcription; μ_1: death rate of infected $CD4^+$ T-cells; δ: death rate of actively infected $CD4^+$ T-cells; N: total number of viral particles produced by an infected $CD4^+$ T-cell; c: clearance rate of virus.

The model presented by Arafa, Rida and Khalil [5], in which fractional derivatives in Caputo's sense have been considered, is the following:

$$\begin{cases} D_C^\alpha(T) &= s - kLT - \mu T + (\eta\epsilon + b)I \quad (A1) \\ D_C^\alpha(I) &= kLT - (\mu_1 + \epsilon + b)I \quad (A2) \\ D_C^\alpha(V) &= (1-\eta)\epsilon I - \delta V \quad (A3) \\ D_C^\alpha(L) &= N\delta V - cL \quad (A4) \end{cases} \tag{A}$$

where $0 < \alpha \leq 1$ is the fractional derivative order.

3. Fractional Calculus

Fractional derivatives have been extensively applied in many fields with an overwhelming growth in the last three decades; for example models admitting backgrounds of heat transfer, viscoelasticity, electrical circuits, electro-chemistry, economics, polymer physics, and biology are concerned with fractional derivative [2, 11, 12, 17, 20]. With particular reference to HIV, fractional differential equations are naturally related to systems with memory which exists in most biological models [4]. Also, they are closely related to fractals [9]. Moreover, the membranes of biological organism cells have fractional-order electrical conductance and then they are classified in groups of non-integer order models [7]. Fractional derivatives embody essential features of cell rheological behavior and they have enjoyed greatest success in the field of rheology [10]. Anomalous diffusion of proteins due to molecular crowding, such as enzymes contained in the HIV, is studied in [6] where

a fractional order model is considered. There are many approaches to the generalization of the notion of fractional differentiation. For the concept of fractional derivative, Caputo's definition is considered because it has the advantage of dealing properly with initial value problems [8, 14, 18].

Definition 1 The Riemann-Liouville fractional integral of order $\alpha > 0$ of a function $f : \mathbb{R}^+ \to \mathbb{R}$ is given by [8]:

$$J^\alpha f(x) = \frac{1}{\Gamma(\alpha)} \int_0^x (x-t)^{\alpha-1} f(t)\, dt,$$

where $J^0 f(x) = f(x),\ x > 0$.

Definition 2 The Riemann-Liouville and the Caputo fractional derivatives of order $\alpha > 0$ of a continuous function $f : \mathbb{R}^+ \to \mathbb{R}$ are respectively given by [8]:

$$D^\alpha f(x) = D^m(J^{m-\alpha} f(x)),$$

$$D_C^\alpha f(x) = J^{m-\alpha}(D^m f(x)),$$

where $m - 1 < \alpha \leq m,\ m \in \mathbb{N}$.

Both definitions of fractional derivative involve an integration which is a non local operator, so fractional derivative is a non local operator. In other words, calculating the fractional derivative of a function $f(t)$ at some time $t = t_1$ requires all the previous history, i.e. $f(t)$ from $t = 0$ to $t = t_1$. Results derived of the fractional systems are of a more general nature. However, fundamental solutions of these equations still exhibit scaling properties that make them useful for applications. One of the basic reasons of using fractional order differential equations is that they are, at least, as stable as their integer order counterpart. [3]

4. Existence and Uniqueness of the Model Solution

Denote $\mathbb{R}^4_+ = \{x \in \mathbb{R}^4 : x \geq 0\}$, and $x(t) = (T(t), I(t), V(t), L(t))$. Let us consider these results given in [5] and [16]:

Theorem 1 [Generalized mean value theorem] Let $f(x) \in AC[0, a]$, where $AC[0, a]$ denotes the set of absolutely continuous functions on $[0, a]$. Then for $0 < \alpha \leq 1$:

$$f(x) = f(0) + \frac{1}{\Gamma(\alpha + 1)} (D_*^\alpha f)(\xi) \cdot x^\alpha,$$

with $0 \leq \xi \leq x,\ \forall x \in [0, a]$.

Proof. Proof is given in [16].

Remark 1 When $\alpha = 1$, the generalized mean value theorem reduces to the classical mean value theorem.

Corollary 1 Suppose that $f(x) \in AC[0, a]$ and $D_*^\alpha f(x) \in C(0, a]$ for $0 < \alpha \leq 1$. If $D_*^\alpha f(x) \geq 0 (D_*^\alpha f(x) > 0), \forall x \in (0, a)$, then $f(x)$ is non-decreasing (increasing) and if $D_*^\alpha f(x) \leq 0\ (D_*^\alpha f(x) < 0), \forall x \in (0, a)$ then $f(x)$ is non-increasing (decreasing) for all $x \in [0, a]$.

Proof. It arises naturally from Theorem 1.

Theorem 2 $\mathbb{R}^4_+$ is a non-negative invariant domain for the model solution.

Proof. It arises from Theorem 1 and Corollary 1, see [5].

Existence and uniqueness of the solution is stated in [5], however it is not explicitly demonstrated. Following, an explicit proof will be given.

Initial value problems for fractional differential equations are stated in the following form:

$$\begin{cases} D_C^\alpha x(t) &= f(t, x(t)), \\ x^{(k)}(t_0) &= x_0^{(k)}, \quad k = 0, 1, \ldots, n-1, \end{cases} \tag{1}$$

where the fractional derivative D_C^α is in the sense of Caputo's definition and the function $f(t, x) : \mathbb{R} \times \mathbb{R}^d \to \mathbb{R}^d$ is called vector field (with dimension $d \geq 1$) [13]. Then, according to Lemma 6.2 in [8], $x(t)$ is a solution of the initial value problem (1) if and only if $x(t)$ is a solution of the nonlinear Volterra integral equation of the second kind:

$$x(t) = \sum_{k=0}^{m-1} \frac{(t-t_0)^k}{k!} x^{(k)}(t_0) + \frac{1}{\Gamma(\alpha)} \int_{t_0}^{t} (t-s)^{\alpha-1} f(s, x(s))\, ds, \tag{2}$$

where $\alpha \in (m-1, m)$, $m \in \mathbb{N}$ and $t \geq t_0$. This allow us to discuss the properties of the solutions of (2) instead of the ones for the initial value problem (1). Besides, considering $\alpha \in (0, 1)$, equation (2) can be written as:

$$x(t) = x_0 + \frac{1}{\Gamma(\alpha)} \int_{t_0}^{t} (t-s)^{\alpha-1} f(s, x(s))\, ds,$$

where $\alpha \in (0, 1)$ and $t \geq t_0$.

Theorem 3 (see [13]) Assume that the vector field $f(t, x)$ satisfies:

(1) $f(t, x)$ is Lebesgue measurable with respect to t on $\mathbb{R}$;
(2) $f(t, x)$ is continuous with respect to x on $\mathbb{R}^d$.

Assume also that:

$$||f(t, x)|| \leq \omega + \lambda ||x||, \tag{3}$$

for almost every $t \in \mathbb{R}$ and for all $x \in \mathbb{R}^d$, where ω, λ are two positive constants.

Then, there exists a function $x(t)$ on $(-\infty, +\infty)$ solving the initial value problem (1).

Remark 2 Besides the hypotheses made in Theorem 3, if $\partial f(t, x)/\partial x$ is further assumed to be continuous with respect to x, then the solution $x(t)$ on $(-\infty, +\infty)$ solving (1) exists and it is unique since the hypotheses of Theorem 2.2 in [13] are fulfilled.

Theorem 4 There exists an unique solution $x(t) = (T(t), I(t), V(t), L(t))$ for system (A) with $t \geq 0$.

Proof. From (A):

$$f(t, x) = (s - kLT - \mu T + (\eta\epsilon + b)I,\ kLT - (\mu_1 + \epsilon + b)I,\ (1-\eta)\epsilon I - \delta V,\ N\delta V - cL).$$

$f(t, x)$ satisfies the first two conditions of Theorem 3 in the global space. Now it will be shown that (3) is satisfied to ensure global existence. Considering the norm $||x|| = ||x||_1 = \sum_{i=1}^{4} |x_i|$, and taking into account the positivity of the parameters, the non-negativity of the variables and that $\eta < 1$, results:

$$||f(t, x)||_1 \leq s + 2kLT + \mu T + (2b + \mu_1 + 2\epsilon)I + \delta(N+1)V + cL. \tag{4}$$

Looking at (A1-2), and considering the linearity of the Caputo fractional derivative operator, it can be deduced that:

$$D_C^\alpha (T + I) \leq s - \mu_m (T + I), \text{ where } \mu_m = \min\{\mu, \mu_1\}.$$

From this it follows that $\limsup_{t\to\infty}(T+I) \leq s/\mu_m$. Being T and I non-negative, it is concluded that $\limsup_{t\to\infty} T \leq s/\mu_m$ and $\limsup_{t\to\infty} I \leq s/\mu_m$. Therefore, $0 < T(t) < M$, $0 < I(t) < M$ for some $M > 0$, for all $t \geq 0$. Thus, a bound for T is obtained and then from (4):

$$||f(t,x)||_1 \leq s + [2kM + \mu + (2b + \mu_1 + 2\epsilon) + \delta(N+1) + c]\,||x||_1.$$

Therefore, taking $\omega = s > 0$ and $\lambda = 2kM + \mu + (2b + \mu_1 + 2\epsilon) + \delta(N+1) + c > 0$, the result follows. Finally, from Remark 2 it follows naturally that the solution not only exists but it is globally unique.

5. Positive invariance

It will be proved that (A) is positively invariant, i.e., it does not exhibit neither negative nor zero values of the variables for similar initial conditions. Let $\mathcal{B} = \{(T,I,V,L), T > 0, I \geq 0, V \geq 0, L \geq 0\}$ and $\mathring{\mathcal{B}} = \{(T,I,V,L), T > 0, I > 0, V > 0, L > 0\}$. Remark that $\mathcal{B}$ is the subset of $\mathbb{R}^+_4$ with all the possible states with biological sense for both infected and non-infected patients. To prove that $\mathring{\mathcal{B}}$ is a positively invariant domain, the following lemma states that the number of susceptible CD4$^+$ T-cells does not vanish in finite time.

Lemma 1 If the initial condition (T_0, I_0, V_0, L_0) is in $\mathcal{B}$ then $T(t) > 0$ for all time for which T, I, V, L are defined.

Proof. Suppose that there exists at least one time t such that $T(t) = 0$. Let t^* be the smallest time. Due to the hypotheses, $t^* > 0$. Then (A1) can be put as:

$$D^\alpha_C T(t^*) = s + (\eta\epsilon + b)I(t^*) > 0.$$

As a consequence of Corollary 1, taking $\widetilde{t}$ below and sufficiently close to t^*, $T(\widetilde{t}) < 0$. This contradicts Theorem 2 and completes the proof.

Theorem 5 $\mathring{\mathcal{B}}$ is a positively invariant domain for the model solution.

Proof. Cases where one, two or three variables vanish simultaneously will be discussed. Recall that it is already known that T does not vanish by Lemma 1.

Let us assume that I vanishes first and alone (before the other variables) and let us denote t^* the smallest time for which I vanishes. On $[0, t^*)$:

$$I(t) > 0, V(t) > 0, L(t) > 0,$$

and in $t = t^*$:

$$I(t^*) = 0, V(t^*) > 0, L(t^*) > 0.$$

in addition to the fact that $T(t) > 0$ on $[0, t^*]$, according to Lemma 1. From (A2):

$$D^\alpha_C I(t^*) = kL(t^*)T(t^*) > 0.$$

This implies that there exists a time $\widetilde{t}$ smaller than t^* at which $I(\widetilde{t}) < 0$. This contradicts Theorem 2 and therefore I does not vanish first and alone. Identical arguments enable to prove that V and L does not vanish first and alone.

All the cases where two variables vanish simultaneously could be easily analyzed in the same way.

In the case where I, V and L vanish at the same time, the following initial value problem appears:

$$\begin{cases} D^\alpha_C T(t) & = s - \mu T(t) \\ T(0) & = T_0. \end{cases}$$

The solution for this problem is:

$$T(t) = s\alpha \int_0^t E'_\alpha(-\mu r^\alpha) r^{\alpha-1} dr + T_0 E_\alpha(-\mu t^\alpha).$$

If t^* is the smallest vanishing time for I, V and L, applying Theorem 4 with reversed time, it can be concluded that the (unique) solution is such that $T(t) = s\alpha \int_0^t E'_\alpha(-\mu r^\alpha) r^{\alpha-1} dr + T_0 E_\alpha(-\mu t^\alpha)$ and $I = V = L = 0$ for all time $t < t^*$. This contradicts the definition of t^* as the smallest vanishing time and finishes the proof.

Corollary 2 There exists an unique solution $x(t) = (T(t), I(t), V(t), L(t))$ for (A) with $t \geq 0$ and it is positively invariant.

6. Equilibrium Points and Stability of the Model

Definition 3 Consider the following differential equation:

$$D^\alpha_C x(t) = f(t, x(t)), \tag{5}$$

with $\alpha \in (0, 1)$.

Then if $f(t, x(t)) = (f_1(t, x(t)), f_2(t, x(t)), \ldots, f_d(t, x(t)))$, the equilibrium points are defined as the solutions of $f_i(t, x(t)) = 0,\ i = 1, \ldots, d$ (see [1]).

From (A) and (5), let us put:

$$\begin{cases} s - k\bar{L}\bar{T} - \mu\bar{T} + (\eta\epsilon + b)\bar{I} & = 0 \\ k\bar{L}\bar{T} - (\mu_1 + \epsilon + b)\bar{I} & = 0 \\ (1-\eta)\epsilon\bar{I} - \delta\bar{V} & = 0 \\ N\delta\bar{V} - c\bar{L} & = 0. \end{cases}$$

Solving, it turns out that there are two equilibrium points: $E_1 = (s/\mu, 0, 0, 0)$ and $E_2 = (\bar{T}, \bar{I}, \bar{V}, \bar{L})$, where:

$$\bar{T} = \frac{(\mu_1 + \epsilon + b)c}{Nk\epsilon(1-\eta)}, \quad \bar{I} = \frac{s - \mu\bar{T}}{\epsilon(1-\eta) + \mu_1}, \quad \bar{V} = \frac{(1-\eta)\epsilon}{\delta}\bar{I}, \quad \bar{L} = \frac{N\delta}{c}\bar{V}.$$

Remark 3 Note that the equilibrium point E_1 is a non-infectious state since there are no infected CD4$^+$ T-cells and no virus density present, while the equilibrium point E_2 is an infectious state as susceptible CD4$^+$ T-cells coexist with infected cells and virus. It can be seen that given certain conditions, the solution tends to the non-infectious state. Therefore necessary and sufficient conditions for the non-infectious state E_1 to be asymptotically stable will be analyzed.

Theorem 6 A necessary and sufficient condition for the local asymptotic stability of an equilibrium point is that the eigenvalues λ of the Jacobian matrix $A = (a_{ij}) = (\partial f_i / x_j)$ evaluated at that point of equilibrium satisfy the following condition:

$$|\arg(\lambda)| > \frac{\alpha\pi}{2}. \tag{6}$$

Proof. See Theorem 7.20 from [8].

Remark 4 Note that this Theorem confirms that fractional-order differential equations with $\alpha \in (0, 1)$ are, at least, as stable as their integer order counterpart since if (6) is satisfied when $\alpha = 1$, then it is also satisfied when $\alpha \in (0, 1)$.

Let us consider for $\alpha = 1$ the classical Routh-Hurwitz conditions [15], this is $det(H_j) > 0,\ j = 1, 2, \ldots, n$ being:

$$H_1 = (a_1),\ H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix},\ H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix},$$

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & \ldots & 0 \\ a_3 & a_2 & a_1 & 1 & \ldots & 0 \\ a_5 & a_4 & a_3 & a_2 & \ldots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ldots & \vdots \\ a_{2n-1} & a_{2n-2} & a_{2n-3} & a_{2n-4} & \ldots & a_n \end{pmatrix},$$

where $a_j = 0$ if $j > n$. To verify (6), for $\alpha \in (0, 1)$, these conditions are sufficient but not necessary. In [1] the following result is established:

Theorem 7

(1) For $n = 1$, the condition for (6) is $a_1 > 0$.
(2) For $n = 2$, the conditions for (6) are either Routh-Hurwitz conditions or:

$$a_1 < 0,\ 4a_2 > (a_1)^2,\ \left|\tan^{-1}\left(\frac{\sqrt{4a_2 - (a_1)^2}}{a_1}\right)\right| > \frac{\alpha\pi}{2}.$$

(3) For $n = 3$:
   (a) If the discriminant of $P(\lambda)$, $D(P) = 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2$ is positive, then Routh-Hurwitz conditions are the necessary and sufficient conditions for (6) to be satisfied, i.e.:

$$a_1 > 0,\ a_1a_2 > a_3,\ a_3 > 0.$$

   (b) If $D(P) < 0$ and $\alpha < 2/3$, then sufficient conditions for (6) to be satisfied are $a_1 \geq 0,\ a_2 \geq 0,\ a_3 > 0$.
   (c) If $D(P) < 0$ and $\alpha \in (0, 1)$, then sufficient conditions for (6) to be satisfied are $a_1 > 0$, $a_2 > 0, a_1a_2 = a_3$.

The Jacobian matrix $J(x)$ for system (A) is the following:

$$J(x) = \begin{pmatrix} -kL - \mu & \eta\epsilon + b & 0 & -kT \\ kL & -(\mu_1 + \epsilon + b) & 0 & kT \\ 0 & (1 - \eta)\epsilon & -\delta & 0 \\ 0 & 0 & N\delta & -c \end{pmatrix}.$$

Thus:

$$\begin{aligned} \det(J(E_1) - \lambda I) &= (\lambda + \mu)\left\{\lambda^3 + (\mu_1 + \epsilon + b + \delta + c)\lambda^2\right. \\ &+ [(\mu_1 + \epsilon + b)(\delta + c) + c\delta]\lambda \\ &\left. + c\delta(\mu_1 + \epsilon + b) - N\delta\epsilon(1 - \eta)ks/\mu\right\}. \end{aligned}$$

Then, the characteristic polynomial for $J(E_1)$ is $(\lambda+\mu)(\lambda^3+a_1\lambda^2+a_2\lambda+a_3) = 0$ being:

$$\begin{aligned} &a_1 = \mu_1 + \epsilon + b + \delta + c; \\ &a_2 = (\mu_1 + \epsilon + b)(\delta + c) + c\delta; \\ &a_3 = b_1 - b_2(1 - \eta) \ \text{ where } b_1 = c\delta(\mu_1 + \epsilon + b) \ \text{ and } \ b_2 = N\delta\epsilon ks/\mu. \end{aligned} \tag{7}$$

Note that $\lambda = -\mu$ is a real negative eigenvalue and therefore verifies the condition (6). Hence the cubic polynomial $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$ must be analyzed.

According to Theorem 7 (item 3) let us evaluate the sign of the discriminant $D(P) = 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2$. As in general $a_1a_2 \neq a_3$ and remembering that $\alpha \in (0,1)$, let us begin by obtaining conditions for $D(P) > 0$.

Theorem 8 Let $a_1, a_2, b_1, b_2 > 0$, $\beta \in (0,1]$. If the following conditions are simultaneously satisfied:

$$\begin{cases} \dfrac{a_2(a_1^4+3a_2^2)}{3(a_1a_2)^2+\frac{a_1^6}{9}} < 1; \\ \\ b_1\left(\dfrac{9}{2}a_1a_2 - a_1^3 - \dfrac{27}{2}b_1\right) > \min\left\{0;\, a_2^2\left(a_2 - \dfrac{a_1^2}{4}\right) - \dfrac{27}{4}b_1^2\right\}; \\ \\ b_2\left(a_1^3 + \dfrac{27}{2}b_1 - \dfrac{9}{2}a_1a_2 - \dfrac{27}{2}b_2(1-\beta)\right) > \min\left\{0;\, a_2^2\left(a_2 - \dfrac{a_1^2}{4}\right)\right. \\ \left. +a_1\left(a_1^2 - \dfrac{9}{2}a_2\right)(b_1 + b_2\beta) + \dfrac{27}{2}b_1\left(\dfrac{b_1}{2} + b_2\beta\right) - \dfrac{27}{4}b_2^2(1-\beta^2)\right\}. \end{cases} \tag{8}$$

then $D(P) = 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27a_3^2 > 0$, where $a_3 = b_1 - b_2(1-\eta)$ for every $\eta \in [\beta, 1]$.

Proof. Writing $D(P)$ in terms of η:

$$\begin{array}{l} D(P)(\eta) = -27b_2^2\eta^2 + (18a_1a_2b_2 - 4a_1^3b_2 - 54b_1b_2 + 54b_2^2)\eta \\ +18a_1a_2b_1 - 18a_1a_2b_2 + a_1^2a_2^2 - 4a_1^3b_1 \\ +4a_1^3b_2 - 4a_2^3 - 27b_1^2 - 27b_2^2 + 54b_1b_2. \end{array} \tag{9}$$

The roots of (9) are:

$\eta_{1,2} = \frac{1}{27b_2}\left(9a_1a_2 - 2a_1^3 - 27b_1 + 27b_2 \pm \sqrt{108a_1^2a_2^2 + 4a_1^6 - 36a_1^4a_2 - 108a_2^3}\right)$.

Clearly, $D(P)(\eta)$ is positive for $\eta \in (\eta_1, \eta_2)$ Then, it is enough to ask:

$$\begin{cases} \Delta(D(P)) > 0 \\ \eta_2 > 1 \\ \eta_1 < \beta, \end{cases}$$

which are respectively translated to (8).

This theorem allow us to consider any value of η between β and 1, so β should be interpreted biologically as the actual efficacy of the RT inhibitor. Now let us analyze the Routh-Hurwitz conditions from Theorem 7. However, due to the positivity of all parameters, condition $a_1 > 0$ is trivially verified. Condition $a_1a_2 > a_3$ is also always verified since:

$$\begin{array}{rl} a_1a_2 & = (\mu_1+\epsilon+b+\delta+c)[(\mu_1+\epsilon+b)(\delta+c)+c\delta] > \\ & > c\delta(\mu_1+\epsilon+b) - N\delta\epsilon(1-\eta)ks/\mu = a_3. \end{array}$$

Therefore, it should only be verified $a_3 > 0$ so that the non-infectious state E_1 is asymptotically stable, this is:

$$c\delta(\mu_1+\epsilon+b) - N\delta\epsilon(1-\eta)\frac{ks}{\mu} > 0 \implies \frac{c(\mu_1+\epsilon+b)}{N\epsilon(1-\eta)k} > \frac{s}{\mu} \implies \bar{T} > \frac{s}{\mu}.$$

In terms of η this translates to $\eta > \eta_{crit}$ where:

$$\eta_{crit} = 1 - \frac{\mu c(\mu_1+\epsilon+b)}{N\epsilon ks}.$$

Theorem 9 Let system (A) be. If equations (8) are satisfied by (7), then

$$\eta > 1 - \mu c(\mu_1 + \epsilon + b)/N\epsilon ks, \tag{10}$$

is the necessary and sufficient condition for the asymptotically stability of the non-infectious state E_1.

Remark 5 Condition (10) is a sufficient condition for the non-infection state to be asymptotically stable, but it is not always necessary.

According to the biological literature [19], let us consider the values of the parameters shown in Table 1.

Parameter	*Value*	*Unit*
s	10	$mm^{-3}day^{-1}$
k	0.000024	mm^3day^{-1}
μ	0.01	day^{-1}
ϵ	0.4	day^{-1}
b	0.05	day^{-1}
μ_1	0.015	day^{-1}
δ	0.26	day^{-1}
N	1000	dimensionless
c	2.4	day
$T(0)$	300	mm^{-3}
$I(0)$	10	mm^{-3}
$V(0)$	10	mm^{-3}
$L(0)$	10	mm^{-3}
α	0.99	dimensionless

TABLE 1. Values of the parameters

Now let us consider the stability results obtained in the previous section, in accordance to the values of the established parameters and remembering that the value of the efficacy of RT inhibitor $\eta \in [\beta, 1]$.

The non-infectious equilibrium E_1 turns out to be $E_1 = (s/\mu, 0, 0, 0) =$
$= (1000, 0, 0, 0)$. In order to ensure the conditions of its asymptotic stability, it is easy to check conditions (8) with (7) and $\beta = 0.6$ (actual efficacy of a RT inhibitor). Now referring to Theorem 9, let us compute the value of $\eta_{crit} = (b_2 - b_1)/b_2 = \eta_{crit} = 0.88375$.

Therefore, if the reverse transcriptase inhibitor has an efficacy η greater than $\eta_{crit} = 0.88375$, then the non-infectious state E_1 is asymptotically stable, thus achieving the undetectable viral load of the patient.

Remark 6 Given the fact that the actual efficacy of the RT inhibitor is approximately 0.6 (i.e., approximately 60%) , ARTs must use combinations of three or more drugs to achieve the needed efficacy.

7. Conclusions

A model of HIV infection has been analyzed along with the immune system cells, the $CD4^+$ T-lymphocytes, where a reverse transcriptase inhibitor was provided [5]. Four variables were taken into account: susceptible cells, virus density, infected cells pre-reverse transcription (i.e. they do not produce viruses), and infected cells post-reverse transcription (cells that produce viruses). A fractional order model

was considered, in view of the advantages that this entails. It was explicitly proved that the solution of this model exists, it is unique and it is positively invariant. After analyzing the stability of the solution, it was concluded that if the efficacy of the drug is greater than 88.375%, then an undetectable level of virus density will be achieved.

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A. J. Ferrari
Facultad de Ciencias Exactas, Ingeniería y Agrimensura, Universidad Nacional de Rosario - CONICET, Rosario, Argentina
Email address: aferrari@fceia.unr.edu.ar; albertoferrari1991@gmail.com

E. A. Santillan Marcus
Facultad de Ciencias Exactas, Ingeniería y Agrimensura, Universidad Nacional de Rosario, Rosario, Argentina
Email address: edus@fceia.unr.edu.ar