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RESEARCH ARTICLE

Maintenance of the latent reservoir by pyroptosis and superinfection in a fractional order HIV transmission model

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ABSTRACT

We focus on the importance of pyroptosis and superinfection on the maintenance of the human immunodeficiency virus (HIV) latent reservoir on infected patients. The latent reservoir has been found to be crucial to the persistence of low levels of viral loads found in HIV-infected patients, after many years of successfully suppressive anti-retroviral therapy (ART). This reservoir seems to act as an archive for strains of HIV no longer dominant in the blood, such as wild-type virus. When a patient decides to quit therapy there is a rapid turnover and the wild-type virus re-emerges. Thus, it is extremely important to understand the mechanisms behind the maintenance of this reservoir. For that, we propose a fractional order model for the dynamics of HIV, where pyroptosis and superinfection are considered. The model is simulated for biological meaningful parameters and interesting patterns are found. Our results are interpreted for clinical appreciation.

1. Introduction

HIV is associated with impairment and destruction of the immune system's response, mostly by depletion of $CD4^+$ T cells. HIV infects several types of these cells, but its primary targets are the $CD4^+$ T helper cells. The depletion of these cells may have destructive effects in immune regulation [1]. These include reduced antibody development capacity for new attackers, abnormal function of macrophages and decrease in production of chemical messengers.

A fraction of HIV infected $CD4^+$ T cells enter a latency state. In this state, the cells do not produce new virus. HIV can remain inside these cells for years, forming reservoirs, which constitute major obstacles for the eradication of HIV. Cells in the latent state escape treatment for HIV. Current anti-retroviral drugs can suppress HIV to undetectable levels, but cannot completely eradicate it [2]. Latently infected cells may be infected by HIV, although with slower kinetics than activated T cells. Productive superinfection of these latent cells would eliminate virus genome through cell death. A similar effect may be obtained from the induction of pyroptosis of latent cells, in cell-to-cell transmission. Pyroptosis is a process which leads to the destruction of latent T cells, by causing an intensely inflammatory form of programmed cell death, where cytoplasmic contents and pro-inflammatory cytokines are released [3].

Mathematical models have largely been used to predict the dynamics of infections. In 2006, Kim *et al* [4] study the factors influencing the persistence of the latent reservoir and of low viral load in HIV infected patients, under anti-retroviral therapy (ART). They consider that T

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cells can undergo bystander proliferation, without producing active virus, and assume that the latent cells' activation rate decreases with time on ART. The results of the model point to a combined contribution of intrinsic physiological patients' parameters, such as the minimum activation rate or the net regeneration rate of latently infected cells, to explain the persistence of the latent reservoir and of low viral loads. In 2009, Rong *et al* [5] review several mathematical models for HIV dynamics proposed in the literature. They focus on the quantitative events underlying HIV latency, on the reservoir stability, on the low-level viremia persistence and on the emergence of intermittent viral blips. The authors also distinguish treatment options for each case. In 2015, Wang *et al* [6] develop a mathematical model to study the pyroptosis mechanism, a programmed cell death, and show how pyroptosis explains the slow time scale of $CD4^+$ T cells depletion and its contribution to the persistence of latently infected cells. Conway *et al* [7] describe a mathematical model for the dynamics of HIV to capture the interactions between target cells, productively infected cells, latently infected cells, virus, and cytotoxic T lymphocytes (CTLs). The model provides a CTL response interval for which patients either present viral rebound or post-treatment control, depending on the size of the latent reservoir when treatment finishes. Outside this interval, for lower values, the patients always rebound and for higher values the patients behave as elite controllers. In 2017, Wodarz *et al* [8] use mathematical models to explain the fundamental mechanisms of the size and of the composition of the latent reservoir in HIV infection. The analysis of the model suggests that though pyroptosis/superinfection are significant factors that influence the dynamics of latency, additional mechanisms might also play a significant role. In particular, abortative infections, higher activation status of cells due to high virus load, the carrying capacity of the latent reservoir.

1.1. Fractional calculus

Many mathematical models have a close proximity to reality, however, they are not able to describe it perfectly. Therefore, there is a need to build more accurate models, with the aim of providing better fittings to real data. As such, the Fractional Calculus is one of the most precise tools to refine the description of a series of phenomena present in the most diverse areas of knowledge, namely in engineering, physics, biology, and others [9–14].

There are several and important definitions for a fractional order derivative. The most well-studied are the Riemann-Liouville (RL), the Grünwald-Letnikov (GL), and the Caputo formula (C). We consider the interval $(0,t)$ instead of (a,t), for simplification. Now, let $y(\tau)$ be a smooth function in every interval $(0,t)$, $t \leq T$. The RL definition reads:

$$D^{\alpha}_{RL}y(t) = \begin{cases} \frac{1}{\Gamma(m-\alpha)}\frac{d^m}{dt^m}\int_0^t \frac{y(\tau)}{(t-\tau)^{\alpha+1-m}}, & m-1 \leq \alpha < m \\ \frac{d^m y(t)}{dt^m}, & \alpha = m \end{cases}$$

The Caputo definition is written as:

$$D^{\alpha}_{C}y(t) = \begin{cases} \frac{1}{\Gamma(m-\alpha)}\int_0^t \frac{y^m(\tau)}{(t-\tau)^{\alpha+1-m}}, & m-1 \leq \alpha < m \\ \frac{d^m y(t)}{dt^m}, & \alpha = m \end{cases}$$

The GL definition is equivalent to the RL formula and is based on finite differences. It is given by:

$$D^{\alpha}_{GL}y(t) = \lim_{h\to 0} \; h^{-\alpha}\sum_{k=0}^{n}(-1)^k \frac{\Gamma(\alpha+1)}{k!\Gamma(\alpha-k+1)} y(x-kh), \; nh = x.$$

Diethelm [10] demonstrates that a non-integer order model simulates the dynamics of data from the 2009 outbreak of dengue fever, on the Cape Verde islands, more accurately than an integer first order model. The author also shows that the dynamics of the human and of the mosquito populations are modeled by different orders of the fractional derivative. In 2017, Pinto *et al* [11] study a fractional order model for HIV infection where the dynamics of the latent $CD4^+$ T cells, macrophages and cytotoxic T lymphocytes (CTLs) are considered. The simulations of the model suggest that the order of the fractional derivative is associated to a decrease in the severity of the disease. Namely, are observed decreased values of infected $CD4^+$ T cells and virus with α. Moreover, the results of the simulations of the model for relevant parameters, such as the fraction of uninfected $CD4^+$ T cells that become latently infected, and the CTLs proliferation rate due to infected $CD4^+$ T cells, are biologically acceptable, for all values of α. Arshad *et al* [13] present a non-integer order mathematical model for HIV infection, to study the degree of T cell depletion caused by viral cytopathology. The results of the model point to the use of the fractional derivative as a parameter to vary to provide better fits to the data of each HIV infected individual. Each individual has its own specificities which are better captured by a non-integer model. Moreover, these models can help doctors choosing the optimal dosage and verify its effects for each individual.

With the aforesaid ideas in mind, in this paper, we propose a fractional order model for HIV dynamics, where latency, pyroptosis and superinfection are considered. The model is given in Section 2. Its reproduction number and the stability of the disease-free equilibrium are done in Section 3. In Section 4, we analyze the global stability of the disease free equilibrium, and the sensitivity analysis is done in Section 5. In Section 6, we simulate the model for epidemiologically relevant parameters and discuss the results. Finally in Section 7, we state the main conclusions of this work.

2. The model

The uninfected CD4$^+$ T cells, $T(t)$, are produced at rate s and die at rate d. These cells proliferate exponentially at a rate r, until reaching the carrying capacity K. They are infected by HIV or by infected CD4$^+$ T cells at rates β and β_1, respectively. A fraction, $(1-q)$, of infected CD4$^+$ T cells becomes latently infected, $L(t)$, and the other fraction, q, is actively infected, $I(t)$. The latently infected CD4$^+$ T cells become productively infected at a rate g and die at a rate a_L. The latently infected cells can be successfully superinfected by productive virus at rate $fq\beta$. As the productive infection rate of latently CD4$^+$ T cells is lower than that of infected CD4$^+$ T cells, we considered the parameter $f < 1$. When infected by CD4$^+$ T cells, the latently CD4$^+$ T cells die by pyroptosis, which is a form of cell death. Thus, cell-to-cell transmission contributes for cells' death at rate β_1. The infected CD4$^+$ T cells, $I(t)$, die at a rate a_I. HIV, $V(t)$, is produced by the infected CD4$^+$ T cells at a rate p and is cleared at a rate c. The nonlinear system of fractional-order differential equations describing the dynamics of the model is given by:

$$\begin{aligned}
\frac{d^\alpha T}{dt^\alpha} &= s^\alpha - d^\alpha T + r^\alpha T\left(1-\frac{T}{K}\right) - \beta^\alpha TV - \beta_1^\alpha TI \\
\frac{d^\alpha L}{dt^\alpha} &= (1-q)(\beta^\alpha TV + \beta_1^\alpha TI) - a_L^\alpha L - fq\beta^\alpha LV \\
&\quad -\beta_1^\alpha LI - g^\alpha L \\
\frac{d^\alpha I}{dt^\alpha} &= q(\beta^\alpha TV + \beta_1^\alpha TI) - a_I^\alpha I + fq\beta^\alpha LV + g^\alpha L \\
\frac{d^\alpha V}{dt^\alpha} &= p^\alpha I - c^\alpha V
\end{aligned} \tag{1}$$

where $\alpha \in (0,1]$ is the order of the fractional derivative, and $\cdot^\alpha$ represents the $\cdot$ to the power of α. When $\alpha = 1$, then the model is the integer order counterpart. The fractional derivative of the proposed model is used in the Caputo sense.

3. Reproduction number

In this section, we compute the reproduction number of model (1), R_0, and the local stability of its disease-free equilibrium. The basic reproduction number is defined as the number of CD4$^+$ T cells which are infected by one single cell entering a completely susceptible population. We begin by computing the reproduction number of system (1), R_0. We use the next generation method [15]. The disease-free equilibrium of model (1) is given by:

$$\begin{aligned}
P_0 &= (T_0, L_0, I_0, V_0) \\
&= \left(\frac{K^\alpha\left[r^\alpha - d^\alpha + \sqrt{(r^\alpha - d^\alpha)^2 + \frac{4r^\alpha s^\alpha}{K}}\right]}{2r^\alpha}, 0, 0, 0 \right)
\end{aligned} \tag{2}$$

Using the notation in [15] on system (1), matrices for the new infection terms, F, and the other terms, V , are given by:

$$F = \begin{pmatrix} 0 & (1-q)\beta_1^\alpha T_0 & (1-q)\beta^\alpha T_0 \\ 0 & q\beta_1^\alpha T_0 & q\beta^\alpha T_0 \\ 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} g^\alpha + a_L^\alpha & 0 & 0 \\ -g^\alpha & a_I^\alpha & 0 \\ 0 & -p^\alpha & c^\alpha \end{pmatrix}$$

The associative basic reproduction number is written as:

$$R_0 = \rho(FV^{-1}) = \frac{T_0(p^\alpha\beta^\alpha + c^\alpha\beta_1^\alpha)(qa_L^\alpha + g^\alpha)}{c^\alpha a_I^\alpha (g^\alpha + a_L^\alpha)} \tag{3}$$

where ρ indicates the spectral radius of FV^{-1}.
The linearization matrix of model (1) around the disease-free equilibrium, P_0, is:

$$M_1 = \begin{pmatrix} -\sqrt{(r^\alpha - d^\alpha) + \frac{4r^\alpha s^\alpha}{K}} & 0 & -\beta_1^\alpha T_0 & -\beta^\alpha T_0 \\ 0 & -a_L^\alpha - g^\alpha & (1-q)\beta_1^\alpha T_0 & (1-q)\beta^\alpha T_0 \\ 0 & g^\alpha & q\beta_1^\alpha T_0 - a_I^\alpha & q\beta^\alpha T_0 \\ 0 & 0 & p^\alpha & -c^\alpha \end{pmatrix}$$

Stability of P_0 can be determined using the following lemmas:

Lemma 1. *(Theorem 2, [16])*
Let $\alpha\left(=\frac{p}{q}\right)$ where $p, q \in \mathrm{Z}^+$ and $gdc(p,q) = 1$. Define $M = q$, then the disease-free equilibrium P_0 of the system (1) is asymptotically stable if $|\arg(\lambda)| > \frac{\pi}{2M}$ for all roots λ of the following equation

$$\det\left(\mathrm{diag}\left[\lambda^{M\alpha}\lambda^{M\alpha}\lambda^{M\alpha}\lambda^{M\alpha}\right] - M_1\right) = 0$$

Lemma 2. *The disease-free equilibrium P_0 of the system (1) is unstable if $R_0 < 1$.*

Proof. Expanding,

$$\det\left(\operatorname{diag}\left[\lambda^{M\alpha}\lambda^{M\alpha}\lambda^{M\alpha}\lambda^{M\alpha}\right]-M_1\right)=0$$

we have the following equation in terms of λ:

$$\begin{aligned}&\left[\lambda^{M\alpha}+\sqrt{(r^\alpha-d^\alpha)+\frac{4r^\alpha s^\alpha}{K}}\right]\left[\lambda^{3M\alpha}+(a_L^\alpha+g^\alpha+a_I^\alpha+c^\alpha-q\beta_1^\alpha T_0)\,\lambda^{2M\alpha}\right.\\&+(c^\alpha(a_L^\alpha+g^\alpha+a_I^\alpha)+(a_L^\alpha+g^\alpha)a_I^\alpha-T_0(\beta_1^\alpha(qc^\alpha+qa_L^\alpha+g^\alpha)+\beta^\alpha qp^\alpha))\,\lambda^{M\alpha}\\&\left.+(a_L^\alpha+g^\alpha)a_I^\alpha c^\alpha(1-R_0)\right]=0\end{aligned}\tag{4}$$

Now arguments of the roots of the equation, $\lambda^{M\alpha}+\sqrt{(r^\alpha-d^\alpha)+\frac{4r^\alpha s^\alpha}{K}}=0$, are given by:

$$\arg(\lambda_k)=\frac{\pi}{M\alpha}+k\frac{2\pi}{M\alpha}>\frac{\pi}{M}>\frac{\pi}{2M}$$

where $k=0,1,..,(M\alpha-1)$.

Thus, using Lemma 1, we show that the disease-free equilibrium, P_0, of system (1) is stable if all roots of the polynomial:

$$\begin{aligned}&\lambda^{3M\alpha}+(a_L^\alpha+g^\alpha+a_I^\alpha+c^\alpha-q\beta_1^\alpha T_0)\,\lambda^{2M\alpha}\,(c^\alpha(a_L^\alpha+g^\alpha+a_I^\alpha)+(a_L^\alpha+g^\alpha)a_I^\alpha\\&-T_0(\beta_1^\alpha(qc^\alpha+qa_L^\alpha+g^\alpha)+\beta^\alpha qp^\alpha))\,\lambda^{M\alpha}+(a_L^\alpha+g^\alpha)a_I^\alpha c^\alpha(1-R_0)=0\end{aligned}\tag{5}$$

have argument greater than $\frac{\pi}{2M}$, for $R_0<1$.

Finally, using Descartes' rule of signs in equation (5), we find that there is exactly one sign change for $R_0>1$. Thus there is exactly one positive real root of the aforesaid equation for which the argument is less than $\frac{\pi}{2M}$. We concluded that, if $R_0<1$, the disease-free equilibrium P_0 of the system (1) is stable. □

4. Global stability of the disease-free equilibria

In this section, we compute the global stability of the disease-free equilibrium of the model (1). We rewrite model (1) as:

$$\begin{aligned}\frac{d^\alpha X}{dt^\alpha}&=F(X,Z)\\\frac{d^\alpha Z}{dt^\alpha}&=G(X,Z),\qquad G(X,0)=0\end{aligned}\tag{6}$$

where $X=T$ and $Z=(L,I,V)$, with $X\in\mathbf{R}_+$ being the number of uninfected CD4$^+$ T cells and $Z\in\mathbf{R}_+^3$ denoting the number of latent and infected CD4$^+$ T cells, and virus.

The disease-free equilibrium is written as $U=(X^\star,0)$, where $X^\star=\left(\frac{K^\alpha\left[r^\alpha-d^\alpha+\sqrt{(r^\alpha-d^\alpha)^2+\frac{4r^\alpha s^\alpha}{K}}\right]}{2r^\alpha},0\right)$.

The conditions (H_1) and (H_2) must be met to guarantee the global asymptotic stability of the disease-free equilibrium of the model (1):

$$\begin{aligned}(H_1):&\ \text{For }\tfrac{d^\alpha X}{dt^\alpha}=F(X,0),\\&\ X^\star\ \text{is globally asymptotically stable}\\(H_2):&\ G(X,Z)=AZ-\hat{G}(X,Z),\ \hat{G}\geq 0,\\&\ \text{for }(X,Z)\in\Upsilon_1\end{aligned}\tag{7}$$

where $A=D_ZG(X^\star,0)$ is a M-matrix (the off-diagonal elements of A are non-negative) and Υ_1 is the region where the model makes biological sense. If the system (6) satisfies the conditions in (7) the following theorem holds.

Theorem 1. *The fixed point $U=(X^\star,0)$ is a globally asymptotically stable equilibrium of the system (6) provided that $R_0<1$ and that the assumptions in (7) are satisfied.*

Proof. Let

$$F(X,0)=\left(s^\alpha-d^\alpha T+r^\alpha T\left(1-\tfrac{T}{K}\right)\right)\tag{8}$$

and

$$A=\begin{pmatrix}-g^\alpha-a_L^\alpha & (1-q)\beta_1^\alpha T_0 & (1-q)\beta^\alpha T_0\\ g^\alpha & q\beta_1^\alpha T_0-a_I^\alpha & q\beta^\alpha T_0\\ 0 & p^\alpha & -c^\alpha\end{pmatrix}\tag{9}$$

and

$$\begin{aligned}\hat{G}(X,Z)&=\begin{pmatrix}\hat{G}_1(X,Z)\\\hat{G}_2(X,Z)\\\hat{G}_3(X,Z)\end{pmatrix}\\&=\begin{pmatrix}(1-q)T_0\left(1-\frac{T}{T_0}\right)(\beta_1^\alpha I+\beta^\alpha V)+fq\beta^\alpha LV+\beta_1^\alpha LI\\qT_0\left(1-\frac{T}{T_0}\right)(\beta_1^\alpha I+\beta^\alpha V)-fq\beta^\alpha LV\\0\end{pmatrix}\end{aligned}\tag{10}$$

Thus $\hat{G}_1(X,Z),\hat{G}_2(X,Z)\geq 0$ and $\hat{G}_3(X,Z)=0\Rightarrow\hat{G}(X,Z)\geq 0$. Conditions in (7) are satisfied, thus the disease-free equilibrium of the model (1) is globally asymptotically stable for $R_0<1$. □

5. Sensitivity analysis

In this section we compute the sensitivity indexes of the reproduction number, R_0 (1). Sensitivity indexes are given in Table 1 and provide information on the variation of the value of R_0 as a function of each parameter. We follow the procedure proposed in [17]. Generically, when $R_0>1$, the epidemics spreads, on the other hand, for $R_0<1$ the epidemics halts.

Table 1. Sensitivity indexes for relevant parameters of model (1).

Parameter	Sensitivity index sign
β	+
β_1	+
p	+
q	+
g	+
c	-
a_L	-
a_I	-

6. Numerical results

We simulate the model (1) for different values of the order of the fractional derivative, α and for epidemiologically valid parameters. The parameters used in the simulations, based on [7, 8], are: $s = 10$ day^{-1}, $d = 0.015$ day^{-1}, $r = 0.03$ day^{-1}, $K = 1500$ mm^{-3}, $\beta = 0.0001$ mm^3 day^{-1}, $\beta_1 = 0.0001$ mm^3 day^{-1}, $q = 0.95$, $g = 0.001$ day^{-1}, $a_L = 0.03$ day^{-1}, $f = 1/7$, $a_I = 0.45$ day^{-1}, $p = 2000$ day^{-1}, $c = 23$ day^{-1}, and the initial conditions are: $T(0) = 700$, $L(0) = I(0) = 0$ and $V(0) = 10$.

Fiures 1-3 depict the number of latently infected cells in the cases of existence and absence of pyroptosis/superinfection. It is observed a higher number of latent cells when there is no pyroptosis/superinfection, for the three values of the order of the fractional derivative, α. In both cases, with and without pyroptosis, there is a first increase in the number of latent cells towards a peak and then a convergence to an asymptotic state. Moreover, the behaviour with pyroptosis/superinfection at $\alpha = 1$ shows a minimum after the peak and then a rise to the equilibrium state. This may be due to the variation of the HIV viral load, which is related with the phenomenon of pyroptosis/superinfection, as follows. The HIV viral load increase from lower levels is followed by the rise of the latent cells. When the HIV load reaches its peak value, the number of latent cell decreases due to cell death by pyroptosis or by superinfection. As the viral load declines and tends asymptotically to its equilibrium, the latent pool rebounds and increases to some value. Lower viral loads are associated with less pyroptosis and less superinfection, which translates in the perseverance of the latent cells' pool. This rebound feature is rapidly forgotten for smaller values of the order of the fractional derivative α, probably due to the memory property, which causes transients to be faster in these systems than in integer order ones.

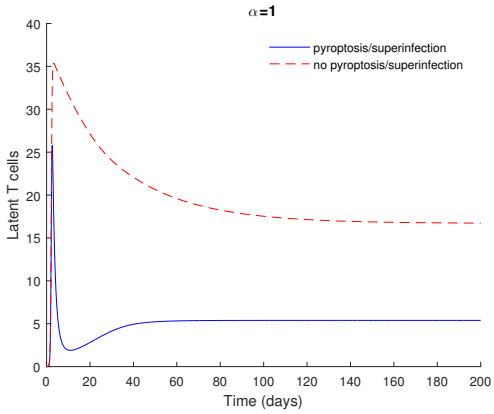

Figure 1. Number of latent cells with and without pyroptosis/superinfection, for $\alpha = 1$. Parameter values and initial conditions in the text.

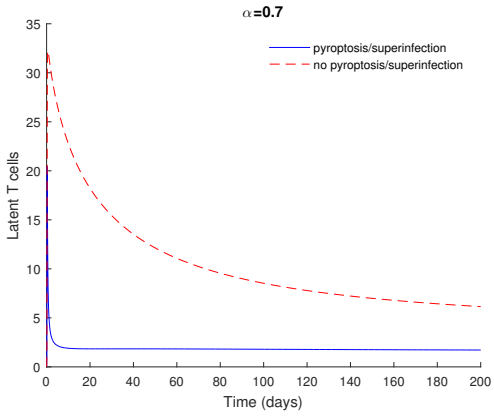

Figure 2. Number of latent cells with and without pyroptosis/superinfection, for $\alpha = 0.7$. Parameter values and initial conditions in the text.

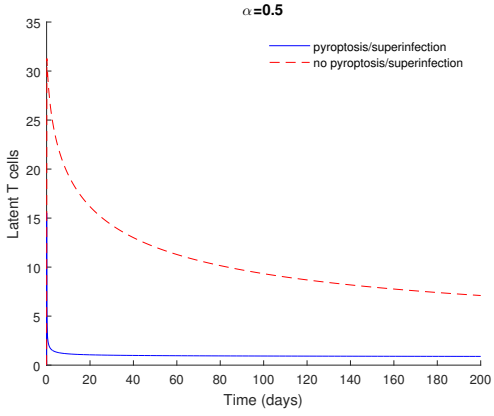

Figure 3. Number of latent cells with and without pyroptosis/superinfection, for $\alpha = 0.5$. Parameter values and initial conditions in the text.

7. Conclusion

We proposed a non-integer order mathematical model for HIV infection to study the influence of pyroptosis and superinfection on the maintenance of the latent reservoir. We computed the basic reproduction number and the stability of the disease-free equilibrium. The simulations of the model provide good agreement with experimental data available in the literature concerning the maintenance of the latent reservoir. It is observed that as HIV load increases from lower levels, the latent cells' population also rises. When the viral load reaches its peak, the number of latent cells decreases, due to cell death by pyroptosis and superinfection. As the viral load declines and tends asymptotically to its equilibrium, the latent pool rebounds and increases to some threshold. Thus, pyroptosis and superinfection, are important players in the perseverance of the latent cells' pool in HIV infection.

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