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A latency fractional order model for HIV dynamics

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ABSTRACT

We study a fractional order model for HIV infection where latent T helper cells are included. We compute the reproduction number of the model and study the stability of the disease free equilibrium. We observe that the reproduction number varies with the order of the fractional derivative α. In terms of epidemics, this suggests that varying α induces a change in the patients' epidemic status. Moreover, we simulate the variation of 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. The model produces biologically reasonable results.

1. Introduction

The human immunodeficiency virus (HIV) is associated to the impairment and destruction of the immune system's response. The mechanism behind these events is extremely complex, since HIV affects a wide variety of elements of the immune system. Moreover, the effects vary within the different stages of infection, namely, acute, chronic and AIDS stage.

HIV main target are the white blood cells with CD4 receptors known as $CD4^+$ T cells [1]. HIV infects several types of these cells, but its primary targets are the $CD4^+$ T helper cells. After attacking these cells, HIV introduces itself in the cells' DNA, producing virions that are released in the blood stream and can infect other healthy cells [2]. The depletion of $CD4^+$ T cells may have destructive effects in immune regulation [3]. These include reduced antibody development capacity for new attackers, abnormal function of macrophages and decrease in production of chemical messengers [1].

Macrophages play a major role in adaptive and innate immune response [4]. However, their relevance for HIV transmission, propagation and pathogenesis is not yet completely understood [5]. This is mainly due to the variation of macrophages' susceptibility to infection and capacity to actively replicate the virus, with the tissue localization and cytokine activity. Nevertheless, macrophages, due to telomerase activity, live longer and become good HIV reservoirs [6], preventing its eradication from the body. The cytotoxic T lymphocytes (CTLs) are critical players in the control of viral infections. CTL response to HIV infection during the acute stage is crucial, since it is believed that it determines the viral set-point, influencing the rate of HIV disease progression [7].

Antiretroviral drugs are used to treat HIV virus. The standard antiretroviral therapy consists of a combination of three or more antiretroviral drugs, such as protease inhibitors and reverse transcriptase inhibitors. These drugs suppress HIV viral load below the limit of detection (50 *copies*/*ml*), particularly if initiated in early stages of infection.

Many mathematical models have been proposed for dynamics of HIV infection [8–11]. In 2000, Arnaout et al. [8] conclude that during the administration of antiretroviral drugs, priming the CTL response can lead to better immune responses from

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the patients. Viral load decreases rapidly when CTLs are abundant and less quickly otherwise. Asquith et al. [12] analyse multiple sets of HIV data and estimate that only 2% of infected $CD4^+$ T cells is due to CTLs, recognizing only one epitope. The authors suggest that CTLs are responsible for the killing of a considerable number of infected T helper cells, but nonetheless the majority of infected cells are killed by other cells of the immune system. Chan et al. [9] study a model for primary and secondary CTL response cells. The model exhibits rich dynamics and the authors observed oscillatory patterns for a wide parameter range. Carvalho et al. [13] propose a model for the dynamics of HIV epidemics under distinct HAART regimes, and study the emergence of drug-resistance. The model predicts HIV dynamics of untreated HIV patients for all stages of the infection. Protease inhibitors-drug based regimes appear to induce better results, leading to reduced infection, than reverse transcriptase inhibitors based drugs.

Fractional differentiation

In the last few decades, the theory of Fractional Calculus (FC) has undergone a huge development. FC is extensively used to solve distinct real world problems. Some important applications are in engineering, physics, biology, and others [14–24], and others. Recently, Caputo and Fabrizio [25] propose a new definition for the fractional order derivative. Their new operator has non-singular kernel and has been applied in several real world problems, namely in groundwater and thermal science. Atangana and co-workers [26,27] present useful tools about the new derivative and apply it to the nonlinear Fisher's reaction–diffusion equation and the nonlinear Baggs and Freedman model. In order to solve some issues concerning the non-locality of the kernel of the Caputo–Fabrizio derivative, Atangana and Baleanu [28] introduced a new fractional derivative with non-local and non-singular kernel based upon the Mittag-Leffler function. The authors use it to find the solution of the fractional heat transfer model. This new derivative is employed in [29] to investigate new chaotic behaviour in the Lorenz attractor model. In what concerns epidemiological models, in 2014, Pinto et al. [22] study a model for HIV and TB co-infection and concluded that the dynamics of the integer and the fractional order versions of the model are very rich and that together these versions may provide a better understanding of the dynamics of the co-infection. In 2015, Pinto et al. [30] propose a fractional complex-order model for drug resistance in HIV infection. Authors observe that the variation of the complex-order fractional derivative can be compared to the variation of the delay in integer-order systems, in biologically meaning intervals. Finally, Pinto et al. [31] study a fractional order model for the three stages of HIV epidemics with drug-resistance. The different routes of progression to AIDS, namely rapid progressors and long-term non progressors, are considered.

In this paper, we propose a fractional model for HIV infection that includes $CD4^+$ T helper cells, macrophages, CTLs and virus. In Section 2, we describe the model. In Section 3, we compute the reproduction number of the model and the local stability of the disease-free equilibrium. In Section 4, we analyse several simulations of the model and discuss the biological relevance of the results. In Section 5, we close our work.

2. Description of the model

The proposed model for the dynamics of HIV infection consists of seven compartments: the uninfected $CD4^+$ T cells, T, the latently infected $CD4^+$ T cells, L, the productively infected $CD4^+$ T cells, I, the uninfected macrophages, M, the infected macrophages, M_I, the virus, V and the CTLs, Z.

The uninfected $CD4^+$ T cells are produced at rate s and die at rate μ_T. When in contact with the virus, the uninfected $CD4^+$ T cells are infected at a rate k_1. Upon infection, a fraction, η, of uninfected $CD4^+$ T cells become latently infected, L. The latently infected $CD4^+$ T cells become productively infected at a rate a_L and die at a rate μ_L. The productively infected $CD4^+$ T cells, I, die at a rate δ and are killed by CTLs at a rate k_2. Macrophages are infected by virus at rate k_M, and die at rate δ_M. Their production rate is s_M. CTLs kill infected macrophages at rate k_3. The virus particles are produced by productively infected $CD4^+$ T cells at rate p and by infected macrophages at rate p_M. Virus particles are cleared at rate c. Finally, CTLs are produced at rate s_C and die at rate δ_C. They proliferate by productively infected $CD4^+$ T cells at rate k_4 and by infected macrophages at rate k_5. The nonlinear fractional order system describing the dynamics of the model is:

$$\begin{aligned}
\frac{dT^\alpha(t)}{dt^\alpha} &= s - \mu_T T - k_1 VT \\
\frac{dL^\alpha(t)}{dt^\alpha} &= k_1 \eta VT - a_L L - \mu_L L \\
\frac{dI^\alpha(t)}{dt^\alpha} &= k_1(1-\eta)VT + a_L L - \delta I - k_2 IZ \\
\frac{dM^\alpha(t)}{dt^\alpha} &= s_M - k_M MV - \delta_M M \\
\frac{dM_I^\alpha(t)}{dt^\alpha} &= k_M MV - \delta_M M_I - k_3 M_I Z \\
\frac{dV^\alpha(t)}{dt^\alpha} &= pI + p_M M_I - cV \\
\frac{dZ^\alpha(t)}{dt^\alpha} &= s_C + k_4 IZ + k_5 M_I Z - \delta_C Z
\end{aligned} \tag{1}$$