Contributions of the latent reservoir and of the pool of long-lived chronically infected $CD4^+$ T cells in HIV dynamics: a fractional approach

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Summary. In this paper, we study the effect of the size of the latent reservoir and of the pool of long-lived chronically infected $CD4^+$ T cells in a non-integer model for HIV dynamics with drug-resistance. We calculate the reproduction number and study the local stability of the disease-free equilibrium. The effects of the sizes of the latent reservoir and of the pool of long-lived chronically infected $CD4^+$ T cells were analyzed numerically, for distinct values of the order of the fractional derivative, α. Our results are biologically reasonable. We found that the latent reservoir in resting $CD4^+$ T cells appears to be sufficient to maintain the plasma viral load in patients under HAART. Moreover, the pool of long-lived chronically infected cells promotes an increase in drug-resistant virus, that escape treatment, which turns the eradication of the plasma virus an impossible goal. These results are biologically acceptable and are observed for all values of α.

Introduction

Over the years, the development of suitable mathematical models and the clinical practice have boosted a greater understanding of HIV dynamics. HIV infection damages the immune system and attacks preferentially $CD4^+$ T cells, leading to their depletion [18].
Treatment for HIV infected patients is extremely important. Nowadays, it consists of a cocktail of drugs, such as reverse transcriptase inhibitors (RTIs), which inhibit the infection of $CD4^+$ T cells by virus, and protease inhibitors (PIs), which prevent the infected cells from producing new infectious virions. This therapy is commonly known as highly active antiretroviral therapy (HAART). But even with treatment, HIV stays dormant within reservoirs, such as the latently infected $CD4^+$ T cells. These cells are infected during the primary phase of infection and remain at a resting state. This is an obstacle for HIV eradication [9]. Latently infected cells take 6 to 48 months to be activated [29]. When they do, they produce new virus and a viral-blip may be observed in patients.
The $CD4^+$ T cells may be characterized as short-lived and long-lived cells. Short-lived infected $CD4^+$ T cells produce more virus than long-lived infected $CD4^+$ T cells. On the other hand, the short-lived infected $CD4^+$ T cells die more rapidly [10].
In the literature several mathematical models have been proposed to describe the dynamics of HIV infection [17, 32, 35]. Existing models for HIV with treatment predict a rapid decline in viral load, in the first phase of infection, if treatment is 100% effective. This decline is exponential and is defined mainly by the rate of decay of productively infected $CD4^+$ T cells. If treatment is not 100% effective, the decline in the viral load is given, additionally, as a function of the drug efficacy. In the second phase of infection, the decay in the viral load is slower. This is attributed to the emergence of drug-resistant virus strains and the production of new virus by the long-lived $CD4^+$ T cells. In this phase, viral load levels often reach values of pre-treatment stage [14]. In 1998, Wein et al [33] present a mathematical model to predict the role of drug regimens, based on combinations of PIs and RTIs, in the eradication of HIV-1 or in the maintenance of low viral loads. The model includes the $CD4^+$ T cells, macrophages (as long-lived cells) and sensitive and resistant virus. From the model the authors infer that the behaviour of the cells and virus, and the eradication of the virus, are dependent on the strength of the combined therapy against the mutant strain and the maximum achievable increase in the uninfected $CD4^+$ T cell concentration. Under certain conditions, the model suggests that a successful formula to control HIV infection would be to start with a strong inductive therapy to reduce viral load, and proceed with a weaker maintenance regime. In 2006, Kim and Perelson [19] study the persistence of the latently infected cells and low levels of plasma virus in HIV-infected patients. Simulations of the model reveal that the intrinsic stability of latently infected resting memory $CD4^+$ T cells is the key factor to their long-term persistence. The role of ongoing viral replication to the stability of the latent reservoir is meaningless. The presented model is also used to assess the contribution of long-lived infected cells to plasma virus. It is found that these cells have a significant contribution to plasma virus only in the first few months of therapy, when the viral load is above 50 copies/ml.

Fractional differentiation

Calculus of non-integer order, or Fractional Calculus (FC) has its birth in 1695 when, in a letter exchange, L'Hôpital asks Leibniz the possible meaning of a $1/2$-order derivative. Since then, several definitions for the fractional order (FO) derivatives and integrals have been proposed and their properties studied, by mathematicians, such as Euler, Abel, Liouville, and Riemann. In 2015, Caputo and Fabrizio [11] propose a new definition for the FO derivative with non-singular kernel. The Caputo-Fabrizio derivative has some problems with respect to the locality of its kernel. In order to overcome this difficulty, Atangana and Baleanu [2] present, based on the Mittag-Leffler function, a new derivative

of FO, with non-local and non-singular kernel. A few decades ago, FC starts to be widely applied in distinct areas of engineering, such as electronics, viscoelasticity, biology, physics, to name some [20, 7, 8, 5, 21, 28, 27, 26, 22, 15, 6, 3]. For instance, applications of the Caputo-Fabrizio derivative to the nonlinear Fisher's reaction-diffusion equation and the nonlinear Baggs and Freedman model can be found in [1, 4]. In epidemiology, fractional models are applied to study the dynamics of HIV, malaria, to name a few. In 2015, Pinto *et al* [23] apply the fractional complex-order derivative to a model of drug resistance in HIV dynamics. From the results of the model, the authors infer that the role of the complex-order derivative is similar to the role of the delay in integer-order systems. The fractional order dynamics of the three stages of HIV infection with drug-resistance is studied in [24]. In 2016, it is analysed a FO model for HIV infection where latent T helper cells are included [25]. The order of the fractional derivative is associated to a decrease in the severity of the disease. Moreover, the results of the simulations 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, are biologically acceptable, for all values of the order of the fractional derivative.
Driven by the aforesaid research, in this paper we propose a FO model for the dynamics of HIV infection and analyse the roles of the latent reservoir and of the size of the pool of long-lived chronically infected CD4$^+$ T cells in the persistence of the disease. The paper is organized as follows. In Section , we present the model. In Section , we compute the reproduction numbers of the model. Moreover we prove the local stability of the disease-free equilibrium. In Section , we show simulations of the full model for distinct sizes of the latent reservoir and of the pool of long-lived chronically infected CD4$^+$ T cells. In Section , we conclude our work.

The model

The population is partitioned into nine classes, namely, the uninfected CD4$^+$ T cells, T, the sensitive latently infected CD4$^+$ T cells, L_S, the resistant latently infected CD4$^+$ T cells, L_R, the short-lived sensitive productively infected CD4$^+$ T cells, I_{S_S}, the short-lived resistant productively infected CD4$^+$ T cells, I_{S_R}, the long-lived chronically sensitive productively infected CD4$^+$ T cells, I_{C_S}, the long-lived chronically resistant productively infected CD4$^+$ T cells, I_{C_R}, the sensitive infectious virus, V_{I_S}, the resistant infectious virus, V_{I_R}, the non-infectious virus, V_{NI}, the cytotoxic T lymphocytes (CTLs), E.
The uninfected CD4$^+$ T cells are produced at rate λ_T and die at rate d_T. The healthy CD4$^+$ T cells are assumed to proliferate exponentially at rate r, until reaching the maximum carrying capacity T_{max}, in the absence of virus or infected CD4$^+$ T cells. The uninfected CD4$^+$ T cells are infected by virus at a rate k_1 and by infected CD4$^+$ T cells at a rate k_2. The infection rate by virus, k_1, is reduced by a quantity, $(1-\epsilon_{RT})$, where ϵ_{RT}, $(0 \leq \epsilon_{RT} \leq 1)$ is the efficacy of RTIs. The infection rates by mutated virus are considered to be smaller. As such, we assume that mutated virus is less fit than the wild-type. In the model, this is accounted by the parameter ψ. Upon infection, a fraction, α_L, of uninfected CD4$^+$ T cells become latently infected. The latently infected CD4$^+$ T cells become productively infected at rate a and die at rate d_L. A fraction, α_C, of productively infected CD4$^+$ T cells become long-lived chronically infected T cells. The short-lived and long-lived chronically productively infected CD4$^+$ T cells die, respectively, at rates d_{I_S} and d_{I_C}. Both are killed by CTLs at rate k_3. The sensitive virus particles are produced by short-lived and long-lived chronically sensitive productively infected cells at rates $N_s d_{I_S}$ and $N_s d_{I_C}$, respectively. Similarly, the resistant virus particles are produced by short-lived and long-lived chronically resistant productively infected cells at rates $N_r d_{I_S}$ and $N_r d_{I_C}$, respectively. Viral mutations are accounted in the model by parameter u, which represents the probability of mutation per replication cycle. PIs prevent virions to become productively infected. Thus, only a fraction, $(1-\epsilon_{PI})$, of newly produced virus is infectious, where ϵ_{PI}, $(0 \leq \epsilon_{PI} \leq 1)$ is the PIs efficacy. The virus particles die at rate c. The CTLs are produced at rate λ_E and die at rate d_E. The proliferation rate of CTLs by infected CD4$^+$ T cells is k_6. The integer order system of ordinary differential equations for the proposed model is given by:

$$
\begin{aligned}
\dot{T} &= \lambda_T + rT\left(1 - \tfrac{T+I_{S_S}+I_{S_R}+I_{C_S}+I_{C_R}+L_S+L_R}{T_{max}}\right) - k_2 T(I_{S_S}+I_{S_R}+I_{C_S}+I_{C_R}) - (1-\epsilon_{RT})k_1 V_{I_S} T - \psi k_1 V_{I_R} T - d_T T \\
\dot{L}_S &= \alpha_L(1-\epsilon_{RT})k_1 V_{I_S} T + k_2 \alpha_L T(t)(I_{S_S}+I_{C_S}) - (a+d_L)L_S \\
\dot{L}_R &= \alpha_L \psi k_1 V_{I_R} T + k_2 \alpha_L T(I_{S_R}+I_{C_R}) - (a+d_L)L_R \\
\dot{I}_S &= (1-\alpha_C)(1-\alpha_L)(1-\epsilon_{RT})k_1 V_{I_S} T + k_2(1-\alpha_L)T I_{S_S} + (1-\alpha_C)aL_S - k_3 E I_{S_S} - d_{I_S} I_{S_S} \\
\dot{I}_R &= (1-\alpha_C)(1-\alpha_L)\psi k_1 V_{I_R} T + k_2(1-\alpha_L)T I_{S_R} + (1-\alpha_C)aL_R - k_3 E I_{S_R} - d_{I_S} I_{S_R} \\
\dot{I}_{C_S} &= \alpha_C(1-\alpha_L)(1-\epsilon_{RT})k_1 V_{I_S} T + k_2(1-\alpha_L)T I_{C_S} + \alpha_C aL_S - k_3 E I_{C_S} - d_{I_C} I_{C_S} \\
\dot{I}_{C_R} &= \alpha_C(1-\alpha_L)\psi k_1 V_{I_R} T + k_2(1-\alpha_L)T I_{C_R} + \alpha_C aL_R - k_3 E I_{C_R} - d_{I_C} I_{C_R} \\
\dot{V}_{I_S} &= N_s(1-u)(1-\epsilon_{PI})(d_{I_S} I_{S_S} + d_{I_C} I_{C_S}) - cV_{I_S} \\
\dot{V}_{I_R} &= N_r \psi(d_{I_S} I_{S_R} + d_{I_C} I_{C_R}) + N_s u(1-\epsilon_{PI})(d_{I_S} I_{S_S} + d_{I_C} I_{C_S}) - cV_{I_R} \\
\dot{V}_{NI} &= \epsilon_{PI} N_s(d_{I_S} I_{S_S} + d_{I_C} I_{C_S}) - cV_{NI} \\
\dot{E} &= \lambda_E + k_6(I_{S_S}+I_{S_R}+I_{C_S}+I_{C_R})E - d_E E
\end{aligned}
\tag{1}
$$

The fractional order model, where $\alpha \in (0,1]$ is the order of the fractional derivative, is given below.

$$
\begin{aligned}
\tfrac{dT^\alpha(t)}{dt^\alpha} &= \lambda_T^\alpha + r^\alpha T\left(1-\tfrac{T+I_{S_S}+I_{S_R}+I_{C_S}+I_{C_R}+L_S+L_R}{T_{max}}\right) - k_2^\alpha T(I_{S_S}+I_{S_R}+I_{C_S}+I_{C_R}) - (1-\epsilon_{RT})k_1^\alpha V_{I_S}T - \psi k_1^\alpha V_{I_R}T - d_T^\alpha T\\
\tfrac{dL_S^\alpha(t)}{dt^\alpha} &= \alpha_L(1-\epsilon_{RT})k_1^\alpha V_{I_S}T + k_2^\alpha\alpha_L T(t)(I_{S_S}+I_{C_S}) - (a^\alpha+d_L^\alpha)L_S\\
\tfrac{dL_R^\alpha(t)}{dt^\alpha} &= \alpha_L\psi k_1^\alpha V_{I_R}T + k_2^\alpha\alpha_L T(I_{S_R}+I_{C_R}) - (a^\alpha+d_L^\alpha)L_R\\
\tfrac{dI_{S_S}^\alpha(t)}{dt^\alpha} &= (1-\alpha_C)(1-\alpha_L)(1-\epsilon_{RT})k_1^\alpha V_{I_S}T + k_2^\alpha(1-\alpha_L)TI_{S_S} + (1-\alpha_C)a^\alpha L_S - k_3^\alpha EI_{S_S} - d_{I_S}^\alpha I_{S_S}\\
\tfrac{dI_{S_R}^\alpha(t)}{dt^\alpha} &= (1-\alpha_C)(1-\alpha_L)\psi k_1^\alpha V_{I_R}T + k_2^\alpha(1-\alpha_L)TI_{S_R} + (1-\alpha_C)a^\alpha L_R - k_3^\alpha EI_{S_R} - d_{I_S}^\alpha I_{S_R}\\
\tfrac{dI_{C_S}^\alpha(t)}{dt^\alpha} &= \alpha_C(1-\alpha_L)(1-\epsilon_{RT})k_1^\alpha V_{I_S}T + k_2^\alpha(1-\alpha_L)TI_{C_S} + \alpha_C a^\alpha L_S - k_3^\alpha EI_{C_S} - d_{I_C}^\alpha I_{C_S}\\
\tfrac{dI_{C_R}^\alpha(t)}{dt^\alpha} &= \alpha_C(1-\alpha_L)\psi k_1^\alpha V_{I_R}T + k_2^\alpha(1-\alpha_L)TI_{C_R} + \alpha_C a^\alpha L_R - k_3^\alpha EI_{C_R} - d_{I_C}^\alpha I_{C_R}\\
\tfrac{dV_{I_S}^\alpha(t)}{dt^\alpha} &= N_s(1-u)(1-\epsilon_{PI})(d_{I_S}^\alpha I_{S_S} + d_{I_C}^\alpha I_{C_S}) - c^\alpha V_{I_S}\\
\tfrac{dV_{I_R}^\alpha(t)}{dt^\alpha} &= N_r\psi(d_{I_S}^\alpha I_{S_R} + d_{I_C}^\alpha I_{C_R}) + N_s u(1-\epsilon_{PI})(d_{I_S}^\alpha I_{S_S} + d_{I_C}^\alpha I_{C_S}) - c^\alpha V_{I_R}\\
\tfrac{dV_{NI}^\alpha(t)}{dt^\alpha} &= \epsilon_{PI}N_s(d_{I_S}^\alpha I_{S_S} + d_{I_C}^\alpha I_{C_S}) - c^\alpha V_{NI}\\
\tfrac{dE^\alpha(t)}{dt^\alpha} &= \lambda_E^\alpha + k_6^\alpha(I_{S_S}+I_{S_R}+I_{C_S}+I_{C_R})E - d_E^\alpha E
\end{aligned}
\tag{2}
$$

When $\alpha = 1$, then the model is the integer order counterpart. The fractional derivative of model (2) is used in the Caputo sense, i.e.:

$$\frac{d^\alpha y(t)}{dt^\alpha} = I^{p-\alpha}y^{(p)}(t), \quad t>0$$

where $p=[\alpha]$ is the value of α rounded up to the nearest integer, $y^{(p)}$ is the p-th derivative of $y(r)$, I^{p_1} is the Riemman-Liouville fractional integral given by:

$$I^{p_1}z(t) = \frac{1}{\Gamma(p_1)}\int_0^t \left(t-t^{'}\right)^{p_1-1} z(t^{'})dt^{'}$$

where $\Gamma(p_1)$ is the gamma function.

Reproduction numbers and local stability of the disease-free equilibrium

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 secondary infections due to a single infection in a completely susceptible population.

We begin by considering two sub-models of model (1). Model (3) arises from model (1) by setting the variables concerning resistant populations (L_R, I_{S_R}, I_{C_R} and V_{I_R}) to zero, and model (5) follows from model (1) by setting the variables concerning sensitive populations (L_S, I_{S_S}, I_{C_S} and V_{I_S}) to zero.

We start by computing the reproduction number of model (3), R_s, using the next generation method [16], and the local stability of its disease-free equilibrium.

$$
\begin{aligned}
\tfrac{dT^\alpha(t)}{dt^\alpha} &= \lambda_T^\alpha + r^\alpha T\left(1-\tfrac{T+I_{S_S}+I_{C_S}+L_S}{T_{max}}\right) - k_2^\alpha T(I_{S_S}+I_{C_S}) - (1-\epsilon_{RT})k_1^\alpha V_{I_S}T - d_T^\alpha T\\
\tfrac{dL_S^\alpha(t)}{dt^\alpha} &= \alpha_L(1-\epsilon_{RT})k_1^\alpha V_{I_S}T + k_2^\alpha\alpha_L T(t)(I_{S_S}+I_{C_S}) - (a^\alpha+d_L^\alpha)L_S\\
\tfrac{dI_{S_S}^\alpha(t)}{dt^\alpha} &= (1-\alpha_C)(1-\alpha_L)(1-\epsilon_{RT})k_1^\alpha V_{I_S}T + k_2^\alpha(1-\alpha_L)TI_{S_S} + (1-\alpha_C)a^\alpha L_S - k_3^\alpha EI_{S_S} - d_{I_S}^\alpha I_{S_S}\\
\tfrac{dI_{C_S}^\alpha(t)}{dt^\alpha} &= \alpha_C(1-\alpha_L)(1-\epsilon_{RT})k_1^\alpha V_{I_S}T + k_2^\alpha(1-\alpha_L)TI_{C_S} + \alpha_C a^\alpha L_S - k_3^\alpha EI_{C_S} - d_{I_C}^\alpha I_{C_S}\\
\tfrac{dV_{I_S}^\alpha(t)}{dt^\alpha} &= N_s(1-u)(1-\epsilon_{PI})(d_{I_S}^\alpha I_{S_S} + d_{I_C}^\alpha I_{C_S}) - c^\alpha V_{I_S}\\
\tfrac{dV_{NI}^\alpha(t)}{dt^\alpha} &= \epsilon_{PI}N_s(d_{I_S}^\alpha I_{S_S} + d_{I_C}^\alpha I_{C_S}) - c^\alpha V_{NI}\\
\tfrac{dE^\alpha(t)}{dt^\alpha} &= \lambda_E^\alpha + k_6^\alpha(I_{S_S}+I_{C_S})E - d_E^\alpha E
\end{aligned}
\tag{3}
$$

The disease-free equilibrium of model (3) is given by:

$$P_0^1 = (T^0, L_S^0, I_{S_S}^0, I_{C_S}^0, V_{I_S}^0, V_{NI}^0, E^0) = \left(\frac{T_{max}\left[(r^\alpha - d_T^\alpha)+\sqrt{(r^\alpha-d_T^\alpha)^2+\frac{4r^\alpha\lambda_T^\alpha}{T_{max}}}\right]}{2r^\alpha}, 0,0,0,0,0, \frac{\lambda_E^\alpha}{d_E^\alpha}\right) \tag{4}$$

Using the notation in [16] on system (3), matrices for the new infection terms, F_s, and the other terms, V_s, are computed to be:

$$F_s = \begin{pmatrix} 0 & k_2^\alpha \alpha_L T^0 & k_2^\alpha \alpha_L T^0 & \alpha_L(1-\epsilon_{RT})k_1^\alpha T^0 \\ 0 & k_2^\alpha(1-\alpha_L)T^0 & 0 & (1-\alpha_C)(1-\alpha_L)(1-\epsilon_{RT})k_1^\alpha T^0 \\ 0 & 0 & k_2^\alpha(1-\alpha_L)T^0 & \alpha_C(1-\alpha_L)(1-\epsilon_{RT})k_1^\alpha T^0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V_s = \begin{pmatrix} a^\alpha + d_L^\alpha & 0 & 0 & 0 \\ -(1-\alpha_C)a^\alpha & k_3^\alpha E^0 + d_{I_S}^\alpha & 0 & 0 \\ -\alpha_C a^\alpha & 0 & k_3^\alpha E^0 + d_{I_C}^\alpha & 0 \\ 0 & -N_s(1-u)(1-\epsilon_{PI})d_{I_S}^\alpha & -N_s(1-u)(1-\epsilon_{PI})d_{I_C}^\alpha & c^\alpha \end{pmatrix}$$

The associative basic reproduction number is thus:

$$R_s = \rho(F_s V_s^{-1}) = \frac{1}{2}\frac{T^0}{c^\alpha(k_3^\alpha E^0 + d_{I_S}^\alpha)(k_3^\alpha E^0 + d_{I_C}^\alpha)(a^\alpha + d_L^\alpha)} \Big[\Big[(1-\epsilon_{PI})^2((k_3^\alpha(1-\alpha_C)E^0 + d_{I_C}^\alpha)d_{I_S}^\alpha + k_3^\alpha d_{I_C}^\alpha \alpha_C E^0)^2 k_1^{2\alpha}((1-\alpha_L)d_L^\alpha + a^\alpha)^2$$

$$(1-\epsilon_{RT})^2(1-u)^2 N_s^2 + 2(1-\epsilon_{PI})k_1^\alpha \Big(\big(((1-\alpha_L)d_L^\alpha + a^\alpha(1-\alpha_L(1+\alpha_C)))(-1+\alpha_C)k_3^\alpha E^0 + \big(2(1-\alpha_L)(\alpha_C - \tfrac{1}{2})d_L^\alpha + a^\alpha((2-\alpha_L)\alpha_C + \alpha_L - 1)\big)d_{I_C}^\alpha\Big)d_{I_S}^{2\alpha}$$

$$+ \Big(a^\alpha k_3^{2\alpha}\alpha_L(1-\alpha_C)E^{0^2} + 2k_3^\alpha d_{I_C}^\alpha\big(\tfrac{1}{2}(1-\alpha_L)d_L^\alpha + a^\alpha\big(\alpha_C^2\alpha_L - \alpha_L\alpha_C + \tfrac{1}{2}\alpha_L + \tfrac{1}{2}\big)\big)E^0 + \big(2(1-\alpha_L)\big(\tfrac{1}{2} - \alpha_C\big)d_L^\alpha + a^\alpha(1 + (\alpha_L - 2)\alpha_C)\big)d_{I_C}^{2\alpha}\Big)d_{I_S}^\alpha$$

$$+(a^\alpha k_3^\alpha \alpha_L E^0 - ((1-\alpha_L)d_L^\alpha + a^\alpha(\alpha_C\alpha_L - 2\alpha_L + 1))d_{I_C}^\alpha)E^0\alpha_C k_3^\alpha d_{I_C}^\alpha\big)((1-\alpha_L)d_L^\alpha + a^\alpha)c^\alpha k_2^\alpha(1-\epsilon_{RT})(1-u)N_s + c^{2\alpha}k_2^{2\alpha}\big(((1-\alpha_L)d_L^\alpha + a^\alpha(\alpha_C\alpha_L - \alpha_L + 1))^2 d_{I_S}^{2\alpha}$$

$$+\big(2a^\alpha\big(2(1-\alpha_L)\big(\alpha_C - \tfrac{1}{2}\big)d_L^\alpha + a^\alpha((2-\alpha_L)\alpha_C + \alpha_L - 1)\big)\alpha_L k_3^\alpha E^0 - 2d_{I_C}^\alpha\big((1-\alpha_L)^2 d_L^{2\alpha} + a^\alpha(1-\alpha_L)(2-\alpha_L)d_L^\alpha + a^{2\alpha}(\alpha_C\alpha_L^2(\alpha_C - 1) + 1 - \alpha_L)\big)\big)d_{I_S}^\alpha$$

$$+E^{0^2}a^{2\alpha}\alpha_L^2 k_3^{2\alpha} + 2a^\alpha\alpha_L(2(1-\alpha_L)\big(\tfrac{1}{2} - \alpha_C\big)d_L^\alpha + a^\alpha(1 + (\alpha_L - 2)\alpha_C))k_3^\alpha d_{I_C}^\alpha E^0 + d_{I_C}^{2\alpha}((\alpha_L - 1)d_L^\alpha + (\alpha_C\alpha_L - 1)a^\alpha)^2\big)\Big]^{1/2} + (1-\epsilon_{PI})(((1-\alpha_C)d_{I_S}^\alpha + \alpha_C d_{I_C}^\alpha)k_3^\alpha E^0$$

$$+d_{I_C}^\alpha d_{I_S}^\alpha)((1-\alpha_L)d_L^\alpha + a^\alpha)k_1^\alpha(1-\epsilon_{RT})(1-u)N_s + ((2(1-\alpha_L)d_L^\alpha + a^\alpha(2-\alpha_L))k_3^\alpha E^0 + ((1-\alpha_L)d_L^\alpha + a^\alpha(\alpha_C\alpha_L - \alpha_L + 1))d_{I_S}^\alpha + ((1-\alpha_L)d_L^\alpha + (1-\alpha_C\alpha_L)a^\alpha)d_{I_C}^\alpha)k_2^\alpha c^\alpha\Big]$$

where ρ indicates the spectral radius of FV^{-1}. By Theorem 2 in [16], we have the following lemma:

Lemma 1 *If $R_s < 1$, then P_0^1 is locally asymptotically stable; if $R_s > 1$, P_0^1 is unstable.*

We proceed with the computation of the reproduction number of model (5), R_r, and the local stability of its disease-free equilibrium.

$$\begin{aligned}
\frac{dT^\alpha(t)}{dt^\alpha} &= \lambda_T^\alpha + r^\alpha T\left(1 - \frac{T + I_{S_R} + I_{C_R} + L_R}{T_{max}}\right) - k_2^\alpha T(I_{S_R} + I_{C_R}) - \psi k_1^\alpha V_{I_R} T - d_T^\alpha T \\
\frac{dL_R^\alpha(t)}{dt^\alpha} &= \alpha_L \psi k_1^\alpha V_{I_R} T + k_2^\alpha \alpha_L T(I_{S_R} + I_{C_R}) - (a^\alpha + d_L^\alpha)L_R \\
\frac{dI_{S_R}^\alpha(t)}{dt^\alpha} &= (1-\alpha_C)(1-\alpha_L)\psi k_1^\alpha V_{I_R} T + k_2^\alpha(1-\alpha_L)TI_{S_R} + (1-\alpha_C)a^\alpha L_R - k_3^\alpha E I_{S_R} - d_{I_S}^\alpha I_{S_R} \\
\frac{dI_{C_R}^\alpha(t)}{dt^\alpha} &= \alpha_C(1-\alpha_L)\psi k_1^\alpha V_{I_R} T + k_2^\alpha(1-\alpha_L)TI_{C_R} + \alpha_C a^\alpha L_R - k_3^\alpha E I_{C_R} - d_{I_C}^\alpha I_{C_R} \\
\frac{dV_{I_R}^\alpha(t)}{dt^\alpha} &= N_r\psi(d_{I_S}^\alpha I_{S_R} + d_{I_C}^\alpha I_{C_R}) - c^\alpha V_{I_R} \\
\frac{dE^\alpha(t)}{dt^\alpha} &= \lambda_E^\alpha + k_6^\alpha(I_{S_R} + I_{C_R})E - d_E^\alpha E
\end{aligned} \tag{5}$$

The disease-free equilibrium state, P_0^2, of model (5) is given by:

$$P_0^2 = (T^0, L_R^0, I_{S_R}^0, I_{C_R}^0, V_{I_R}^0, E^0) = \big(T^0, 0, 0, 0, 0, E^0\big) \tag{6}$$

Using the notation in [16] on system (5), matrices for the new infection terms, F_r, and the other terms, V_r, are computed to be:

$$F_r = \begin{pmatrix} 0 & k_2^\alpha \alpha_L T^0 & k_2^\alpha \alpha_L T^0 & \alpha_L \psi k_1^\alpha T^0 \\ 0 & k_2^\alpha(1-\alpha_L)T^0 & 0 & (1-\alpha_C)(1-\alpha_L)\psi k_1^\alpha T^0 \\ 0 & 0 & k_2^\alpha(1-\alpha_L)T^0 & \alpha_C(1-\alpha_L)\psi k_1^\alpha T^0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V_r = \begin{pmatrix} a^\alpha + d_L^\alpha & 0 & 0 & 0 \\ -(1-\alpha_C)a^\alpha & k_3^\alpha E^0 + d_{I_S}^\alpha & 0 & 0 \\ -\alpha_C a^\alpha & 0 & k_3^\alpha E^0 + d_{I_C}^\alpha & 0 \\ 0 & -N_r\psi d_{I_S}^\alpha & -N_r\psi d_{I_C}^\alpha & c^\alpha \end{pmatrix}$$

The associative basic reproduction number is given by:

$$R_r = \rho(F_r V_r^{-1}) = \frac{1}{2}\frac{T^0}{c^\alpha(k_3^\alpha E^0+d_{I_S}^\alpha)(k_3^\alpha E^0+d_{I_C}^\alpha)(a^\alpha+d_L^\alpha)}\Big[\Big[\big((d_{I_C}^\alpha+(1-\alpha_C)k_3^\alpha E^0)^2N_r^2((1-\alpha_L)d_L^\alpha+a^{2\alpha})k_1^{2\alpha}\psi^4+2N_r((1-\alpha_L)d_L^\alpha+a^\alpha)k_2^\alpha(((2\alpha_C-1)d_{I_C}^\alpha+(-1+\alpha_C)k_3^\alpha E^0)(1-\alpha_L)d_L^\alpha$$

$$+((d_{I_C}^\alpha+E^0k_3^\alpha(\alpha_C+1))(1-\alpha_C)\alpha_L+(2\alpha_C-1)d_{I_C}^\alpha-(1-\alpha_C)k_3^\alpha E_0)a^\alpha)k_1^\alpha c^\alpha\psi^2+k_2^{2\alpha}((1-\alpha_L)d_L^\alpha+(1+(-1+\alpha_C)\alpha_L)a^\alpha)^2c^{2\alpha}\big)d_{I_S}^{2\alpha}+\big(2d_{I_C}^\alpha(d_{I_C}^\alpha+(1-\alpha_C)k_3^\alpha E^0)N_r^2((1-\alpha_L)d_L^\alpha+a^\alpha)^2E^0k_3^\alpha k_1^{2\alpha}\alpha_C\psi^4$$

$$+4\Big(d_{I_C}^\alpha\big(\big(\tfrac{1}{2}-\alpha_C\big)d_{I_C}^\alpha+\tfrac{1}{2}k_3^\alpha E^0\big)(1-\alpha_L)d_L^\alpha+\Big(\Big(\tfrac{1}{2}\alpha_C d_{I_C}^{2\alpha}+E^0k_3^\alpha\big(\alpha_C^2-\alpha_C+\tfrac{1}{2}\big)d_{I_C}^\alpha+\tfrac{1}{2}E^{0^2}k_3^{2\alpha}(1-\alpha_C)\Big)\alpha_L+\big(\tfrac{1}{2}-\alpha_C\big)d_{I_C}^{2\alpha}+\tfrac{1}{2}E^0k_3^\alpha d_{I_C}^\alpha\Big)a^\alpha\Big)N_r((1-\alpha_L)d_L^\alpha+a^\alpha)k_2^\alpha k_1^\alpha c^\alpha\psi^2$$

$$+2\big(-d_{I_C}^\alpha(1-\alpha_L)^2d_L^{2\alpha}+2\big(\big(\tfrac{1}{2}d_{I_C}^\alpha+\big(\alpha_C-\tfrac{1}{2}\big)k_3^\alpha E^0\big)\alpha_L-d_{I_C}^\alpha\big)a^\alpha(1-\alpha_L)d_L^\alpha+((1-\alpha_C)(E^0k_3^\alpha+\alpha_Cd_{I_C}^\alpha)\alpha_L^2+(d_{I_C}^\alpha+(2\alpha_C-1)k_3^\alpha E^0)\alpha_L-d_{I_C}^\alpha)a^{2\alpha}\big)k_2^{2\alpha}c^{2\alpha}\big)d_{I_S}^\alpha$$

$$+d_{I_C}^{2\alpha}N_r^2((1-\alpha_L)d_L^\alpha+a^\alpha)^2E^{0^2}k_3^{2\alpha}k_1^{2\alpha}\alpha_C^2\psi^4+2d_{I_C}^\alpha N_r((1-\alpha_L)d_L^\alpha+a^\alpha)k_2^\alpha(-d_{I_C}^\alpha(1-\alpha_L)d_L^\alpha+(((2-\alpha_C)d_{I_C}^\alpha+k_3^\alpha E^0)\alpha_L-d_{I_C}^\alpha)a^\alpha)E^0k_3^\alpha k_1^\alpha c^\alpha\alpha_C\psi^2+\big(d_{I_C}^{2\alpha}(1-\alpha_L)^2d_L^{2\alpha}+4d_{I_C}^\alpha\big(\big(\tfrac{1}{2}\alpha_Cd_{I_C}^\alpha+(\alpha_C$$

$$-\tfrac{1}{2}\big)k_3^\alpha E^0\big)\alpha_L-\tfrac{1}{2}d_{I_C}^\alpha\big)a^\alpha(-1+\alpha_L)d_L^\alpha+\big((E^0k_3^\alpha+\alpha_Cd_{I_C}^\alpha)^2\alpha_L^2-4d_{I_C}^\alpha\big(\tfrac{1}{2}\alpha_Cd_{I_C}^\alpha+\big(\alpha_C-\tfrac{1}{2}\big)k_3^\alpha E^0\big)\alpha_L+d_{I_C}^{2\alpha}\big)a^{2\alpha}\big)k_2^{2\alpha}c^{2\alpha}\big]^{1/2}+k_3^\alpha(N_r((1-\alpha_L)d_L^\alpha+a^\alpha)k_1^\alpha\psi^2(1-\alpha_C)d_{I_S}^\alpha+(1-\alpha_L)(N_r\alpha_Cd_{I_C}^\alpha k_1^\alpha\psi^2$$

$$+2c^\alpha k_2^\alpha)d_L^\alpha+(d_{I_C}^\alpha\psi^2\alpha_CN_rk_1^\alpha+c^\alpha k_2^\alpha(2-\alpha_L))a^\alpha)E^0+((1-\alpha_L)(N_rd_{I_C}^\alpha k_1^\alpha\psi^2+c^\alpha k_2^\alpha)d_L^\alpha+a^\alpha(d_{I_C}^\alpha\psi^2N_rk_1^\alpha+(1-(1-\alpha_C)\alpha_L)k_2^\alpha c^\alpha))d_{I_S}^\alpha+((1-\alpha_L)d_L^\alpha+a^\alpha(1-\alpha_C\alpha_L))d_{I_C}^\alpha k_2^\alpha c^\alpha\Big]$$

where ρ indicates the spectral radius of FV^{-1}. By Theorem 2 in [16], we have the following lemma:

Lemma 2 *If $R_r < 1$, then P_0^2 is locally asymptotically stable; if $R_r > 1$, P_0^2 is unstable.*

We now turn our attention to the full model (1). We calculate its reproduction number, R_0, and the local stability of its disease-free equilibrium.
The disease-free equilibrium, P_0, of model (1) is given by:

$$P_0 = (T^0, L_S^0, L_R^0, I_{S_S}^0, I_{S_R}^0, I_{C_S}^0, I_{C_R}^0, V_{I_S}^0, V_{I_R}^0, V_{NI}^0, E^0) = \big(T^0, 0, 0, 0, 0, 0, 0, 0, 0, 0, E^0\big) \tag{7}$$

Using the notation in [16] on system (1), matrices for the new infection terms, F, and the other terms, V, are computed to be:

$$F = \begin{pmatrix} 0 & 0 & k_2^\alpha\alpha_L T^0 & 0 & k_2^\alpha\alpha_L T^0 & 0 & \alpha_L(1-\epsilon_{RT})k_1^\alpha T^0 & 0 \\ 0 & 0 & 0 & k_2^\alpha\alpha_L T^0 & 0 & k_2^\alpha\alpha_L T^0 & 0 & \alpha_L\psi k_1^\alpha T^0 \\ 0 & 0 & k_2^\alpha(1-\alpha_L)T^0 & 0 & 0 & 0 & (1-\alpha_C)(1-\alpha_L)(1-\epsilon_{RT})k_1^\alpha T^0 & 0 \\ 0 & 0 & 0 & k_2^\alpha(1-\alpha_L)T^0 & 0 & 0 & 0 & (1-\alpha_C)(1-\alpha_L)\psi k_1^\alpha T^0 \\ 0 & 0 & 0 & 0 & k_2^\alpha(1-\alpha_L)T^0 & 0 & \alpha_C(1-\alpha_L)(1-\epsilon_{RT})k_1^\alpha T^0 & 0 \\ 0 & 0 & 0 & 0 & 0 & k_2^\alpha(1-\alpha_L)T^0 & 0 & \alpha_C(1-\alpha_L)\psi k_1^\alpha T^0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

$$V = \begin{pmatrix} a^\alpha+d_L^\alpha & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a^\alpha+d_L^\alpha & 0 & 0 & 0 & 0 & 0 & 0 \\ -(1-\alpha_C)a^\alpha & 0 & k_3^\alpha E^0+d_{I_S}^\alpha & 0 & 0 & 0 & 0 & 0 \\ 0 & -(1-\alpha_C)a^\alpha & 0 & k_3^\alpha E^0+d_{I_S}^\alpha & 0 & 0 & 0 & 0 \\ -\alpha_C a^\alpha & 0 & 0 & 0 & k_3^\alpha E^0+d_{I_C}^\alpha & 0 & 0 & 0 \\ 0 & -\alpha_C a^\alpha & 0 & 0 & 0 & k_3^\alpha E^0+d_{I_C}^\alpha & 0 & 0 \\ 0 & 0 & -N_s(1-u)(1-\epsilon_{PI})d_{I_S}^\alpha & 0 & -N_s(1-u)(1-\epsilon_{PI})d_{I_C}^\alpha & 0 & c^\alpha & 0 \\ 0 & 0 & -N_su(1-\epsilon_{PI})d_{I_S}^\alpha & -N_r\psi d_{I_S}^\alpha & -N_su(1-\epsilon_{PI})d_{I_C}^\alpha & -N_r\psi d_{I_C}^\alpha & 0 & c^\alpha \end{pmatrix}$$

The associative basic reproduction number is computed to be:

$$R_0 = \rho(FV^{-1}) = \max\{R_s, R_r\} \tag{8}$$

where ρ indicates the spectral radius of FV^{-1}. By Theorem 2 in [16], we have the following lemma:

Lemma 3 *If $R_0 < 1$, then P_0 is locally asymptotically stable; if $R_0 > 1$, P_0 is unstable.*

Numerical Results

In this section, we show the results of the numerical simulations of model (1). The initial conditions used are $T_0 = 486$, $L_{S_0} = L_{R_0} = 0.5 \times 10^5$, $I_{S_0} = I_{R_0} = 10$, $I_{C_{S_0}} = I_{C_{R_0}} = 40$, $V_{I_{S_0}} = V_{I_{R_0}} = 100$, $V_{NI_0} = 50$ and $E_0 = 333$.
In Figures 1-3, we show the dynamics of the relevant variables of system (2) for different values of α_C, the fraction of productively infected CD4$^+$ T cells that become long-lived chronically infected cells. When α_C increases, the pool of long-lived chronically productively infected CD4$^+$ T cells grows. The later promotes the appearance of a larger number of resistant infectious virus, which makes the eradication of HIV extremely difficult, since the drug-resistant strains escape treatment [10]. In the literature, it was found that the contribution of the long-lived chronically productively infected CD4$^+$ T cells to the growth of plasma virus is more significant when the viral load is above 50 copies/ml [19].
In Figures 4-6, we depict the dynamics of the relevant variables of system (2) for different values of α_L, the fraction of uninfected CD4$^+$ T cells that become latently infected. When α_L increases, it is observed an increase in the number of latently infected CD4+ T cells. This means that the reservoirs of these cells are enlarged, which promotes an increase in the amount of virus that escapes treatment [9]. Subsequently, after activation of the latent cells, new virus will be produced and released into the blood stream. The later guarantees the persistence of HIV-1 in most patients under HAART regimens. It is clear an increase in the number of sensitive virus for larger values of α_L.

Parameter	Figs. 1-3	Figs. 4-6
λ_T	10	100
λ_E	5	5
r	0.03	0.072
T_{max}	1500	1500
k_1	1×10^{-5}	0.7×10^{-5}
k_2	2.4×10^{-4}	1.1×10^{-3}
k_3	9.9×10^{-6}	9.9×10^{-6}
k_6	3.3×10^{-5}	3.3×10^{-5}
ψ	0.9	0.9
d_T	0.01	0.01
d_L	0.05	0.02
d_{I_S}	0.7	0.7
d_{I_C}	0.04	0.07
d_E	0.015	0.015
c	23	10
α_L	0.02	varied
α_C	varied	0.195
a	3×10^{-4}	2×10^{-4}
u	3×10^{-5}	3×10^{-5}
N_s	3000	3000
N_r	2500	2500
ϵ_{RT}	0.8	0.4
ϵ_{PI}	0.2	0.2

Table 1: Parameter values used in the simulations of model (2) based in [13, 34, 12].

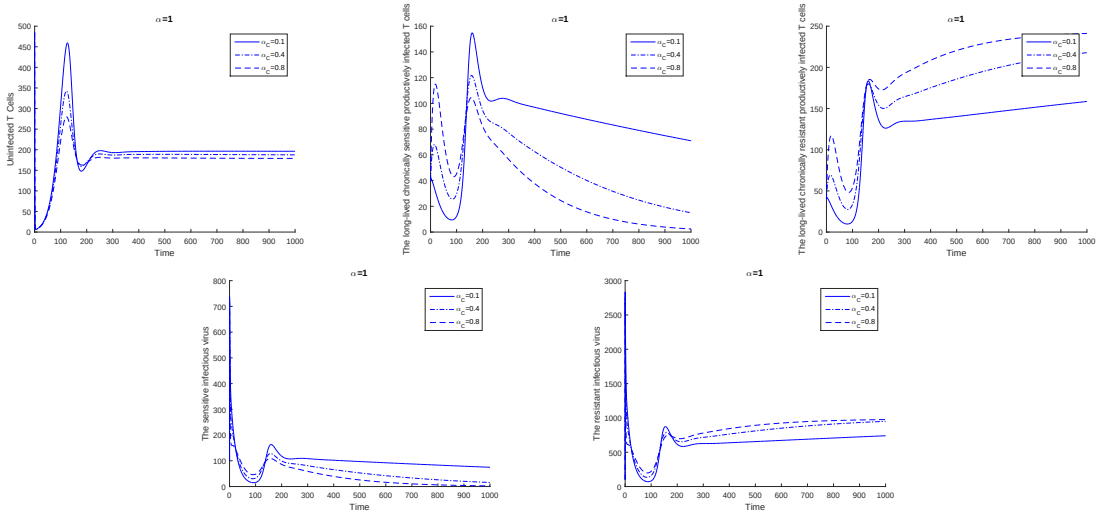

Figure 1: Dynamics of the variables of system (1) for different values of α_C, the fraction of the productively infected CD4$^+$ T cells that become long-lived chronically infected cells. Parameter values and initial conditions are given in the text.

Conclusions

We analyzed the effect of the size of the latent reservoir and of the pool of chronically productively infected CD4$^+$ T cells in a model for HIV infection with drug resistance. We proved that for $R_0 < 1$, the disease-free equilibrium is locally asymptotically stable. When $R_0 > 1$, the disease-free equilibrium becomes unstable. Outcomes of the numerical simulations of the model show that the size of the latent reservoir is extremely important in the persistence of the plasma viral load. The intrinsic stability of the resting memory CD4$^+$ T cells is responsible for their longevity, which in turn allows for longer shelter for wild-type HIV-1 virus and drug-resistant virus. In what concerns the pool of long-lived productively infected CD4$^+$ T cells, the results show that an increase in its size favours the appearance of more resistant virus, that escape treatment, which turns the eradication of the plasma virus an impossible mission. Future work will focus on the effect of distinct HAART regimens in the dynamics of the proposed model.

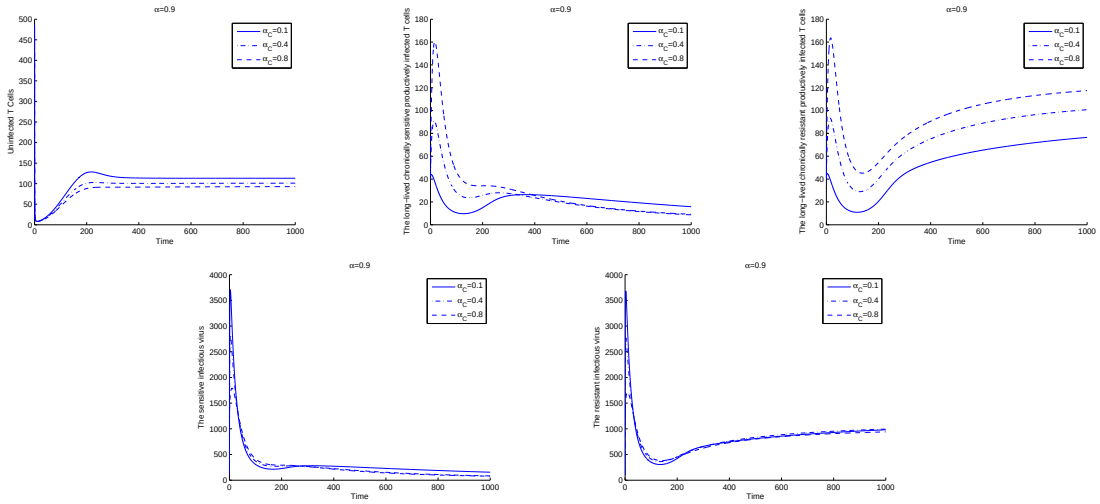

Figure 2: Dynamics of the variables of system (1) for different values of α_C, the fraction of the productively infected CD4$^+$ T cells that become long-lived chronically infected cells. Parameter values and initial conditions are given in the text.

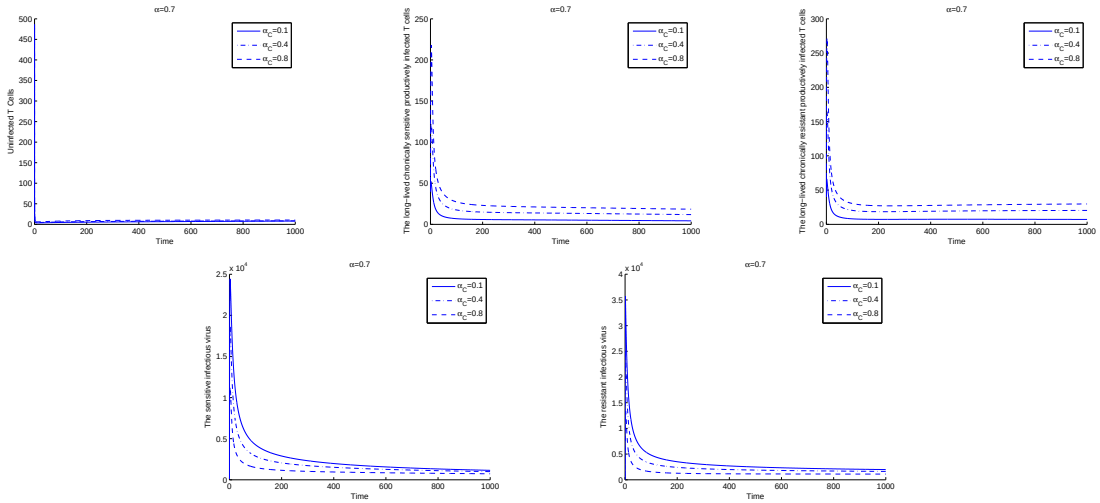

Figure 3: Dynamics of the variables of system (1) for different values of α_C, the fraction of the productively infected CD4$^+$ T cells that become long-lived chronically infected cells. Parameter values and initial conditions are given in the text.

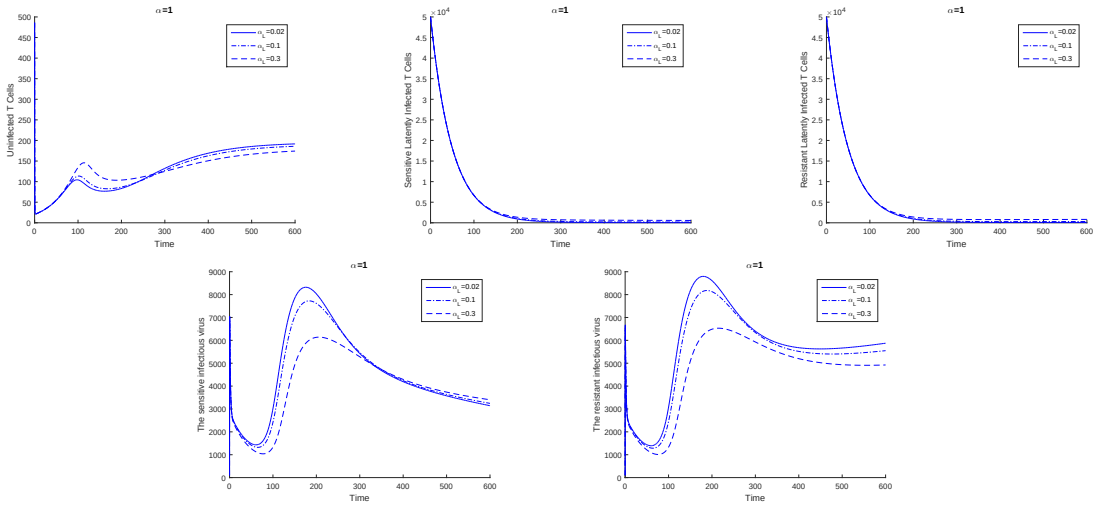

Figure 4: Dynamics of the variables of model (2) for different values of α_L, the fraction of uninfected CD4$^+$ T cells that become latently infected. Parameter values and initial conditions are given in the text.

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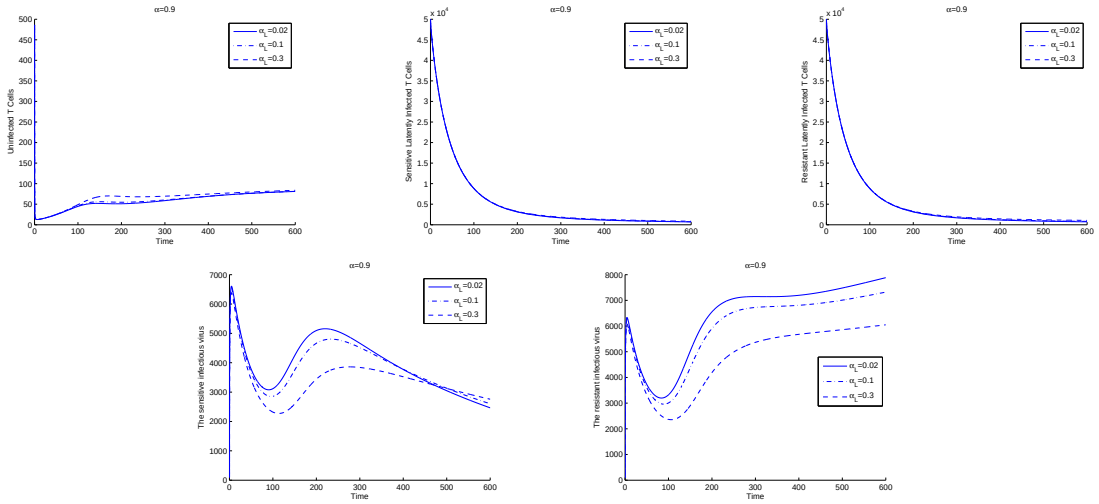

Figure 5: Dynamics of the variables of model (2) for different values of α_L, the fraction of uninfected CD4$^+$ T cells that become latently infected. Parameter values and initial conditions are given in the text.

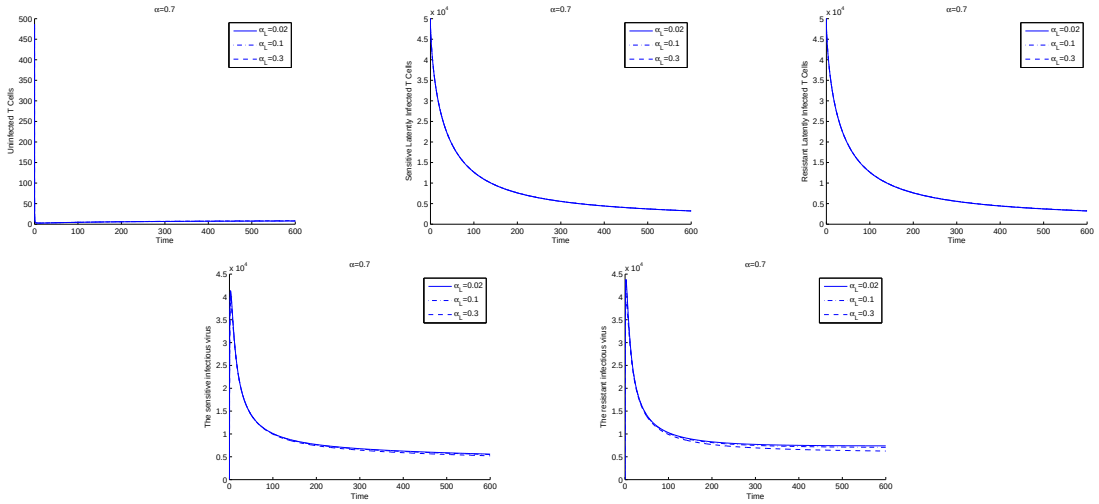

Figure 6: Dynamics of the variables of model (2) for different values of α_L, the fraction of uninfected CD4$^+$ T cells that become latently infected. Parameter values and initial conditions are given in the text.

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