Modelling the influence of activation-induced apoptosis of CD4$^+$ and CD8$^+$ T-cells on the immune system response of a HIV infected patient

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Abstract

Based on the HIV infection dynamics model proposed by Adams et al. in [1], we propose an extended model represented by a set of nonlinear Ordinary Differential Equations (ODEs) that aims at incorporating the influence of activation-induced apoptosis of CD4$^+$ and CD8$^+$ T-cells on the immune system response of HIV infected patients. Through this model we study the influence of this phenomenon on the time evolution of specific cell populations such as plasma concentrations of HIV copies, or blood concentrations of CD4$^+$ and CD8$^+$ T-cells. In particular, this study shows that depending on its intensity, the apoptosis phenomenon can either favor or mitigate the long-term evolution of the HIV infection.

Introduction

Human Immunodeficiency Virus (HIV) is a retrovirus that may lead to the lethal Acquired Immune Deficiency Syndrome (AIDS). Progression from HIV infection to AIDS is primarily due to an extensive depletion of CD4$^+$ T-cells.

T-cell loss may be due to direct destruction by the virus (direct virus-induced cytolysis) or to defective T-cell generation.

In 1991, **apoptosis, also called programmed cell death, has been suggested as another mechanism responsible for T-cell depletion during the evolution of HIV-1 infection** and an extensive body of recent literature is supporting this hypothesis. To the best of our knowledge, no mathematical model has yet tried to explain the influence of the activation-induced apoptosis phenomenon on the HIV infection dynamics.

We propose here a modification of the model proposed by Adams et al. in [1]. **This modification aims at modelling the activation-induced apoptosis phenomenon and at analyzing its influence on the HIV infection dynamics.**

The Model of Adams et al.

$$\dot{T}_1 = \lambda_1 - d_1 T_1 - k_1 V T_1 \quad (1)$$
$$\dot{T}_2 = \lambda_2 - d_2 T_2 - k_2 V T_2 \quad (2)$$
$$\dot{T}_1^* = k_1 V T_1 - \delta T_1^* - m_1 E T_1^* \quad (3)$$
$$\dot{T}_2^* = k_2 V T_2 - \delta T_2^* - m_2 E T_2^* \quad (4)$$
$$\dot{V} = N_T \delta \left(T_1^* + T_2^*\right) - cV - \left(\rho_1 k_1 T_1 + \rho_2 k_2 T_2\right) V \quad (5)$$
$$\dot{E} = \lambda_E + \frac{b_E \left(T_1^* + T_2^*\right)}{\left(T_1^* + T_2^*\right) + K_b} E - \frac{d_E \left(T_1^* + T_2^*\right)}{\left(T_1^* + T_2^*\right) + K_d} E - \delta_E E \quad (6)$$

T_1 (T_1^*) : number of non-infected (infected) CD4$^+$ T-lymphocytes (in $cells/ml$)
T_2 (T_2^*) : number of non-infected (infected) macrophages (in $cells/ml$)
V : number of free HIVs (in $virions/ml$)
E : number of HIV-specific cytotoxic CD8$^+$ T-cells (in $cells/ml$)

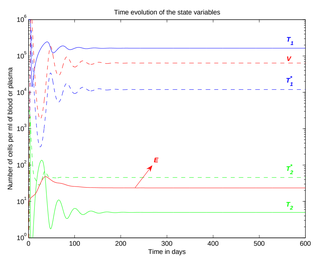

FIG. 1: Time evolution of the state variables of the model (1)-(6) starting from the primo-infection initial condition $(T_1, T_2, T_1^*, T_2^*, V, E) = (10^6, 3198, 0, 0, 1, 10)$.

Apoptosis-compliant model for the HIV infection dynamics

$$\dot{T}_1 = \lambda_1 - d_1 T_1 - k_1 V T_1 - a_{T_1} T_1^* T_1 \quad (7)$$
$$\dot{T}_2 = \lambda_2 - d_2 T_2 - k_2 V T_2 \quad (8)$$
$$\dot{T}_1^* = k_1 V T_1 - \delta T_1^* - m_1 E T_1^* \quad (9)$$
$$\dot{T}_2^* = k_2 V T_2 - \delta T_2^* - m_2 E T_2^* \quad (10)$$
$$\dot{V} = N_T \delta \left(T_1^* + T_2^*\right) - cV - \left(\rho_1 k_1 T_1 + \rho_2 k_2 T_2\right) V \quad (11)$$
$$\dot{E} = \lambda_E + \frac{b_E \left(T_1^* + T_2^*\right)}{\left(T_1^* + T_2^*\right) + K_b} E - \frac{d_E \left(T_1^* + T_2^*\right)}{\left(T_1^* + T_2^*\right) + K_d} E - \delta_E E - a_E T_1^* E \quad (12)$$

a_{T_1} and a_E are expressed in $\frac{ml}{cells \times day}$.

Analysis of the apoptosis-compliant model

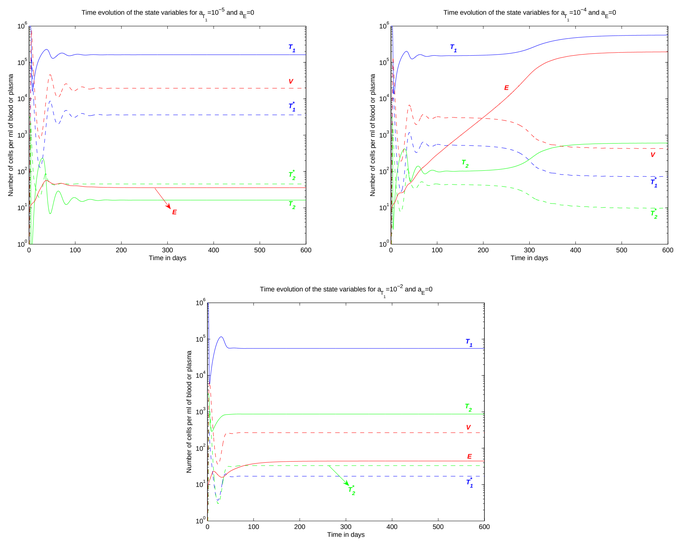

FIG. 2: Time-evolution of the state variables of the model (7)-(12) for $a_{T_1} = 10^{-5}$, $a_{T_1} = 10^{-4}$, and $a_{T_1} = 10^{-2}$ starting from the primo-infection initial condition with a_E=0. **The apoptosis phenomenon can either favor or mitigate the long-term evolution of the HIV infection.**

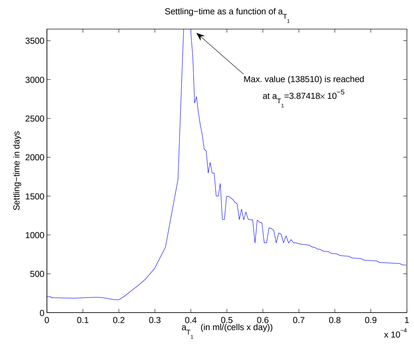

FIG. 3: Evolution of the settling-time (minimum time required for the state variables to be within an infinite-norm distance of 1 percent of their asymptotic value) as a function of the apoptosis parameter a_{T_1} with a_E=0.

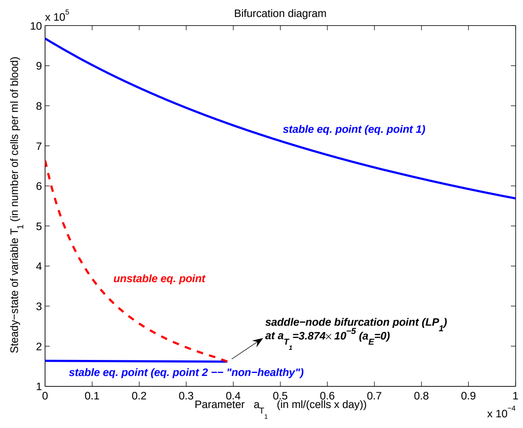

FIG. 4: Bifurcation diagram of the equilibrium concentrations of non-infected CD4$^+$ T-cells ($T_{1_{eq}}$) when the bifurcation parameter a_{T_1} varies from 0 to 10^{-4}. A saddle-node bifurcation point (LP_1) exists at $a_{T_1} = 3.874 \times 10^{-5}$. Only the infected equilibrium points (equilibrium points 2, 3 and 4) are represented and a_E is chosen equal to 0.

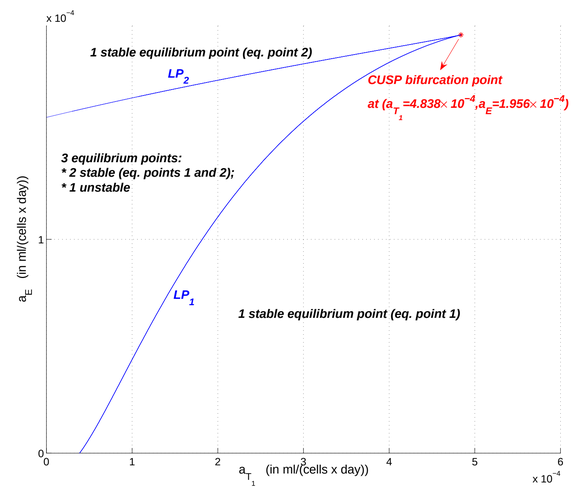

FIG. 5: Two-parameter continuation of the saddle-node bifurcation point LP_1 corresponding to $(a_{T_1}, a_E) = (3.87418 \times 10^{-5}, 0)$. A CUSP bifurcation point appears at $(a_{T_1}, a_E) = (4.838 \times 10^{-4}, 1.956 \times 10^{-4})$.

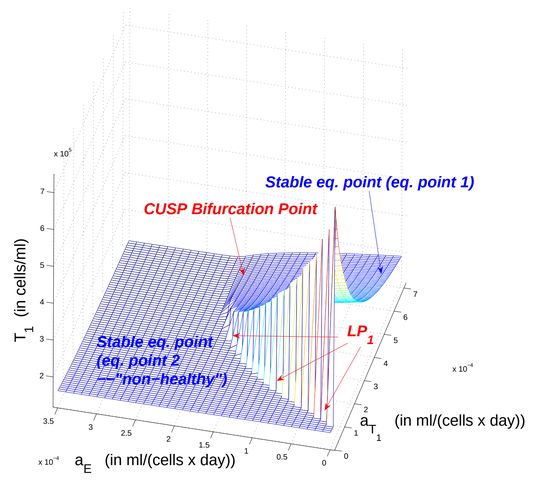

FIG. 6: Concentrations of non-infected CD4$^+$ T-cells (T_1) corresponding to the equilibrium point to which the patient's state converges when starting from the primo-infection initial condition.

Discussion

Using a combination of numerical simulations and bifurcation analysis, we found that for some ranges of values of theapoptosis parameters, **these activation-induced apoptosis phenomena had non-linear effects that could be beneficial to the immune system during the HIV infection**. On the other hand, when the magnitude of the apoptosis parameters becomes too large, this potential beneficial effect disappears and activation-induced apoptosis mechanisms were then found to aggravate the HIV infection. Furthermore, since the HIV infection worsens when these activation-induced apoptosis rates become too large, one could also relate the progression of the HIV infection to AIDS to a change of magnitude in these rates. These findings need to be taken with caution since they are dependent on several modelling assumptions that would certainly require careful experimental validation.

These results could potentially help in designing new anti-HIV therapies based on a drug-mediated regulation of the activation-induced apoptosis factors (such as gp120) in HIV infected patients. These therapies could be based on the injection of some specific interleukins to HIV positive patients, such as for example IL-2, IL-7 and IL-15 [2, 3, 5], although the role of interleukins on the immune system of HIV-infected patients/macaques is still a controversial issue since other studies (see e.g. [4]) have shown that they could have a detrimental effect.

References

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