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Stability in a mathematical model for HIV–1 infection*

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Abstract

We extend a previous epitope model for HIV-1 infection originally developed by Nowak et al. (1995) by considering not only continually mutant free virions but also viral reservoirs as monocytes. The immunological system response to viral infections includes the attack to monocytes by specific cytotoxic cells addressed against each one of the exhibiting epitope monocytes and the removal of free viral particles by T cell mediated interactions. We obtain a non lineal system of equations that allows only numerical treatment. Under the additional hypothesis that there is no immune attack to monocytes and only a viral variant, we got a simpler model that admits the usual linearization procedure. The inclusion of immune attack against infected monocytes in general stabilizes previously unstable solutions, but if new viral variants appear the system becomes unstable. These results suggest that the whole role played by reservoirs in HIV infection is a very important one and therapy should not go on ignoring it.

Key words: HIV-1; virions; reservoirs; immune response; viral growth.

Estabilidad en un modelo matemático para infección VIH-1

Resumen

En este trabajo extendemos un modelo previo de epitopes para describir el proceso de infección VIH-1 originalmente desarrollado por Nowak et al. (1995) al considerar no solo virus continuamente mutantes sino también reservorios como los monocitos. La respuesta del sistema inmunológico a la infección viral incluye tanto el ataque a los reservorios por células citotóxicas específicas, como también la eliminación de partículas virales en sangre a través de interacciones mediadas por células T. El sistema resultante de ecuaciones es no lineal ya que sólo admite análisis numérico. Bajo la suposición adicional de que no hay ataque inmune sobre los monocitos, y sólo una variante viral, el modelo se puede linealizar de la forma usual. La inclusión del ataque inmune sobre los monocitos generalmente tiende a estabilizar soluciones previamente inestables. Si nuevas variantes virales aparecen el sistema inevitablemente se torna inestable. Estos resultados sugieren tomar en mayor consideración el papel que juegan

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los monocitos en el mantenimiento de la infección por VIH-1 y las terapias propuestas no pueden seguir sin considerarlo.

Palabras clave: HIV-1; crecimiento viral; viriones; reservorios; respuesta inmune.

1. Introduction

The present work pretends to incorporate in a simple manner the effect of monocyte cells to a model already proposed by Nowak et al. (1995). Nowak (1) uses the concept of immune-dominance to explain variations in the immune response against virus that possess continuously mutating epitopes. On the other hand, some authors (2–4) claim the importance of macrophages and/or mononuclear phagocytes in the promotion and persistence of some types of HIV infections, but the whole role played by reservoirs (latently infected cells) remain unclear (5,6). In this work, the original equations proposed by Nowak have been modified and new differential equations were introduced to describe the different roles played by the mononuclear cells and free viral particles. Also, healthy monocytes and infected ones are treated separately. The equations that describe the immune response by cytotoxic cells are kept without modification. The stability of the present model, in the case of a single viral variant is discussed under the approximation that there is no activity present of cytotoxic cells, i.e., a situation that can be related to some absence of immune response, and we got full agreement among our analysis and numerical integration. When cytotoxic cells are introduced, the system becomes more stable, although there are several sets of parameter values that causes virus proliferation. Mutations are also capable to promote viral escape. These last two situations are only treated numerically. Finally we appoint that there exist models dealing with antiviral drug effects (7, 8), a situation not considered by us.

2. The Model

We use a mixed predator-prey model (9) that considers the existence of free virions that could exhibit two epitopes *A* and *B*, each one of them with variants $i_1, i_2,..., i_{n1}$ for the epitope *A*, and $j_1, j_2,..., j_{n2}$ for the epitope *B*. There are healthy monocytes m_0, infected monocytes m_{ij} and CD4+ helper T cells given by *z*. Cytotoxic cells directed against the variant *i* of the epitope *A* are designated as x_i and those against variant *j* of epitope *B* as y_j. and the remaining symbols, unless so stated, keep identical meaning as in [1]. The general equations for the present model are:

$$\frac{dm_0}{dt} = am_0(1-m_0) - m_0(\gamma_{ij}\nu_{ij})^* \qquad [1]$$

Monocytes are produced at the hematopoietic organs from which they migrate to the blood stream and in absence of any interaction their population evolves according to a logistic law.

$$\frac{dm_{ij}}{dt} = \gamma_{ij} m_0 \nu_{ij} - m_{ij}(p_i x_i + q_i y_j) - \omega_1 m_{ij} \qquad [2]$$

Monocytes are infected with a velocity $\gamma_{ij} m_0 \nu_{ij}$ as a result of their interaction with free viral particles (ruled by a dynamic parameter γ_{ij}) and from that moment they exhibit viral epitopes. They are taken away from the blood stream by the action of cytotoxic cells x_i (and y_j), with velocities ($q_j y_j m_{ij}$), and p_i (q_j) is the dynamical parameter that rules this interaction. Monocytes eventually die with a lifetime of $t_1 = 1/\omega_1$.

$$\frac{dx_i}{dt} = nc_i z m_{i*} + c_i z m_{i*} x_i - \omega_1 x_i \qquad [3]$$

$$\frac{dy_j}{dt} = nk_j z m_{*j} + k_j z m_{*j} y_j - \omega_1 y_j \qquad [4]$$

Cytotoxic cells, i.e., x_i (y_j) are produced by activation from precursor cells with a velocity $nc_i z m_{i*}$ ($nk_j z m_{*j}$) or by proliferation from previous activated ones with a velocity

$c_i z m_{i*} x_i (k_j z m_{*j} y_j)$, both regulated by the presence of helper T cells. It is assumed that they die within the same lifetime as monocytes do, t_1.

$$\frac{dz}{dt} = \lambda - (u\nu)^* z - \omega_2 z \qquad [5]$$

T cells are produced in thymus with rate λ, they are destroyed by any viral variant with speed $u_{ij}\nu_{ij}z$ (u_{ij} is the destruction rate), and eventually die after a lifetime $t_2 = \frac{1}{\omega_2}$.

$$\frac{d\nu_{ij}}{dt} = g_{ij} m_{ij} + (\gamma u_{ij} - f_{ij}) z\nu_{ij} - \gamma_{ij} m_0 \nu_{ij} \qquad [6]$$

Virions are liberated by infected monocytes with a velocity $g_{ij} m_{ij}$ or by infected T cells with a velocity $\gamma u_{ij} (z\nu_{ij})$, this term being proportional to the rate of T-helper cell infection, they infect the monocytes with a velocity $\gamma_{ij} m_0 \nu_{ij}$ and are destroyed by the humoral response, by the presence of antibodies produced by B cells, a process which is also mediated by helper T cells. This interaction could be described by the function $f(B,z)\nu_{ij}$, where B stands for plasma cell concentration and we have assumed for simplicity that $f(B,z) = f_{ij} z$ with f_{ij} the parameter ruling a Lotka-Volterra type interaction, and

$$m_{i*} = \sum_j m_{ij} \qquad m_{*j} = \sum_i m_{ij}$$

$$(u\nu)^* = \sum_{i,j} u_{ij}\nu_{ij} \qquad (\gamma_{ij}\nu_{ij})^* = \sum_{i,j} \gamma_{ij}\nu_{ij}$$

3. Approximations

In order to simplify the model, let us consider the existence of just one viral variant, ν_{11}, and therefore one type of infected monocytes, m_{11}. The decay of healthy monocytes by viral infection is negligible $\gamma_{ij} m_0 \nu_{ij} = 0$, and the same stands for the attack of cytolytic cells to infected monocytes. The system reduces to:

$$\frac{dm_0}{dt} = a m_0 (1 - m_0) \qquad [7]$$

$$\frac{dm_{11}}{dt} = \gamma_{11} m_0 \nu_{11} - \omega_1 m_{11} \qquad [8]$$

$$\frac{d\nu_{11}}{dt} = g_{11} m_{11} + (\gamma u - f) z\nu_{11} \qquad [9]$$

$$\frac{dz}{dt} = \lambda - u\nu_{11} z - \omega_2 z \qquad [10]$$

Prior to any detailed analysis, we note that for a healthy organism there must be $\frac{d\nu_{11}}{dt} = 0$ and $\frac{dm_{11}}{dt} = 0$. These conditions are fulfilled if both $\nu_{11} = m_{11} = 0$ (absence of infection). Then [7] and [10] become independent and T cell and monocyte populations evolve toward their stable equilibrium values, $m_0 = 1$, $z = \frac{\lambda}{\omega_2}$. We emphasize that prevention of virus infection is the best procedure against the development of AIDS. We note also, that $\lambda(f - \gamma u)$ is the rate of T-cell production times rate of net viral depletion, so we introduce the term "immune response" for this factor. Moreover, $g_{11}\gamma_{11} \approx \left(\frac{1}{\nu_{11}}\frac{d\nu_{11}}{dt}\right)\left(\frac{1}{m_{11}}\frac{dm_{11}}{dt}\right)$, i.e., the product of viral and infected monocytes growth rates respectively, and we minted this factor "viral growth". We obtain that our approximate system owns a null, stable solution (no virions) if $\frac{\lambda}{\omega_2}(f - \gamma u) > \frac{\gamma_{11} g_{11}}{\omega_1}$, this is, if mean immune response is stronger than mean viral growth.

4. Particular cases

i) We first consider conditions related to monocytes: $g_{11} = 0$ (monocytes do not pour free virions into blood stream),

and/or $\gamma_{11\gamma} = 0$, (there is no viral invasion to mononuclear cells). In both situations the system attains a non-trivial equilibrium population $m_0 = 1, z = \frac{\lambda}{\omega_2}$, $v_{11} = m_{11} = 0$, stable if $\frac{\lambda}{\omega_2}(f - \gamma u) > 0$ and unstable otherwise. We obtain that the control of the viral effects upon T-cells is just enough to stop the infection if it is possible to neglect the existence of viral sources.There is no viral invasion to T-cells, $u = 0$. Then the non-trivial equilibrium population is the same as in the precedent case, and the system is stable if $\frac{\lambda f}{\omega_2} > \left(\frac{\gamma_{11} g_{11}}{\omega_1}\right)$ and unstable otherwise, then a moderately strong immune response is enough to control viral growth.

iii)Let us consider only the effect of the immune T-cell control upon the viral population. If both $(f - \gamma u) = 0$ and $g_{11} \neq 0$ (there is no viral growth due to the T-cell effects, but monocytes are still producing free virions). Then any viral population is unstable. This situation seems to be the present therapy status.

iv) If $(f - \gamma u) = 0$ and $g_{11} = 0$, we get $\frac{dv_{11}}{dt} = 0$. Analytical criteria fail to deal with this case, but numerical analysis shows that there exists a stable equilibrium population $m_0 = 1$, $v_{11} = v_0, m_{11} = \left(\frac{\gamma_{11}}{\omega_1}\right) v_0$ and $z = \frac{\lambda}{\omega_2 + u v_0}$, where v_0 stands for the initial viral population.

Figure 1 shows the typical behavior of the equilibrium points as a function of $\lambda(f - \gamma u)$. It is worthy to mention that initially positive populations can not become negative (non-biological situation) due to the fact that $z = 0$ ($v = 0$) acts as a barrier, it is a repulsor. Observe from equations (9) and (10) that $\frac{dz}{dt} > 0$ if $z = 0\left(\frac{dv}{dt} > 0 \text{ if } v = 0\right)$.

We took $\alpha = 0.9$, $f = 3.5$, $u = 2.5$, $\lambda = 4.0$, $\omega_1 = 0.28$, $\omega_2 = 7.0$, $\gamma_{11} = 2.0$, $g_{11} = 0.2$.

5. Inclusion of cytotoxic cells

If cytotoxic cells are included, a fifth grade analytically unmanageable eigenvalue equation is obtained, so it is necessary the numerical treatment. Inclusion of cytotoxic cells produces more control on viral variables and convergence of the system that otherwise was diverging. Figure 2 shows this behavior for the same set of common parameter values as in Figure 1, $p_1 = q_1 = 2.05$, $c_1 = k_1 = 0.45$, $\eta = 0.02$.

6. The full system

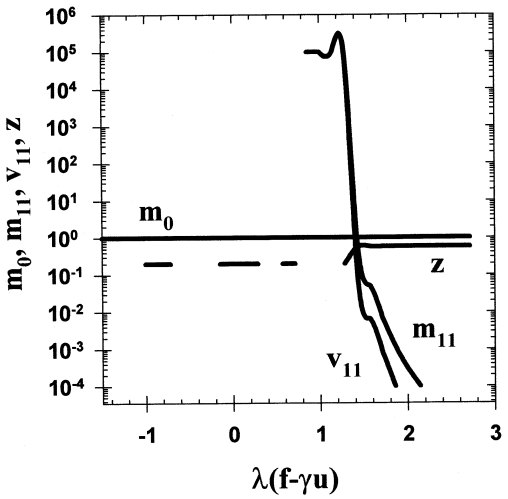

Figure 1 Equilibrium values for viral and immune variables as a function of $\lambda(f - \gamma u)$, i.e., the strength of the immune response in absence of cytolytic cells. Viral and reservoirs concentrations stay high although immune response is strong, but if immune parameters grow further, virions and reservoirs disappear, and z and m_0, T-helper cel and reservoirs populations tend to their equilibrium

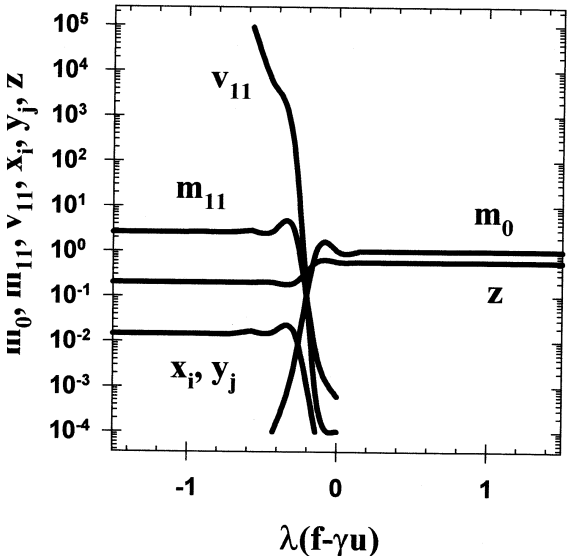

Figure 2. Equilibrium values for viral and immune variables as a function of $\lambda(f-\gamma u)$, i.e., the strength of the immune response with the presence of cytolytic cells. Killer cell populations stay high while there exist free virions or reservoirs in blood stream. More important, note the leftward shifting of the convergence values.

Situations with more than one viral variant was treated numerically and we obtained always the same result: appearance of new viral mutants drives the system to unstability.

7. Conclusions

We have obtained an approximate analytical approach to viral infection that shows: (C-1) It is important to block viral production and/or invasion of reservoirs, if this condition is fulfilled, then a moderately strong immune response suffices for control of viral infection, (C-2) Control just over T-cell action but not on viral reservoirs leads to full disease under any type of immune response. To annihilate viral population it is necessary to annihilate also reservoirs. Complete system, including attack to monocytes by cytotoxic cells, shows more stable situations. (C-3) Viral mutability may lead to more efficient viral variants or simply viral accumulation and concerted attack over T-cells as stated by Nowak et al (1). In both cases there appears viral breakthrough. Recent literature (10) mention damage to stromal cells which could lead to decreasing of plasma cells population and therefore antibodies production (f goes down). Non decisive results on drug-mediated virus suppression (10) could be caused not only for the development of new, resistant viral variants, but also for persistence of old ones inside reservoirs. We stress then, that any future therapy must include not only control of T-cells viral infection. We recall that many changes in vision of HIV related disease have occurred in the last couple of years (10,11). Unless these changes are accompanied by similar ones in therapy, avoiding infection seems to be the best measure against AIDS.

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