Stability analysis of simple models for immune cells interacting with normal pathogens and immune system retroviruses

(human immunodeficiency virus/acquired immunodeficiency syndrome)

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Communicated by Leon N Cooper, December 15, 1988 (received for review August 22, 1988)

ABSTRACT A mathematical analysis is presented for several simple dynamical systems that might be considered as crude descriptions for the situation when an immune system retrovirus, immune cells, and normal autonomously replicating pathogens interact. By stability analysis of the steady-state solutions, the destabilizing effect of the immune system retrovirus is described. The qualitative behavior of the solutions depending on the system parameters is analyzed in terms of trajectories moving in a phase space in which the axes are defined by the population numbers of the interacting biological entities.

An intact immune system is usually capable of eliminating infectious pathogens or at least is capable of efficiently controlling and limiting their spread within the organism. The human immunodeficiency virus (HIV), however, has been strongly implicated in a striking impairment of immune functions that eventually has fatal consequences (1). HIV infects cells by way of the CD4 surface antigen. This molecule is present on a variety of cells but is most prominent on CD4+ T helper/inducer lymphocytes, a regulatory lymphocyte of pivotal importance for proper immune responses. By mechanisms that are not completely elucidated, the infection by HIV leads to functional impairment and death of the infected cells either directly by cytopathicity of HIV or indirectly, e.g., by immune reactions. As a consequence, the exceedingly complicated network of interactions within the immune system collapses. As this scenario varies widely, at least kinetically, in infected subjects, there may be other cofactors that sustain the progression of the disease. Among these cofactors, immunological activation by various pathogens seems to be of particular importance (2–5).

Many details of how HIV affects the immune system remain to be clarified. Theoretical models might accompany the experiments since they enable investigation of possible consequences of a defined set of assumptions in some depth.

In two previous models for interactions involving the immune system, immune system retroviruses, and normal replicating pathogens (6, 7), the description of at least some of the interactions that are known to be important has involved relatively complicated dynamical systems consisting of several coupled nonlinear differential equations that cannot be readily analyzed in a mathematical sense.

Here, an opposite approach is presented. A few interactions that are deemed to be of uppermost importance for an understanding of the possible catastrophic effect of HIV on the immune response are embedded into simple mathematical equations that can be analyzed, at least to some degree. The solutions are described either in terms of the time dependence or by “trajectories” that describe the mutual dependence of the various interacting species in a phase space defined by the populations of these components of the system (8–10).

Model 1

The starting point of the present discussion is the following simple system of two coupled, nonlinear differential equations, with a, b, c, and d denoting nonnegative constants:

\[
\frac{dX_1}{dt} = \dot{X}_1 = (a - bX_2)X_1
\]

and

\[
\frac{dX_2}{dt} = \dot{X}_2 = (c + dX_2)X_1. \tag{E1}
\]

Let \(X_1\) be the population size of a pathogen and \(X_2\) be the population size of the immune cells specific for this pathogen. The first differential equation indicates that the pathogen population grows exponentially in the absence of a specific immune response; the immune response, however, tries to eliminate the pathogen. The growth rate of \(X_2\), described by the second equation, is proportional to the population size of the pathogen and is further sustained by an autocatalytic component that is in action as long as there is pathogen present.

In its simplicity, this model resembles the well known predator–prey models of Lotka (8) and Volterra (9). There are, however, characteristic differences in the behavior of the solutions. Whereas the Lotka–Volterra system leads to conservative motions of the trajectories in the phase space spanned by \(X_1\) and \(X_2\), the present model has the following analytical solution:

\[
X_1 = (1/d^2)(ad + bc)\log(c + dX_2) - (b/d)X_2 + \text{const},
\]

and, for \(X_1(t = 0) = X_1^0, X_2(t = 0) = X_2^0\):

\[
\text{const} = X_1^0 + (b/d)X_2^0 - (1/d^2)(ad + bc)\log(c + dX_2^0).
\]

Looking for stationary points (i.e., \(X_i^0 = 0\), where \(i = 1, 2\)), there is, first, the trivial solution with \((X_1^0, X_2^0) = (0, 0)\), which corresponds to an immunologically virgin state. Simple inspection of model 1 shows that at \(X_2 = 0\) the system is stationary for any value of \(X_2\) but for \(X_1 > 0\) it is impossible for the system to be stationary. Thus, this primitive immune system is in fact invulnerable: any nonzero population of the pathogen will lead to elimination of the pathogen; after which the immune cell population will persist on a constant level (memory state). If we start with the virgin state and introduce pathogen at an initial concentration, \(X_1^0 (X_2^0 = 0)\), the pathogen population initially increases and reaches a maximum when \(X_2 = a/b\). The value of \(X_1^0\) at this turning point:

Abbreviation: HIV, human immunodeficiency virus.

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point can be estimated from the above solution. After the turning point, the trajectory is attracted by the axis at $X_1 = 0$ if it approaches asymptotically at a value $X_2^*$, given by the implicit equation

$$(1/d^2)(ad + bc)\log(c + dX_2^*) = (b/d)X_2^* - \text{const.}$$

Fig. 1 shows the time dependence of the solutions as well as the behavior of the trajectories in the phase plane. Notably, repeated stimulations with the pathogen increase the steady-state level of the immune cells; in the phase plane, they simply are represented by a jump to a trajectory with higher $X_2^*$ value.

**Model 2**

As a possible step to make the above model more realistic, one could assume that for both interacting populations, $X_1$ and $X_2$, there are elimination mechanisms with rates that depend on the present population size (i.e., normal decay processes such as cell death).

This extension yields

$$\dot{X}_1 = (a - bX_2)X_1 - k_1X_1$$

[i.e., $\dot{X}_1 = (k_1 - bX_2)X_1$ with $k_1 = a - k_1$] and

$$\dot{X}_2 = (c + dX_2)X_1 - k_2X_2. \quad \text{[E2]}$$

Here, only cases are considered with $k_1 > 0$, which means considering only normal pathogens that are capable of autonomous growth (i.e., simple antigens such as toxoids or proteins are excluded).

There are two stationary points, a virgin state $(0, 0)$ and a nontrivial solution with coexisting populations,

$$X_1^* = k_1k_2/(kd + bc)$$

and

$$X_2^* = k_1/b.$$  

In Appendix A it is shown by eigenvalue analysis of the representative linearized system that $(0, 0)$ is an unstable saddle point: Infection with $X_1$ will result in a final state that is different from $(0, 0)$. The nontrivial solution represents a stable node: The system returns to this same stationary state, even after repeated perturbations with any values of $X_1$. In contrast to model 1, in this model a persistent nonvanishing level of $X_1$ is obtained depending mainly on the net reproduction rate of the pathogen $k_1$ and the elimination rate of the immune cells $k_2$. Fig. 2 shows the behavior of the system represented by model 2.

**Model 3**

Next, consider the following system:

$$\dot{X}_1 = (a - bX_2)X_1$$

$$\dot{X}_2 = (c + dX_2)X_1 - eX_2X_3$$

and

$$\dot{X}_3 = (fX_2 - g)X_3. \quad \text{[E3]}$$

where $X_3$ is the immune system retrovirus and $e$, $f$, and $g$ are nonnegative constants.

This system may be interpreted as a model, albeit very crude, for the situation when an immune system retrovirus is present: The equations simply indicate that the retrovirus in-

![Fig. 1. Time dependence and trajectories of the system E1. Initial values are $X_1^0 = 5$, $X_2^0 = 0$. The rate constants used are $a, b, c, d = 0.05$. At time $t = 30$, the system is perturbed by a new infection with 5 units of the pathogen $X_1$ (indicated by the interrupted line). The stationary solutions are not really stable: Perturbation of the system leads to a new stationary state. The trajectories of the system are shown in the insert; the arrows indicate the direction of motion. The numerical integration of the coupled differential equations was done using program D02EBF from the NAG (Numerical Algorithm Group) library as implemented on the CDC CYBER 74 computer of the University of Innsbruck.](image1)

![Fig. 2. Time dependence and trajectories of the system E2. Initial values are $X_1^0 = 3$, $X_2^0 = 0$. Rate constants are $k_1, b, c, d, k_3 = 0.20$. The nontrivial steady-state solution is $[k_1k_2/(kd + bc), k_3/b] = (1/2, 1)$. At time $t = 100$, the system is perturbed by a new infection with 3 units of pathogen $X_1$ (indicated by the interrupted line). The stationary solution represents a genuine stable state: After a perturbation, the system returns to the same stationary state. The trajectories of the system are shown in the insert; the arrows indicate the direction of motion.](image2)
Appendix B that in this situation the following relation holds as a special case:

\[ \frac{X_1(t)}{X_3(t)^b} = X_1^e X_3^{eb} \exp(aft) \]

(i.e., that the product of the population sizes of \( X_1 \) and \( X_3 \) approaches infinity in the limit of an infinitely long growing time). The introduction of the agent \( X_2 \) has in fact destroyed any possibility for \( X_2 \) to control the growth of \( X_1 \) and \( X_3 \).

A more interesting, and perhaps also more realistic, behavior is obtained when \( X_3 \) is subject to an elimination mechanism with a rate that is set proportional to the size of the population of \( X_2 \) (i.e., \( g > 0 \)).

The trivial solution \((0, 0, 0)\) is stationary, but unstable (see Appendix A). Clearly, if \( X_3 = 0 \) in the beginning, the situation is described by Eq. E1. There is, however, a further nontrivial stationary point, if \( a/b = g/f \). In this case,

\[ X_1^s = aeX_3^s/(ad + bc) \]

and

\[ X_3^s = a/b = g/f. \]

In Appendix B it is shown that for Eq. E3 at any time

\[ \frac{X_1(t)}{X_3(t)^b} = X_1^e X_3^{eb} \exp((af - bg)t). \]

In the long term, \( X_1 \) and \( X_3 \) show, after a transient of oscillations, unlimited growth, if \( af > bg \). In contrast, if \( af < bg \), they will decay exponentially in the long term. In the special case \( a/b = g/f \), the time dependence of this solution vanishes, and

\[ X_3^{(b+g)} = X_3^e X_3^{eb}[(ad + bc)/ae]^t, \]

and \( X_1^s \) follows from the above relation.

It is obvious that the condition \( a/b = g/f \) is a razor’s edge;

FIG. 4. Time dependence and trajectories for the system E3 for \( a/b > g/f \). Initial values are \( X_1^e = X_3^e = 1, X_3^s = 0 \). The growth rate constant \( a \) for the pathogen \( X_1 \) is set equal to 0.3, all remaining rate constants are set equal to 0.2 (the decay terms for the pathogen \( X_1 \) and the immune cells \( X_3 \) are neglected). No stationary solution exists; rather, the populations of pathogen \( X_1 \) and the retrovirus \( X_3 \) grow unrestricted after an initial phase of oscillations. A projection of the trajectories of the system onto the \( X_1, X_3 \) phase plane is shown in the insert; the arrows indicate the direction of motion.

even the slightest deviation from this condition will prevent the steady state. Fig. 3 shows what happens when this condition is fulfilled: A stationary state is reached after a primary infection with both the pathogen and the retrovirus. Stability analysis of model 3 when \( a/b = g/f \) reveals that the determinant of the Jacobian vanishes at the nontrivial stationary point; therefore, this state is not stable. Whereas the stationary value for \( X_2 \) is determined by the above ratio, the stationary levels of \( X_1 \) and \( X_3 \) depend obviously on the initial conditions (see Appendix B). Therefore, in contrast to Eq. E2, the system does not return to the same stationary state when being disturbed but switches to another stationary state [e.g., a new infection with \( X_1 \) leads to a new stationary state with different levels of \( X_1 \) and \( X_3 \) (Fig. 3)].

The condition \( a/b > g/f \) (Fig. 4) means that the proliferation of the normal pathogen \( X_1 \) cannot be controlled by the immune cells since the efflux or destruction of the immune system retrovirus \( X_3 \) is not great enough to limit the population of these immune system-destroying agents. At least for small deviations from the stationary condition, we can have a long series of damped oscillations that apparently tend asymptotically to a stable focus, just as if \( a/b = g/f \) holds, but the mean level of the oscillations of \( X_1 \) and \( X_3 \) increases with time. Therefore, after a transient, the oscillations vanish and exponential growth of \( X_1 \) and \( X_3 \) remains. (Conversely, if \( a/b < g/f \), the populations of both agents decay exponentially in the long term, the population of \( X_2 \) remains on a constant level.)

It should be noted that in Figs. 3 and 4, the two-dimensional trajectories seem to have intersections. Actually, the three-dimensional trajectories being depicted obey the requirement of the classical analysis of dynamical systems that trajectories cannot cross other trajectories or themselves.

When one introduces in this model a decay term for \( X_1 \) and \( X_3 \) in analogy to Eq. E2, essentially the same situation is obtained with the exception that the conditions for the stationary state now are

\[ X_1^s = (ek_1X_3^s + k_1k_2)/(k_1d + bc), \]

\[ X_3^s = k_1/b = g/f \]

and for the time dependence we obtain

\[ X_1(t)/X_3(t)^b = X_1^e X_3^{eb} \exp[(fk_1 - bg)t]. \]
Discussion

The models studied show, in mathematical terms, the expected destabilizing effect of the immune system retrovirus: In the absence of this agent, the model immune response successfully eliminates the pathogen (model 1) or controls it at a persistent level (model 2). Introducing the immune system retrovirus leads either to unlimited growth of both the normal pathogen and the immune system retrovirus itself or, under certain requirements, again to elimination of both pathogenic agents. These conditions depend on the growth rates and elimination rates of both pathogens. Thus, this behavior might suggest why a large proportion of people infected with HIV show no symptoms for a long period of time and why in HIV infection there is a surprisingly high variability in time from infection to outbreak of clinical disease.

One should keep in mind that the assumption of rate constants that are independent of time certainly will not hold in an actual HIV infection; e.g., it may be that the situation in HIV-infected individuals who are in good health corresponds to model 3 in the more favorable case that the elimination processes of the normal pathogen and the immune system retrovirus are sufficiently rapid to prevent unlimited growth. In contrast, continuous immunological stimulation might have negative effects on the ability of the immune system to respond adequately. This could be represented, e.g., by steadily decreasing rate constants for the elimination of the pathogen, whereby the system’s response might switch to the situation in which the population size of the pathogen eventually explodes.

One reason why mathematical models are being studied is that potential implications of a well defined set of hypotheses can be formulated and studied unambiguously. The models presented herein should be considered solely with this in mind. By no means can they be expected to give a theory of real HIV infection. The simplicity in the models presented must not obscure the exceedingly complex reality: The immune system consists, in fact, of a multitude of mutually dependent and independent components. Cells such as monocytes/macrophages are known to serve as reservoirs of HIV. Each normal pathogen has its characteristic peculiarities. The nonlinearities of the interactions between the interacting partners are in fact unknown. In the models, the immune system retrovirus is not considered as immunogenic per se, which is not necessarily true for real HIV. Consequently, no attempt was made to adjust, e.g., the rate constants used to a “real” situation.

There are several possible routes along which these models could be refined; e.g., one could replace the exponential growth model by the more realistic logistic model that allows one to take limitations of resources into consideration. Additionally, the simple product terms representing the interactions could be replaced by sigmoid terms [11, 12] that allow one to adjust the strength of the cooperativity as well as possible saturation effects. Alternately, one could refine the description from a biological point, e.g., by taking into account the complexities of the internal regulation of the immune system.

Model 3, despite its lack of detail, provides a starting point for in-depth study of the fatal phenomena associated with the strategy of HIV. In the current scientific discussion about the potential relevance of other cell types as HIV reservoirs (e.g., macrophages), the models studied here may at least hint that the effects on the T lymphocytes (which would correspond most closely to the studied immune cells) alone might already suffice to understand a great part of the HIV-related immune deficiency.

Appendix

A: Stability Analysis. In the paper, the indirect method of Lyapunov is applied. In the vicinity of the stationary point under consideration, the system of differential equations is developed in a Taylor series and only the linear terms are retained.

System E2. For the point (0, 0) the linear system is simply

\[ \dot{u}_1 = k_1 u_1 \]

and

\[ \dot{u}_2 = cu_1 - k_2 u_2. \]

The characteristic equation is

\[ \det \begin{pmatrix} k_1 - \lambda & 0 \\ c & -k_2 - \lambda \end{pmatrix} = 0, \]

and the eigenvalues are \( \lambda_1 = k_1, \lambda_2 = -k_2. \) Since one of the eigenvalues has a positive real part, (0, 0) represents an unstable saddle point. For the nontrivial point, the following transformation is applied:

\[ u_1 = X_1 - X_1^* = X_1 - k_1 k_2 / (k_1 d + bc) \]

and

\[ u_2 = X_2 - X_2^* = X_2 - k_1 / b. \]

Transforming Eq. E2 and retaining only the terms linear in \( u_1 \) and \( u_2 \), the following characteristic equation is finally obtained:

\[ \lambda^2 + \left[ b c k_2 / (b c + d k_1) \right] \lambda + k_1 k_2 = 0, \]

and it is easily seen that for positive \( k_1 \) and \( k_2 \) the eigenvalues are either real or complex conjugates, but the real parts are invariably negative for both eigenvalues. Therefore, this stationary solution represents a stable node.

System E3. First, the stationary solution (0, X_1^*) for the case of vanishing elimination rate of \( X_3 \) (i.e., \( g = 0 \)) is analyzed by the transformation

\[ u_1 = X_1 \]

\[ u_2 = X_2 \]

and

\[ u_3 = X_3 - X_3^*. \]

This yields

\[ \dot{u}_1 = au_1 \]

\[ \dot{u}_2 = cu_1 - e_2 X_3^* u_2 \]

and

\[ \dot{u}_3 = f X_3^* u_2. \]

Inspection of the characteristic equation shows that the eigenvalues are \( \lambda_1 = a, \lambda_2 = -e_2 X_3^* > 0, \lambda_3 = 0. \)

Since one eigenvalue is zero and, moreover, one has a positive real part, this system is unstable. Similar arguments show that for the more complex systems (with nonvanishing decay terms for \( X_1 \) and \( X_2 \) in analogy to model 2) where either \( g \) alone or both \( g \) and \( k_2 > 0 \), at least one eigenvalue vanishes and, therefore, the stationary solutions are not genuine stable points.

B: Time Dependence of the Solutions of System (Eq. E3). By rearrangement of Eq. E3 it follows that

\[ X_2 = (1/b)(a - \dot{X}_1/X_1) = (1/f)(g + \dot{X}_3/X_3), \]
and, after integration with respect to time,

\[ b \log(X_3) + f \log(X_1) + \log(\text{const}) = (af - bg)t. \]

With initial values \( X_1^0 \) and \( X_3^0 \), the constant is obtained as

\[ \text{const} = \frac{1}{(X_1^0)^f(X_3^0)^b}. \]

Taking the exponential of the integrated equation yields the required solution:

\[ X_1(t)^fX_3(t)^b = X_1^0X_3^0e^{((af - bg)t)}. \]