

Diversity and virulence thresholds in AIDS

(human immunodeficiency virus/immunity/bifurcations/separatrix/incubation period)

ROB J. DE BOER AND MAARTEN C. BOERLIJST

Theoretical Biology, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

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ABSTRACT We propose a model for the interaction between human immunodeficiency virus and the immune system. Two differential equations describe the interactions between one strain of virus and one clone of T lymphocytes. We use the model to generalize earlier results pertaining to the AIDS diversity threshold [Nowak, M. A., Anderson, R. M., McLean, A. R., Wolfs, T. F. W., Goudsmit, J. and May, R. M. (1991) *Science* 254, 963–969]. Our model has (i) a stable steady state corresponding to the “controlled” persistence of the virus and (ii) a region corresponding to AIDS. The separatrix between the two regimes is formed by the stable manifold of a saddle point. We define a dimensionless “virulence” parameter which combines the infectivity and antigenicity of a virus strain. We derive analytically two parameter conditions involving virulence. The first corresponds to a saddle–node bifurcation which causes AIDS due to the loss of the stable equilibrium. The second corresponds to a global bifurcation which causes AIDS due to a change in the basins of attraction. Incorporating diversity into the model, we derive a diversity threshold corresponding to the saddle–node bifurcation. In this threshold condition diversity and virulence have an equivalent effect. By studying the effect of diversity on the critical virulence that is required for a new mutant to cause AIDS, we again establish that diversity and virulence are equivalent parameters. Because in our model increasing diversity decreases the critical virulence, the strain that eventually causes AIDS need not be a virulent one.

The development of AIDS is associated with the selective depletion of the most crucial cell type of the immune system: the CD4⁺ helper T cell. The human immunodeficiency virus (HIV) infects helper T cells by binding the gp120 virus envelope glycoprotein to CD4⁺ molecules (1). The selective infection and death of CD4⁺ T cells provides a simple explanation for the impairment of the immune system (2, 3). This explanation, however, is widely debated (4–7).

One hallmark of HIV infection is the long and variable incubation period. Although the processes of infection and immune activation have a short time scale, a typical time scale for the incubation period is 10 years (8). Another hallmark of HIV is its enormous genetic diversity. The dominant surface antigen for the immune response is the V3 loop of gp120 (9, 10). This V3 loop is hypervariable: virus isolates from one infected individual have genetically different V3 loops (11, 12). Since HIV accumulates one point mutation per genome during an average replication cycle (12, 13), the genetic variability will grow exponentially. However, antigenic variability is not unique to HIV: several pathogens possess antigenic variability which lets them “run ahead” of the immune response.

A recent model (14–17) combines these two hallmarks of AIDS in that it attributes the long and variable incubation period to genetic variability. The authors of the model coined

the term “diversity threshold” for the critical variability beyond which the immune system is no longer capable of controlling the virus. The diversity threshold emerges mathematically from their simple and quite reasonable model. The diversity threshold (14–17) is a generic property of a wide variety of models. (See refs. 17 and 18 for recent reviews of mathematical models for the various pathogenic effects of HIV.)

The virus quasispecies (19) not only increases in diversity but also evolves physiologically different strains. Virus strains evolve different replication rates, cytotrophisms, and antigenicities (20–22). Here we develop a model that allows us to study the relation between the diversity of the virus quasispecies and the “virulence” of each virus strain. We derive a dimensionless virulence parameter and show that it is involved in well-known local and global bifurcations.

Models of the Immune Response to HIV

Our models describe the interactions between one strain of virus v_j , where j is the strain number, and the clone(s) of CD4⁺ T cells t_j that recognizes this strain specifically. We assume that for each strain of virus there will always be a clone of T cells. Upon interaction with the virus the T cells will either proliferate or become infected. Infection of the T cells leads to cell death. The T cells have a constant turnover and receive a constant supply of new cells from the thymus. The virus grows exponentially and declines as a function of the immune reaction. The latter is supposedly due to specific antibodies and/or to cytotoxic T cells (3, 21, 23, 24). For simplicity, we here assume that the immune reaction is proportional to the concentration of HIV-specific CD4⁺ helper T cells.

These interactions are formalized in the model

$$\dot{t}_j = s + t_j \left(\frac{pv_j}{k + v_j} - 1 - iv_j \right), \quad [1]$$

$$\dot{v}_j = v_j(r - ct_j), \quad [2]$$

where we have scaled time with respect to the turnover of T cells, which is on the order of days (25). In our model r is the maximum replication rate of the virus, s represents the supply of specific T cells from the thymus, p is the maximum rate of proliferation of the T cells, and k is the saturation constant of the proliferation process. The parameter k is an “antigenicity” parameter: highly antigenic strains will have a low k value. The term cv_jt_j represents the immune response and the term iv_jt_j represents the infection of T cells by the virus. A very similar model has been developed independently by Harnevo (26).

The nontrivial equilibrium of Eq. 2 corresponds to $t_j = r/c$. Thus we make the model dimensionless by scaling

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Abbreviation: HIV, human immunodeficiency virus.

$$T_j = \frac{ct_j}{r} \quad \text{and} \quad V_j = \frac{v_j}{k}, \quad [3]$$

to obtain

$$\dot{T}_j = \sigma + T_j \left(\frac{pV_j}{1+V_j} - 1 - \nu V_j \right), \quad [4]$$

$$\dot{V}_j = rV_j(1 - T_j), \quad [5]$$

where $\sigma \equiv cs/r$ is the dimensionless source of T cells, and $\nu \equiv ik$ combines the virus antigenicity and infectivity. We treat ν as a ‘‘virulence’’ parameter: increasing ν increases the deleterious effects of the virus strain in the organism. The dimensionless model has four parameters $r, p, \sigma,$ and ν . When stimulated optimally, T-cell populations have a doubling time of about 1 day—i.e., $p = 2$. To allow for analytical treatment we assume that the maximum growth rate of the virus is the same as that of the T cells—i.e., $r = p - 1 = 1$. Since the virus probably grows much more slowly, this assumption will later be relaxed. (See refs. 17, 27, and 28 for a discussion of parameter values.) The source of specific T cells, s , and the elimination of virus by T cells, c , are typically small parameters. Our default value for the dimensionless source is therefore small—i.e., $\sigma = 0.01$. To allow for T-cell growth we let $\nu < p$; see Eq. 4.

For reasons of simplification, our model ignores the dependency of the replication of the virus on T-cell numbers. We have several arguments to support this assumption. First, we consider just one clone of T cells which represents only a small fraction of the total T-cell population. Second, the virus replicates not only in T cells (29). Third, we study the early development of AIDS, which is a stage during which T-cell depletion is not yet severe.

Equilibria. Fig. 1a shows the nullclines of the model for $\nu = 10^{-3}$. The $\dot{V}_j = 0$ nullcline is a straight line at $T_j = 1$. The $\dot{T}_j = 0$ nullcline corresponds to the curved lines. The model has three equilibria for these parameters. The T-cell clone is

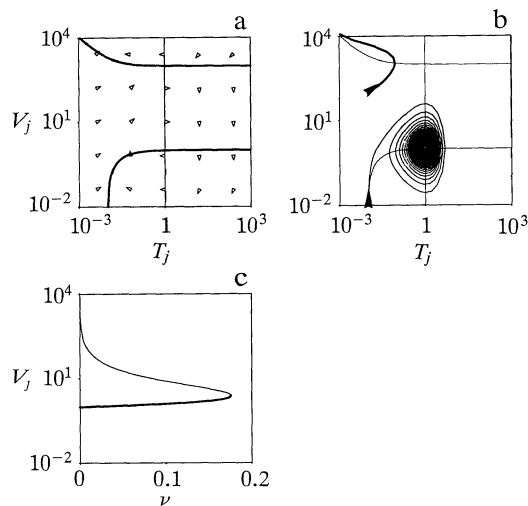


FIG. 1. Nullclines and trajectories of Eqs. 4 and 5. Parameters: $p - 1 = r = 1$, $\sigma = 0.01$, and $\nu = 0.001$. (a) The light line forms the $\dot{V}_j = 0$ and the heavy lines form the $\dot{T}_j = 0$ nullcline. Arrows indicate the vector field. (b) Two trajectories for two initial conditions, i.e., $(T_j, V_j) = (\sigma, 0.01)$ and $(\sigma, 100)$. A small dose of virus leads to a trajectory spiraling into the immune state. A high dose of virus leads to AIDS (see the heavy line). (c) The saddle-node bifurcation. Beyond the critical value $\nu = 0.172$ the virus strain is lethal (see text). The heavy line corresponds to the stable immune state, the light line corresponds to the Rubicon steady state. Numerical results were obtained with GRIND (30).

at rest in a ‘‘virgin’’ state at $T_j = \sigma$ and $V_j = 0$. This state is a saddle point: it is unstable to the introduction of virus. The T-cell clone proliferates in the two other equilibria. They correspond to the two intersects of the $\dot{V}_j = 0$ and the $\dot{T}_j = 0$ nullclines. The upper steady state is a saddle point (as can be seen from the arrows), and the lower one is a stable spiral (Fig. 1b). We call the upper equilibrium the ‘‘Rubicon’’ steady state and the lower one the ‘‘immune’’ steady state. In the top left-hand corner we have a region where virus increases and T cells decline. This region is the ‘‘AIDS regime.’’ Trajectories attaining this region approach $T_j \rightarrow 0$, $V_j \rightarrow \infty$ (Fig. 1b).

The two horizontal asymptotes of the $\dot{T}_j = 0$ nullcline, which exist for $\nu \ll p$, are found by setting $\dot{T}_j = 0$ in Eq. 4; i.e.,

$$T_j = - \frac{\sigma}{pV_j/(1+V_j) - 1 - \nu V_j}. \quad [6]$$

The asymptotes correspond to those values of V_j for which the denominator of Eq. 6 equals zero. Since this expression is a quadratic there may be two asymptotes. For $\nu \ll p$ the approximate values of V_j can be found by considering two cases. First, when $V_j < 1$, we can ignore the νV_j term to obtain

$$V_j \approx 1/(p - 1).$$

Second, when $V_j \gg 1$, we approximate $pV_j/(1+V_j)$ by p to obtain

$$V_j \approx (p - 1)/\nu.$$

For our default value $p = 2$ the two asymptotes approximately correspond to $V_j = 1$ and $V_j \approx \nu^{-1} = 10^3$.

Virulence

Virus strains usually appear in low numbers facing a T-cell clone that is at rest. Thus, we will say a strain is introduced in the virgin state at an infinitesimal value. For strains that are introduced in the virgin state we distinguish two kinds: ‘‘lethal’’ strains that cause AIDS and ‘‘sublethal’’ strains that are controlled by the immune system. Fig. 1b shows how a sublethal virus strain expands but is eventually controlled by the immune system. Any sublethal virus, however, ‘‘escapes’’ from immune control, thus causing AIDS, when it is introduced in a sufficiently large dose (Fig. 1b). We derive two parameter conditions that determine whether or not a strain is lethal. The first condition is based upon a local bifurcation, the second upon a global bifurcation.

Existence of the Immune State. The effect of the virulence ν on the Rubicon and the immune steady states is studied in Fig. 1c. Continuing ν as a bifurcation parameter, we observe that the steady states disappear at a saddle-node bifurcation. This local bifurcation point is obtained analytically by solving $\dot{T}_j = 0$ for ν in Eq. 4. Because in these steady states $T_j = 1$, we obtain

$$\bar{\nu} = \frac{\sigma - 1}{V_j} + \frac{p}{1 + V_j}. \quad [7]$$

Since the saddle-node bifurcation corresponds to the maximum value of $\bar{\nu}$ as a function of V_j (Fig. 1c), we set $\partial \bar{\nu} / \partial V_j = 0$ and solve for V_j . Substituting this value of V_j into Eq. 7 and letting $\sigma \rightarrow 0$ gives us the ‘‘existence’’ condition

$$\nu = \left(\sqrt{p} - 1 \right)^2. \quad [8]$$

For $p = 2$, Eq. 8 corresponds to $\nu \approx 0.172$ (Fig. 1c). Thus, a single strain is lethal when $\nu > (\sqrt{p} - 1)^2$. For such a strain

there is no equilibrium in which the strain can be controlled by the immune system.

Basins of Attraction. The existence of a stable equilibrium is a necessary but not a sufficient condition for the control of a single strain. In Fig. 1*b* we saw that a large dose of a sublethal virus—i.e., one for which $\nu < (\sqrt{p} - 1)^2$ —may lead to AIDS. The escape of sublethal virus is determined by the separatrix between the basins of attraction of the immune state and the AIDS regime. This separatrix is formed by the stable manifold of the Rubicon equilibrium.

Such a separatrix imposes a condition not only on the virus dose but also on the virulence ν . Thus, studying a small virus dose and various values of ν , we numerically found at $\nu = 0.01$ a global bifurcation that corresponds to a heteroclinic connection involving the Rubicon state and the virgin state (Fig. 2*b* and *d*). This heteroclinic connection turned out to be a straight line. For $\nu < 0.01$ the ω -limit set of the neighborhood of the virgin state is the immune state; for $\nu > 0.01$ it corresponds to AIDS (Fig. 2*a* vs. *c*). This suggests that any virus for which $\nu > 0.01$ is lethal.

We have been able to prove that the straight line between the two saddle states is invariant. The heteroclinic connection involves the stable manifold of the Rubicon steady state and the unstable manifold of the virgin state. (Both manifolds are one-dimensional.) The latter is calculated from the eigenvectors of the Jacobian matrix of the virgin state: if the connection forms a straight line, the unstable manifold is identical to the eigenvector that corresponds to the positive eigenvalue.

In the virgin state $V_j = 0$ and $T_j = \sigma$. For $r = p - 1 = 1$ the Jacobian matrix is

$$J = \begin{bmatrix} -1 & \sigma(2 - \nu) \\ 0 & 1 - \sigma \end{bmatrix}. \quad [9]$$

The eigenvalues of this matrix are $\lambda_+ = 1 - \sigma$ and $\lambda_- = -1$. The eigenvector corresponding to λ_+ in the $[T_j, V_j]$ state space

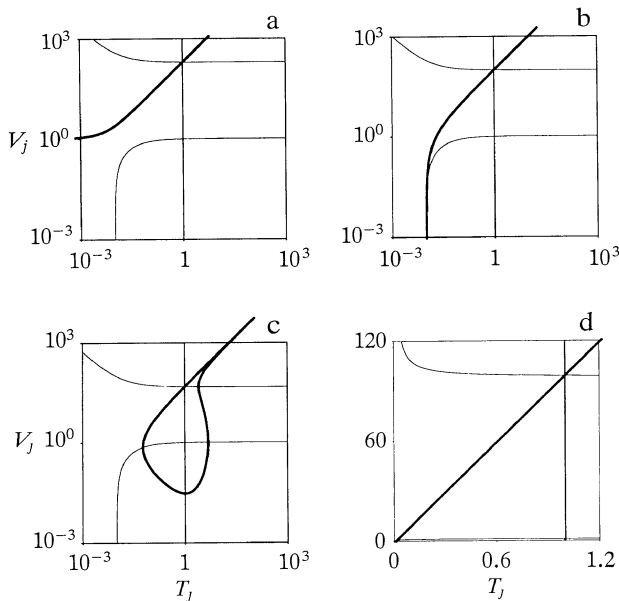


FIG. 2. Nullclines and the separatrix between the immune state and the AIDS regime. Parameters: $p - 1 = r = 1$, $\sigma = 0.01$, and $\nu = 0.005, 0.01, 0.02$. The heavy line depicts the unstable manifold of the Rubicon steady state. (a) With $\nu = 0.005$, the virgin state lies in the basin of attraction of the immune state. (b) With $\nu = \sigma = 0.01$, there is a heteroclinic connection between the virgin and the Rubicon steady state. (c) With $\nu = 0.02$, the virgin state is no longer in the basin of attraction of the immune state. (d) Same as *b* but for a linear state space: the heteroclinic connection forms a straight line. Numerical results were obtained with GRIND (30).

is $[1, (2 - \sigma)/\sigma(2 - \nu)]$. Extending this eigenvector in a straight line from the virgin state $[\sigma, 0]$ to the T-cell value in the Rubicon state $T_j = 1$ gives the point

$$[T_j, V_j] = \left[1, \frac{(1 - \sigma)(2 - \sigma)}{\sigma(2 - \nu)} \right]. \quad [10]$$

We are interested in the parameter values for which this point corresponds to the Rubicon steady state. Since $T_j = 1$, $\bar{V}_j = 0$ is always satisfied. Substituting Eq. 10 into Eq. 4 and solving $\dot{T}_j = 0$ yields a fourth-order equation with three roots:

$$\nu = \sigma, \quad \text{with} \quad \bar{V}_j = \frac{1 - \sigma}{\sigma}, \quad [11a]$$

$$\nu = 1 + 2/\sigma, \quad \text{with} \quad \bar{V}_j = \sigma - 1, \quad [11b]$$

$$\sigma = 1, \quad \text{with} \quad \bar{V}_j = 0. \quad [11c]$$

Only the first root, Eq. 11*a*, is of interest here. Since σ is small, the second root violates our condition $\nu < p$ (see Eq. 4) and is physically meaningless because $\bar{V}_j < 0$. The third root corresponds to the virgin state and not to the Rubicon state.

Finally, we have to verify that, for $r = p - 1 = 1$ and Eq. 11*a*, this connection is indeed a trajectory. On the line from $[\sigma, 0]$ to $[1, (1 - \sigma)/\sigma]$, we have $V_j = (T_j - \sigma)/\sigma$. Substituting this into Eqs. 4 and 5, we obtain $\dot{T}_j = \sigma \dot{V}_j$. This does indeed give a straight trajectory with a slope $1/\sigma$.

In summary, at $\nu = \sigma$ the separatrix corresponds to a heteroclinic connection between the virgin and the Rubicon state. Thus, a strain is lethal when $\nu > \sigma$ (see Eq. 11*a*). In Eq. 8 we derived that strains are lethal when $\nu > (\sqrt{p} - 1)^2$. However, since $\sigma \ll (\sqrt{p} - 1)^2$, the separatrix condition (Eq. 11*a*) is much more important than the existence condition (Eq. 8).

Diversity

T-cell activation by HIV is specific; i.e., only V_j will activate T_j . Conversely, T-cell infection by HIV is nonspecific; i.e., any virus strain may infect any clone. This means that the diversity of the virus quasispecies (19) appears only in the infection term. Consider a model with n strains of virus and n T-cell clones,

$$\dot{T}_j = \sigma + T_j \left(\frac{pV_j}{1 + V_j} - 1 - \sum_{i=1}^n v_i V_i \right), \quad [12a]$$

where $i, j = 1, \dots, n$. We first develop a ‘‘toy’’ model by assuming that all strains have the same virulence and that all strains have the same concentration. Note that the latter assumption is valid if all strains attain the immune steady state. The T-cell equation of the toy model is

$$\dot{T}_j = \sigma + T_j \left(\frac{pV_j}{1 + V_j} - 1 - n\nu V_j \right), \quad [12b]$$

where $j = 1, \dots, n$. To study the effect of diversity on the escape of the virus quasispecies, we have to restrict ourselves to sublethal strains—i.e., we have to satisfy $\nu < \sigma$.

Diversity Threshold. Eqs. 4 and 12*b* differ only in the infection parameters, in ν and $n\nu$, respectively. Thus, all results obtained with Eq. 4 also apply to Eq. 12*b* if we replace ν by $n\nu$. Hence, the model has a diversity threshold corresponding to the saddle-node bifurcation of Fig. 1*c* at

$$n\nu = \left(\sqrt{p} - 1 \right)^2, \quad \text{or} \quad n = \nu^{-1} \left(\sqrt{p} - 1 \right)^2. \quad [13]$$

This means that a quasispecies that is increasing its diversity by mutation will escape from immune control when $n > \nu^{-1}(\sqrt{p} - 1)^2$. Here the system loses the equilibrium in which the quasispecies is kept under control. Hence, all virus strains composing the quasispecies suddenly start to grow, and AIDS develops.

This confirms the result of Nowak *et al.* (14–17): a quasispecies that is composed of sublethal strains causes AIDS simply because it increases its diversity. The biological mechanism by which AIDS develops in this model is an increase in the total virus concentration. A quasispecies of a diversity of n strains that are kept under control in the immune state has a dimensionless total virus concentration $V_j = n$.

With respect to the diversity threshold, Eq. 13 shows that the diversity n and the virulence ν are equivalent parameters in this model. Doubling the diversity has the same effect as doubling the virulence. Thus, Eq. 13 is not strictly a diversity threshold but is a condition in terms of the “accumulated virulence” of the quasispecies. In fact, one can regard the term $n\nu V_j$ as a dimensionless total virus concentration.

Diversity and Virulence. Studying the effect of diversity on the basins of attraction is more involved because different strains need not be in the same equilibrium. We therefore have to extend the toy model in order to make a distinction between the established quasispecies nV_j and a new mutant V_* . Given the presence of a quasispecies that is kept under control in the immune state, what is the critical virulence at which a new mutant escapes? Our extended model is

$$\dot{V}_j = rV_j(1 - T_j), \tag{14a}$$

$$\dot{T}_j = \sigma + T_j \left(\frac{pV_j}{1 + V_j} - 1 - n\nu V_j - \nu_* V_* \right), \tag{14b}$$

and for the new mutant we have

$$\dot{V}_* = rV_*(1 - T_*), \tag{15a}$$

$$\dot{T}_* = \sigma + T_* \left(\frac{pV_*}{1 + V_*} - 1 - n\nu V_j - \nu_* V_* \right), \tag{15b}$$

where ν is the “average” virulence of the established strains, and ν_* is the virulence of the mutant.

The equilibria of this four-dimensional system resemble those of the toy model. The system has a virgin state $V_j = V_* = 0$ with $T_j = T_* = \sigma$. When $V_j, V_* > 0$, the system can have equilibria only when $T_j = T_* = 1$ (see Eqs. 14a and 15a). Solving $\dot{T}_j = \dot{T}_* = 0$ for $T_j = T_* = 1$ implies that $V_j = V_*$ (see Eqs. 14b and 15b). When $V_j = V_*$ we may rewrite Eq. 14b as

$$\dot{T}_j = \sigma + T_j \left(\frac{pV_j}{1 + V_j} - 1 - \eta V_j \right), \tag{16}$$

where $\eta \equiv n\nu + \nu_*$. Eqs. 4 and 16 differ only in the infection parameters—i.e., in ν and η , respectively. Thus, all results obtained with Eq. 4 also apply to Eq. 16 if we replace ν by η . This means that the four-dimensional system has a Rubicon state and an immune state, with $T_j = T_* = 1$ and $V_j = V_*$, which disappear by a saddle-node bifurcation at $\eta = (\sqrt{p} - 1)^2$. The Rubicon state is a saddle with a three-dimensional stable manifold. This three-dimensional surface forms the separatrix between the basins of attraction of the stable immune state and the AIDS regime.

In addition to the three symmetric equilibria, there are two asymmetric steady states where $V_j \neq V_*$ and $T_j \neq T_*$. The steady state that is relevant for our question on the critical virulence is a combination of an immune state, $V_j \approx T_j \approx 1$,

for the quasispecies, and a virgin state, $T_* \approx \sigma$ and $V_* \approx 0$, for the new mutant. We call this the “infected” state. It is a saddle point with a one-dimensional unstable manifold: it is unstable to the introduction of V_* . The other infected saddle state, where $V_j = 0$ and $V_* \approx 1$, is not of interest here.

For answering our question we have to introduce small doses of the mutant strain in the infected state to check at what combination of its virulence, ν_* , and the accumulated virulence, $n\nu$, the mutant escapes. Because the eigenvector corresponding to the unstable manifold of the infected state has V_* as its dominant component, we can also study our question by following the fate of this unstable manifold as a function of ν_* and $n\nu$. Biologically this is approximately the same as following the fate of mutant strains appearing in the infected state. Mathematically this corresponds to a global bifurcation analysis.

In Fig. 3 we follow the fate of unstable manifold of the infected state systematically in a two-parameter bifurcation diagram. Our approach is as follows. For any value of $n\nu$, we select $V_j = T_j = 1$, $T_* = \sigma$, and $V_* = 0$ as an initial guess for a Newton-Raphson iteration. This reliably attained the infected state. Subsequently, the system is perturbed by making a small step along the eigenvector corresponding to the unstable direction (which largely corresponds to introducing a small dose of V_*). We study the unstable manifold by numerical integration from this initial condition. Changing $n\nu$ and ν_* we plot a dot whenever the unstable manifold approaches the immune state (Fig. 3). Otherwise it attains the AIDS regime. Thus, at the boundary between the dotted and the white area the system is involved in a global bifurcation in which the unstable manifold of the infected state glues with the separatrix—i.e., with the three-dimensional stable manifold of the Rubicon state. This global bifurcation defines the critical virulence of the mutant; i.e., in the dotted area the mutant is not lethal. We have found no indication for a heteroclinic connection between the infected state and the Rubicon state.

The relation between ν_* (the critical virulence of the mutant) and $n\nu$, (the virulence of the quasispecies) is fairly linear (Fig. 3). Thus, diversity and virulence again appear as equivalent parameters: doubling the diversity corresponds to halving the critical virulence. We finally study a virus that grows more slowly than the T cells, with $r = 0.1$ (Fig. 3b, note the change in scaling). Qualitatively, this does not affect the results.

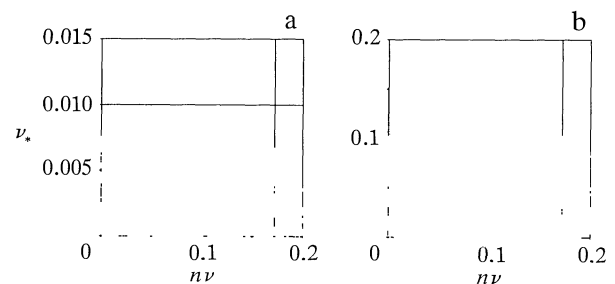


FIG. 3. Effect of diversity (i.e., $n\nu$) on the critical virulence of a new mutant. Biologically, each dot corresponds to a mutant safely attaining the immune state. The horizontal and vertical lines corresponds to the conditions 11a and 13, respectively. This two-parameter bifurcation diagram depicts the global bifurcation of the unstable manifold of the infected state. In the dotted area the unstable manifold approaches the immune state; in the white area the unstable manifold attains the AIDS regime. The global bifurcation at the boundary defines the critical virulence ν_* . We observe a fairly linear relationship between ν_* and $n\nu$. (a) $\sigma = 0.01$, $r = p - 1 = 1$. (b) $\sigma = 0.01$, $r = 0.1$, $p = 2$. Numerical results were obtained with GRIND (30).

Thus, mutants below the threshold conditions (Eqs. 11a and 13) may escape by the presence of an established quasispecies. Escaping mutants grow monotonically and evoke an immune response corresponding to proliferation of T_* (data not shown). When the mutant population gets large—i.e., $V_* > \nu_*^{-1}$ —all T cells, T_* and T_j , start to decline. This allows the entire quasispecies, nV_j , to escape also. Because the escaping mutant is generally much larger than all other strains, it looks as if AIDS is caused by one particular strain. Surprisingly, this mutant causing AIDS may have a lower virulence than any of the strains that were kept under control.

Discussion

The biological mechanism by which the diversity threshold causes AIDS is an increase in the total virus load. The total virus concentration is the sum of all strains that are kept at a low equilibrium. The fact that strains persist and fail to be eliminated is in agreement with recent immunological results. After an immune reaction various antigens persist in the system, thus contributing to immunological memory (31, 32). However, since the concentrations of the persisting antigens are probably small, it is questionable whether the total virus concentration will ever be able to account for a critical increase in the rate of T-cell infection. Additionally, interesting characteristics of AIDS, such as polyclonal lymphocyte activation and its similarities to autoimmune disease (5–7, 33), are not addressed by these simple models.

In our diversity model (Eqs. 14 and 15) it is assumed that new mutants appear after the established strains of the virus quasispecies have attained the immune steady state. This assumption is valid only when mutants appear on a slow time scale. Harnevo (26) has studied the full model numerically (our Eq. 12a) by varying the time scale at which mutants are introduced. Her results show that shortening the time scale at which mutant strains appear decreases the critical diversity at which AIDS develops. Our conjecture is that the results based upon our toy model provide an upper bound for the onset of AIDS. The original model of Nowak *et al.* (14–17) has recently (34) been analyzed in a similar way. This numerical study suggests that for one value of the diversity threshold the onset to AIDS may strongly depend on the actual parameters and the initial conditions (34). It seems interesting to repeat this analysis for our model.

The virulence ν that we have defined forms a dimensionless weighting factor for the virus concentration. Our results suggest that the diversity and the virulence are equivalent parameters. Since increasing $n\nu$ decreases the critical virulence, the continuous increase in the diversity of the quasispecies increases the probability that the next mutant will escape. If individual strains generally have a low virulence—i.e., if $\nu \ll \sigma$ —our model predicts that the frequency distribution of incubation times will be skewed. The distribution should have a slow rising part because initially the diversity is small and we expect most mutants to be controlled by the immune system. It should have a steeply falling part because mutants are likely to escape when the diversity is high. However, the AIDS epidemic is too young to allow for an analysis of the distribution of long incubation times.

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