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# Antigenic Diversity Thresholds and Hazard Functions

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ABSTRACT

In this paper, we answer some points made in a recent paper by N. I. Stilianakis and coworkers on the antigenic diversity threshold model for acquired immune deficiency syndrome pathogenesis. An extended version of the model is then used to compute hazard functions for the human immunodeficiency virus incubation period that are in agreement with empirically observed hazard functions. © *Elsevier Science Inc., 1997*

## 1. A COMMENT ON STILIANAKIS *ET AL.*

Stilianakis et al. [1] have recently published an interesting and constructive elaboration of "antigenic diversity threshold" models for human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and related infections in other primates [2–8]. These authors use numerical simulations to explore the details of the stochastic dynamical behavior associated with the appearance of mutant strains of HIV. They emphasize several findings: (1) "the model dynamics depend crucially on the HIV mutation rate"; (2) "the model dynamics equally strongly depend on the initial size of the virus population and the initial virus density"; (3) the statistical descriptions of incubation periods (from infection with HIV to the onset of AIDS), and the corresponding hazard functions, are in conflict with empirically established distributions of hazard functions [9, 10]; and (4) the detailed time scales, and the proportion of those infected who progress to AIDS within 50 years, depend on the parameters characterizing the system dynamics and not simply on the dimensionless combination involved in the "diversity threshold," $n_c$. Stilianakis et al. conclude that their "simulations question the significance of the concept of an antigenic diversity threshold because it has been demonstrated to characterize the model dynamics only partially."

We welcome these criticisms and detailed analyses that make explicit some of our findings in [2] (see below). But we are surprised—particu-

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larly in the light of our earlier conversation and correspondence with the authors—at the clear impression given in [1] that the first, second, and fourth findings above are new—"new insights into some effects of the model that have not yet been investigated" [1].

Relevant to points 1 and 2, our first paper—Sections 3 and 4 in [2]—derives an explicit criterion for a combination of parameters that characterize the rate of appearance of new mutants and further notes that (regardless of the magnitude of the antigenic diversity threshold parameter) the diversification process obviously cannot proceed unless the mutation rate exceeds a critical value. Indeed, we explicitly define a "basic reproductive ratio" for the process whereby new strains are produced—the final equation in Section 3 in [2]; as derived, the quantity $R$ explicitly involves the intrinsic mutation rate, as well as the initial viral load [denoted $v_i(0)$]. In deriving this expression for $R$, we assumed that the initial virus population was small. Specifically, Eq. 4 in [2] corresponds to assuming that $v_i(0)$ is significantly smaller than $2r'^2/pk$, which we think is a biologically sensible starting point. (We use the parameter symbols of our earlier paper [2], as explicitly defined in Eqs. 1–3 below; Stilianakis et al. use a different set of symbols for the same parameters). If, on the other hand, $v_i(0)$ is not small in this sense, then it can be seen that $R$ depends approximately on $[v_i(0)]^{1/2}$, which implies that the mutation-driven diversification process proceeds increasingly fast as $v_i(0)$ increases. These analytic insights from [2] illuminate Fig. 2 of [1], where Stilianakis et al. have chosen parameter values such that $2r'^2/pk = 0.1$, whereas $v_i(0) = 0.001$, 0.01, and 0.1; thus they move from a region where $R$ does not depend significantly on $v_i(0)$ [for $v_i(0) = 0.001$, and approximately for 0.01] into the region where this is no longer true [for $v_i(0) = 0.1$]. Insights into most of the other computer simulations reported by Stilianakis et al. can be similarly obtained from the analytic results presented and discussed in [2].

Although not referred to by Stilianakis et al., we have also explored the stochastic dynamics of the antigenic diversity threshold model. Figure 4 in [6] and a different Fig. 6 in [7] each display representative collections of simulations of HIV infections in 100 different hosts, illustrating how chance events early in the course of the infection (resulting in the model from different "seeds" in the random number generator) lead to different outcomes. Figure 7 in [7] gives a rough analytic estimate of the distribution of incubation periods, and its general shape is very similar to those found by simulation by Stilianakis et al. (their Figs. 1b, 2b, and 4b).

Turning to point 4, in all our illustrative simulations of the viral and antigenic dynamics [2–7], we have emphasized that the time scales are arbitrary, depending on the details of the rate parameters in the models.

The qualitative dynamics are characterized by the parameter combination $n_c$: if $n_c < 1$, a single strain cannot be regulated by the immune system; if $n_c > 1$, we have the potential for a "diversity threshold" situation. On the other hand, the time scales for these events to unfold, the magnitude of the viral burdens, and all other quantitative details obviously depend on the several dynamic parameters in the model. This, we believe, is clearly stated in all our papers. In particular, our discussion of the "basic reproductive ratio" of the mutation process, referred to above, has the obvious implication that—given that the diversity threshold is exceeded ($n > n_c$)—the fraction of those infected with HIV who actually go on to eventually develop AIDS may be large or small; we thus are not at all surprised that "the same diversity threshold may lead to substantially different results" [1] for the fraction of those infected who go on to develop AIDS.

There remains Stilianakis et al.'s important point (3) that the distribution of incubation intervals from HIV infection to AIDS onset (and the associated hazard functions) are significantly discrepant with those actually observed, for the limited period of 10 years or so over which data have been accumulated. We now turn to this point, showing how these problems may be resolved by using an extended model that we introduced earlier [7].

## 2. CALCULATION OF HAZARD FUNCTIONS

Stilianakis et al. [1] use simulations to estimate hazard functions for the model for a variety of parameter values. The functions that they obtain rise from zero to a peak after about 5 years and then decline to values very close to zero (their Figs. 1b, 2b, and 4b). We agree with Stilianakis et al. in that these results seem to be in conflict with empirically established hazard functions for AIDS progression [8, 9]. Stilianakis et al., however, choose to use the very simplest model that can display the diversity threshold dynamics [4]. This simplest model for the immune response against HIV does not include a term that describes the decline of anti-HIV immune response in the absence of stimulation. As we have previously emphasized, such a term appears to be necessary for a more realistic description of the dynamics of the immune system [7].

In this paper, we calculate the hazard function for the expanded model and show that it is in good agreement with empirical observation. The model is exactly the one described in [7]. The equations are:

$$\frac{dv_i}{dt} = v_i(r - px_i - sz), \qquad i = 1, \ldots, n, \tag{1}$$

$$\frac{dx_i}{dt} = kv_i - bx_i - uvx_i, \qquad i = 1,\ldots,n, \tag{2}$$

$$\frac{dz}{dt} = k'v - bz - uvz. \tag{3}$$

The variables $v_i$ denote the population sizes of the different strains of virus. Specific to each viral strain $i$, there is an immune response denoted $x_i$, which includes both cell-mediated and humoral immune responses and which acts only against that viral strain. Variable $z$ denotes the cross-reactive immune responses that act against all viral strains. Equation (1) describes the population dynamics of the different viral strains. Each strain reproduces at rate $r$ and proportional to the level of virus present. Virus is removed both by strain-specific and cross-reactive immune responses. With rate constants $p$ and $s$, respectively. Equation (2) describes the dynamics of the strain-specific immune responses. The immune response is activated at rate $k$ and proportional to the level of the strain of virus that it is directed against. In the absence of stimulation, the immune response decays at rate $b$. The model used by Stilianakis et al. assumes that $b = 0$. The assumption that $b = 0$ would be valid if the time scale of immune deactivation were very much slower than the time scale for HIV infection. We think that, because HIV infection occurs on a time scale of 10 years, this assumption may be unrealistic. The final term of these equations represents the impairment of the immune response as a result of the presence of the HIV virus. For the total virus population, the notation $v = \sum_{i=1}^{n} v_i$ is used. Equation 3 models the cross-reactive immune response. It is very similar to Eq. 2, but the rate of activation of the cross-reactive immune response $k'$ is allowed to differ from that of the specific responses. More generally, of course, the parameters $r$, $p$, $s$, $k$, and $b$ can all be taken to be strain specific [6].

The total number of different viral strains is given by $n$. At the start of the simulation, $n$ is very small, typically 1. A new strain of virus arises as a result of mutation. The probability of a mutation occurring during the time interval $[t, t + \delta t]$ is equal to $qv(t)\delta t$, where, in the simplest case, $q$ is constant.

This model and related models have been analyzed in depth by Nowak and coworkers [2–8]. It is seen that this model displays three distinct behaviors, corresponding to three different regions of parameter space:

(1) There is no asymptomatic phase, and the virus population quickly reaches high levels.

(2) The virus produces a persistent infection, but is successfully controlled by the immune system.

(3) There is a long asymptotic phase in which the virus level is controlled by the immune system, followed by disease in which the virus reaches high levels.

In the third-parameter region, the immune system is capable of controlling the virus population as long as the number of strains $n$ is below the "antigenic diversity threshold" given by

$$n_c = \frac{pk}{ru - sk'}. \tag{4}$$

Once $n$ rises above this threshold, the virus population escapes immune response and grows to arbitrarily high levels. For $n < n_c$, it can be shown that the total virus level $v$ converges to the steady-state

$$v(n) = \frac{rb}{sk' + \dfrac{pk}{n} - ru}. \tag{5}$$

### 1.1. *A SIMPLIFIED STOCHASTIC PROCESS*

It is possible to derive an analytic approximation for the hazard function by making the assumption that, for each $n$, the probability of a new virus mutant being generated in a time interval $[t, t + \delta t]$ is equal to $qv(n)\delta t$, where $v(n)$ is the steady-state level of virus when there are $n$ strains present. This approximation is valid in the limiting case of very low mutation rates, in which the viral population reaches steady state before new mutations arise. $n(t)$ may now be considered generated by the following stochastic process:

$$1 \xrightarrow{qv(1)} 2 \xrightarrow{qv(2)} \cdots \xrightarrow{qv(m-1)} m \xrightarrow{qv(m)} m+1.$$

Here $m$ is the largest integer less than $n_c$. The process starts in state 1 (corresponding to a single strain). While at each state $i$, the process moves to the next state as an exponentially distributed variable with parameter $qv(i)$. The process is stopped when it reaches state $m+1$ (and the antigenic diversity threshold is attained).

To calculate the hazard function $h(t)$ for this process, it is easiest to start by calculating the density function $f(t)$. The density function for time spent in each state $i$, denoted $f_i(t)$, is given by

$$f_i(t) = qv(i)e^{-qv(i)t}. \tag{6}$$

Because the times spent in each state are independent, the time taken to reach the diversity threshold has density function $f(t)$ given by

$$f(t) = \bigotimes_{i=1}^{m} f_i(t). \tag{7}$$

Here $\bigotimes$ denotes the $m$-fold convolution of the $f_i(t)$. This convolution can be calculated by using the Laplace transform. The Laplace transform of $f_i$ can be easily calculated to be

$$(\mathscr{L}f_i)(y) = \frac{qv(i)}{y + qv(i)}, \tag{8}$$

and so

$$(\mathscr{L}f)(y) = \mathscr{L}\left( \bigotimes_{i=1}^{m} f_i \right)(y) = \prod_{i=1}^{m} (\mathscr{L}f_i)(y) = \prod_{i=1}^{m} \frac{qv(i)}{y + pv(i)}. \tag{9}$$

The inverse Laplace transform of the expression on the right-hand side of Eq. (9) can be calculated by using the Bromwich integral. This gives

$$f(t) = \sum_{y \in \{\text{poles of } (\mathscr{L}f)\}} e^{-yt} \text{ residue of } \mathscr{L}f \text{ at } y. \tag{10}$$

Observe, from Eq. (5), that, if $i \neq j$, then $v(i) \neq v(j)$, and thus all the poles of $\mathscr{L}f$ are simple poles. This gives the following expression for $f(t)$:

$$f(t) = \sum_{i=1}^{m} \left[ \prod_{j \neq i} \frac{v(j)}{v(j) - v(i)} \right] qv(i) e^{-qv(i)t}. \tag{11}$$

Thus the distribution function $F(t)$ is given by

$$F(t) = 1 - \sum_{i=1}^{m} \left[ \prod_{j \neq i} \frac{v(j)}{v(j) - v(i)} \right] e^{-qv(i)t}. \tag{12}$$

The hazard function $h(t)$ satisfies

$$h(t) = \frac{f(t)}{1 - F(t)}. \tag{13}$$

Therefore $h(t)$ is given by the expression

$$h(t) = \frac{\Sigma_{i=1}^{m}\left[\Pi_{j\neq i}\frac{v(j)}{v(j)-v(i)}\right]qv(i)e^{-qv(i)t}}{\Sigma_{i=1}^{m}\left[\Pi_{j\neq i}\frac{v(j)}{v(j)-v(i)}\right]e^{-2qv(i)t}}. \tag{14}$$

Expression (14) can be calculated explicitly [remember that $v(i)$ is given by Eq. (5)]. This function is plotted in Fig. 1. It can be seen that the hazard function increases monotonically and tends to an asymptotic value. As such, the shape of the hazard function is very different from the shape of the function seen in Stilianakis et al. and more in line with what we would expect from a realistic model. We have chosen parameter values that try to reflect the recent findings of Wei et al. [11] and Ho et al. [12] on the rates of turnover of HIV virus. Thus the parameter

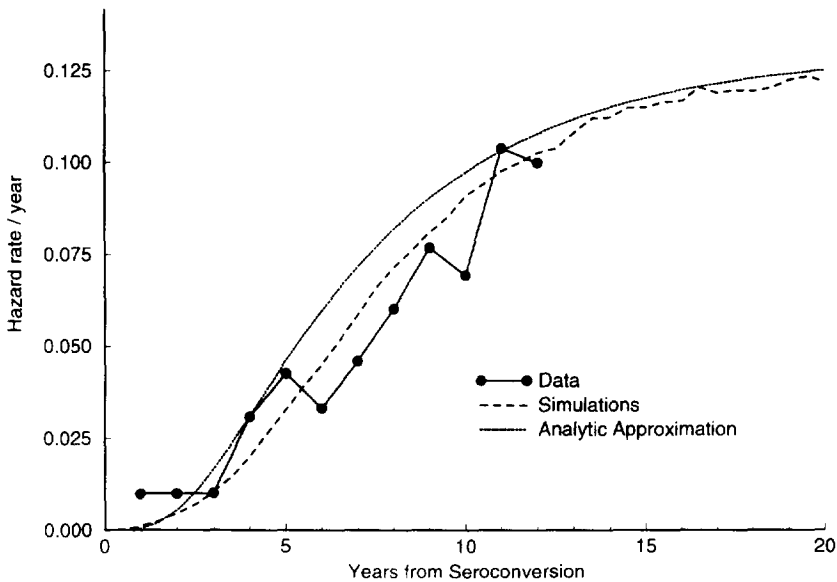


FIG. 1. Hazard rates for the analytic approximation to the model, for 10,000 realizations of the model, and calculated from a recent study of hemophiliacs in the United Kingdom [12]. For the analytic approximation, the probability of a new virus mutant being generated in a time interval $[t, t + \delta t]$ is equal to $qv(n)\delta t$, where $v(n)$ is the steady-state level of virus when there are $n$ strains present. The parameters used in both models, with units in years, are $q = 0.1$, $r = 95$, $p = 84$, $s = 83$, $k = k' = u = 9.5$, and $b = 9.37$.

values differ from those in our earlier papers, but it is important to note that the shape of the hazard function remains the same throughout parameter region 3 described above. This result can be seen from expression (14) for $h(t)$. As $t$ tends to infinity, expression (14) gives, to leading order,

$$h(t) \sim \frac{\left[\prod_{j \neq k} \frac{v(j)}{v(j)-v(k)}\right] q v(k) e^{-q v(k) t}}{\left[\prod_{j \neq k} \frac{v(j)}{v(j)-v(k)}\right] e^{-q v(k) t}} = q v(k) = q v(1). \quad (15)$$

Here $v(k) = \min_i v(i)$, the least of the $v(i)$, which, by inspection of Eq. (5) for the $v(i)$, is equal to $v(1)$. Thus it can be seen that the hazard function will reach an asymptotic level for all parameter values for which the model exhibits the above behavior and will not tend to zero.

## 3. NUMERICAL ESTIMATION OF THE HAZARD FUNCTION

When the mutation rate is higher, the foregoing approximation is no longer valid, because the virus level does not have time to reach its steady-state value before new mutants arise. The hazard function has been estimated numerically from 10,000 simulations performed with the use of the same parameter values that we have used in the simplified version of the model above. The simulations give a series of discrete time points ($t_j$) at which events (progression to AIDS) may or may not have occurred. At each $t_j$, we define $r_j$ (the risk set) to be the number of patients in the simulations who had not progressed to AIDS by time $t_j$, and $d_j$ to be the number of patients who progressed to AIDs precisely at time $t_j$. The maximum likelihood estimate of the hazard function at each time $t_j$, denoted $h_j$, is then given by $h_j = d_j / r_j$. The $h_j$ must then be smoothed to remove the statistical artefacts arising from the use of discrete time steps, whereby at many time points there will be no patients who progressed to AIDS. We have used square-window smoothing, in which the calculated hazard function $h(t)$ is given by

$$h(t) = \frac{1}{2t_0} \int_{t-t_0}^{t+t_0} \hat{h}(\tau)\, d\tau, \quad (16)$$

where

$$\hat{h}(\tau) = \sum_j h_j \delta(\tau - t_j). \quad (17)$$

Here $\delta$ denotes the Kronecker delta function, and $t_0$ is a constant determining the time interval over which the integration is performed.

It can be seen in Fig. 1 that the function is almost identical in shape with the analytic calculation, despite the high mutation rate, suggesting that the mutation rate plays little role in the overall form of the hazard function, although it plays a major role in the time scale of the infection process. Both hazard rates are close to the hazard rate estimated from the survival curve from a recent study of hemophiliacs in the United Kingdom [13].

Thus the simple model given by Eqs. (1)–(3) can provide a correct distribution of incubation periods. Therefore the criticism of Stilianakis et al. that the "antigenic diversity threshold" model cannot provide a realistic hazard function is not valid. In addition, one should keep in mind that different infected individuals may greatly differ in their ability to mount immune responses against HIV, which can give rise to large differences in virus load [14] and can greatly affect the rate of disease progression [15].

## 4. SUMMARY

In summary, our earlier intention was to propose a simple and novel mechanism—the antigenic diversity threshold—that could (at least under certain conditions, $n_c$ large but not too large) explain the long and variable interval observed between HIV infection and AIDS onset. Our models were clearly identified as deliberately oversimplified, and our emphasis was on the qualitative features [the diversity threshold ($n_c$), the basic reproductive ratio for newly appearing mutants ($R$), and so on]; detailed time scales were identified as arbitrary on illustrative figures, dependent on specific parameter choices. Against this background, we welcome the further and careful analyses made and the interesting questions raised by Stilianakis et al. [1]. But three of their main points (1, 2, and 4 above) are, to the contrary of the claims in [1], covered in our earlier work.

The emphasis on the shape of distributions of incubation intervals and hazard functions (their point 3 above), on the other hand, does seem to us important and raises valid questions about the simplicity of our earlier models. We have shown, however, that, for our later models, which use simple and biologically reasonable assumptions, the hazard functions that we derive, both analytically and numerically, are in line with those empirically estimated from the data on AIDS patients.

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