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Metastability with Probabilistic Cellular Automata in an HIV Infection

R. B. Pandey[1] **and D. Stauffer**[1,2]

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Assuming a small failure probability for the interleukin production, a discrete model of HIV infection leads to transitions between fixed points. Eventually all initial configurations for the cellular automata lead to the destruction of the immune system, i.e., to AIDS.

KEY WORDS: Cellular automata; HIV; AIDS; probability.

The description of immune response by discrete models[1] has become an alternative to more traditional continuum models studied by differential equations[2]; see ref. 3 for an overview of the field. Also, infection by the human immunodeficiency virus (HIV), which leads to AIDS, has been described by various cellular automata models[4] as well as by differential equations.[5]

One characteristic of HIV and AIDS is the long latency period of typically about 10 years between the initial HIV infection and the outbreak of the full AIDS disease. This time is about three decades longer than the normal response time of the immune system. A realistic simulation of this latency time by a cellular automata approximation thus requires a time of about 1000 iterations to reach a fixed point or limit cycle corresponding to the final state. None of the cellular automata models suggested so far give such long relaxation times, though for other automata[6] metastability with even longer times was found. The present paper thus uses probabilistic cellular automata instead of the previous deterministic ones.[4] We find

[1] Department of Physics and Astronomy, University of Southern Mississippi, Hattiesburg, Mississippi 39406-5046.

[2] Permanent address: HLRZ, c/o KFA, 5170 Julich 1, West Germany.

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only one fixed point, but by letting the probability go to zero, we can make the time to reach that fixed point arbitrarily large. In that sense we have an admittedly primitive model for the long relaxation or metastability observed for HIV infection.

Our model consists of several elements: virus V, helper cells T4, cytotoxic cells T8, interleukin molecules I, and macrophages APC ("antigen-presenting cells") (see ref. 2 for a short summary of immunology). As soon as viruses enter the human body, some of them are captured by the macrophages, which present parts of the virus on their surface. Since these macrophages shelter the HIVs and act as a reservoir, we assume these APCs to be present during the whole computer simulation after the HIV infection. For the other elements V, T4, T8, and I we assume the concentration to be either higher or low. Thus, the states of V, T4, T8, and I are Boolean or integer variables taking on the values true (1, high concentration) or false (0, low concentration) only. This approximation is very frequently used in the discrete cellular automata models of the immune response[1,3,4] however, this discrete version captures most of the equilibrium aspects of the continuum model.[9] Our model differs from some earlier AIDS models[4] in taking into account the role of interleukin molecules (which serve as important mediators); furthermore, it is simpler than Pandey's eight-cell model.[4]

We assume the interactions between two different elements to be either $+1$, -1, or 0. If the sum of the interactions is positive, then at the next time step the Boolean variable influenced by this interaction is true (high concentration); for zero or negative sums of interaction the variable is false (low concentration) at the next time step. Of course, only elements which are present (high concentration) can influence others. The interactions from the virus V to the helper cells T4 are negative (this is the deadly effect leading to AIDS[4,10]), those from APC to T4 and to V, those from the helper cells T4 to V and to I, and those from I to T4 and T8 are positive, whereas we have negative interactions from the cytotoxic cells T8 on the virus V. All other interactions are zero. Figure 1 summarizes our assumptions. For the detailed justification of specific stimulatory and inhibitory functions of these cellular elements, we refer to refs. 4 and 10 in the context of HIV infections. As usual for cellular automata, all variables are updated simultaneously.

Since we fix the APC concentration as high, the dynamics after an HIV infection is quite simple in this model: The T8 variable at the next time steps equals the I variable at the present time step; the I variable at the next time step equals the T4 variable at the present time step. Viruses are present if and only if T4 is present or T8 is absent; T4 cells are present if and only if I is present or V is absent. In summary, we have

$$V = T4 \text{ or not } T8$$

$$T4 = I \text{ or not } V$$

$$T8 = I$$

$$I = T4$$

where the rhs refers to time t and the lhs to time $t+1$; in addition, APC = true always.

This set of interactions captures the main features of the cell-mediated immune response.[11] The helper/inducer T4 cells play a crucial role in coordinating the functions of all cell types by releasing a variety of mediators/effectors such as lymphokines (which include interleukin 2). T4 cells cannot recognize the free antigens on their own; antigens must be presented in a specific form by APC along with MHC II markers ("major histocompatibility complex") for T4 cells to interact and recognize the antigens.[11] The conformational complementarity of the surface markers such as CD4 on T4 cells and that of gp120 (a protein section which is part of the virus) leads the virus to be more reactive with T4 cells. The HIV behaves like a retrovirus; what makes these HIVs unique and complex is the path of their sporadic growth[10]: On the hand, the HIVs seem to manipulate the genetic transformations (with the help of reverse

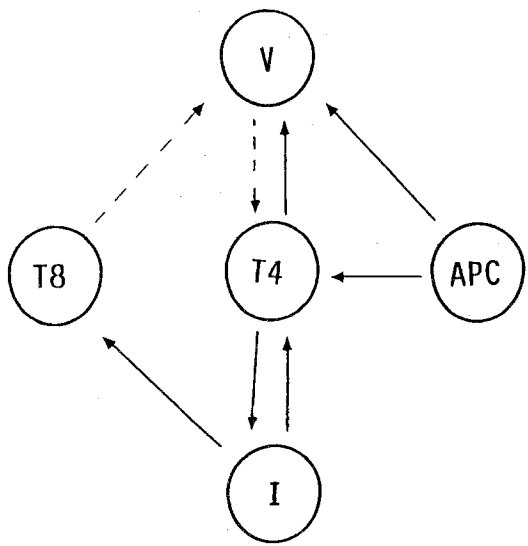

Fig. 1. Schematic representation of the interactions among virus, T4 cells, T8 cells, and interleukin molecules. The concentration of APC macrophages is kept high.

transcriptase and host enzymes) to remain latent in the T4-cell nucleus as a provirus; on the other hand, they multiply with the help of integrase (along with other effectors with the help of messenger RNA within the cell), leading to a burst of virus by rupturing the T4 cell. This sporadic growth of virus therefore leads to irregular stimulations in the growth of T4 cells, and so in the production of interleukins. These facts are taken into account in the following with the help of the above set of interactions after an HIV infection; for example, T4 cells can produce virus. (Our model does not describe the naive state before an HIV infection.)

The simulation of the above set of four equations is quite trivial. Going through all 16 possible initial configurations for the four Boolean variables, we found two fixed points and one limit cycle. The fixed points are (V, T4, T8, I) = (1000), which corresponds to the complete destruction of the immune system by the virus, and (1111), which corresponds to an infected but still fully present immune system. The limit cycle is an oscillation between the two states (1110) and (1001) where the infected immune system is partially destroyed. (Oscillations in cellular automata are often the result of the simultaneous updating procedure and thus may lack biological significance[7]. They may be relevant, however, in an HIV infection.) Thus, when a healthy body is just infected it is in the state (1111), which is a fixed point and never changes. In this approximation, therefore, an HIV infection of a healthy immune system does not destroy this immune system.

So far we have considered the mean-field approach[1,3,4] in which each cellular element interacts with all others with the same strength no matter how far away they are located, i.e., the interaction is of infinite range. To analyze the extreme opposite case to the mean-field description and to take into account the effects of various mediators, growth factors, effectors, etc.[4,11] we consider a $36*36*36$ lattice system. We introduce a nearest neighbor intracell interaction along with the intercell intrasite interaction as follows.[4] Each cell of four different types are placed at each lattice site. A cell type k with its current binary state, say C_k, is selected at a site i; the binary states of cell type k at the neighboring sites are added to C_k at site i. If the sum of seven binary states (on the simple cubic lattice) of the cell type k is positive, then a temporary binary state C'_k of high concentration (state 1) is assigned to this cell. Otherwise its binary state remains at 0. Similar temporary binary states are assigned to all other cell types at site i and to each cell type at all lattice sites using this cellular automata rule of a logical "or" operation for the intersite intracell interactions. With their temporary binary states, all four cells at a site i interact with each other according to the above intercell interaction and the resulting state is then considered as a final state at the next time step for each cell type at site i.

This process is repeated again and again for all cell types at each lattice site with several independent runs for the time steps in which the populations of all cell types reach their steady-state value. Starting with any initial configuration, we observe that all sites finally go to the fixed point (1111). We also observe similar results on a two-dimensional lattice. Note that, apart from eliminating the other fixed points, we do not get any new result different from those with the mean-field approach. We therefore limit ourselves here to the mean-field treatment in the following.

These results unfortunately are clearly unrealistic, and thus we now assume that at every time step with probability p the interleukin concentration is set to zero independent of the other elements. This small probability p may correspond to an infection with another virus,[8] effects of dysfunction of infected T4 cells, or some other rare event peculiar to HIV infection.[10] For nonzero failure probabilities p, the simulation results are now dramatically different: All 16 initial configurations lead after sufficiently long time to the same fixed point (V, T4, T8, I) = (1000), i.e., to AIDS; the other fixed point and the limit cycle have vanished. This minor modification thus approximates reality much better.

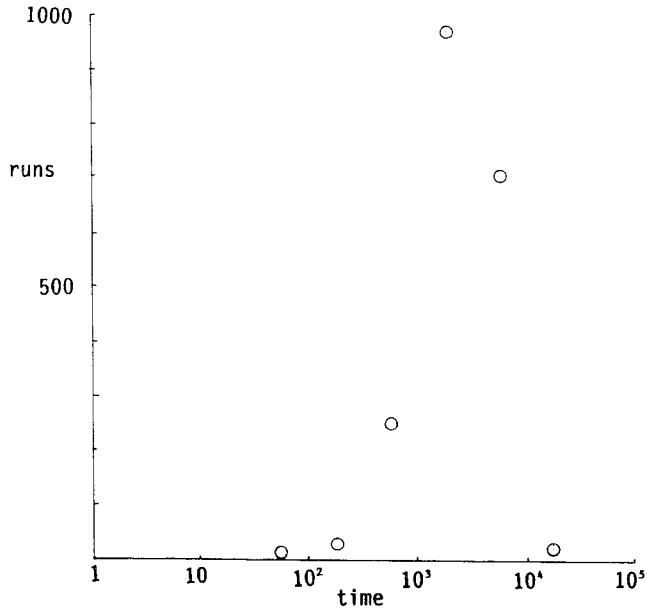

Fig. 2. Distribution of times needed to go to state (1000) from state (1111). We use a logarithmic time binning with two intervals per decade, and 2000 runs. The time at the peak could be identified with the 10-year latency period after an HIV infection.

The time needed to reach this fixed point depends on the starting configuration and on the random numbers used. Even if we take only the biologically most plausible starting configuration (1111), the number of iterations needed to reach the fixed point fluctuates over more than an order of magnitude in several hundred samples with $p = 0.001$. The most probable time to get to the fixed point is of the order of $1/p$; the distribution of times seems to be between normal and log-normal, as seen in Fig. 2. The small failure probability of the interleukins leading to long relaxation time may well be interpreted in the framework of HIV infection. Usually, a very small concentration of foreign elements (HIV) enters the body where they manipulate the immune mechanism in order to multiply.[10] However, the latent nature of HIVs as proviruses in the nucleus of the infected cell[10] reduces their effects detected by the immune system. The resulting low degree of immune dysfunction may lead to low probability of interleukin failure, which may give rise to a long incubation time. Thus, with a small probability of failure for the interleukin production, we found a primitive cellular automata model with a long relaxation rate proportional to this probability.

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