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Simulating the Immune Response to the HIV-1 Virus with Cellular Automata

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Two cellular automata models are presented which simulate the immune response to the HIV-1 virus at the early stage of the infection. The simple model A is based on the generalized nearest neighbor interaction, and the complex model B on the explicitly defined local interactions between the neighboring sites. These two models are discussed in the context of related work by Pandey.

KEY WORDS: Cellular automata; HIV-1 virus; immune response.

Cellular automata[1] are dynamical systems, discrete in space and time, evolving on a lattice according to some local synchronous updating rule, which is a mapping of the Boolean set onto itself. Although the rule is in most cases simple, the long-time behavior of the automata can be very complex. Due to this complex behavior and to the Boolean character of each element, cellular automata are an efficient computational tool for modeling complex systems, such as biological processes, hydrodynamics, or Ising models.

In recent years the study of immune response systems with conventional mathematical methods, i.e., differential equations (see, e.g., ref. 2 and references therein), and with cellular automata[3–8] has been investigated with increasing effort. Some related work[9–11] deals with the immune response to the HIV virus.

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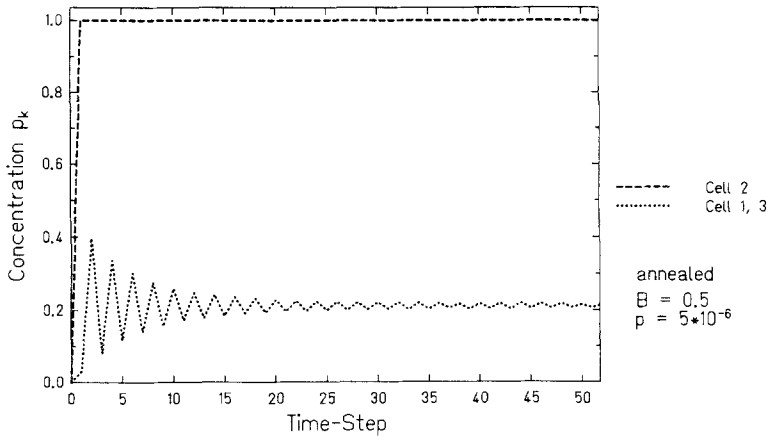
In the human immunodeficiency[4] the role of the T4 helper and inducer cells is considered to be the fulcrum of the macroscopic immune reaction in the acquired immunodeficiency syndrome (AIDS). T4 cells, previously informed about the existence of the virus and of viral infected cells by macrophages, send out lymphokines, i.e., chemical signals, regulating T-type (mature in thymus) and other cells. The interaction of macrophages, T4 cells, and lymphokines from T4 cells cause the cytotoxic lymphocyte T8 cells to mature and to roam the bloodstream, thus destroying viral infected cells. On the other hand, T4 cells are attacked by HIV-1 virus by its retroviral feature, i.e., T4 cells carry the genetic information of HIV-1. This dramatic feature of the HIV-1 virus and of the free glucoproteins gp120, which mark the retrovirus and all types of HIV-1-infected cells at their surfaces, is responsible for the mechanism that viral infected T4 cells are able to destroy themselves. In the cellular automata models presented here, we simply consider T4 helper cells, T8 cytotoxic cells, and HIV-1 viral infected cells, neglecting the action of other components (B-type cells, antibodies, memory cells, etc.), which are active in the immune system.

Pandey[10] proposed a cellular automata model to simulate the immune response by taking into account the main mechanisms of T4, T8, and virus-infected cells. All calculations were carried out on a 3D cubic periodic lattice of $60 \times 60 \times 60$ sites ($3 \times 216{,}000$ cells). The cells interact by two different sets of rules (sets I and II), coupled by a coupling constant B. The latter is the probability that at a given site the rules of set I will be applied, while for set II the assigned probability is $1 - B$. In the quenched version of the model the distribution of B over the lattice remains constant with time, while in the annealed version, B is randomly distributed each time step. We calculated the same model using a 2D square periodic lattice with 512×512 sites ($3 \times 262{,}144$ cells). All other parameters, such as the initial cell concentration and the coupling constant, were kept identical. The resulting cell concentration, the phase transition in the quenched and annealed models, and the oscillation of T4 and viral infected cells agree nearly perfectly (Fig. 1). Only the temporal development of the immune reaction is speeded up to some extent. Thus, instead of a 3D lattice, a 2D lattice can be used, offering greater computational efficiency. This statement agrees with the conclusion of Wiesner[12] for the generalization of the Weisbuch–Atlan model.[6,7] We also investigated the oscillation between the fixed points. In both 3D and 2D models the oscillation of concentration for certain coupling constants immediately changes at each time step from low to high concentration (not shown in ref. 10). We carried out calculations of a localized infection and found that the changes do not depend on

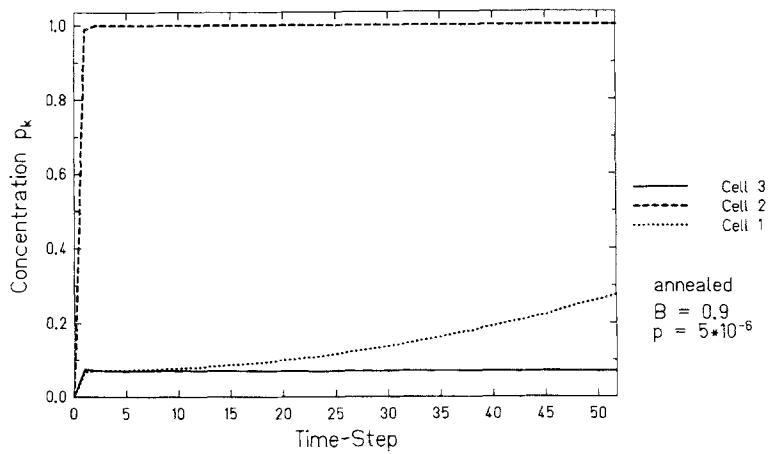
[4] See the single-topic issue of *Scientific American* (September 1988).

the initial local concentration. We also found a creation of viral infected cells from zero concentration, which should not occur in a healthy system. We found no biological justification for the coupling constant B.

For the early stage of the infection we propose the following two models taking into account T4, T8, and viral infected cells. We consider a 2D square lattice with 512×512 sites and periodic boundary conditions



(a)



(b)

Fig. 1. Calculations of the annealed model by Pandey[10] with coupling constant (a) $B = 0.5$ and (b) $B = 0.9$, carried out on a 2D lattice of 512×512 sites. The concentration is normalized to the total number of cells c_k on the lattice, the timesteps are, as in ref. 10, in units of 5. The results nearly perfectly agree with those in ref. 10.

(torus). At each site of the lattice we assume three different types of cells c_k $(k=1, 2, 3)$ treated as Boolean variables, where c_1 represents T4 helper cells, c_2 T8 cytotoxic cells, and c_3 viral infected cells. A high local concentration of cell c_k is represented by 1, a low concentration by 0. The average concentration of c_k on the lattice is given by $p_k=(1/N)\sum_{j=1}^{N} c_k(j)$, N being the total number of sites. We formulate the interactions between these cells using the Boolean operations AND, OR, Exclusive-OR and NOT $(\wedge, \vee, \otimes, \bar{})$.

Simple Model A. The model A is based on the interactions between different cells of the same site and on the generalized nearest neighbor interaction between cells of the same type. By means of the generalized nearest neighbor interaction[7,10] the local concentration of a cell $c_k(x, y)$ at the particular site (x, y) interacts with all next neighboring cells of the same type by a logical OR summation, and thus the information can be spread over the lattice. A temporary value C_k is assigned to this cell as follows:

$$C_k(x, y)=c_k(x, y)\vee c_k(x+1, y)\vee c_k(x-1, y)\vee c_k(x, y+1)\vee c_k(x, y-1) \tag{1}$$

We now define the rules which describe the interactions between the different types of cells and apply them to the temporary values [Eq. (1)] at each site of the lattice:

$$c_1'=C_3\otimes C_1 \tag{2}$$

$$c_2'=[C_3\wedge C_1]\vee C_2 \tag{3}$$

$$c_3'=[C_3\vee C_1]\wedge \overline{C_2} \tag{4}$$

The primed cells c_k' represent the status of the cells at a particular site after one time step. The local concentration of c_1 cells at a particular site [Eq. (2)] can only grow if c_3 cells are present. This is the first response of a healthy immune system. If viral infected cells c_3 are detected, c_1 cells will be produced. On the other hand, as c_3 cells attack c_1, they destroy them by changing the high local concentration of c_1 cells to a low one. The concentration of c_1 does not change in case the concentration of c_3 cells is low. According to Eq. (3), c_2 cells will be activated if c_1 cells have recognized viral infected cells (logical AND in the bracket), which implicitly simulates lymphokine proliferation by macrophage-prepared c_1 cells. This expression, together with the state of concentration of c_2 at the considered site, takes care of the controlled growth of c_2 cells. Since we consider the early stage of the viral infection, c_2 cells are not allowed to decrease or to be infected

by c_3 cells. The viral infected c_3 cells [Eq. (4)] grow proportionally to c_1 cells and only at low concentration of cytotoxic c_2 cells.

In the mean field approach, where each cell type has the same concentration everywhere (thus dealing with only one site),[6,7,10] model A yields three stable fixed points, as shown in Table I.

We carried out a calculation starting with a uniform random distribution of c_1, c_2, and c_3 cells over the lattice. The initial average concentration is $p_1 = p_2 = p_3 = 0.001$, which means that HIV-1 virus has been inserted in a healthy organism. The simulation started with an increase of c_3 cells and a simultaneous decay of c_1 cells, while c_2 cells grow continuously (Fig. 2). The growth of the c_2 cells causes c_3 cells to vanish (T8 cytotoxic cells attack viral and viral infected cells). The system reaches the equilibrium (1, 1, 0), which is one of the three fixed points (Table I).

In order to see what happens in the case of a localized infection, we initialized the lattice by randomly distributing c_1, c_2 cells with mean concentration $p_1 = p_2 = 0.001$ and setting zero the concentrations of these cells in a sublattice of 64×64 sites. In the same sublattice we assigned the value 1 to all c_3 cells. The qualitative results (Fig. 3) are the same as those in Fig. 2, but the growth of c_3 cells at the first time steps is now more clear and the system reaches equilibrium faster.

We also checked a probabilistic approach of model A, where the interaction probability β is the probability that at a particular site (active site) the averaging of Eq. (1) and the rules (2)–(4) will be applied. On the other hand, if a site remains nonactive (with probability $1 - \beta$), the cells c_k of this site keep their previous value ($c'_k = c_k$). In the case of the "quenched" ver-

Table I. Fixed Points and Related Biological States in the Mean Field Approach for Model A

Input state (c_1, c_2, c_3)	Fixed point (c_1, c_2, c_3)	Biological state
(0, 0, 0)	(0, 0, 0)	Healthy
(0, 1, 0) (1, 1, 1)	(0, 1, 0)	Immunized
(0, 0, 1) (0, 1, 1) (1, 0, 0) (1, 0, 1) (1, 1, 0)	(1, 1, 0)	Susceptible

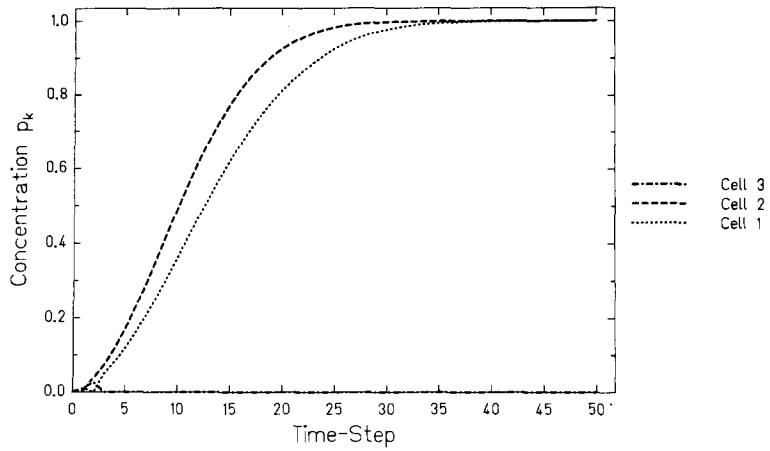


Fig. 2. Time evolution of model A. The average initial concentration is $p_1 = p_2 = p_3 = 0.001$ and is uniformly distributed over the lattice.

sion of this probabilistic approach, where the distribution of the active sites over the lattice with a certain β remains constant with the time, we found that the final concentrations of c_1 and c_2 lie much lower than those in Fig. 2 and that they depend on the β (Fig. 4a). The reason is that stable islands on the lattice are built up, as shown in Fig. 4c. For the "annealed" version of model A, where the active sites are redistributed each time step

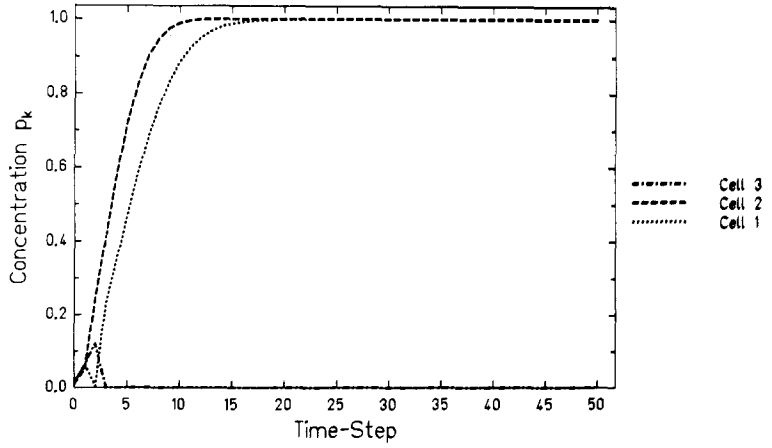


Fig. 3. Time evolution of model A starting from a localized initial infection. The average initial concentration is now $p_1 = p_2 = 0.001$, $p_3 = 0.0$ uniformly distributed over the lattice, except for a subregion of 64×64 sites, where $p_1 = p_2 = 0.0$, $p_3 = 1.0$.

with certain probability β, a delay of the final state has been observed, which is proportional to β (Fig. 4b). Finally, the same state as in Fig. 2 has been reached.

Complex Model B. In the complex model B the action of the components of the immune response remain as in model A, except for the

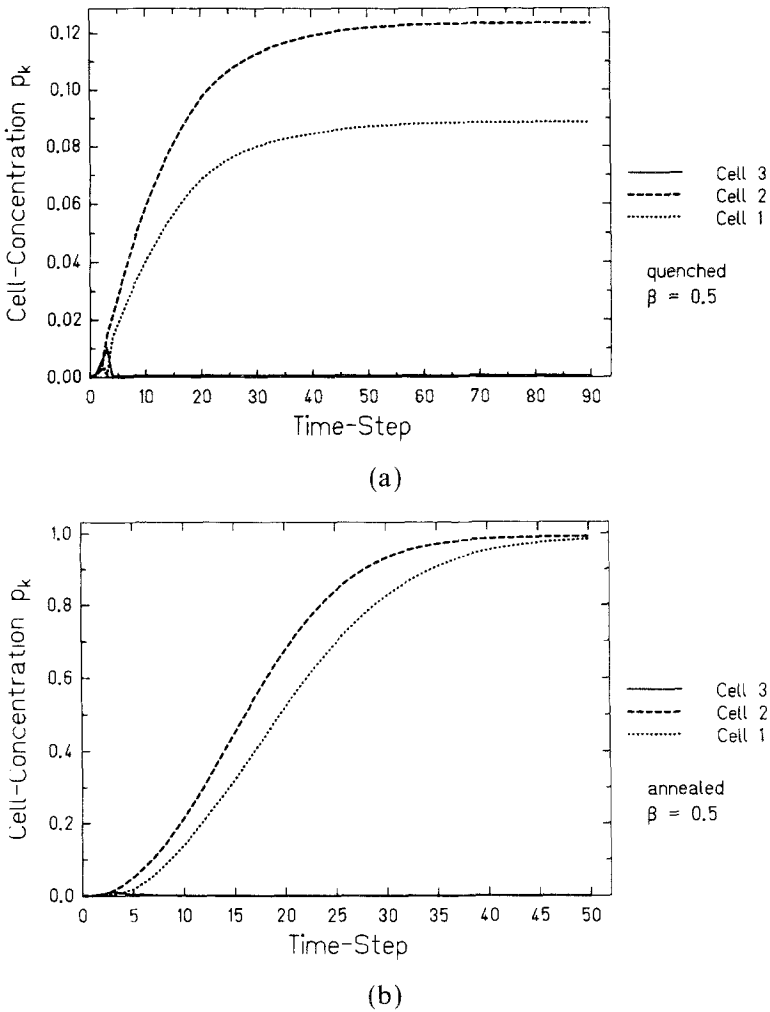
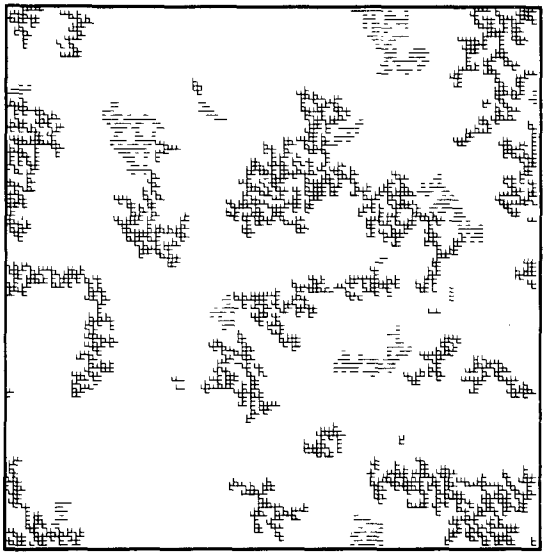


Fig. 4. Probabilistic approach of model A. The probability β is 0.5. (a) A quenched and (b) an annealed version are presented. The initial concentrations are the same as in Fig. 2. (c) Formation of stable islands for the quenched version (a). We denote c_1 with | and c_2 with · The lattice size is 128×128.



(c)

Fig. 4. (*Continued*)

interactions between the neighboring cells. The set of rules is defined as follows:

$$c_1' = \left(\sum_{*}{}' \left[c_3(*) \right] \otimes c_1 \right) \wedge \overline{c_3} \tag{5}$$

$$c_2' = \left(\sum_{*} \left[c_3(*) \wedge c_1(*) \right] \right) \vee c_2 \tag{6}$$

$$c_3' = \left(\sum_{*} \left[c_3(*) \wedge c_1(*) \right] \vee c_3 \right) \wedge \overline{c_2} \tag{7}$$

The primed cells c_k' represent the status of the cells at a particular site, after one time step, as in model A. The summation $\sum_*$ is a logical OR summation of the bracket expression over the next neighboring cells of the particular site and the particular site itself (denoted as $*$); in the primed summation ($\sum_*'$) the center site is excluded from the sum. Both summations denote the weight of the strength of the rule.

If the c_3 cells are highly concentrated in the neighborhood of a particular site [the summation in Eq. (5) results in a logical 1], there will be a production of c_1 cells which will survive in case the concentration of c_3 cells at the site is low. If there is high concentration of c_3 cells at the

neighborhood of the site or at the site itself, then c_1 cells will be destroyed. The bracket expression in Eq. (6) takes into account the concentration of c_3 and c_1 cells in the surrounding site and the site considered itself. If c_1 cells have recognized viral infected cells (logical AND in the bracket), c_2 cells will be activated. The viral infected c_3 cells [Eq. (7)] are allowed to grow if the neighborhood of the cell consists of contaminated c_1 cells, and diminish if the local concentration of cytotoxic c_2 cells at the site is high.

We investigated the behavior of the model B starting from a low concentration for all cell types, i.e., $p_k = 0.1$, randomly distributed over the lattice. Several low initial concentrations have been tested. In all cases the qualitative results are the same and, in addition, the lower the initial concentration, the longer is the time needed to reach the equilibrium. The immune reaction starts immediately with an oscillatory activation of c_1 cells (Fig. 5). This oscillatory behavior, with a constant amplitude, is the equilibrium state of the c_1 cells. Their inducing function on the roaming cytotoxic c_2 cells results in a monotonic increase of their concentration up to limiting saturation; contrary to model A and to the model by Pandey, it lies below the system saturation. The viral infected cells c_3, origin of the stimulated immune reaction, start to populate their initial concentration. After some time steps they fall victim to the immune reaction and their concentration decreases below their initial concentration. The distribution of c_1, c_2, and c_3 cells over the lattice is uniform and homogeneous and no formation of islands has been observed.

We also investigated a probabilistic approach of model B, similarly to model A. Both the quenched and the annealed versions yield the same

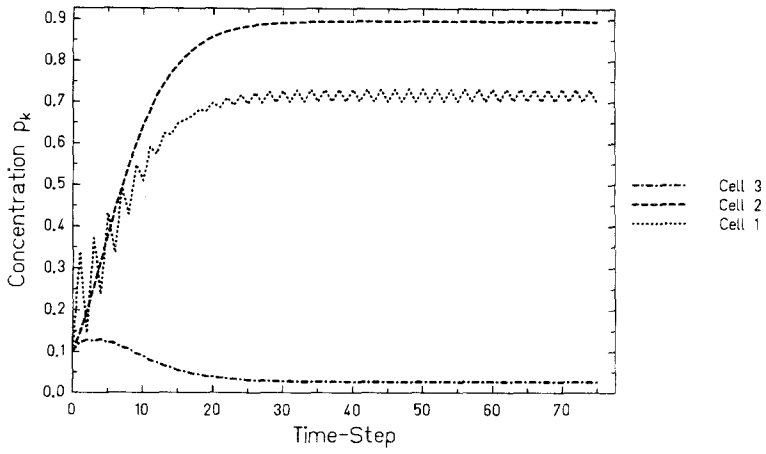


Fig. 5. Time evolution of model B based on the explicitly defined local interactions. The average initial concentration is $p_1 = p_2 = p_3 = 0.1$.

qualitative results; only the final concentrations decrease as the interaction probability β decreases (Fig. 6). We have also studied the spatial spreading of an initially localized infection as in model A. In this case, as expected, no reaction of the system is observed.

In conclusion, we have presented two cellular automata models which seem to simulate reasonably the early stage of the macroscopic biological immune response to HIV-1 infection. Model B, based on the explicitly defined local interactions, gives more detailed information about this

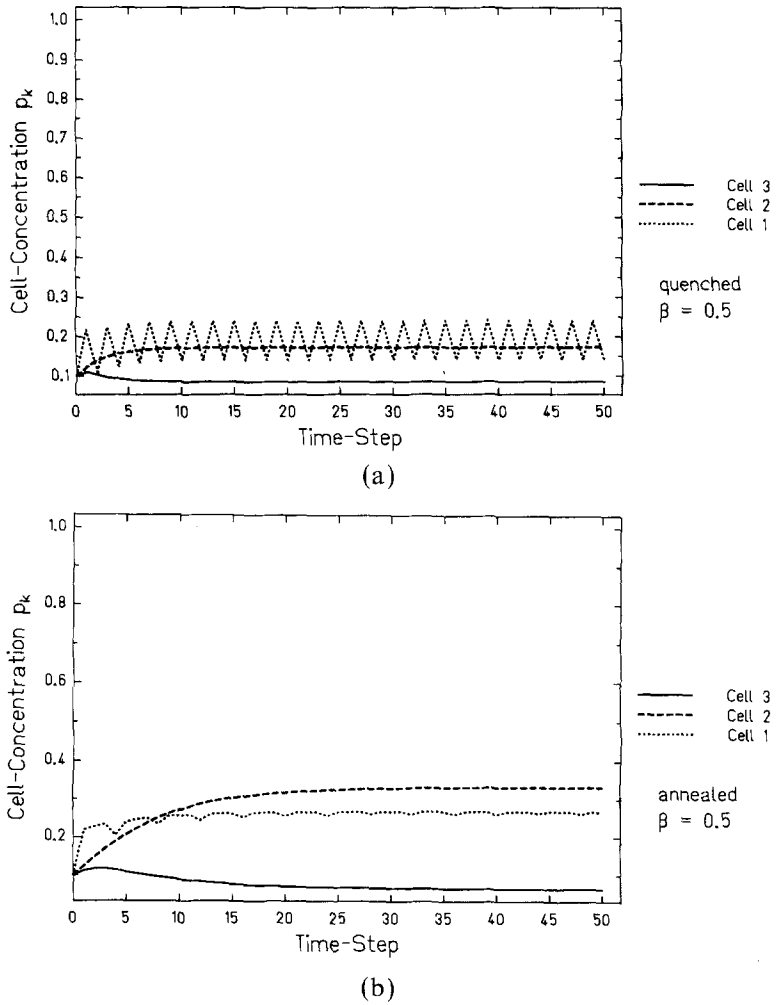


Fig. 6. Probabilistic approach of model B. The probability β is 0.5. (a) A quenched and (b) an annealed version are presented. The initial concentrations are the same as in Fig. 5.

response than model A, which was based on the generalized nearest neighbor interaction. Thus, we tend to assume that the local interaction model B reflects the localized biological interactions of the cells and model A, in addition, reflects a biological interaction of the system which is distributed over the lattice through the averaging of Eq. (1). The biological interpretation of this averaging might be a mechanical mixing of the system. Further investigation of the given models, which simulate the intermediate and final stages of the infection, respectively, including external intervention (vaccination), is the subject of forthcoming work.[13]

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REFERENCES

1. S. Wolfram, *Theory and Applications of Cellular Automata* (World Scientific, Singapore, 1986).
2. U. Behn and J. L. van Hemmen, *J. Stat. Phys.* **56**:533 (1989).
3. S. A. Kauffman, *J. Theor. Biol.* **22**:437 (1969).
4. M. Kaufman, J. Urbain, and R. Thomas, *J. Theor. Biol.* **114**:527 (1985).
5. Z. Agur and M. Kerszberg, *Am. Nat.* **129**:862 (1987).
6. G. Weisbuch and H. Atlan, *J. Phys. A* **21**:L189 (1988).
7. I. Dayan, D. Stauffer, and S. Havlin, *J. Phys. A* **21**:2473 (1988).
8. D. Chowdhury and D. Stauffer, Systematics of the models of immune response and autoimmune disease, *J. Stat. Phys.*, submitted.
9. A. R. McLean and T. B. L. Kirkwood, HIV infection in single T helper cell clones, *J. Theor. Biol.*, submitted.
10. R. B. Pandey, *J. Stat. Phys.* **54**:997 (1989).
11. R. B. Pandey, Interacting cellular network model for the dynamics of cell population in an early HIV infection, *J. Theor. Biol.*, submitted.
12. U. Wiesner, *J. Undergrad. Res. Phys.* **7**:15 (1988).
13. Ch. F. Kougias and J. Schulte, in preparation.

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