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Computer Simulation of a Cellular Automata Model for the Immune Response in a Retrovirus System

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Immune response in a retrovirus system is modeled by a network of three binary cell elements to take into account some of the main functional features of T4 cells, T8 cells, and viruses. Two different intercell interactions are introduced, one of which leads to three fixed points while the other yields bistable fixed points oscillating between a healthy state and a sick state in a mean field treatment. Evolution of these cells is studied for quenched and annealed random interactions on a simple cubic lattice with a nearest neighbor interaction using inhomogenous cellular automata. Populations of T4 cells and viral cells oscillate together with damping (with constant amplitude) for annealed (quenched) interaction on increasing the value of mixing probability B from zero to a characteristic value B_{ca} (B_{cq}). For higher B, the average number of T4 cells increases while that of the viral infected cells decreases monotonically on increasing B, suggesting a phase transition at B_{ca} (B_{cq}).

KEY WORDS: AIDS; virus; cells; immune response; network; cellular automata.

1. INTRODUCTION

The study of immune response, using theoretical models[1–5] as well as cellular automata simulations,[6–9] has attracted a great deal of interest in recent years. Introduction of a certain amount of antigens inside the body as a result of viral infection, bacterial attack, or vaccination stimulates the immune system to respond. Immune systems consist of a variety of cellular elements which participate in chain reactions with a complex web of interactions, leading to virus growth and lymphocyte expansion.[10–12] The

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list of varieties in immune response is large and growing, and the reaction mechanism of the response is complex and varied. Although there exists a huge amount of experimental data for the studies ranging from microscopic facts [i.e., the study of cell transformation and growth (clonal expansion), structural transformation of macromolecules such as proteins in expressing the genetic codes, etc.] to macroscopic findings (i.e., the study of the growth of viral infected cases, overall symptoms, and related statistics), understanding the immune response via theoretical means is limited. However, attempts have been made in recent years to study some of the problems involving general aspects such as immunological memory in a neural-network-type model for the idiotypic network,[3,4] control of immune response using models of interacting binary cells,[5–9] etc., as well as specific issues such as viral growth and lymphocyte expansion in response to the retrovirus[2] for the acquired immune deficiency syndrome (AIDS). Since the binary cell interacting models[10] have shown some success in describing some of the general aspects of immune response, I limit myself here to such simple models but attempt to address a more specific issue of viral growth and lymphocyte expansion.

In Section 2, I briefly describe the cellular components of the immune system with reference to retrovirus[11]; this may help in an understanding of the simplifications used in modeling which is introduced in Section 3. In Section 4, I give the details of implementing the basic interactions of the model on a cubic lattice with a nearest neighbor interaction. Results are presented in Section 5, with a summary and discussion in Section 6.

2. IMMUNE SYSTEM AND IMMUNE RESPONSE

In immune response,[10–12] multipotential stem cells differentiate into three main classes[11]: (i) B cells (from bone marrow), which, on contact with antigen, differentiate into plasma cells which secrete antibody and memory cells responsible for lasting immunity. (ii) T cells, which mature in the thymus gland and then are released into the blood or lymph, where they take on distinct biochemical and functional identities in which two types of T4 cells act as helper and inducer, respectively, while two types of T8 cells act as cytotoxic (killer) and suppressor. T8 cells recognize the antigens which contain class I MHC (Major Histocompatibility Complex) proteins (these molecules are present on the surface of nucleated cells). On the other hand, T4 cells respond to antigens which contain class II MHC proteins, which are found primarily on the surface of antigen-presenting cells. (iii) Myeloid stem cells which produce macrophages among various classes of white blood cells. The macrophages, one of the main antigen-presenting cells, interact with virus or other intruder in a highly specific

way and display the antigenic protein fragments on the cell membrane together with class II MHC proteins, which are then recognized by T4 cells. Apart from these three main classes of cells, there are other cells which also participate in immune response.[11] All these cells act randomly but cooperatively in a very complex fashion to fight against viral infection.

In general, when a virus invades the body, the immune system responds in a variety of complex ways depending upon the kind of infection. In some viral infections, natural killers respond at first, followed by a complex interaction and reaction of virus-infected cells with macrophages; helper and inducer T4 cells then come into play, which induces cytotoxic T8 cells to fight against the infection. While the plasma cell produces antibodies, suppressor T8 cells help to shut down the T-cell response and memory cells guard against further infection. The immune reaction involves interactions among many cellular elements which pass through various stages of their complex path of transformations during the course from beginning to complete recovery; we leave the specific details to the experts in this field.

In AIDS,[11] viruses have the ability to avoid destruction by the immune system and there may be several possibilities to achieve this. One possibility could be that its proteins change frequently because of mutation causing any antigen-specific immune response to miss its mark. Again several interrelated possibilities can be suspected. For example, the virus may undergo steady genetic change, probably due to its rapid and inaccurate replication leading to genetic drift. Instead of evasion, the human immunodeficiency virus (HIV) seems to avoid destruction by preemptively destroying the immune system which produces a lasting depression of immune response. It is believed that the cause of this deadly infection is a retrovirus which involves a complex interaction on a microscopic level in the biological sequence of molecular transformation involving DNA, RNA, and proteins in reverse order of sequences to that of its usual biological sequence in transcribing the genetic information. Once this happens, the immune system fails to respond to other infections as well. On a microscopic level it is rather difficult at present to understand the complex reaction among the molecules, cells, and their transformations. Even the experimental data sometimes lead to conflicting speculations. However, on a global scale, it is believed that in the case of HIV, immunosuppression results from viral infection of T4 lymphocytes and here we address the effects of interplay between these interacting components.

In culture the HIV[11] seems to alter and ultimately slow the growth of infected T4 cells while other kinds of T cells continue to multiply normally. As inducer and helper, T4 lymphocytes play a vital role in immune response and therefore the reduction of the T4 cell population has severe

consequences in failing immunity. B cells are unable to produce adequate quantities of specific antibody to the virus due to lack of appropriate amount of helper T4 cells, which also hampers the response of cytotoxic T8 cells. The crucial roles of B cells (as memory cells for lasting immunity and a constant production of antibodies) and of T cells (T8 suppressor cells) to shut down the response and macrophages to prepare infected cells are severely interrupted. It is extremely difficult to incorporate all interacting cellular elements in a theoretical model in order to study the kinetics of evolution of these cells. Nevertheless, to initiate a preliminary study it is worth looking into some of the essential features of main cellular elements; toward this end I introduce here a simplified model.

3. MODEL

Consider a network[5,10] of these binary cell types in which cell type 1 represents the T4 cell, cell type 2 the T8 cell, and cell type 3 the antigen produce by virus; I call cells of type 3 the viral infected cells. Here, I do not distinguish between different functions of the T4 cells and that of the T8 cells, although I mainly emphasize the helper function of T4 cells and the killer function of T8 cells (i.e., cytotoxic T8 cells). For simplicitly, I do not consider explicitly the B cells, antigen-producing cells, and natural killer cells along with other cellular elements of the immune system. In a sense, the aftereffects of the immune response (suppressor function of T8 cells and memory function of the B cells), i.e., the immune resistance, is ignored, and therefore the model may only be useful to understand some of the features during the initial stage of the response. The components of the immune system (i.e, the cells) are embedded inside the body in a space shared by organisms along with body fluids. The cells are mobile in an inhomogeneous three-dimensional space and to take into account their conformational morphology along with other constraints (say, the steric hindrances) on their multiplication and expansion adds more complexities. I, however, model the host space for the cells as a three-dimensional lattice in which all the lattice sites have potential to accommodate each type of cell, neglecting the mobility of the cells altogether. In this approximate model, I do take into account some of the structural constraints in which two cells of the same type are not allowed to occupy the same lattice site, whereas cells of different types (say, a T4 cell, a T8 cell, and a viral infected cell) can be at the same site; a lattice site, therefore, represents a local space of the equivalent biological system (of thymus as an example). Inhomogeneity and randomness are incorporated via random interactions among the cells with their random growth and decay. At this stage, only some of these basic features of the random chain reaction of the immune

response are considered in this primitive model, which will be further developed to take into account more microscopic details. In the following, I first analyze the interactions among the three cell types, in the so-called mean field description, where a cell at a site interacts with other cells of the same type at all other sites; all sites becomes equivalent in this infinite-range interacting neural network type of model, which reduces the problem to a single-site interacting network. Nearest-neighbor interacting networks will be considered in the next section. One may write a variety of three-cell interactions to describe some of the features of immune weakness mentioned above; I consider two such interactions here.

(i) I define the current status of a cell type i by $IC(i)$, which acquires binary[5,10] values 0 (false) and 1 (true) for its low and high concentration, respectively. Similarly, the new binary state of the cell type i is represented by $ICN(i)$, which emerges after the interaction. I propose a possible interaction among the 4 million mathematical possibilities as

$$\begin{aligned} ICN(1) &= IC(1) \text{ .and. } [\text{.not. } IC(3)] \\ ICN(2) &= IC(1) \text{ .or. } IC(2) \\ ICN(3) &= [IC(1) \text{ .and. } IC(3)] \text{ .and. } [\text{.not. } IC(2)] \end{aligned} \tag{1}$$

where the first Boolean expression describes that T4 cells can grow at a site when the concentration of viral infected cell is low at that site. The second expression describes the self-interaction of T8 cells, which expands also with the help of T4 cells. Since the cytotoxic T8 cells (cell type 2) attempt to kill only those viral cells which are prepared by helper T4 cells (cell type 1), viral infected cells may grow when the concentration of cytotoxic T8 cells is low and this mechanism is represented by the third expression. Note that this equation involves only one site with 2^3 possible states of three cell types $\{IC(1), IC(2), IC(3)\}$ and that all sites of a lattice can be treated independently with this interaction (1) in the spirit of the mean field description of Weisbuch and Atlan.[5] If we start randomly from one of these eight initial states, then this interaction (1) leads to three fixed points: immunized $\{010\}$, healthy but susceptible $\{110\}$, and perfectly healthy $\{000\}$ with probabilities 1/2, 1/4, and 1/4 respectively.

(ii) Alternatively, I propose the following interaction:

$$\begin{aligned} ICN(1) &= \text{.not. } [IC(1) \text{ .and. } IC(3)] \\ ICN(2) &= IC(1) \text{ .or. } IC(2) \\ ICN(3) &= \text{.not. } [IC(1) \text{ .and. } IC(3) \text{ .and. } IC(2)] \end{aligned} \tag{2}$$

One can interpret these logical expressions in the same way as those of Eq. (1). Here the first expression implies that cell type 1 can expand when

both cell types 1 and 3 or one of the two are in low concentration, while the third expression suggests that viral infected cells (type 3) can grow if either one of these is in low concentration; the second expression remains the same as that in Eq. (1). Starting from any one of the eight initial configurations randomly, this interaction leads to an oscillatory state of sick $\{111\}$ and immunized $\{010\}$. To my knowledge, such oscillatory behavior in the flow phase space of interaction is observed for the first time in the study of immune response via a network of binary cellular elements.

4. MIXED INTERACTION ON A SIMPLE CUBIC LATTICE

Now I consider nearest neighbor interactions among the cells of the same type (intracell interactions) on a simple cubic lattice. The basic interactions (1) and (2) of the preceding section describe only two features of the numerous possible effects caused by retrovirus in immune response. In order to understand a variety of mysterious reactions exhibited by retrovirus systems, it is worth exploring a number of complex interactions among various cells. To understand the irregular course of reactions in such retrovirus systems and their time-dependent effects (such as varying incubation time), I attempt to incorporate randomness using interactions (1) and (2). I study two kinds of random binary interactions[9,13,14]: (a) Annealed interactions in which, at each time step, each lattice site is randomly assigned interaction (1) with probability B and interaction (2) with probability $1-B$ with $0 \leqslant B \leqslant 1$; and (b) quenched interactions, where interactions (1) and (2) are assigned with probabilities B and $1-B$ to cells at each lattice site randomly at the beginning and are kept the same throughout the evolution of the simulation. Rules for nearest neighbor interactions on the lattice and the basic computer algorithms are the same as those of a previous study[9] that uses similar random mixing for the inhomogeneous cellular automata. In the following I briefly mention the procedure of implementing these rules.

Each of the three type of cells is placed at each lattice site. A fraction p of each type of these cells is assigned a binary state 1 (of high concentration). First we select a cell type, say k, with its current binary state $IC(k)$ at site i; then we add the binary state of this cell with those of its six neighboring cells of the same type k. If this sum (logical or) of seven binary states of the cell type k is positive, then a temporary state $s'(k)$ of high concentration $[IC'(k)=1]$ is assigned to the cell type k at site i; otherwise, the binary state of this cell type remains zero. Using the same interaction rule of addition of binary states of the neighboring cells of the same type, each of the three cells $(k=1, 2, 3)$ is assigned a temporary binary state. Now, all three cells at site i interact with each other with a temporary

binary state according to specified intercell (quenched or annealed random) interactions, Eq. (1) or (2), which govern the final states of these cells at the next time step. Similar updates are made for three cell types at all lattice sites and this completes one time step of the simulation. This process of updating the configurations of the cells is repeated again and again for a desired number of time steps each with a number of independent sample. I have studied the temporal evolution of the average number of three cell types as a function of mixing probability B with various initial concentrations p for both quenched and annealed interactions which are discussed in the following.

5. RESULTS

5.1. Annealed Interaction

I use $60 \times 60 \times 60$ lattices with five independent samples to produce data for the growth of cells for various initial concentrations p. A typical variation of the number of T4 cells, T8 cells, and viral infected cells is presented in Fig. 1 for various values of mixing probability B. We know that at extreme values of B there is no random mixing and either fo the two interactions (1) and (2) on the lattice governs the evolution. For $B = 0$, we observe that the number of T4 cells and viral infected cells oscillates between two extreme values of 0 and the size of the sample (216,000); the number of T8 cells approaches very fast to a maximum saturation value, i.e., the size of the sample. Here the two types of cells, the T4 cells and viral infected cells, stay together at the same sites and this is obvious from the first and third Boolean expressions of Eq. (2) when T8 cells expand to all sites, i.e., $ICN(1) = ICN(3)$ for $ICN(2) = 1$; the oscillations in their number is due to simultaneous updating of these cell types. A similar oscillation has been also observed by Dayan *et al.*[6] in a somewhat different study. On the other hand, at $B = 1$, there is no oscillation in the variation in the number of cells of types 1 and 3; instead, the number of T4 and T8 cells increase with time, expanding to all lattice sites, and the number of viral infected cells goes down to its zero level.

On increasing the value of mixing probability B, the numbers of T4 cells and viral infected cells still oscillate, but the amplitude of oscillations decreases with time, which implies that this interacting system has damping. The higher the value of B, the faster is the decay of oscillations, though the numbers of T4 cells and viral infected cells remain equal. This trend continues until a certain value B_{ca} (~ 0.7) beyond which the number of T4 cells increases with time, approaching a certain asymptotic value

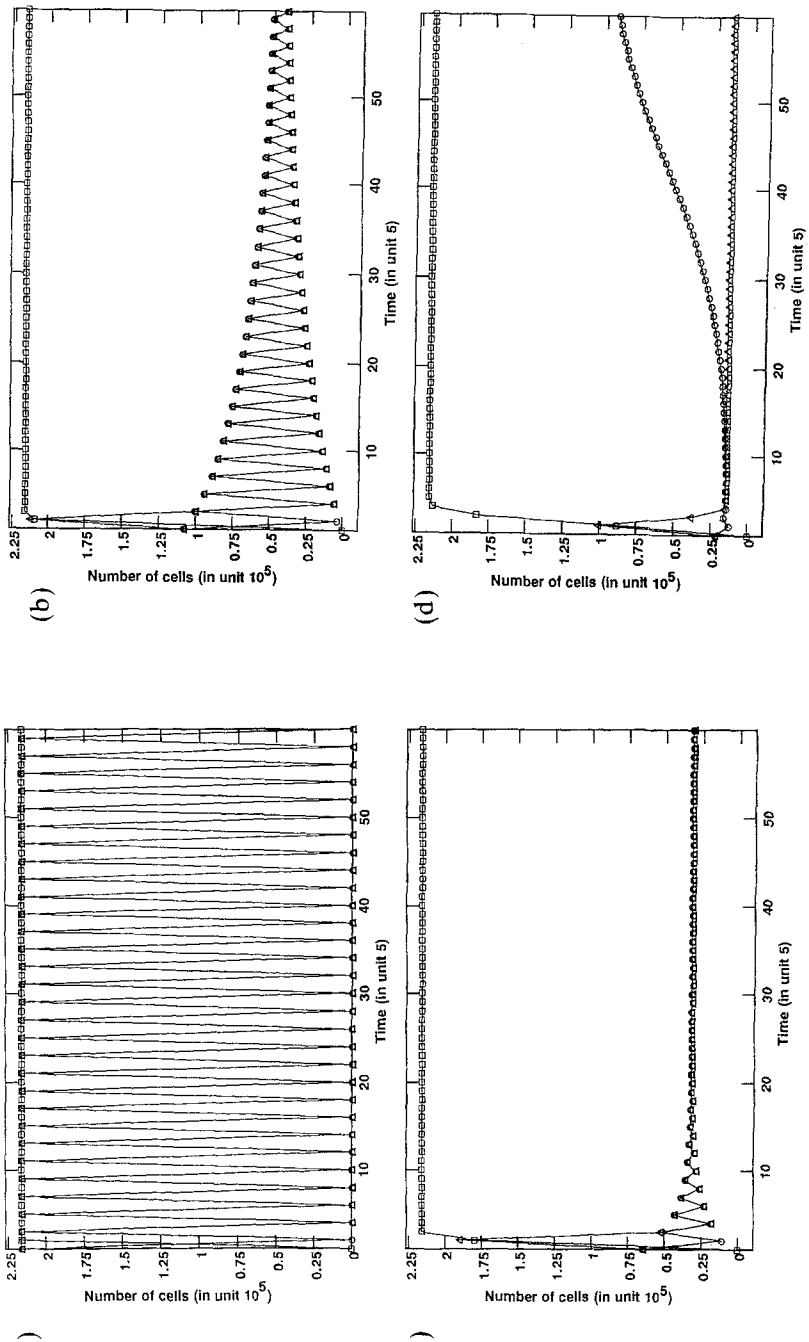

Fig. 1. Number of T4 cells (○), T8 cells (□), and viral infected cells (△) versus time at their initial concentration $p = 0.0000005$ for the annealed interaction with mixing probability $B =$ (a) 0.0, (b) 0.5, (c) 0.7, and (d) 0.9. A $60 \times 60 \times 60$ lattice with five independent samples was used.

$N_4(B)$, which increases with B. The number of viral infected cell, on the other hand, quickly reaches a constant value $N_v(B)$, which decreases on increasing B below $N_4(B)$. I define an order parameter $M(B)$ as the difference of these two asymptotic numbers,

$$M(B) = N_4(B) - N_v(B) \tag{3}$$

A plot of $M(B)$ versus B for various values of initial concentration p is shown in Fig. 2; the saturation numbers are calculated from the runs up to 500 time steps, although some test runs were made for time steps up to 10^5 in order to check the saturation time. As is evident, apart from a little statistical fluctuation, the order parameter $M(B)$ remains zero below a characteristic value B_{ca} and it increases monotonically for B above B_{ca}, which suggests a phase transition at about B_{ca}. The qualitative behavior remains the same at all initial concentrations p. Note that cells are interacting with two kinds of interactions (1) and (2) randomly and that B is only a probabilistic measure of the switching on of cell interactions of one kind over the other. It is rather difficult at this stage to provide a more quantitative analysis of the phase transition than to look into the variation in the cell number as a function of B. I hope that a more realistic model will address this issue further.

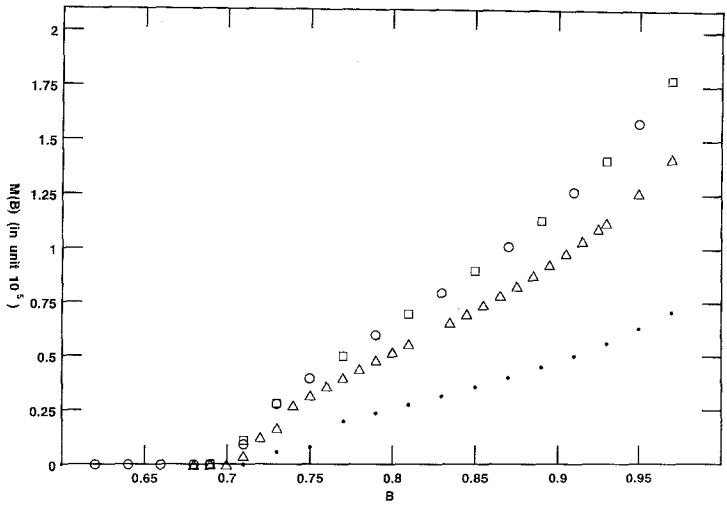

Fig. 2. Order parameter $M(B)$ versus mixing probability B for annealed interaction at initial concentration $p = (\bullet)$ 0.000005, $(\triangle)$ 0.000001, $(\square)$ 0.0001, and $(\circ)$ 0.001. Statistics is the same as that in Fig. 1 except that long-time data (5000–10,000 time steps) were used to evaluate the asymptotic values of the cell numbers.

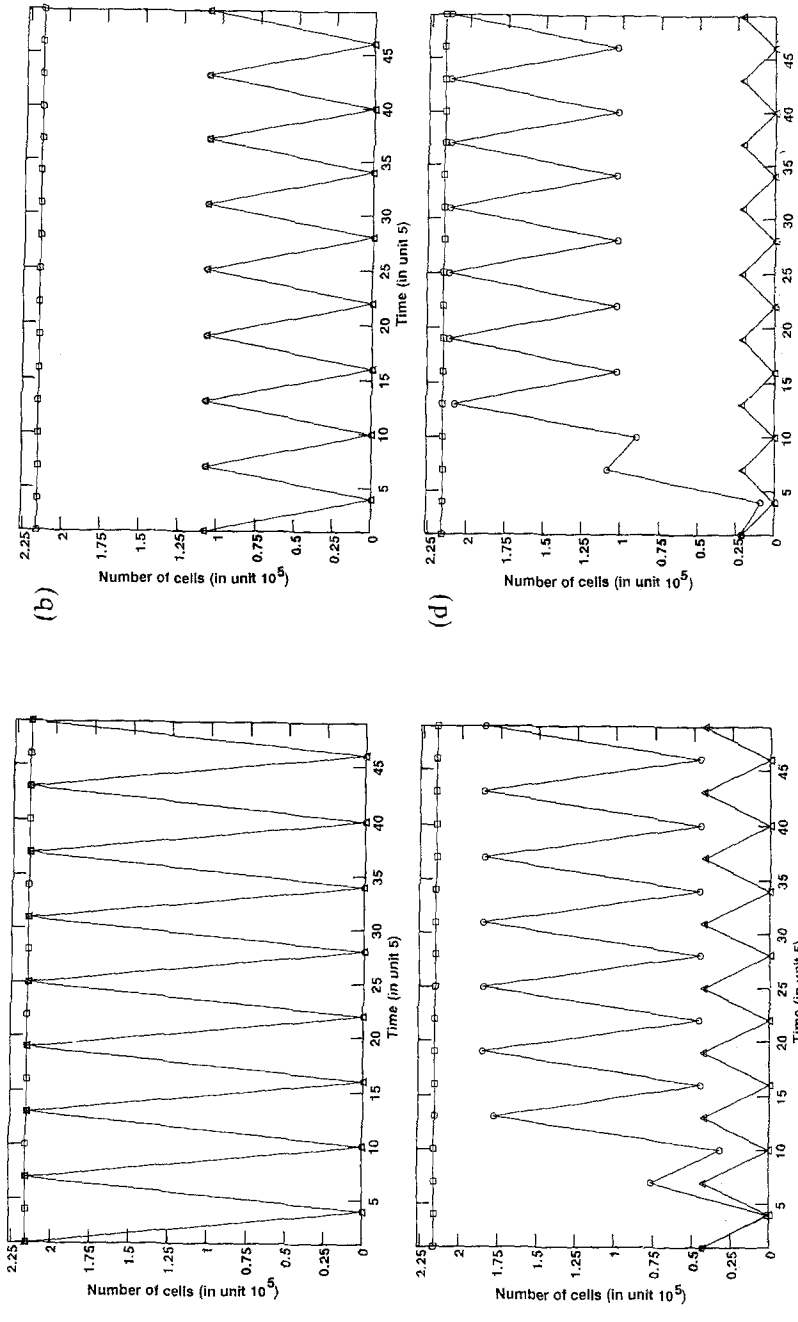

Fig. 3. Number of T4 cells (○), T8 cells (□), and viral infected cells (△) versus time at their initial concentration $p = 0.000005$ for the quenched interaction with mixing probability $B =$ (a) 0.0, (b) 0.5, (c) 0.8, and (d) 0.9, with the same statistics as that used in Fig. 1.

5.2. Quenched Interactions

Statistics for the simulation data here is the same as that of Section 5.1. A typical variation of the number of three cell types is presented in Fig. 3 for various values of mixing probability B. I have already discussed the results at the extreme values of B. For $B = 0$, we saw that the numbers

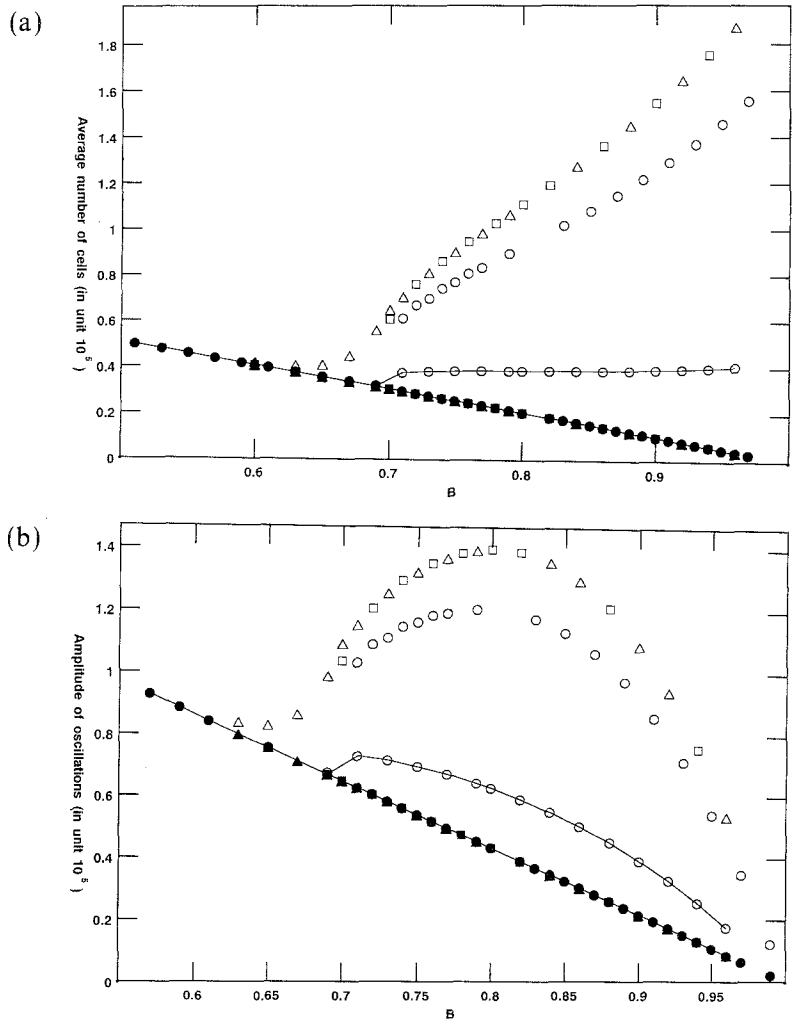

Fig. 4. (a) Average number about which the population of T4 cells (open symbols) and viral infected cells (filled symbols) oscillate versus mixing probability B for the quenched interaction with initial concentration $p = (\bigcirc)$ 0.000005, $(\bigcirc)$ 0.00001, $(\square)$ 0.0001, and $(\triangle)$ 0.001, with the same statistics as that used in Fig. 2. (b) Amplitude of these oscillations versus B for the same data.

of T4 cells and viral infected cells oscillate with a maximum amplitude which stays constant after few initial steps. For intermediate values of the mixing probability B, the numbers of T4 cells and viral infected cells still oscillate in time but their amplitude of oscillation depends on the mixing probability B, while the number of T8 cells reaches quickly to a saturation value, the size of the system. On increasing the value of B from zero, the amplitudes of oscillations for both T4 and viral infected cells remain equal and approach a constant value in time that decreases monotonically until B approaches a characteristic value B_{cq} (~ 0.66) (see Fig. 4). Again for B below B_{cq} both T4 cells and viral infected cells here stay together at the same sites. Therefore the average number about which these oscillations take place is the same for both T4 cells and viral infected cells (Fig. 4a). Beyond this characteristic value (i.e., for $B > B_{cq}$), T4 cells and viral infected cells no longer stay together. The amplitude of oscillations for the viral infected cells continues to fall monotonically and reaches its limiting value of zero at $B = 1$. The amplitude of oscillations for the T4 cells depends non-monotonically on the mixing probability B above B_{cq}; it first increases and then decreases as a function of B (Fig. 4b), showing a maximum at about $B \approx 0.8$; the maximum peak becomes sharper on increasing the value of initial concentration p.

6. SUMMARY AND DISCUSSION

I have introduced a simple model for the interacting network of three binary cells which takes into account the primary functions of T4 cells, T8 cells, and antigens produced by virus. I have proposed two basic interactions, one which gives rise to three fixed points while the other leads to an oscillatory behavior between sick and healthy states even in the mean field case; such oscillatory behavior is found for the first time as far as I know for a network of binary cells in the study of immune response.[5,10] These two basic interactions are randomly mixed with a probability B to form quenched and annealed interactions among the three cellular elements. Evolution of the three cell types is studied on a simple cubic lattice for a nearest neighbor intersite, intracell interaction using inhomogeneous cellular automata with both quenched and annealed intercell interactions. While expansion of cell type 2 (i.e., T8 cells) seems unaffected, I find interesting results for the growth of viral infected cells and T4 cells. For $B = 0$ on the lattice, T4 cells and virus (viral infected cells) always stay together, i.e., they coexist infected. The other extreme case, $B = 1$, indicates a dominant role of immune response where T4 cells grow to a maximum value and viral infected cells tends to vanish.

For quenched interaction, the numbers of both T4 cells and viral infected cells oscillate with equal amplitude on increasing the mixing probability B form zero to characteristic value B_{cq}. Above this characteristic value, both types of cells oscillate independently about their mean number, say $\langle N_4(B)\rangle$ and $\langle N_v(B)\rangle$. I find that $\langle N_4(B)\rangle$ increases and $\langle N_v(B)\rangle$ decreases monotonically with B above B_{cq}; the oscillation in the number of T4 cells about the mean value $\langle N_4(B)\rangle$ depends nonmonotonically on B, while the oscillation in the number of viral infected cells decreases monotonically with B. Thus, T4 cells win over virus for B above B_{cq}, below whch both coexist, and this behavior suggests a phase transition at B_{cq}. There is a similar sign of phase transition for the annealed interaction at about the same value of the mixing probability B_{ca} above which the difference in the numbers of the two cells, i.e., $M(B)=N_4(B)-N_v(B)$, increases with B. For B below B_{ca} in the annealed case, even though the order parameter $M(B)$ is zero, variation in the development of both T4 cells and viral infected cells exhibits a damped oscillation about the same mean; this may be interpreted as a continued coexistence between immune response and virus sustaining a long-lasting infection. Thus, the order parameter $M(B)$ signifies the degree of health.

Thus, this simple model does capture some of the features of the immune response to retrovirus. As stated in the Introduction, the model proposed here is very simple and offers an opportunity for further extension and development. For example, instead of limiting oneself to three interacting cell types, one may consider seven (two T4 cells, two T8 cells, two B cells, and an antigen-producing cell such as macrophages) or more cells to incorporate more details of the immune response. Further, instead of considering only binary cells and a discrete lattice, one should consider cells with continuous variables on lattice, continuum, and random space; I will continue some of these investigations in the future.

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