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Dynamics and Percolation in the Immune System

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The immune system is studied as a dynamical system. A lattice model for the immune system's memory without percolation is given. An upper limit for the probability of the existence of the memory state is derived. It agrees with the numerical results.

1. INTRODUCTION

Biological systems are a rich source for mathematical and physical ideas (West, 1990). From this point of view the immune system (IS) (Perelson, 1988) has many interesting features, e.g., learning, pattern recognition, memory, etc. In this work we study two aspects of the IS. First we study the IS as a dynamical system. It is shown that it has the distinguishing feature of changing its dynamical equations with time. The second aspect is the memory of IS. A model on Bethe and hypercubic lattices in $d \geq 1$ dimensions is given to simulate the memory of the IS.

In Section 2 the lattice model for IS memory is studied. In Section 3 the dynamics of IS is discussed.

2. A LATTICE MODEL FOR IS MEMORY

The study of the immune system (IS) is an interesting problem in biology, physics, and mathematics. One of the most interesting questions is related to the memory of the IS. It is known that IS cells live, at most, for weeks. However, we know immunization against many diseases remains for years. Furthermore, the new IS cells have random shapes; hence they are

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not identical to the already existing cells. Only in the case that a new clone is close enough to an old one will the new clone be stimulated, i.e., the state of memory continues. This, however, is a probabilistic event which may or may not happen, while immunization is an almost deterministic event.

This poses a problem for mathematicians and physicists: to study dynamical systems where the evolution equations change with time. This kind of dynamics is called metadynamics (Farmer *et al.*, 1986) and will be discussed in the next section.

In this study we propose a lattice model for the IS memory. Lattice models for the IS have been proposed before to study others of its features (Chowdhury and Stauffer, 1992).

We study a lattice with coordination number z. In one dimension, chains ($z = 2$) are studied. In two dimensions, a square lattice ($z = 4$) is used; in three dimensions, a simple cubic lattice ($z = 6$) and for $d \geq 3$, hypercubic and Bethe lattices are discussed.

The different clones of the IS are represented by the sites of the lattice. Whether the clones exist (or not) is represented by the occupancy (vacancy) of the corresponding sites.

At each discrete time $t = 1, 2, \ldots, T$, where T is finite, each site is occupied (left vacant) randomly with probability p $(1 - p)$. An exception to this rule are stimulated sites, which will be defined as follows: If two nearest neighboring (nn) sites are simultaneously occupied, they stimulate each other. We model this by the following rule:

Stimulation rule. If two nn sites are occupied at time t, they will be occupied at time $t + 1$. However, at time $t + 2$ they will be included in the random occupation process in order to avoid continuous stimulation.

To include the immunization we choose any site say S and impose the condition that it is occupied at $t = 1$. The system is said to have memory for S if at every time step $T > t > 1$ either S or at least one of its nn sites is occupied. We also require that there is no infinite cluster (percolation) in the system.

The reason is that IS memory is a local effect. If percolation (Stauffer and Aharony, 1992) exists, it will remove all memory effects once a new stimulation occurs.

We begin by studying the system in one dimension. For simplicity we temporarily neglect stimulation. The probability that S or any of its nn sites is occupied at any time step is P_1, where

$$P_1 = 1 - (1 - p)^3 \tag{1}$$

Thus an estimation for the probability that a memory state exists (PM_1) is $P_1 \geq 0.5$, i.e.,

$$PM_1 \geq 0.206, \qquad PM_1 < P_c \tag{2}$$

where P_c $(=1)$ is the critical percolation probability in one dimension. Notice that we are considering only systems at finite time intervals (there are no creatures that live forever), hence it is sufficient that at each time step the memory state probability should be greater than or equal to 0.5; therefore we set $P_1 > 0.5$.

A better estimation for the probability of the memory state (PM) is to include stimulation. This is done by studying two consecutive time steps, say t and $t+1$. Let E_1 (E_2) be the event that there is no (there is) nn occupied sites given that at least one site is occupied at time t. Then the probabilities of E_1 and E_2 are

$$\text{Prob}(E_1) = 3pq^2 + p^2q, \qquad q = 1 - p \tag{3a}$$

$$\text{Prob}(E_2) = 2p^2q + p^3 \tag{3b}$$

At time $t+1$ stimulation implies that the event E_2 guarantees that the occupied sites will remain occupied. Thus after two time steps the probability that there is at least one occupied site is

$$P_2 = (3pq^2 + p^2q)[1 - (1-p)^3] + 2p^2q + p^3 \tag{4}$$

The maintenance of the memory state implies $P_2 > (0.5)^2$, where the square in the RHS is due to the two time steps. This gives an upper limit (UPM) for the probability of the memory state in one dimension,

$$\text{UPM} = 0.188 \tag{4'}$$

The reason that this is an upper limit is that in the previous discussion the stimulated sites at $t-1$ have not been included. Furthermore, the initial condition that S is occupied at $t=1$ has not been included.

We have simulated the 1D model using a Monte Carlo method (Jain, 1992) and obtained

$$\text{PM} = 0.1 \tag{5}$$

where a chain of length 40 has been used, S is chosen to be site number 20 to avoid boundary effects, and the system has been studied up to $t = 100$.

Studying the 2D system, the first (no stimulation) estimate for PM is obtained using $P_1 > 0.5$, where

$$P_1 = 1 - (1-p)^5 \tag{6a}$$

i.e.,

$$\text{PM}_1 = 0.129, \qquad \text{PM}_1 < P_c, \qquad P_c = 0.5 \tag{6b}$$

Including stimulation and following the 1D procedure, one gets

$$\text{Prob}(E_1) = 5pq^4 + 6p^2q^3 + 4p^3q^2 + p^4q, \qquad q = 1 - p \tag{7a}$$

$$\text{Prob}(E_2) = 4p^2q^3 + 6p^3q^2 + 4p^4q + p^5 \tag{7b}$$

$$P_2 = (5pq^4 + 6p^2q^3 + 4p^3q^2 + p^2q)[1 - (1-p)^5] + 4p^2q^3 + 6p^3q^2 + 4p^4q^1 + p^5 \tag{7c}$$

Thus the upper limit UPM for the probability of the memory state in two dimensions is

$$\text{UPM} = 0.121 \tag{8}$$

Using numerical simulation, we obtained

$$\text{PM} = 0.07 \tag{9}$$

where a 15×15 square lattice has been used, S is chosen to be the (8, 8)th site, and $t = 50$.

Generalizing to $d > 3$, the first (no stimulation) estimate for the memory state for a (hyper)cubic lattice and Bethe lattice with coordination number z is given by $P_1 > 0.5$, where

$$P_1 = 1 - (1-p)^{z+1} \tag{10a}$$

Thus

$$\text{PM}_1 = 1 - (0.5)^{1/(z+1)} \tag{10b}$$

An estimate for UPM is given by solving the equation

$$P_2 = (0.5)^2 \tag{11a}$$

$$P_2 = [1 - (1-p)^{z+1}]\left[(z+1)pq^z + \sum_{r=2}^{z} d(z,r)p^r q^{z+1-r}\right] + \sum_{r=2}^{z+1} C(z,r)p^r q^{z+1-r} \tag{11b}$$

where the coefficients $d(z, r)$ and $C(z, r)$ are given by

$$d(z,r) = \binom{z}{r} = z!/[r!(z-r)!], \qquad r = 2, 3, \ldots, z \tag{12a}$$

$$C(z,r) = \binom{z+1}{r} - \binom{z}{r}, \qquad r = 2, 3, \ldots, z \tag{12b}$$

$$C(z, z+1) = 1 \tag{12c}$$

Now we discuss the existence of the memory state. It is clear that UPM > PM and that for many lattices we have $P_c >$ UPM, e.g., 1D and 2D square lattices; therefore we obtain the following existence theorem for the memory state of the IS:

Theorem. Let P_c be the critical probability of the site percolation problem on a graph with coordination number z; then there is a memory state so long as $P_c >$ PM.

Corollary. There is a memory state in 1D and 2D square lattices and 3D simple cubic lattices.

3. METADYNAMICS OF IS

The immune system (IS) is a distinguished dynamical system (Farmer *et al.*, 1986). It has the ability to recruit new clones and to eliminate some clones from the system. This causes the system's equations to change with time. This is the distinguishing feature of metadynamics. An ordinary discrete dynamical system is defined by the equation

$$z_{n+1} = f(\mathbf{r}, z_n), \qquad n = 1, 2, 3, \ldots \tag{13}$$

where $\mathbf{r} = (r_1, r_2, \ldots, r_l)$ is the set of parameters of the system. Notice that $\mathbf{r}$ and f are the same for all n. For a metadynamical system (MDS) describing the IS, f or $\mathbf{r}$ changes slowly compared to n. Therefore we define the MDS as follows:

Definition 1. The MDS is defined by

$$z_{n+1} = f_i(z_n) \tag{14}$$

where $(i-1)N < n < iN$, $i = 1, 2, \ldots$, and N is a large positive integer. N is defined as follows: For any attractor z_i^* for $f_i(z)$ (considered as an ordinary dynamical system) and for any $\epsilon > 0$ then if the sequence $\{z_n\}$, $(i-1)N < n < iN$, exists in the basin of attraction of z_i^*, then there is $N_1 < iN$ such that $n > N_1$ implies $|z_n - z_i^*| < \epsilon$. This means that for all i the transient system

$$z_{n+1} = f_i(z_n), \qquad (i-1)N < n < iN$$

comes very close to its asymptotic behavior. Only the systems for which such N exists will be considered here.

In the IS the equations usually preserve their form, only the parameters change as the clones change. We will concentrate on this type of metadynamics.

As an example, the MDS corresponding to the logistic map can be defined by

$$z_{n+1} = r_i z_n (1 - z_n), \qquad (i-1)N < n < iN \tag{15}$$

where $\{r_i\}$ are real, positive parameters. Numerical study shows that N can be chosen to be greater than or equal to 50.

A corresponding MDS for the Mandelbrot map is

$$z_{n+1} = z_n^2 + C_i, \qquad (i-1)N < n < iN \tag{16}$$

where $\{C_i\}$ are complex parameters.

Definition 2. (a) An n-periodic point z_i^* is defined by

$$z_i^* = f_i^{(n)}(z_i^*), \qquad (i-1)N < n < iN \tag{17}$$

where $f^{(n)} = f, f, \ldots, f$ n-times. If z^* is independent of i, then it is a global n-periodic point.

(b) An attracting (repelling) n-periodic point z_i^* satisfies

$$\left|(df_i^{(n)}/dz)_{z=z_i^*}\right| < 1 \quad (>1)$$

(c) The Julia set for the MDS (13) is the closure of repelling periodic points.

From now on we consider the systems (15) and (16). The behavior of the MDS (15) and (16) is closely related to the asymptotic behavior of the parameter sequences $\{r_i\}$ and $\{C_i\}$, respectively.

Definition 3. A slowly alternating dynamical system corresponds to the parameter sequences $(r_1, r_2, r_1, r_2, \ldots)$ and $(C_1, C_2, C_1, C_2, \ldots)$ for the systems (15) and (16), respectively.

A fast alternating dynamical system, corresponding to $N = 1$, has been defined and used (Ahmed, 1992) to study ac conductivity.

It is straightforward to prove the following proposition:

Proposition. (a) If the sequence $\{r_i\}$ is convergent, then the behavior of MDS is determined by r, where $r = \lim_{i \to \infty} r_i$. In this case the MDS reduces asymptotically to an ordinary dynamical system.

(b) In the slowly alternating MDS corresponding to (15), if $1 < r_1, r_2 < 3$, then the system oscillates between the basins of attraction of one of the following attractors: $1 - 1/r_1$, $1 - 1/r_2$. The attractor $z = 0$ is a global attractor for this system.

(c) Since the point at infinity is a global superattractor for the system (16), the Julia set for this system is contained in a bounded subset of the complex plane.

(d) In the MDS (16), if the sequence $\{C_i\}$ is a subset of the Mandelbrot set, then the MDS is bounded.

It is interesting that the oscillatory behavior shown in part (b) of the proposition is similar to observations of the immune system (Lundkvist *et al.*, 1989).

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