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A Dilute Bootstrap Percolation: Lattice Model for Unresponsiveness in T-Cell Immunology

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The biased majority rule of cellular automata takes a spin up if and only if at least two of its four nearest neighbors on the square lattice are up. We generalize this type of bootstrap percolation by introducing quenched site dilution as well as a random birth and decay process. Our Monte Carlo simulations then give first-order transitions qualitatively similar to our results from mean-field reaction equations describing the induction of T-cell unresponsiveness in the immune system.

KEY WORDS: Immunology; cellular automata; bootstrap percolation; computer simulation.

1. INTRODUCTION

The immune system protects us from invasion by pathogenic agents. In order to perform this task, it has developed highly specific and efficient responses for neutralizing the foreign antigens, i.e., the foreign cells and molecules. The basic defense cells of the immune system are the B and T lymphocytes. B lymphocytes respond to antigen by producing antibody molecules. T lymphocytes are involved in cell–cell interactions. Some T cells are responsible for killing tumors or virus-infected cells. Others, such as the "helper" T lymphocytes have a regulatory function and secrete factors that promote the activation of the B and T effector cells.[1]

It has been reported that these helper T cells may become unresponsive after an antigen-driven stimulation.[2–4] Following a productive activation, a long-lasting phase of "anergy" is observed, presumably related to a

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modification in the state of the T-cell receptors at the surface of these cells.[4–6] This phenomenon is important for the downregulation of immune responses, and might also participate in the mechanisms of self-tolerance.

A theoretical model based on a phosphorylation cascade has been developed for the understanding of T-cell unresponsiveness.[5] It describes a molecular mechanism both for desensitization in the presence of antigen and persistent lowering of cell responsiveness after stimulus removal. Important features of this model can be summarized as follows. (1) T cells are stimulated by antigen immobilized on antigen-presenting cells or unsolubilized antibodies; binding of the T-cell antigen receptors (TCR) to their external ligands is therefore accompanied, as a function of ligand concentration, by an increase in receptor density on the contact area. (2) Receptor aggregation induces the activation of receptor-associated, autophosphorylating enzymes. Autophosphorylation markedly enhances the phosphorylative activity of these enzymes and represents an autocatalytic step in the early events of TCR signaling.[7] (3) Enzyme activation also leads to reversible phosphorylation of the TCR transducing system; phosphorylation has a dual role and is assumed to regulate both positively and negatively the signaling pathway leading to cell activation.

Mean-field equations for these density-dependent phosphorylation/dephosphorylation reactions involving the T-cell receptors have, in some parameter region, given bistable solutions; either the fraction of autophosphorylated enzymes is low or it is high. This existence of a first-order transition did not rely on details like birth and death processes. One prediction of the mean-field model is that, following activation, the phosphorylative activity of the receptor-associated enzymes may remain above background level after removal of the antigen. Residual activity or phosphorylation of the T-cell receptor transducing system could therefore be responsible for deficient signal transduction and lead to a state of prolonged unresponsiveness.[5,6]

The present note tries to find a simple lattice model also giving such first-order transitions due to bistability, but allowing for spatial fluctuations of the various receptor concentrations.

2. THE LATTICE MODEL

The sites of a square lattice symbolizing the surface of a T cell are initialized randomly: either empty (E) with probability $1-x$ or occupied with probability x. An occupied site may be an unphosphorylated (R) receptor or a phosphorylated (P) receptor; again the initial distribution is random, with a probability p for phosphorylated and a probability $1-p$ for unphosphorylated.

After this initialization the empty and occupied sites remain empty and occupied forever, but the phosphorylation state of a receptor can change: a receptor is phosphorylated if and only if at least two of its four nearest neighbors are phosphorylated (parallel updating). This rule is assumed here to account qualitatively and in a compact way for the *autocatalytic* activation of the receptor-associated autophosphorylating enzymes, through interactions between adjacent molecules. It reflects the resulting net balance of phosphorylation/dephosphorylation of the T-cell receptors. Mathematically, we represent a P site by an up spin, and E and R sites by down spins; E sites always remain E, whereas R sites may become P sites and P sites may become R sites.

This mixture of three components E, R, and P is simulated via bit-by-bit parallel updating (multispin coding) on a Cray-YMP, with a speed of 8 sites per microsecond and per processor to initialize a site, and about 600 sites per microsecond and per processor for the later iterations, with systems consisting typically of 10 million sites and up to 256 million sites (four orders of magnitude above the natural size). In two limits we recover known cases:

(a) E and R only ($p=0$): nothing changes, random site percolation.

(b) R and P only ($x=1$): now a spin is down if three or four of its neighbor spins are down; otherwise (i.e., when at least two neighbors are up) it points up (gets phosphorylated). This "reversible" bootstrap[8] percolation problem, also called biased majority rule, was discussed in ref. 9. For small p the fraction of phosphorylated sites remains small, and we end up with oscillations of period two. For intermediate and large p, finally all lattice sites get phosphorylated and the system ends in a fixed point of all spins up. The threshold concentration for this transition varies for $L * L$ lattices asymptotically as $(\log L)^{-1/2}$.

3. DILUTION

As soon as x is slightly below unity, the behavior of the system in case (b) of Section 2 is drastically changed. In a large enough lattice there will necessarily be some isolated clusters of R sites which never can get phosphorylated. Also, the end result is always an oscillation of period two, except for $p=1$, where a fixed point with finite concentrations of all three types was observed. Thus the phase transition of case (b) has vanished completely. Therefore the behavior at $x=1$ is quite different from that for x going to unity. Of course, in a small lattice of size $192 * 192$ this discontinuity is smoothed out and we still see that transition if the lattice is nearly fully occupied. For $x=0.99$, 0.98, 0.96, and 0.94 we find a transition

between oscillations and fixed points at p near 0.3, 0.4, 0.86, and 0.97, respectively. For p smaller than these x-dependent thresholds, an oscillation (limit cycle of period two) was found. As some remmant of the transition of case (b) we found that for x above 0.9 and low p a rather large number of iterations is needed to get to the final limit cycle (1000 iterations at $x=0.99$ and $p=0.2$).

It is doubtful that the distinction between oscillations and fixed points has any immunological significance, since limit cycles may be the result of the parallel (synchronous) updating procedure. More relevant is the final concentration of P sites (presumably more relevant than the question if they percolate[10]). Our simulations for large lattices show that with increasing initial number of phosphorylated sites the final mean number increases roughly as p^2 as long as the number of phosphorylated sites is appreciably smaller than the number of occupied (P and R) sites. For large x and large p, the number of phosphorylated sites levels off to a value close to but always below the number of occupied sites; in other words, some R sites always remain.

For a fixed initial concentration p of phosphorylated sites of 5% the final number of phosphorylated receptors is at high x about two orders of magnitude below the initial number of P sites; it becomes rapidly smaller if x is diminished. That has to be expected, since at small x we will have rarely two P sites close by, since most sites are E; therefore most of the initial P sites are converted to R. Quantitatively, the decay with decreasing x is roughly a stretched exponential. Apart from x near 0.1, we roughly fit the final fraction p_f of phosphorylated sites to

$$\log_{10} p = 4 - 6x^{-1/4}$$

for an initial concentration $p=0.05$. At $x=0$, of course, p is also zero.

So far the transition[9] for $x=1$ has vanished once we dilute the lattice and work with x below unity. Now the final concentration of phosphorylated sites is a smooth but rapidly varying function of the initial concentration p and of x.

4. BIRTH AND DEATH

Sharp transitions are recovered in this model if we include random growth and decay processes to follow the previously described (bootstrap percolation) initialization. Birth and death allow changes of the receptor positions and receptor status and thus get closer to a mean-field description with infinite diffusivity. In addition, this process accounts for the observed recycling and turnover of the T-cell receptors and associated enzymes.

Thus after an oscillation of period two has been reached, we randomly take away receptors (phosphorylated or not phosphorylated) and also randomly add new unphosphorylated receptors; the added receptors get phosphorylated if and only if at least two of their neighbors at that time are phosphorylated.

More precisely, the initialization is followed by many iterations, and each iteration consists of N steps if the lattice contains N sites. For each step a random number z is drawn from the interval between 0 and 1. For $z > x$ a randomly selected site is made empty (independent of whether it was empty or occupied before); otherwise a randomly selected site is occupied and immediately it gets phosphorylated if and only if at least two neighbors are phosphorylated at that time (if for $z < x$ the randomly selected site is already occupied, its status is not changed). In this way the ratio of occupied to empty sites remains unchanged by the growth and decay steps, apart from fluctuations. However, the ratio of phosphorylated and unphosphorylated receptors can change.

Simulations are now orders of magnitude slower, since the growth and decay process is not vectorized and since the repeated call for random numbers makes bit handling inefficient. Thus a standard Fortran program on a SUN sparc2 work station needed nearly 9 μsec/step. We simulated $L * L$ square lattices with $L = 192$ and 1000 with up to 3000 iterations (200 iterations for a test at $L = 4000$, and 20,000 iterations for a test at $L = 500$). Fewer simulations were made for $1000 * 1000$ triangular lattices where receptors were phosphorylated if at least three out of the six neighbors were phosphorylated. Thus on both lattices a receptor gets or remains phosphorylated if and only if at least half of its neighbors are phosphorylated.

Already the small lattices show clear evidence for a transition. For small initial concentrations x of occupied sites the number of phosphorylated receptors goes to zero exactly, whereas for large x it grows until nearly all receptors are phosphorylated. For example, at a fraction $p = 0.3$ of phosphate carriers among the initial receptors (square lattice), we find the phosphorylation ratio to decrease at $x = 0.85$ and to increase at $x = 0.86$, though our 3000 iterations are not long enough to get a stationary equilibrium; at $p = 0.3$ and $x = 0.9$ such equilibrium was obtained after about 2000 iterations for $L = 1000$, with 10% empty sites, 0.4% unphosphorylated receptors, and thus 89.6% phosphorylated sites. Figure 1 gives an example of the time dependence of the fraction of phosphorylated receptors for different dilutions. As shown in Fig. 2, the critical concentration $x_c = x_c(p)$ stayed at about 0.85 if p was at least 0.3, and increased toward unity if p decreased toward zero. For large p nearly all remaining receptors were phosphorylated, whereas for small p at the

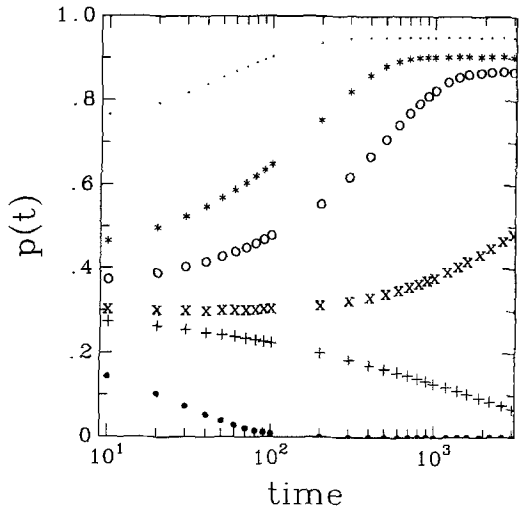

Fig. 1. Time dependence of the fraction of phosphorylated receptors for initial phosphorylation ratio $p \approx 0.3$ in a $1000 * 1000$ lattice. The different symbols correspond to different dilutions: $x = 0.95$, 0.90, 0.88, 0.86, 0.85, and 0.80 from above. (For $x = 1.0$, not shown, finally $p = 1$.)

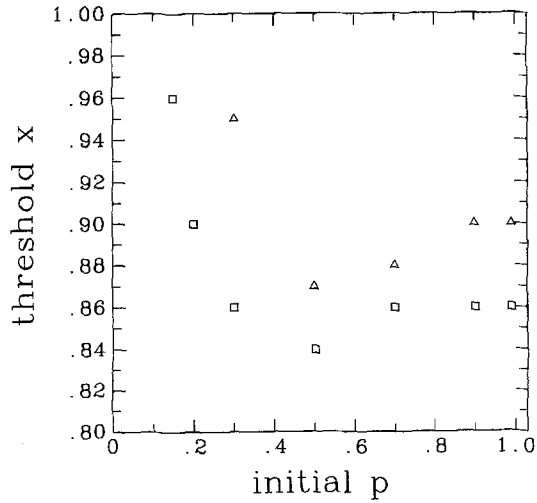

Fig. 2. Phase diagram for the square and triangular lattices, as indicated by the different symbols, in the case of the birth and death simulations. In the upper right part of the figure, many receptors remain phosphorylated, whereas in the left part the number of phosphorylated receptors goes to zero.

Table I

p	x_c(sq)	x_c(tr)
0.10	1.00	—
0.15	0.96	—
0.20	0.90	1.00
0.30	0.86	0.92
0.50	0.84	0.83
0.70	0.86	0.83
0.90	0.86	0.83
0.99	0.86	0.86

transition point most of the receptors carried no phosphate. Thus, by adjusting parameters, jumps in the final concentration of phosphorylated receptors from zero to about any number below 86% could be obtained.

Table I gives the first-order transition points for square (sq) and triangular (tr) lattices. Note the similarity of the results for high p; in this region our results seem to be rather independent of the lattice structure. They are also in qualitative though not in quantitative agreement with the mean-field approach.[5]

In reality, different time scales are involved in the rather slow birth and decay process and the much faster interactions between neighboring receptors. In order to take that aspect into account, we added after each sweep through the lattice (with birth and death processes) a sufficient number (typically of the order of ten) of phosphorylation iterations (P site if and only if at least two neighbors were P sites) until the lattice equilibrated, i.e., until each site became stable or oscillated with period two. Only then was another sweep of birth and death processes started, and so on. The thresholds x_c then were reduced by a few percent to about 0.85, 0.81, and 0.81 at $p = 0.25$, 0.50, and 0.75, respectively. This tendency is in agreement with the mean-field results, where the bistability region is displaced toward lower densities as a function of decreasing recycling rates. The number of birth and death iterations needed to remove all P sites for x below x_c, and the fluctuations in the stationary numbers of P sites for x above x_c, seemed to diverge if x approached the threshold from below and above, respectively. Thus the critical density x_c seems to represent a critical point with divergences of fluctuations and relaxation times, and long times are required to remove all P in the vicinity of the transition point ($x \leqslant x_c$).

5. CONCLUDING REMARKS

Although strongly simplified, our lattice approach shows that bistability due to autophosphorylation can be preserved in the presence of spatial density fluctuations, when random birth and death of receptors are included in the model. Moreover, long-lived metastable states may appear for a system that functions below but close to the critical density if these growth and decay processes occur on a slower time scale than the chemical reactions.

In the framework of our mean-field approach gradual recovery of T-cell immunocompetence in the absence of antigen should arise from a heterogeneity of the cell population: in the course of cell division some cells jump back to their basal state (low level of phosphorylated receptors) and become fully responsive again. As shown here for a probabilistic automata network approach, long-range interactions in a spatially distributed system provide a mechanism of "delayed" removal of phosphorylated receptors that might account for the slow recovery from unresponsiveness that has been observed experimentally.[4] These results also suggest that controlling the rate of turnover and displacement of the cell receptors should strongly influence the rate at which cell competence is reestablished.

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