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COMMENT

Cellular automata generalisation of the Weisbuch–Atlan model for immune response

I Dayan, D Stauffer and S Havlin

Department of Physics, Bar-Ilan University, Ramat-Gan 52100, Israel

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Abstract. Taking into account spatial fluctuations in the discrete model for certain types of immune response, the model of Weisbuch and Atlan is studied on a square lattice. In general, we end up with a healthy carrier state '29' where at all sites all cell types except activated killer cells are present. We study the time it takes to reach this fixed point, as well as effects of disorder and noise.

Weisbuch and Atlan (1988, hereafter referred to as WA) recently suggested a simple discrete model for certain types of immune response: the concentration of killer cells, activated killer cells, helper cells and two types of suppressor cells are approximated as being either one or zero, and the different types of cells influence each other with a strength which is 1, 0 or -1. At the next time step, the concentration of one cell type is unity if the sum of the interactions with the various cell types is positive; for zero or negative sums, the concentration is taken as zero at the next time step. The main result of this WA model is the existence of only two basins of attractions: starting from any one of the 32 possible configurations, we either end up in the empty state where all five concentrations are zero, or in state '29' in the WA notation, where only activated killers have vanished, and the four other concentrations are unity. We leave the biological implications to the experts and deal here with the relations of this model to cellular automata and to percolation (Wolfram 1986, Stauffer 1985).

The WA version corresponds to a mean-field approximation: every killer cell in the system has the same probability of affecting any other cell in the system; no lengths enter the calculation. Thus it is natural to generalise this model to the case of a lattice, where on each lattice site one has five variables (corresponding to the five concentrations) each of which can be 0 or 1 only. Each site influences itself and its nearest lattice neighbours in the same way as in the WA version. Thus for a square lattice of $N = L^*L$ sites one now has $5N$ 'spins' which can be up or down. Again, the sign of the sum of all interactions (five sites on square lattice, with five cell types each) at time t determines the value of the concentration, 0 or 1, at the next time step $t+1$.

More specifically, we number the spin corresponding to the killer cells as S_1, the activated killers correspond to S_2, the suppressor cells to S_3, the helper cells to S_4, and the suppressors produced by the helpers to S_5, with $S_i = 0$ or $= 1$. The state number n, in the WA notation, of a lattice site is defined as $n = S_1 + 2S_2 + 4S_3 + 8S_4 + 16S_5$ and thus varies between 0 and 31 (corresponding to all concentrations zero and unity, respectively). Many properties of the system can be derived directly from the defining

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equations, where $S_i(t)$ denotes the concentration of the ith component at time $t = 0, 1, 2 \ldots$:

$$S_1(t+1) = \operatorname{sgn}\left(\sum S_1(t) + S_4(t) - S_3(t)\right)$$

$$S_2(t+1) = \operatorname{sgn}\left(\sum S_1(t) + S_4(t) - S_3(t) - S_5(t)\right)$$

$$S_3(t+1) = \operatorname{sgn}\left(\sum S_1(t)\right)$$

$$S_4(t+1) = \operatorname{sgn}\left(\sum S_1(t)\right)$$

$$S_5(t+1) = \operatorname{sgn}\left(\sum S_4(t)\right)$$

where the sign function $\operatorname{sgn}(x)$ of integer argument x is 1 if $x > 0$ and is 0 otherwise ($x \leqslant 0$). The summations are performed over the site itself and over its nearest neighbours on the lattice. (The original WA model dealt with 'summation' over the site itself only.)

We see that $S_3(t) = S_4(t)$ for times $t \geqslant 1$ and then $S_1(t+1) = \operatorname{sgn}(\Sigma\, S_1(t))$. Thus for positive times the killer concentration S_1 behaves like a forest fire (Stauffer 1985) or epidemic (Grassberger 1983, 1985) in the percolation model: the sites become infected if at least one neighbour was infected at the previous time step. The behaviour of S_1 is thus known from percolation theory. Furthermore we see that for $t \geqslant 2$ we have $S_4(t) = S_1(t)$, and thus $S_5(t) = S_1(t)$ for $t \geqslant 3$; thus finally $S_2(t) = 0$ for $t \geqslant 4$. Thus if at least one site in the whole lattice has $S_1 = 1$ at some time $t \geqslant 1$ then all lattice sites will finally end up in the stable fixed point 29. Thus the S_1 site can be put there initially, or evolve out of an $S_4 = 1$ neighbour at time $t = 1$. If the lattice initially has not a single killer or helper cell, i.e. if $S_1 = S_4 = 0$ for all sites, then the whole lattice ends up in the completely healthy $n = 0$. Thus normally the whole lattice reaches the fixed point $n = 29$, and in pathological limit cases it reaches the fixed point $n = 0$, for all sites.

Our computer simulations on square lattices started with all spins down, except for the killer cells S_1 of which a fraction p is randomly set to unity. Thus, except for very small p, we avoid the possibility of having not a single killer cell in the system. After a few time steps all lattice sites are in state 29, the healthy carrier state of WA. We do not find any sites in any other states, even though initially the sites were in states $n = 0$ and $n = 1$. The same result is obtained if the initial state is selected randomly from 0 to 31 for each site. This result is in complete agreement with the arguments above.

In contrast, the mean-field model of WA gave, in about half the initial conditions, the final fixed point $n = 0$, and in the remaining ones (including the initial configuration $n = 11$ which was ignored in a figure of WA) the fixed point $n = 29$. Thus our lattice generalisation, with the randomness introduced by the initial conditions, makes the fixed point $n = 0$ unstable and leaves only the unique fixed point $n = 29$. Thus the WA model on a lattice with random initial configurations corresponds to a class-1 cellular automaton (Wolfram 1986). Only if all lattice sites start with the same configuration can we trivially reproduce the mean-field diagram of WA with two large basins of attraction. (If we take the threshold of the sign function not slightly above zero but slightly above 2, we also get sites with $n = 0$, as in WA, and oscillating sites.)

The time after which all sites are in state 29, starting with 12.5% of the sites as killers ($S_1 = 1$), increases with some power of the logarithm of the system size according to our simulations (figure 1). (An IBM 3081 without vector feature took about 34 ns per site and time step.) This result can also be explained: killer and helper cells are able to infect the whole lattice, even if initially only one of them is present. At any finite concentration of killer cells, the infection spreads through the lattice with unit velocity. In a very big lattice there will be a few regions of relatively large size with no killers or helpers initially. These regions will be infected completely only after a relatively long time, since the infection has to travel through these regions. Then it will also take them a relatively long time to settle into the fixed point $n = 29$. The probability of such a large empty square of n^2 sites, if initially all sites except a fraction p are in state zero, varies asymptotically as $(1-p)^{n^2}$, and the number of such empty regions is proportional to the number N of lattice sites in the system. Thus we have on average $N(1-p)^{n^2}$ such large holes in our lattice, and the largest hole one can expect is that where this number is of order unity. Thus the largest n typically observed varies as $(\log N)^{1/2}$, and the time $\frac{1}{2}n$ to infect this hole completely therefore also varies with the square root of the logarithm of the system size.

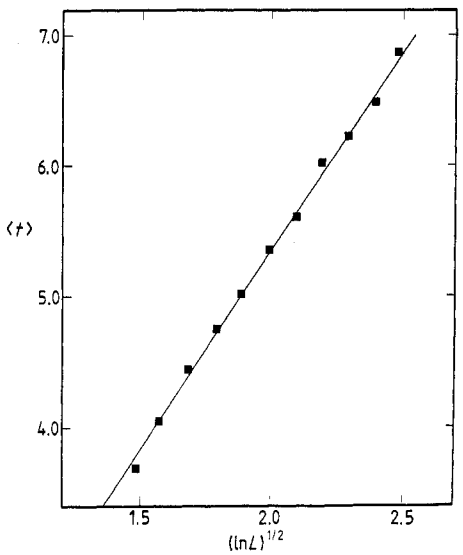

Figure 1. Variation of average time $\langle t \rangle$ for a lattice to reach state 29 at all sites, if initially a random fraction $p = 0.125$ of sites are in state 1 (killer cells), and the others in state zero (healthy). Four thousand lattice configurations of size $N = L^2$ were simulated for each L. Note the logarithmic scale for N. No sites were taken as inert. The size of the squares represents the size of the error bars.

If a randomly selected fraction of all sites is taken as inert, i.e. it always remains at $n = 0$, then the infection spreads through the lattice as in percolation theory (Grassberger 1985, Stauffer 1985). Small clusters of normal sites ($n > 0$ allowed) may be surrounded by inert sites ($n = 0$ always) and if no killer (or helper) cell was initially present in this finite cluster, then the cluster sites move to a fixed point $n = 0$, not to $n = 29$. Thus the combination of the WA model with percolation on a lattice reproduces the original possibility of two different final fixed points $n = 0$ and $n = 29$. The time

development for the spreading infection is now given by the chemical distance (Havlin and Ben-Avraham 1987). As an alternative, we took the inert sites as being in one of the 32 different states, selected randomly for each site, and again never changing throughout the simulation; now some sites end up in a final state different from 0 or 29 since they are influenced by inert neighbours.

We also introduced 'noise' in the WA lattice model (without percolation effects): with a certain probability, the spins do not obey the above rules (Lam 1988) but instead remain for this time step in their old orientation. Again $n = 29$ is the final state but now the number of activated killers remains non-zero over a longer time than without noise. This effect might be relevant biologically. Instead we also let the spin point up if, with the given probability, it did not obey the rules; then we also find $n = 29$, except that some sites also have activated killers ($n = 31$). Finally, if the spins either obeyed the WA rules or were set to zero, then no fixed point for the whole lattice was found.

In summary, the more complicated lattice version of the WA model was found not to have a more complicated behaviour than the mean-field version: the number of fixed points does not increase; instead it may decrease. This conclusion is opposite to that of Kurten (1988) who found additional fixed points if the interactions were allowed to take on all real values between -1 and 1.

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