Cellular Automata Simulation of Medication-Induced Autoimmune Diseases

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Abstract: We implement the cellular automata model proposed by Stauffer and Weisbuch in 1992 to describe the response of the immune system to antigens in the presence of medications. The model contains two thresholds, $\theta_1$ and $\theta_2$, suggested by de Boer, Segel, and Perelson to present the minimum field needed to stimulate the proliferation of the receptors and to suppress it, respectively. The influence of the drug is mimicked by increasing the second threshold, thus enhancing the immune response. If this increase is too strong, the immune response is triggered in the whole immune repertoire, causing it to attack the own body. This effect is seen in our simulations to depend both on the ratio of the thresholds and on their absolute values.

Keywords: cellular automata, phase transitions, thresholds, medical treatment, BSP model

1 Introduction

Too much of a good think may be bad. We know this from alcoholic drinks; few readers have lost as much money as Bill Gates did in 2000; and antibiotics not only saved many human lives but also created resistant strains of bacteria. Our immune system protects us against many diseases but may also go wrong and attack the own body, leading e.g. to many allergic reactions. Allergic reactions are unexpected reactions that are not caused by the normal action of the medicine and are due to stimulation of the immune system by the drug. The immune system may react in a variety of ways, most commonly by causing proliferation of lymphocytes which form antibodies. Antibodies may cause reactions when they combine with the drug.

The present note tries to model something similar: If we apply too much of a medicine strengthening our immune system, can it cause the immune cells to attack “everything” including healthy tissue, besides attacking the foreign antigen (infectious disease)? The antigen-specific immunoglobulin
interacts with mast cells to protect the host against the invading parasite. However, the same antibody-cell combination is also responsible for typical allergy or immediate hyper-sensitivity reactions such as hay fever, asthma, hives and anaphylaxis.

Presumably many immunological models [1, 2, 3] would give such an effect. To avoid adding another example to the already large number of immunology models of the last decades, we selected a variant of the de Boer-Segel-Perelson model [4], which has been cited well in the last decade. We use one of the simplifications of [5] called BSP II there; since an even simpler version, BSP III, has been criticised [6], we take a somewhat more complicated and realistic version BSP II and explain it in the next section. Thereafter we bring our results and summarise our findings.

2 Model

The immune repertoire is represented by a five-dimensional shape space of linear dimension $L$ containing $L^5$ possible types of antibodies, which the immune cells may produce to fight against as many possible types of antigens. Each of the five dimensions corresponds to give different criteria (length, electric charge, curvature, ...) by which our immune system characterises the antigen; for $L = 7$ this parameter may take the values $x = -3, -2, -1, 0, 1, 2, 3$. The five components $x$ then give a five-dimensional vector $r$ such that the null vector is the lattice centre. Just as a key has to fit a lock, apart from minor scratches, the antibody has to be complementary to the antigen in order to detect and neutralise it. Thus an antigen with $x = -2$ may be killed by an antibody with $x = +2$; more generally an antigen at a position $-r$ in the shape space is neutralised by its complementary antibody at a position $r$, or by very similar antibodies. We define as very similar the ten nearest neighbours of $r$, which differ from the fully complementary site $r$ only by a Hamming distance of one; but each of these ten neighbours contributes only one tenth as much to the immune response as the fully complementary $r$. Thus if $b(r)$ is the concentration of B cells (producing antibodies) at a site $r$ of the shape space, then

$$h(-r) = b(r) + 0.1 \sum_{n} b(r_n)$$

is the influence of the immune system on the site $-r$; the sum runs over the
Following the Weber-Fechner law of physiology, that effects increase often only logarithmic with concentration or physical amplitude, we assume the concentrations $b$ to vary exponentially:

$$b = e^B$$

where the B’s are integers varying between 0 and 20. The rule for our simultaneous updating is: $B$ increases by one if and only if the influence $h$ at that site in the shape space lies between two thresholds $\theta_1$ and $\theta_2$; otherwise it decreases by one. (If $B$ is zero it stays at zero; parameters were chosen such that $B$ does not surpass 20). The “naive” immune system thus has $B = 0$ everywhere, i.e. only one B cell per a possible shape. This threshold automata rule mimics the bell-shaped natural immune response. Now we completed the definition of model BSP II.

(Actually the BSP model does not deal with antigen-antibody reactions but with the underlying idiotypic-antiidiotypic reactions within the immune network; therefore a field $h$ of the proper value $\theta_1 < h < \theta_2$ increases and not decreases the corresponding $b$ and $B$.)

Initially we put the whole lattice to $B = 0$ except at one line of length $L$ or one hyper-plane of $L^4$ sites; this initialisation models the initial response to a specific antigen. We then ask whether this initial response remains small and localised around the initial region, or becomes large by spreading over the whole lattice. We thus monitor the sum

$$S = \sum_r b(r)$$

over the whole lattice; since our initially excited region is relatively small, it does not matter whether or not we subtract from this overall sum the sum over only the initially excited region. Thus a healthy localised immune response means $S/L^5 \simeq 1$ while a dangerous over-reaction means $S/L^5 \gg 1$. Our simulations below show a clear separation between these two behaviours. Fortran programs are available from anap@phys.uni-sofia.bg and stauffer@thp.uni-koeln.de.

To simulate the dangers of excessive medication we assume that the medicine helps the immune system by increasing the window between $\theta_1$ and $\theta_2$ within which the immune response is positive. We made a test where the medication takes effect only after a few interactions (much shorter delays
Figure 1: Double-logarithmic plot of normalised response $B/L^5$ versus scaled time $t/L$ where $t$ is the number of sweeps through the lattice. Different symbols correspond to different lattice sizes $L = 31, 37, 47, \text{ and } 53$; $\theta_1 = 10$ throughout. The upper curves have $\theta_2 = 200$, the intermediate curves $\theta_2 = 100$, and the flat line near unity mostly $\theta_2 = 50$. However, one of the $\theta_2 = 100$ curves stays flat, and one of the $\theta_2 = 50$ simulations rises and is the lowest curve in this figure.

than in the aging studies of [7]) and then found the results to be the same as if the medication effects start with the beginning of the simulation. Thus all simulations reported below use one time-independent pair of thresholds, with smaller $\theta_2/\theta_1$ corresponding to no medication, and larger $\theta_2/\theta_1$ to the effect of medicine. At what threshold $\theta_2$, for fixed $\theta_1$, does the system switch from healthy localised to dangerous, huge, spreading immune response?
Figure 2: Semilogarithmic plot of the number $S/L$ of B cells per site as a function of $\theta_2$ for fixed $\theta_1 = 10$ and $L = 31$. We see first a jump (first-order phase transition) from unity to about 100, and then a further jump to about 300. Only in the small left region the immune system works properly, with the first jump it deteriorates, and with the second jump it becomes really bad.

3 Results

Figure 1 shows how the number of B cells per site varies as a function of the second threshold $\theta_2$ for a $\theta_1$ equal to 10. The antigen presentation was simulated by randomizing one line of length $L$, while all other sites were set to $B = 0$. The results usually indicate that for $\theta_2 = 5\theta_1$ the B cell concentration stays small while for $\theta_2 = 10\theta_1$ it spreads. This general trend can be violated in some cases, see the caption to Fig.1. The constant value (the plateau) is higher for an overdosed drug, meaning that the system memorises the amount of medicine absorbed. Figure 2 shows two phase transitions a function of $\theta_2$.

The initial configuration with randomly flipped sites in one hyper-plane
models a higher response than previously. We observe different time behaviours of the system depending on both the ratio $R = \theta_1/\theta_2$ and the $\theta_1$-value.

If the first threshold $\theta_1$ is 50, then the number of B-cells remains basically unchanged for $R$ less or equal to 5, increases smoothly for $R$ about 10, or has a prominent peak for $R$ about 20. The time at which the number of B cells reaches its maximum value increases with the $\theta_2$-value, Fig.3.

A similar study with small $\theta_1$-values (5,10) shows an opposite time dependence: the peak appears at shorter times with the $R$-increase, Fig.4. However, the shapes change similarly, i.e. a smooth increase to the maximum $B$-value for $R = 5,10$. Note that a healthy response (one B cell per a site) is observed for much smaller $R$-values, about 2, e.g. for a narrower window. This is a general trend, the smaller $\theta_1$-value, the narrower window

Figure 3: Double-logarithmic plot of non-normalised response $B$ versus time $t$ for a high value of the first threshold, $\theta_1 = 50$. A healthy response of the system is observed for $R = 5$, i.e. $\theta_1 = 250$ (+). The $R = 10$ ($\theta_1 = 500$) case is shown with (x), and $R = 20$ with (*).
Figure 4: Double-logarithmic plot of non-normalised response $B$ versus time $t$ for a low value of the first threshold, $\theta_1 = 5$. A healthy response of the system is observed for $R = 2$, denoted with (+), while $R = 5$ (x) gives a smoothly increasing curve, similar to the curve for $R = 10$ in Fig.3. The $R=20$ case is shown with (*).

for a healthy response.

A different time-dependence of the immune response is sometimes observed: for example, if $\theta_1 = 30$ and $R = 20$, the number of the $B$ cells increases again after some time being almost constant (at a plateau), Fig.5. Thus it seems that the model is able to describe the 'unhealthy' response of the immune system to drugs if a specific time of treatment is surpassed.

4 Summary

Using a variant of the well-established BSP model we show that a properly working immune system may go wrong completely and attack “everything” if the second threshold is increased too much. This phase transition may
Figure 5: Double-logarithmic plot of non-normalised response $B$ versus time $t$ for one ’special’ case, $\theta_1 = 30$. The system responds normally up to $R = 10$ (+,x); for $R = 20$ (*) the plateau is observed for some time, after then the $B$-cells increase again.

explain some autoimmune diseases arising from medication.

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References

[1] A.S. Perelson and G. Weisbuch, Rev. Mod. Phys. 69 (1997) 1219.

[2] R. M. Zorzenon dos Santos and S. Countinho, Phys. Rev. Lett. 87 (2001) 168102.

[3] U. Hershberg, Y. Louzoun, H. Atlan, S. Solomon, Physica A 289 (2001) 178.
[4] R. J. De Boer, L. A. Segel and A. S. Perelson, J. Theor. Biol. 155 (1992) 295.

[5] D. Stauffer and G. Weisbuch, Physica A 180 (1992) 42.

[6] R. M. Zorzenon dos Santos and A. T. Bernardes, Physica A 219 (1995) 1.

[7] R. M. Zorzenon dos Santos and A. T. Bernardes, Phys. Rev. Lett. 81 (1995) 3034.