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Systematics of the Models of Immune Response and Autoimmune Disease

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A dynamical model of normal immune response has been formulated in terms of cellular automata by Kaufman *et al.* We generalize this model incorporating the antigens as a dynamical variable. This generalized model not only describes the kinetics of primary and secondary responses of humoral immunity, together with the appropriate memory cells, but also describes the vaccinated state as well as the states of low-dose and high-dose paralysis. Recently models of autoimmune response have also been developed in terms of discrete automata. But the models are underdetermined by the experimental facts, i.e., several models can account for the same set of observed biological facts. With an aim to find out how large this underdeterminacy is and how it can be reduced systematically, we have carried out an exhaustive computer-aided search of all those discrete three-cell and five-cell models of autoimmune response which at present cannot be ruled out by the existing biological informations. Out of the 3^{25} possible five-cell models, only one fulfilled our criteria. We also carried out simulations of the dynamics of some of these models on a discrete lattice. We discuss the relevance of random interactions in the context of autoimmune disease.

KEY WORDS: Immune response; cells; networks; automata; attractor; fixed point; limit cycle.

1. INTRODUCTION

For centuries biologists have studied not only the various mechanisms of immune response in living matter, but also developed vaccines against many of the diseases.[1] Physicists, on the other hand, would like to *describe* these apparently diverse phenomena *quantitatively* on the basis of

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the simplest possible dynamical models. Most of the theoretical models so far have been formulated in terms of differential equations.[2] In this work we shall follow a new approach[3,7],[3] formulated in terms of discrete automata.

We would like to emphasize that the new approach in terms of the discrete automata is not necessarily an alternative to the more conventional approach based on differential equations, but is complementary to the latter. In a complex system like living matter it is often very difficult to judge which are the most relevant factors that must be incorporated in a model intended to describe a particular set of biological phenomena. Moreover, it is often difficult to decide *a priori* the appropriate range of allowed values for the relevant parameters of the model. We shall argue later that the discrete automata models not only help to pinpoint the relevant variables and to fix the range of allowed values of the parameters, but also provide the basic theoretical structure that should be considered only as the zeroth approximation to the most appropriate model (see ref. 9 for a detailed justification of the automata-theoretic approach). The next step in the development of the theory would be to take the continuum limit of the dynamical equations so as to get the desired dynamical model in terms of differential equations. This last step, however, has not been carried out in this paper.

Some essential aspects of immune response are reviewed in Appendix A. Here we just explain a few relevant terms. Immune response follows if an *antigen* is recognized by the immune system. The *helper* and *suppressor* T cells, respectively, enhance and inhibit the immune response. Antigens are neutralized either by the *antibodies* produced by the B cells (humoral immunity) or by the *effector* T cells or by natural killer cells (cell-mediated immunity). Autoimmune response (AIR) follows when a part of the body is mistakenly recognized as an antigen by the immune system of the same individual.[10] Such a response can lead to an autoimmune disease, e.g., multiple sclerosis, etc. In this work we focus our attention on simple models describing normal immune response (NIR) and AIR. Whenever we talk about a cell type, we mean only those involved in the considered immune reaction.

2. THE MODELS

Our models fall within the general category of cellular automata, which have already found extensive applications in various branches of

[3] For the continuous version also see refs. 4 and 5. See ref. 6 for a critique, part of which applies to differential equations only.

science.[11] The general framework of our models can be formulated as follows[7,8]: Let us denote the *concentration* of the ith cell by S_i. We assume that each S_i can take one of two possible values: 1 corresponds to high concentration of the cell and 0 to low concentration. Thus, the concentration of each type of cell, rather than each individual cell, is assumed to behave like an automaton. Suppose C_{ij} denotes the interaction *from* the cell j *to* the cell i. Note that C_{ij} is not necessarily equal to C_{ji}. One crucial feature of our models is that the interactions C_{ij} are allowed to take only three integer values, 1, 0, -1. We assume that if the sum $\sum C_{ij}S_j(t)$ at time t is greater than a preassigned threshold, then at time $t+1$ we must have $S_i(t+1)=1$, and otherwise $S_i(t+1)=0$. Formally, this can be written as

$$S_i(t+1)=f\left(\sum C_{ij}S_j(t)\right), \qquad i,j=1,\ldots,n \tag{1}$$

where n is the total number of cell types and f is a function of the argument shown in the parentheses. The general form of the function f assumed most often in this paper is

$$f(x_i)=\theta(x_i-\mu_i) \tag{2}$$

where θ is the step function defined by

$$\begin{aligned} &\theta(y)=0 \qquad \text{for} \quad y\leqslant 0 \\ &\theta(y)=1 \qquad \text{otherwise} \end{aligned} \tag{3}$$

μ_i is a preassigned threshold at which the ith automaton switches on from the state 0 to the state 1. For the sake of simplicity, we assume the same threshold $\mu=0.5$ for all types of cells, if not stated otherwise. Unlike some of the earlier papers,[3,12] which formulated the dynamics in terms of logical operations, e.g., OR, AND, etc., the dynamics has been formulated in terms of algebraic operations in Eqs. (1)–(3). However, the logical expressions can be written in terms of algebraic operations and vice versa.

The states of all the cells are updated synchronously. The state of the whole system is described by the binary representation of the number $(S_nS_{n-1}\cdots S_2S_1)$, which describes the concentration of the n types of cells in the order specified. Therefore, the states in the three-cell model are labeled by the numbers 0 to 7, while those in the five-cell model are labeled by the numbers 0 to 31. For example, in the case of the five-cell models, $13=01101$ describes the state where the concentrations of the *first*, *third*, and *fourth* types of cells are high. For convenience, Tables IA and IB list all these states. We shall not explore any relation between our cellular-automata-type models and spin-glass models[13] in this paper.

Table IA. Eight States of Our Three-Cell Model, Type A, for Autoimmune Response[a]

State number	Cell concentration			Name of fixed point
	S	K	H	
0	0	0	0	Virgin state
1	0	0	1	
2	0	1	0	
3	0	1	1	
4	1	0	0	
5	1	0	1	Immunized state
6	1	1	0	
7	1	1	1	Sick state

[a] We include suppressors S, autoimmune effectors K, and helpers H.

Kaufman *et al.* (KUT)[3] developed a kinetic model of NIR. Unlike the concentrations of the antibody (A), the B cells (B), the T_H cells (H), and T_S cells (S), that of the antigens (E) does not have a natural dynamics in the KUT model; the concentration of the antigen enters the dynamics only as a fixed parameter ($E = 0$ and 1, respectively, corresponding to low and high dose of antigen). In the *virgin* state the concentration of all types of cells is low, the concentration of all but the T_S cells is low in the state of *paralysis*, whereas in the *active* state the concentration of all types of cells, including that of the antibodies, is high. The state in which the concentration of only the T_H and T_S cells is high was identified by KUT as the *memory* state. In the KUT model the *rate of production* of the i-type cells depends not only on the concentration of i-type cells, but also on those of the other types of cells. KUT argue that at a time t the production of a particular type of cell depends on whether the corresponding genes are on or off. However, assuming that the time delay between the switching on of a gene and full production stage is the same for all types of cells, the simple model exhibits several nice features. In the presence of antigen, the fixed points of the KUT model are the state of paralysis and the active state, whereas in the absence of antigen the fixed points are the virgin state, the state of paralysis, and the memory state. Although KUT suggested the scenario that the antigens are neutralized "after enough antibody is produced," their formal model is incapable of demonstrating it explicitly as a consequence of the dynamical evolution. In Section 3 of this paper we generalize the KUT model, incorporating explicit dynamics of the antigen and compare some of the novel features of the model with the corresponding biological phenomena. Kaufman *et al.* have also developed a five-cell

Table IB. The 32 States of Five-Cell Extended KUT Model for Normal Immune Response[a]

State number	Cell concentration					Name of fixed point
	E	B	H	S	A	
0	0	0	0	0	0	Virgin state
1	0	0	0	0	1	
2	0	0	0	1	0	Low-dose paralysis
3	0	0	0	1	1	
4	0	0	1	0	0	
5	0	0	1	0	1	
6	0	0	1	1	0	Vaccinated state
7	0	0	1	1	1	
8	0	1	0	0	0	
9	0	1	0	0	1	
10	0	1	0	1	0	
11	0	1	0	1	1	
12	0	1	1	0	0	
13	0	1	1	0	1	
14	0	1	1	1	0	Immunized state
15	0	1	1	1	1	
16	1	0	0	0	0	
17	1	0	0	0	1	
18	1	0	0	1	0	High-dose paralysis
19	1	0	0	1	1	
20	1	0	1	0	0	
21	1	0	1	0	1	
22	1	0	1	1	0	
23	1	0	1	1	1	
24	1	1	0	0	0	
25	1	1	0	0	1	
26	1	1	0	1	0	
27	1	1	0	1	1	
28	1	1	1	0	0	
29	1	1	1	0	1	
30	1	1	1	1	0	
31	1	1	1	1	1	

[a] We include antibodies A, suppressors S, helpers H, B cells B, external antigen E, and autoimmune effectors K. For five-cell AIR models, A, S, H, B, and E of the KUT table have to be replaced by antigen-specific helpers, autoimmune effectors, anti-idiotypic suppressors, anti-idiotypic helpers, and antigen-specific suppressors in the WAC sense; fixed points for Fig. 3a are virgin state 0, immunized state 29, and sick state 31.

model that distinguishes between the roles played by the immature B cells and mature B cells in immune response. However, in this paper we shall not distinguish between the mature and immature B cells.

Based on a suggestion of Jerne,[14] Weisbuch and Atlan[7] and subsequently Cohen and Atlan[8] developed a class of dynamical models for AIR. (In this paper we shall refer to these models as the WAC model.) The basic idea of this approach, at least in the Cohen–Atlan interpretation, is that for every idiotypic network (a specific set of cells that respond to a specific antigen) there is an anti-idiotypic network that recognizes the idiotypes just as the idiotypes recognize the antigen. Therefore, in the immune system consisting of mutually-interacting idiotypic and anti-idiotypic cells a deterministic dynamics is associated with each type of cell, so that the competing interactions between them lead to the various possible steady states (attractors of the dynamics) which correspond to the various possible conditions of the body, e.g., the healthy state, the immunized state, etc.

The five different types of cells constituting the WAC model can be interpreted as follows: the antigen-specific T_H cell (cell 1) (more appropriately called an *inducer* cell) the autoimmune effector T cell (cell 2), the anti-idiotypic T_S cell (cell 3), the anti-idiotypic T_H cell (cell 4), and the antigen-specific T_S cell (cell 5). In the sick state the concentration of all five types of cell is high. The immunized state corresponds to a high concentration of all but the effector cells. The dynamics in the WAC model is given by Eqs. (1)–(3) with suitable interactions. In the WAC model the immunized state is a fixed point of the dynamics, whereas the state of sickness is not; the latter state decays into the immunized state. (The only other fixed point is the virgin state.) WAC argued that if the patient can survive this critical period of sickness, it would reach the immunized state.

In reality some patients do not recover from autoimmune disease (and eventually die); for such patients only the state of sickness should be the appropriate attractor of the dynamics. On the other hand, for those patients who recover from the disease (and remain immunized against further attack by the same disease) the appropriate attractor of the dynamics is the immunized state. These differences in the final steady state may arise from two different reasons: (i) *Different initial conditions*: the initial states of these two kinds of patients may be different, although the model (i.e., the interactions and the thresholds) is the same for both; in this case the model must have both the states of sickness and immunization as its attractors. We shall refer to such models as models of *type A*. If the attractor states of sickness and immunization form a limit cycle of period two, it can be interpreted as recurring sickness. (ii) *Different dynamical equations*: the equations governing the dynamical evolution of the two

kinds of patients are different. In the latter situation there are two distinct models, one having sickness as a steady state, whereas the immunized state is that of the other. We shall refer to such models collectively as models of *type B*. Thus, models of type A have three attractors: the virgin state, the immunized state, and the sick state. On the other hand, models of type B have only two attractors: either the virgin state and the immunized state or the virgin state and the sick state. The WAC model is a five-cell model of type B and does not contain the sick state as an attractor. In Section 4 we investigate models of type A and type B systematically by computer simulation with an aim to develop three-cell and five-cell analogues of the WAC model imposing the various possible biologically-motivated restrictions on the nature of the interactions. We establish some of the general properties of such three-cell models (details are given in Appendix B). Unfortunately, the properties thus inferred can serve only as guidelines to make educated guesses of the appropriate models in a biological context.

3. EXTENDED KUT MODEL OF NIR

Our main aim in this section is to extend the original KUT model so as to treat the concentration of the antigens E as a dynamical variable rather than just a parameter. Just like the B cells, T cells, and the antibody, we shall also use two-state variables to describe the antigens. Let us denote the states of such a system of five automata by the binary representations of the numbers $(S_5 S_4 S_3 S_2 S_1)$ in that order, where $S_1 = \mathrm{A}$, $S_2 = \mathrm{S}$, $S_3 = \mathrm{H}$, $S_4 = \mathrm{B}$, and $S_5 = \mathrm{E}$. The time evolution of these five variables is given by the following five equations:

$$\mathrm{A} = \mathrm{E.AND.B.AND.H} \tag{4}$$

$$\mathrm{S} = \mathrm{H.OR.S} \tag{5}$$

$$\mathrm{H} = (\mathrm{E.AND.(.NOT.S)}).\mathrm{OR.H} \tag{6}$$

$$\mathrm{B} = (\mathrm{E.OR.B}).\mathrm{AND.H} \tag{7}$$

$$\mathrm{E} = \mathrm{E.AND.(.NOT.A)} \tag{8}$$

We shall call the model defined by Eqs. (4)–(8) the *extended* KUT model. Equation (8) is absent in the KUT model. Moreover, Eq. (7) in the extended KUT model is slightly different from the corresponding form in the KUT model. The rationale behind this latter modification is that the concentration of B cells can be high (i) in the presence of a high dose of antigen when the concentration of $\mathrm{T_H}$ cells is high, (ii) in the memory state, where the concentrations of both the $\mathrm{T_H}$ and B cells are high (although there is no antigen). (See also Neumann.[17])

The *virgin* state can contain a low dose of antigen (i.e., within the tolerance limit). We would like to interpret state 2 as that of *low-dose paralysis*, whereas the state 18 corresponds to *high-dose paralysis*. State 6 is to be interpreted as the *vaccinated* state, whereas the state 14 is the *memory* state. Note that there are high concentrations of T cells as well as B cells in the memory state which follows humoral immunity. On the other hand, the vaccinated state corresponds to a high concentration of T cells only.

The flow diagram for the extended KUT model (4)–(8) is shown in Fig. 1. The fixed points of this model are: the virgin state (0), the vaccinated state (6), the memory state (14), the state of low-dose paralysis (2), and the state of high-dose paralysis (18).

We now summarize some of the nice features of this model.

(i) *Primary response* in humoral immunity: Suppose a high dose (beyond the tolerance limit) of antigen is added to the virgin system. The corresponding initial state is now denoted by 16 (10000). The sequence of the transitions $16 \to 20 \to 30 \to 31 \to 15 \to 14$ describes the sequence of the steps in humoral immunity through NIR; the presence of antigen activates the T_H cells, which then activate the T_S and B cells, the latter then

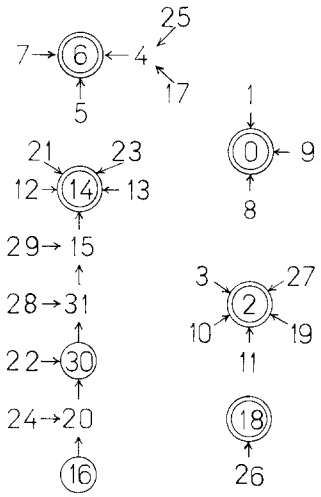

Fig. 1. The flow diagram of the states in the extended KUT model [Eqs. (4)–(8)] of normal immune response. The states are labeled by the binary representation of the numbers $(S_5S_4S_3S_2S_1)$ in the order specified; $S_i = 0$ and 1 represent, respectively, the low and high concentrations of the cells of ith type. The antibodies, the T_S cells, the T_H cells, the B cells, and the antigen correspond, respectively, to $i = 1$, 2, 3, 4, and 5. The virgin state (0), low-dose paralysis state (2), vaccination (6), the high-dose paralysis state (18), and the immunized or memory state (14) are the fixed points of the dynamics.

produces the antibodies which subsequently neutralize the antigen, and then the concentration of the antibodies falls in the absence of the antigen; the memory of the specific antigen is carried by the B and T cells forever (at least for a very long time).

(ii) *Secondary response*: This extended KUT model also describes the secondary response. Suppose antigen in sufficiently high dosage is added to a system in state 14 carrying the memory of this antigen from a previous encounter. The corresponding state now is 30. The sequence of the states $30 \to 31 \to 15 \to 14$ is also fully consistent with the secondary response observed in biological systems.

(iii) *Vaccination*: The virgin system can be vaccinated against a specific antigen by inoculation with a sufficiently high concentration of the corresponding specific T cells. Suppose a sufficiently high dose of the specific T_H cells is inoculated into the virgin system; the corresponding state is now denoted by 4. From the flow diagram in Fig. 1 it is clear that the system then ends up in the vaccinated state 6. Simultaneous inoculation with both the specific T_H and T_S cells also vaccinates the system. Invasion of the vaccinated state with a high dose of antigens takes the system to the initial state 22. Then the sequence of the states $22 \to 30 \to 31 \to 15 \to 14$ describes the NIR that follows, leading finally to the memory state.

(iv) *Paralysis*: The system can get paralyzed if the T_S cells dominate. Low-dose paralysis (state 2) follows a low dose of antigen, whereas a high dose of antigens persist in the state of high-dose paralysis (18). Invasion of the low-dose paralysis state (2) by a high dose of antigen leads to the state of high-dose paralysis (18). The transition $26 \to 18$ implies that even an inoculation of the state of high-dose paralysis with a high dose of the specific B cells fails to trigger the immune response and the system reverts back to the state of high-dose paralysis. On the other hand, the sequence of transitions $18 \to 19 \to 2$ implies that by inoculating a sufficiently high dose of the specific antibodies into the state of high-dose paralysis, it is possible to neutralize the antigens and the system goes to a state of low-dose paralysis. However, if the specific T_H cells are inoculated into the state of high-dose paralysis, the system goes to the state 22 and then the sequence of the transitions $22 \to 30 \to 31 \to 15 \to 14$ implies that a NIR follows, which finally leads to the memory state. This sequence highlights the importance of the regulatory role of the T cells in NIR.

4. DISCRETE AUTOMATA MODELS OF AIR

We have studied the systematics of the fixed points of all possible models of AIR with three and four cells, and of a subset with five cells. For

the models with 3–5 cells we have, respectively, 9, 16, and 25 possible interactions. Since each of the interaction strengths can take the values -1, 0, and $+1$, the total number of possible models with three, four, and five types of cells is $3^9 = 19{,}683$; $3^{16} = 43{,}046{,}721$; and $3^{25} \simeq 10^{12}$; respectively. The number of models having the attractors 0–7 in the three-cell models (and also the attractors 0–15 in the four-cell models), as enumerated by a computer simulation, are listed in Table II. This table shows that, depending on the biological phenomena to be described, there are always a large number of ways to choose the interactions such that the biological steady states correspond to the attractors of the model. However, as we argue in the next subsections, the number of possible choices can often be narrowed down by imposing certain reasonable restrictions on the interactions in order to be consistent with the biological evidence.

Before we begin the computer-aided search of the relevant models, let us establish two important properties of the n-cell models of type A which will be used later to compare these models with living systems. Here cell type 2 corresponds to the autoimmune effector cells and the immunized state means that the concentrations of all cell types except these effector cells are high.

Table II. The Possible Attractors and the Number of Three-Cell and Four-Cell Models of Autoimmune Response Having the Attractors

Cell types	Attractors binary representations of $(S_3S_2S_1)$	Number of models having the attractor	Cell types	Attractors binary representations of $(S_4S_3S_2S_1)$	Number of models having the attractor
	0	19683		0	43046721
	1	4900		1	8799531
	2	4900		2	8799531
	3	2634		3	4763836
3	4	4900		4	8799531
	5	2634		5	4763836
	6	2634		6	4763836
	7	1576	4	7	2783461
				8	8799531
				9	4763836
				10	4763836
				11	2783461
				12	4763836
				13	2783461
				14	2783461
				15	1713465

Theorem 1. For the general n-cell models of type A (thresholds assumed to be 0.5) both the sick state and the immunized state are *fixed points* if and only if $C_{22} = 1$.

Proof. Suppose a certain choice of the set of interactions $\{C_{ik}\}$ $(i, k = 1,..., n)$ ensures that the immunized state is a fixed point. Therefore, $\sum C_{2k} S_k = \sum' C_{2k} < 0.5$, where the prime on the summation indicates that the term $k = 2$ is excluded from the sum. On the other hand, in order to have the sick state also as a fixed point with the same choice of the interactions, we must have $\sum C_{2k} S_k = (\sum' C_{2k} + C_{22}) > 0.5$. Both these requirements can be satisfied simultaneously only if $C_{22} = 1$.

Theorem 2. For the general n-cell models of type A (thresholds assumed to be 0.5) the sick state and the immunized state constitute a *limit cycle* of period two if and only if $C_{22} = -1$.

Proof. Suppose we begin with the sick state. In order that this state makes a direct transition to the immunized state, we must have $\sum C_{2k} S_k = (\sum' C_{2k} + C_{22}) < 0.5$. On the other hand, in order to have the direct transition from the immunized state to the sick state, we must also have $\sum' C_{2k} > 0.5$. Both these conditions can be satisfied simultaneously only if $C_{22} = -1$.

We conclude from Theorems 1 and 2 that there is no model of type A with $C_{22} = 0$. However, there exist models of type B with $C_{22} = 0$. If biological evidence rules out any self-interaction of the effector cells in some biological systems, then the different final states of the different patients could still be explained by those models of type B which do not involve self-interaction of the effector cells. In our computer-aided search we do not allow negative self-interaction of any cell type, and therefore models of type A with limit cycles are excluded. So far as the interpretations of the states are concerned, the virgin state must be interpreted as the tolerant state, just as we did in the case of the NIR.

In order to eliminate the unsatisfactory models and select the most appropriate one, we impose the following *standard* conditions on the models: (i) the helpers (as well as the effectors) must not suppress and the suppressors must not help in the immune response; (ii) none of the n types of cells is allowed to have $n - 1$ vanishing interactions *from* others; trivial dynamical behavior is exhibited by cells receiving $n - 1$ vanishing interactions from others, because even if it has positive self-interaction, it would behave at best only as a fixed parameter; and (iii) two different types of cells must not have identical interactions from the others, because in that case the states of the two types of cells would remain identical for all times $t > 1$ and the n-cell model would become effectively an $(n - 1)$-cell model.

The original Weisbuch–Atlan model[7] does not satisfy condition (iii), because both cell types 3 and 4 receive identical interactions.

4.1. Three-Cell Models of AIR

In the three-cell model, cell 2 is identified as the autoimmune effector T cell; however, cell 1 represents both the antigen-specific as well as anti-idiotypic T_H cells, whereas cell 3 represents the two corresponding suppressor cells. Thus, the three-cell model does not distinguish between the antigen-specific and anti-idiotypic helper cells. The same also holds true for the suppressor cells. The "virgin state," the "state of sickness," and the "immunized state" are labeled by the numbers 0, 7, and 5, respectively, in the three-cell model. The three-cell models of type A must have the three attractors 0, 5, and 7 only, whereas the three-cell models of type B must have either the two attractors 0 and 5 or the two attractors 0 and 7.

It is worth mentioning here that in order to have the states 5 and 7 as the attractors, the interaction C_{12} must be positive whenever $C_{13} = -1$ because the threshold for switching is assumed to be 0.5. This aspect of the three-cell models may be somewhat unsatisfactory, because to our knowledge the effector cells do not act like helpers of the inducer cells in living systems.

The general form of the interaction matrix C and the number of models of types A and B are listed in the Table III. Out of the five models of type A, only one, shown in Fig. 2a, satisfies all the standard conditions (i)–(iii). Note, however, that this model has the drawback that none of the states, other than the state 5 itself, flows into the state 5 following the dynamics.

Out of the 15 three-cell models of type B with the attractors 0 and 5, only three satisfy the standard conditions (i)–(iii). Only two of these, shown in Figs. 2b and 2c, have $C_{22} = 0$. Both models have the nice feature

Table III. The Number of Various Types of Possible Three-Cell Models of Autoimmune Response[a]

Model (interaction matrix)			Attractors	Number of models
0, 1	0, 1	−1, 0	0, 5, 7	5
0, 1	0, 1	−1, 0	0, 5	15
0, 1	0, 1	0, 1	0, 7	26

[a] The symbol x, y for an element of the interaction matrix implies that the element is allowed to have either of the two values x or y.

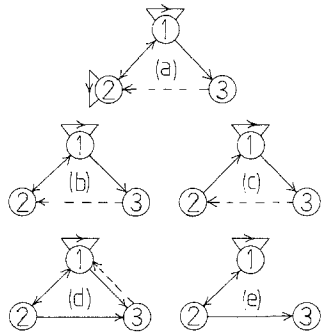

Fig. 2. The three-cell models of autoimmune response. The automata 1, 2, and 3 represent, respectively, the concentrations of the T_H cells, the autoimmune effector cells, and the T_S cells. For the constraints imposed on the interactions see Table III. The virgin state (0), the immunized state (5), and the sick state (7) are the only attractors of model (a). The attractors of models (b) and (c) are 0 and 5, whereas those of models (d) and (e) are 0 and 7.

that state 4, in which the suppressors dominate, flows into the virgin state (i.e., the tolerant state) without passing through the sick state. In order to decide which of these two models is more realistic, we examined the detailed features of their flow diagrams. For example, the sequence of states that lead from state 1 to state 5 are $1 \to 7 \to 5$ in model 2b and $1 \to 5$ in the model 2c. In our view, the former is more realistic than the latter. In fact, beginning from any of the states 1, 2, 3, or 6, the system reaches state 5 in model 2b always passing through the sick state. On the other hand, the system becomes immunized starting from the states 1, 2, 3, or 6 without ever becoming sick. Although there is no natural route to the sick state in model 2c, the sick state, once prepared, decays into the immunized state. Therefore, we believe that model 2b is more realistic than model 2c.

Out of the 26 three-cell models of type B with the attractors 0 and 7, only 9 satisfy all the standard conditions (i)–(iii). Only two of these, shown in Figs. 2d and 2e, have $C_{22} = 0$. Both models have the common feature that state 4 flows into the virgin state. But, states 2, 5, and 6 end up in the virgin state in model 2d, whereas the same states end up in the sick state in model 2e. Therefore, we consider model 2e to be more satisfactory than model 2d. Thus, we conclude that so far as the three-cell models of type B are concerned, the models of Fig. 2b (having the attractors 0 and 5) and Fig. 2e (having the attractors 0 and 7) are the most satisfactory.

4.2. Five-Cell Models of AIR

The automata 1, 2, 3, 4, and 5 describe, respectively, the antigen-specific T_H cell, the autoimmune effector cell, the anti-idiotypic T_S cell, the

anti-idiotypic T_H cell, and the antigen-specific T_S cell, as in the WAC model. The five-cell models of type A must have the attractors 0, 29, and 31 only, whereas the five-cell models of type B must have either the two attractors 0 and 29 only or the two attractors 0 and 31 only.

We begin the computer-aided search of the five-cell models of AIR with the following assumptions: (a) The antigen-specific effector cells do not send any stimuli to the other cells in the same antigen-specific network, i.e., $C_{12} = 0 = C_{52}$; this restriction was also imposed by Weisbuch and Atlan on their model of AIR. (b) The helper-to-effector, the suppressor-to-effector, and the helper–suppressor interactions within the antigen-specific idiotypic network are never broken, i.e., $C_{21} = 1$, $C_{25} = -1$, $C_{15} = -1$, and $C_{51} = 1$. These restrictions are different from the corresponding ones in the WAC models; cells 1 and 5 do not interact directly in the latter models. (c) None of the cell types is allowed to have negative self-interaction. However, only the cells of the antigen-specific idiotypic network are allowed to maintain their concentration through positive self-interaction in the absence of inputs from other cells, i.e., $C_{kk} = 0$ or 1 for $k = 1$, 2, and 5, but $C_{kk} = 0$ for $k = 3$ and 4. (d) Since direct helper–suppressor interaction within the anti-idiotypic network is not required for its coupling to the idiotypic network, we assume $C_{34} = 0 = C_{43}$. (e) A high concentration of the suppressors in one network does not directly influence the helpers and suppressors of the other network, i.e., $C_{45} = 0 = C_{13}$ and $C_{35} = 0 = C_{53}$. The assumptions (a)–(e) lead to the interaction matrix of the form shown in Table IV; the corresponding numbers of models of type A and type B are also listed.

Out of the nine five-cell models of type A, only two, shown in Figs. 3a and 3b, satisfy all the standard conditions (i)–(iii). Of these, model 3a seems to be more realistic than model 3b because cell 3 does not influence

Table IV. The Number of Various Types of Possible Five-Cell Models of Autoimmune Response[a]

Model (interactions matrix)					Attractors	Number of models
0, 1	0	0	0, 1	−1	0, 29, 31	9
1	0, 1	−1, 0	0, 1	−1		
0, 1	0, 1	0	0	0	0, 29	30
0, 1	0, 1	0	0	0		
1	0	0	0, 1	0, 1	0, 31	35

[a] The symbol x, y for an element of the interaction matrix implies that the element is allowed to have either of the two values x and y.

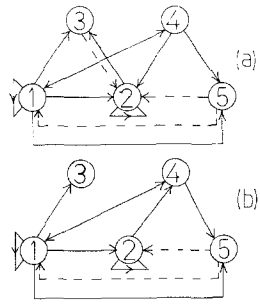

Fig. 3. The five-cell models of autoimmune response. The automata 1, 2, 3, 4, and 5 represent, respectively, the antigen-specific T_H cell, the autoimmune effector, the anti-idiotypic T_S cell, the anti-idiotypic T_H cell, and the antigen-specific T_S cell. For the constraints imposed on the interactions see the text. The virgin state (0), the immunized state (29), and the sick state (31) are the only attractors of the dynamics of each of these two models.

any other cell in the latter. The flow diagram of the model in Fig. 3a is shown in Fig. 4. The symmetry requirements of Hoffmann[6] are fulfilled in Fig. 3, at least for $C_{14} = C_{41}$, $C_{35} = C_{53}$.

Of the 30 models of type B with the attractors 0 and 29, there are only 6 with vanishing C_{22} which satisfy all the standard conditions (i)–(iii). These 6 models are shown in Figs. 5a–5f. Because of our assumption (b), the models shown in Fig. 5 possess nonzero C_{15} and C_{51}, unlike the WAC models, which have $C_{15} = 0 = C_{51}$. There are several common features of these 6 models, e.g., state 3 leads to the immunized state via the sick state.

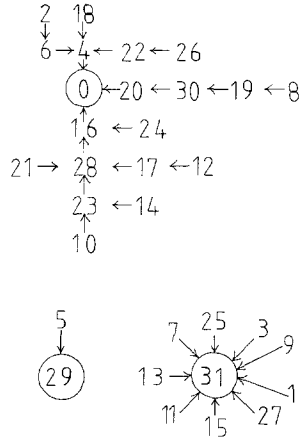

Fig. 4. The flow diagram of the states in the five-cell model of AIR shown in Fig. 3a. The fixed points are 0, 29, and 31.

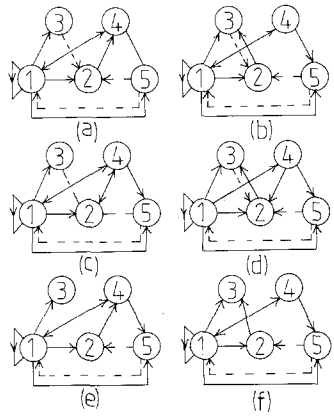

Fig. 5. Same as Fig. 3, except that the attractors are the virgin state (0) and the immunized state (29).

However, only model 5c leads from the state 10 (= 1010) to the immunized state via the sick state, as it should. Therefore, we believe the model in Fig. 5c is more realistic than the other five models in Fig. 5. The flow diagram of the model in Fig. 5c is shown in Fig. 6. This diagram shows that there are some differences between the dynamics of this model and those of the Weisbuch–Atlan model[7] and Cohen–Atlan models.[8] These differences arise from the differences in the interaction matrices of these models.

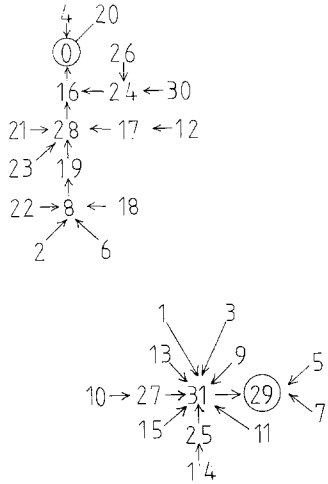

Fig. 6. The flow diagram of the states in the five-cell model of AIR shown in Fig. 5c. The fixed points are 0 and 29.

Let us now briefly compare the various models studied in this section. The five-cell models distinguish between the idiotypic and the anti-idiotypic networks, whereas the three-cell models do not. The four-cell models treat the helper and the suppressor cells differently. Although we have also studied the four-cell models, we do not present those results in this paper. However, all the n-cell models of type A require self-interaction of the effector cells.

5. CONCLUSION

In this paper we have carried out a systematic investigation of a class of models of NIR and AIR where the *concentrations* of the various cells are represented by discrete automata and the set of interacting automata are assigned a rule of dynamical evolution. Some special features of these models[7,8] are: (i) the number of cell types is small (typically three to five); (ii) each of the automata can assume only one of two possible values, 0 and 1, i.e., only two levels of concentration of the cells are distinguished, low and high; (iii) only three values of the strengths of the interactions are allowed, -1, 0, and 1; and (iv) each automaton switches on from the 0 state to the 1 state at a preassigned threshold value of the sum of the stimuli it receives from the other automata.

So, even within the general framework of discrete automata, there are several possible ways of generalizing these models. (a) If it is found necessary to include more types of cells, the number of automata in the theory can be easily increased. (b) In order to describe various levels of concentration of the cells, the number of allowed values of the automata can also be increased. (c) More flexibility in the magnitudes of the interactions would allow one to express the relative strengths of the various positive (also negative) interactions.[18] (d) The thresholds assigned to the different automata can also be varied according to necessity.

Finally, once a small number of possible models has been selected in terms of the discrete automata, the corresponding differential equations can be written by following well-established procedures.[3,19]

In this paper we have studied only models with discrete automata. We have proposed a simple generalization of the KUT model for NIR which provides a more satisfactory description of the observed biological phenomena. We have also investigated the models of AIR of the type proposed recently by Weisbuch, Atlan, and Cohen. Atlan *et al.*[8,9] state that at present the models are underdetermined by experimentally known biological facts, i.e., often several models can explain the same set of biomedical phenomena. In this work we have laid down some reasonable restrictive criteria which help in reducing this underdeterminacy in the

context of AIR. Within these restrictions, we made a *systematic* search of the satisfactory models, i.e., we went through *all* possible n-cell models for $n = 3$, 4, and 5. This systematic aspect distinguishes our work from the previous work known to us.[3–9,12]

From the point of view of biology, several further extensions of these models are possible: (i) different responses of the immature and mature B cells should be distinguished by the theory, (ii) the two types of B cells, namely those which differentiate into plasma cells (which in turn produce the antibodies) and those which become memory cells, should also be distinguished, and (iii) inclusion of both humoral immunity and cell-mediated immunity and also both NIR and AIR in the same model would be more satisfactory than having separate models.

Further progress in this field of study requires further experimental input into the theory as well as theoretical output in terms of an experimentally verifiable description of a wider variety of biological phenomena.

APPENDIX A. A BRIEF INTRODUCTION TO IMMUNE RESPONSE

The immune system consists of *fixed* components, e.g., the bone marrow, the thymus, lymph nodes, spleen, etc., and *circulating* components, e.g., the lymphocytes and the phagocytes. When challenged by invading microbes, generally called the *antigen*, the *macrophages* (large mononuclear phagocyte cells) respond in a non-antigen-specific manner. In contrast to this process of *phagocytosis*, the response of the lymphocytes is antigen-specific, as explained below.

The lymphocytes are broadly divided into two classes: the *B cells* (produced from the stem cells in the bone marrow) and the *T cells* (matured in thymus); they are distinguished by the presence of different surface molecules and by their modes of response to the antigens. In addition to the B and T cells, there are small populations of *natural killer cells* which are capable of neutralizing the antigen by killing the target cells. The T cells can be divided further into two functionally different classes; these are called T4 cells (having CD4 membrane glycoprotein) and T8 cells (having CD8 membrane glycoproteins). The T4 and T8 *effector cells* are *cytotoxic* (killers of target cells). Usually, T4 regulator cells are helpers that help in the response of macrophages and specific B lymphocytes, whereas T8 regulators are suppressors which inhibit (sometimes even terminate) an immune response.

For an antigen-specific response the antigen must be recognized by the specific lymphocytes. The membrane immunoglobulins on specific B cells

can directly recognize a specific antigen in its native form by a procedure analogous to key-and-lock matching. A pattern stored in a part of the antigen, called the *epitope*, is the analogue of the lock, and the surface immunoglobulin receptors of the B cells are the analogues of the key. The T cells, on the other hand, cannot recognize the antigen unless the antigen is presented properly. Antigen presentation is a process whereby a cell (either a macrophage or a B cell or a target cell) expresses antigen on its surface in a form recognizable by a T cell. Each lymphocyte possesses membrane immunoglobulin receptors of a single specificity. Therefore, subsequent to the receptor–epitope matching, a specific lymphocyte proliferates rapidly into a *clone* (a population of genetically identical cells) and the corresponding process is called *clonal selection.* The lymphocytes and macrophages coordinate their action through lymphokines.

Rapidly proliferating B cells play a crucial role in *humoral immunity.* Terminal differentiation of a fraction of this B-cell population lead to *plasma cells* which synthesize and secret immunoglobulins, called *antibodies*, having the same specificity as the membrane receptors of the original B cells. The antibodies react with the antigen and neutralize it. During their proliferation some B cells become dormant and do not differentiate into plasma cells. These dormant B cells carry the memory of the antigen encountered and therefore are called memory B cells.

The T cells are responsible for *cell-mediated immunity* as well as regulation of the growth and differentiation of the B cells in humoral immunity. *Inducer* T-cells activate T_H, T_S, and cytotoxic T cells, whereas T_H cells activate the B cells. Unlike the B cells, the T cells cannot produce antibodies, though cytotoxic T cells can neutralize antigens. Memory T cells, together with the memory B cells, patrol the body and provide quicker secondary response on future encounter with the same antigen.

Note that immune response follows if and only if the dose of antigen exceeds a certain tolerance limit. Immunological tolerance can be a consequence of inactivation of the B or T_H cells or activation of T_S cells. Tissues located at anatomically privileged sites not in contact with the circulation do not induce tolerance of lymphocytes. When such tissues somehow come in contact with lymphocytes, the latter can respond in a manner as if the tissue is an antigen, and the response that follows is called an autoimmune response. (An alternative origin of AIR is a change in the network.[8])

Just as tissues can be recognized by the immune system of the same individual, the lymphocytes can also be recognized by other lymphocytes. The network of B, T_H, and T_S cells that defend the individual against a certain antigen constitute an *idiotypic network.* Those lymphocytes which get stimulated following a recognition of the idiotypic network are said to form the *anti-idiotypic network.* Thus, in principle every idiotypic network

has an anti-idiotypic network; the balance between the two is disrupted when the idiotypic network recognizes an antigen. Subsequently, the anti-idiotypic network must respond and bring the system to a steady state. This is a crucial mechanism for recovery from autoimmune diseases.

APPENDIX B. GENERAL PROPERTIES OF THREE-CELL MODELS OF TYPE A

In this appendix we list some of the special properties of the three-cell models of type A. By the term *restricted* model in this appendix we mean only those models having the general form of the interactions shown in Table III.

Theorem B.1. The self-interaction of cell 1, C_{11}, in restricted three-cell models of type A must be positive.

Proof. For the three-cell models of type A we must have

$$C_{11} + C_{13} > 0.5 \tag{B.1}$$

Since C_{13} cannot be positive, we must have $C_{11} = 1$. Note also that if $C_{13} = -1$, condition (B.1) would be violated. This leads to the following corollary.

Corollary B.1. Restricted three-cell models of type A must have $C_{13} = 0$.

Theorem B.2. The self-interaction of cell 3, C_{33}, in restricted three-cell models of type A must vanish.

Proof. The three-cell models of type A must satisfy the condition

$$C_{31} + C_{33} > 0.5 \tag{B.2}$$

This condition would be violated if $C_{33} = -1$. On the other hand, since both C_{13} and C_{23} cannot be positive and since the thresholds are 0.5, state 4 would become a spurious fixed point if $C_{33} = 1$. Thus, the only allowed value of C_{33} is zero. This result, together with condition (B.2), leads to the next corollary.

Corollary B.2. The restricted three-cell model of type A must have $C_{31} = 1$.

Theorem B.3. For stable fixed points (no limit cycles) in the restricted three-cell models of type A, we must have $C_{21} = 1$ whenever $C_{23} = -1$.

Proof. State 7 would be a fixed point provided

$$C_{21} + C_{22} + C_{23} = C_{21} + C_{23} + 1 > 0.5 \tag{B.3}$$

If $C_{23} = -1$, the only way to satisfy condition (B.3) is to choose $C_{21} = 1$.

APPENDIX C. LATTICE MODELS OF IMMUNE SYSTEMS

Only the *global* concentration of each cell type enters into the KUT and WAC models and therefore there is no intrinsic length scale in these models. In order to take into account the local fluctuations, if any, of the five different types of cells in the Weisbuch–Atlan model, Dayan *et al.*[15] introduced an extended version of the WA model. The model of Dayan *et al.* consists of N sites on a d-dimensional lattice, each lattice site containing five different types of cells. Each of the lattice sites has been interpreted as a local neighborhood in the immune system. Each cell interacts not only with the other cells at the same site, but also with those at the $2d$ nearest-neighbor sites on the d-dimensional hypercubic lattice. The results of computer simulation of the lattice models in two[15] and three[12,16] dimensions have already been reported. Very recently, Neumann[17] has simulated the KUT model on a lattice. The WAC and KUT models can be regarded as the mean-field approximations, respectively, to the models of Dayan *et al.*[15] and Neumann.[17] We have also simulated the lattice versions of our models. From the point of view of statistical mechanics such short-range lattice models are more interesting than the corresponding mean-field (infinite-range interaction) models. However, in the present context the biological relevance of the lattice model is not clear, because usually cells and antigens spread relatively fast within the body.

C.1. Nonrandom Lattice Models of Immune Response

As emphasized elsewhere,[12,17] for a given model of immune response, there is no unique prescription for formulating the corresponding lattice versions. However, our final results are not sensitive to these finer details. We simulated systems as large as 9600×9600 on a Cray-YMP and could update up to 1600 cells/μsec per processor. So far as the initial states are concerned, in the case of the extended KUT model on a lattice, 1% of the sites are assumed to have a high concentration of antigen, and in the case of the models of AIR, 1% of the sites are assumed to have a high concentration of the inducers. The choice of 1% is, of course, arbitrary. In the case of the extended KUT model the state 14 is found to spread over the

whole lattice just like forest fire. Similarly, in the case of the models of AIR, depending on the particular model, either the immunized state or the sick state spreads. The time taken to get into the final state varies as $(\log L)^{1/2}$ for $L \times L$ lattices. This spreading phenomenon is very similar to that observed by Dayan *et al.* and can be explained in the same way. More interesting phenomena are observed in these lattice models if the thresholds for the cells are increased to 5/2, as suggested by Weisbuch.[20]

C.2. Randomly Mixed Lattice Models of Autoimmune Response

Let us first give the motivation for constructing such random models.[12] Suppose the *local neighborhoods* in a biological system can be perturbed independently by some means such that the interaction between two types of cells can be broken at some parts of the body. In order to describe such a situation, it would be appropriate to have a lattice model where each lattice site chooses one of the two possible dynamics with a given probability. This is the motivation behind the choice of randomly mixed interactions.

Although the principles are quite general, we use specific examples just to illustrate the main features. We begin by defining two three-cell models on a d-dimensional lattice. Model I is defined by

$$\begin{aligned} S_1(t+1) &= \theta\left\{\sum [S_1(t) + S_2(t)]\right\} \\ S_2(t+1) &= \theta\left\{\sum [S_1(t) - S_3(t)]\right\} \\ S_3(t+1) &= \theta\left\{\sum S_1(t)\right\} \end{aligned} \tag{I}$$

and model II is given by

$$\begin{aligned} S_1(t+1) &= \theta\left\{\sum [S_1(t) + S_2(t)]\right\} \\ S_2(t+1) &= \theta\left\{\sum S_1(t)\right\} \\ S_3(t+1) &= \theta\left\{\sum S_2(t)\right\} \end{aligned} \tag{II}$$

where $\theta(x)$ is the same function as defined by Eq. (3). The summations are

to be performed over the site i as well as the nearest-neighbor sites of i on the lattice.

In this random model at every instant of time each of the lattice sites randomly chooses to follow dynamics I (or dynamics II) with probability p (with probability $1-p$). Randomness enters this model through the probabilistic choice of the dynamics by each lattice site at every time step. Since randomness in this model is a function of time, it is an *annealed* model. One can also develop the corresponding *quenched* model, where the rules of dynamical evolution, once chosen probabilistically for the various sites at $t=0$, remain unchanged for all later times. The reason we chose these two particular models for illustration is that the mean-field versions of these two models are the two satisfactory models of type B, shown in Figs. 2b and 2e.

The special cases $p=1$ and $p=0$ correspond, respectively, to the two nonrandom models I and II. Only 1% of the lattice sites are assumed to have initially high concentration of the inducer cells. It is quite straightforward to see that in the case of models I and II, respectively, states 5 and 7 spread over the whole lattice, just like the spreading phenomenon in the case of the other nonrandom models described in the preceding subsection.

For $0<p<1$ we observed that in the steady state of both the annealed and quenched models a fraction p of the lattice sites are in state 5, whereas the remaing sites are in state 7. In the annealed case the state of an individual lattice site keeps fluctuating between 5 and 7 for all times, although at every instant of time the fraction of the sites in state 5 (and also in 7) remains p, except for small statistical fluctuations arising from the finite lattice size. This is analogous to an annealed random spin system.

A different type of lattice model[21] regards an occupied site as a single cell or antibody and observes the motion and reaction of such cells on a sparsely populated lattice. We did not use this method here.

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