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An Immune System Model in Discrete Time Based on the Analogy with the Central Nervous System

K. E. Kürten[1]

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Jerne's model for the immune system formulated in terms of a neural network recently proposed by Weisbuch and Atlan is generalized to interactions with continuous coupling coefficients. It is shown that even the extended model can be solved analytically without the aid of computer simulations and exhibits one additional attractor, which corresponds to a configuration with high concentrations of active killer cells eventually causing death of the organism.

KEY WORDS: Immune system; neural networks; Weisbuch–Atlan model; nonlinear phenomena.

It has long been known that the immune system and the central nervous system share many striking features at the level of system behavior, suggesting that similar mathematical models might be appropriate for each of them.[1,2] Though the two systems penetrate most other tissues of the body, the lymphocytes (white blood cells) never come into direct contact with nerve cells, being separated by the blood–brain barrier. Both biological systems consist of several billions of highly specialized cells connected by excitatory and/or inhibitory interactions to a small subset of the system, exhibit memory related to the existence of attractors, and learn from experience by building up a memory sustained by reinforcement, which might be formulated in terms of Hebbian-like self-organization rules.[3] In humans, the central nervous system consists of about 10^{10} neurons, whereas the immune system contains roughly 10^{12} lymphocytes moving freely, unlike nerve cells, which remain in fixed positions in the brain. Meanwhile, there is compelling evidence from experiments for Jerne's postulate that the immune system can be described by a functional network.[1,2]

[1] Institut für Zoologie, Sektion Biophysik, Johannes Gutenberg-Universität, 6500 Mainz, West Germany, and Institut für Theoretische Physik, 5000 Cologne, West Germany.

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In the spirit of Jerne,[1] Weisbuch and Atlan[4] recently discussed a fairly simplified immune network model guided by Cohen's experimental findings on autoimmune encephalomyelitis.[5] The proposed network consists of five interacting binary pools of interconnected formal threshold cells, killer cells C_1, activated killer cells C_2, helper cells C_4, and two kinds of suppressor cells C_3 and C_5, induced by the killer cells C_1 and the helper cells C_4, respectively. The state of each pool can either take the value $\sigma_i = 1$ or $\sigma_i = 0$, $i = 1,..., 5$, depending on the existence of high or low concentrations with respect to different cell types. The synchronous and fully deterministic dynamics of this network is reminiscent of the pioneering discrete-time neural network model of McCulloch and Pitts[6] and can be described by the following set of equations of motion, where the five spins are supposed to be updated simultaneously according to (Fig. 1)

$$\sigma_1(t+\tau) = \Theta\{c_{11}\sigma_1(t) - c_{13}\sigma_3(t) + c_{14}\sigma_4(t)\} \tag{1a}$$

$$\sigma_2(t+\tau) = \Theta\{c_{21}\sigma_1(t) - c_{23}\sigma_3(t) + c_{24}\sigma_4(t) - c_{25}\sigma_5(t)\} \tag{1b}$$

$$\sigma_3(t+\tau) = \Theta\{c_{31}\sigma_1(t)\} \tag{1c}$$

$$\sigma_4(t+\tau) = \Theta\{c_{41}\sigma_1(t)\} \tag{1d}$$

$$\sigma_5(t+\tau) = \Theta\{c_{54}\sigma_4(t)\} \tag{1e}$$

The theta function is supposed to be unity for positive arguments and zero elsewhere. The bracket terms in Eq. (1) have their analog in the membrane potential in a neural network. The quantity τ may be interpreted as the scale of the generation time, presumably of the order of a few days. Without loss of generality, the strengths of the interactions between the cells specified by the quantities c_{ij} can be chosen arbitrarily in the interval [0, 1], whereas Weisbuch and Atlan assume that the coupling coefficients c_{ij} are all equal to one. Note that in the present model the coupling coefficients are in general not symmetric, in contrast to the immune network recently proposed by Hoffmann and accepted by Jerne.[2] The minus signs in the dynamical equations (1.1) and (1.2) correspond to the inhibitory character of the suppressor cells C_3 and C_5 with respect to their target cells C_1 and C_2, respectively.

The time evolution of any physical quantity of interest follows immediately from the rather elementary mathematical nature of the model. Since the crucial active killer cells C_2 inducing the disease do not give any input to the other cells of the network, they have no impact on the dynamical evolution of the system. The same arguments hold for the suppressor cells C_5 with respect to the pools C_1, C_3, and C_4. Hence, the equations of motion for the pools C_2 and C_5 decouple. Moreover, after the

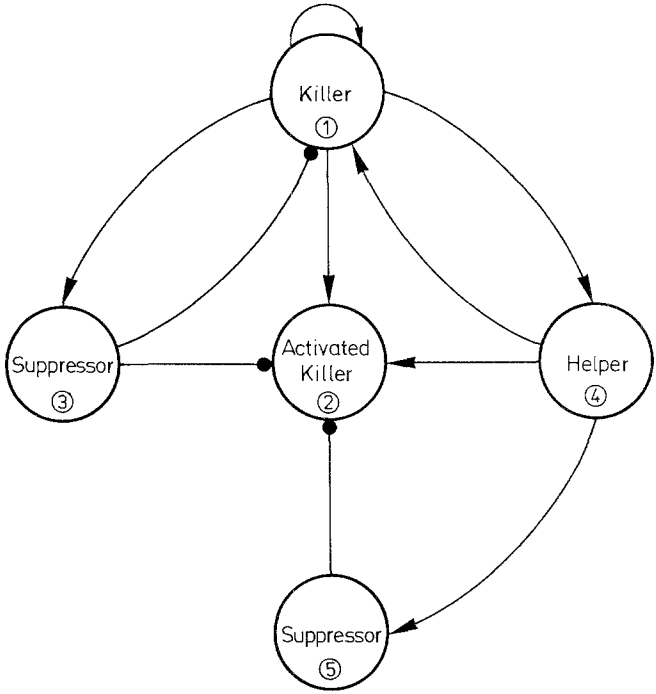

Fig. 1. Schematic representation of positive (arrows) and negative (dots) couplings among the five pools.

first time step the state of C_3 equals the state of C_4 and the problem can be reduced to the two-pool system with the dynamical evolution

$$\begin{aligned} \sigma_1(t+\tau) &= \Theta\{\sigma_1(t) + x_1\sigma_3(t)\} \\ \sigma_3(t+\tau) &= \Theta\{\sigma_1(t)\} \end{aligned} \tag{2}$$

where $x_1 = (c_{14} - c_{13})/c_{11}$ serves as a convenient control parameter, properly describing all the relevant configurations of the efficacies contributing to the dynamics of the killer pool C_1. It is straightforward to verify that, independent of the choice of the coupling coefficients in the interval [0, 1] for $t \geqslant 3$,

$$\sigma_1(t) = \sigma_3(t) = \sigma_4(t) \tag{3}$$

holds. This result eventually implies

$$\sigma_1(t) = \sigma_3(t) = \sigma_4(t) = \sigma_5(t) \tag{4}$$

and the relevant state of the active killer cells C_2 can the finally be determined from

$$\sigma_2(t+\tau) = \Theta\{x_2\sigma_1(t)\} \tag{5}$$

The coefficient

$$x_2 = c_{21} + c_{24} - (c_{23} + c_{25}) \tag{6}$$

serves as a second control parameter describing the balance of the strength of the inhibitory and excitatory activations of the killer, helper, and suppressor cells C_1, C_3, C_4, and C_5 on their targets, the activated killer cells C_2. Their state evidently depends uniquely on whether or not the sum of the efficiencies of the helper cells exceeds the sum of the efficiencies of the suppressor cells. Thus, only for $x_2 > 0$, when the efficacies of the helper and killer cells are dominant, will the pool of the active killer cells C_2 always be in state one, supposing that all the other cells are present in high concentrations. On the other hand, if the suppressive weights are dominant, $x_2 \leqslant 0$, the active killer cells will always be in state zero. The "number" of an attractor with respect to its configuration is defined in terms of its decimal representation according to[4]

$$\underline{n} = \sigma_1 + 2\sigma_2 + 2^2\sigma_3 + 2^3\sigma_4 + 2^4\sigma_5 \tag{7}$$

varying between $\underline{0}$ and $\underline{31}$.

Thus, Eqs. (3) and (4) imply that the model exhibits only three stable fixed points: the healthy virgin state $\underline{0} = (0, 0, 0, 0, 0)$, the healthy carrier state $\underline{29} = (1, 0, 1, 1, 1)$, where active killer cells are only present in small concentrations, and the totally infected state $\underline{31} = (1, 1, 1, 1, 1)$. It is interesting to note that by introducing a nonzero threshold for the theta function in Eq. (1) a variety of different attractors can be reached, depending on the choice of the coupling coefficients. Since in the model proposed by Weisbuch and Atlan,[4] where the coupling coefficients are restricted to unit magnitude, the control parameter x_2 is strictly zero, attractor $\underline{31}$ does not occur in their model.

Table I shows which attractors are reached from different initial concentrations of the pools C_1, C_3, and C_4 as a function of the control parameters x_1 and x_2. The initial concentrations of the pools C_2 and C_5 can be chosen arbitrarily.

One finds that for the choice $x_1 \leqslant -1$ $(c_{11} + c_{14} \leqslant c_{13})$, meaning that the sum of the efficacies of the helper and killer cells C_1 and C_2 is less than or equal to the efficacy of the suppressor cells C_3, the state of all pools will eventually be zero for arbitrary initial concentrations. On the other hand,

Table I. Stable Attractors Corresponding to Different Initial Concentrations for Different Control Parameter Regimes

C_1	C_3	C_4	Attractor	Control parameter regimes
1	1	1	31	$x_1 > -1$ and $x_2 > 0$
1	0	1	29	$x_1 > -1$ and $x_2 \leqslant 0$
0	0	1	0	$x_1 \leqslant -1$
1	0	0		
0	1	1	31	$x_1 > 0$ and $x_2 > 0$
1	1	0	29	$x_1 > 0$ and $x_2 \leqslant 0$
			0	$x_1 \leqslant 0$
0	0	0	0	
0	1	0		

for the choice $x_1 > 0$ ($c_{14} > c_{13}$), when the efficacy of the killer cells C_1 exceeds the efficacy of the suppressor cells C_3, the system falls on attractor 29 or 31 independent of the initial condition except if there are *neither* killer *nor* helper cells present in the initial configuration. For the parameter choice $-1 \leqslant x_1 < 0$ ($c_{11} + c_{14} > c_{13} > c_{14}$), when the efficacies of the sum of the killer and helper cells C_1 and C_4 exceed or equal the efficacy of the suppressor cells C_3, which themselves have a higher efficacy than the killer cell, the final state depends on whether the initial concentrations of the killer and helper cells are larger or smaller than the concentration of the suppressor cells. In the latter case the fixed point 0 is reached for half of the possible initial concentrations, whereas the fixed points 29 and 31 are reached in the first case.

The model proposed by Weisbuch and Atlan,[4] where the quantities x_1 and x_2 are strictly zero, is a special case of the latter constellation ($0 \leqslant x_1 < -1$), only leading to the attractor 29 for 16 initial conditions, when the sum of the initial concentrations of the killer and helper cells C_1 and C_4 exceed the concentration of the suppressor cells C_3; for the remaining 16 initial conditions, where the inhibitory effect is dominant, the system falls evidently on attractor 0. Thus there is always a 100% chance of surviving $[C_2(t) = 0]$ if the scale of the incubation time for intermediate states like 31 is not too long.

In the model generalized to continuous coupling coefficients, the situation is somewhat different. Assuming that the coupling coefficients are chosen randomly according to a uniform distribution $\rho(z)$ in the interval $[0, 1]$, the probabilities $P(x_1 > 0)$, $P(x_1 > -1)$, and $P(x_2 > 0)$ with respect to Table I can be calculated by evaluating the integrals

$$P(x_1 > 0) = \iint \rho(z_1)\, \rho(z_2)\, \Theta(z_1 - z_2)\, dz_1\, dz_2 \tag{8a}$$

$$P(x_1 > -1) = \iiint \rho(z_1)\, \rho(z_2)\, \rho(z_3)\, \Theta(z_1 - z_2 + z_3)\, dz_1\, dz_2\, dz_3 \tag{8b}$$

$$P(x_2 > 0) = \iiiint \rho(z_1) \cdots \rho(z_4)\, \Theta(z_1 - z_2 + z_3 - z_4)\, dz_1 \cdots dz_4 \tag{8c}$$

$P(x_1 > 0)$ as well as $P(x_2 > 0)$ evidently take the value one-half, whereas $P(x_1 > -1)$ can be calculated analytically for the uniform distribution, taking the value $P(x_1 > -1) = 5/6$. Consequently, the attractor $\underline{0}$ is reached with a probability ~ 0.46, whereas attractors $\underline{29}$ and $\underline{31}$ are reached with the same probability ~ 0.27, still giving rise to an $\sim 73\%$ chance of surviving for a random distribution of the initial concentrations as well as the coupling coefficients.

Preliminary computer simulations on a generalization of the Weisbuch–Atlan model to extended systems containing large numbers of units, each of them consisting of five pools of the different cell types interacting with itself and four randomly chosen units in the same way as the single pool with itself in the original model, indicate again that essentially the healthy carrier state $\underline{29}$ and the totally infected state $\underline{31}$ survive within each unit. The attractor $\underline{0}$ is only reached with a very small probability decreasing with increasing system size. This more realistic model with infinitely ranged neighbor interactions between the units more attuned to immunological reality shows the remarkable effect that the presence of one single killer cell in a network turns out to be able to infect large populations of units being connected by a topological path within the network. This study parallels a current work of Dayan *et al.*,[7] where, in analogy with cellular automata, the basic units reside on a regular lattice exclusively interacting with *nearest* neighbors—somewhat less in accord with biological reality—and coupling coefficients are constrained to unit magnitude. They report that the system in general falls on attractor $\underline{29}$, whereas only in pathological limit cases is the attractor $\underline{0}$ reached in their model.

An alternative description of the problem can be formulated in continuous time by introducing nonlinear differential equations, thus breaking the artifical synchronism, where the concentration rate of each individual pool represents the basic dynamical *continuous* variable. Even now the dynamics with respect to the original Weisbuch–Atlan version with couplings of equal magnitude is not richer, but reveals only one single stable fixed point corresponding to attractor $\underline{29}$ in the discrete-time model.

All the above findings, essentially exhibiting general truisms so far,

point to the idea that the model proposed by Weisbuch and Atlan, even in extended versions, is a pragmatic but evidently still limited approach to the problem, partly due to the simple interconnectivity of the network explaining its elementary mathematical nature. However, it might nevertheless serve as a reasonable starting point constituting a new direction for a network approach to the immune system as an interacting manylymphocyte assembly based on synchronized binary threshold elements operating in discrete time. The basic model can easily be generalized to include external signals of antigens and to incorporate activity-dependent plastic coupling coefficients in analogy to Hebb's postulate.[3]

It would be of interest to study an extension of the connectivity of the network systematically, although an additional inhibitory link from the suppressor pool C_5 to the killer pool C_1 as suggested in ref. 8 only leads to the final virgin state $\underline{0}$, in contrast to their report. One should expect that feedback interactions with respect to the active killer cells, while preventing the problem from being completely solved analytically, open the way to cycling activities of the network corresponding to periodic diseases found in physiological systems,[9] thus giving rise to more complexity and richer dynamical behavior.

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