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LETTER TO THE EDITOR

Control of the immune response

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Abstract. According to the Jerne hypothesis, the control of the immune response is due to interactions among anti-idiotypic antibodies which recognise each other. We present here a model based on a network of interacting binary automata and we compare its dynamics with the evolution of a typical auto-immune disease, experimental auto-immune encephalomyelitis.

When foreign substances (macromolecules, bacteria or viruses, hereafter to be referred to as antigens and abbreviated as Ag) attempt to invade our body, a strong reaction, specific to the antigen, is triggered (we shall not describe here the mechanisms that are not specific to the Ag). The so-called immune reaction consists of the secretion of macromolecules (antibodies, abbreviated as Ab) and cells in the bood and the lymph (the lymphocytes) which participate in the recognition and destruction of the antigens. Recognition is the process by which a site of the surface of an antigen is fixed by the specific site of an immunoglobulin (an Ab) or the receptor on the membrane of a lymphocyte. Specificity is ensured by the steric complementarity of the van der Waals link. The transformation of the Ab or cell receptor then gives rise to a series of cellular transformations, secretions and multiplication which result in the subsequent destruction of the foreign antigens. At the very simple level of our description, all we say about one mechanism, whether molecular with Ab or cellular with lymphocyte, is valid for the other and we shall not distinguish further between the two immune responses.

Even this simple description readily raises a number of fundamental issues.

The first one concerns the origin of the specificity and the diversity of the response. How can any foreign Ag be specifically recognised? The idea of an active 'measurement' process allowing a further design of antibodies with the right complementary surface has to be rejected in the absence of any experimental evidence or any similar process in the living world. The prevailing theory, clonal selection [1], is that of a selection process among a large number of pre-existing cellular receptors and Ab. Ab (and cell receptors) have an invariant part, identical for all Ab, and a variable part specific to those Ag with which it can react. The presence of the Ag triggers the reproduction of the cells which react with it, thus increasing considerably their relative proportion inside the body.

Another general issue concerns auto-immunity. How does the immune system make distinctions between foreign Ag and our own body? Several possible mechanisms with sound biological evidence have been proposed. Burnet's 'educative' theory [1] is based on a selection process occurring in the thymus of the embryo. Because of the

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existing screening by the mother, all the Ag 'seen' by the embryo, are self-Ag. All the corresponding Ab and cell receptors are then eliminated by the thymus. When the animal is born the elimination process stops. 'New' Ag are now recognised as foreign and treated accordingly. Another mechanism is the existence of cellular markers specific to the individual which exist in the membrane of all the cells of the body: the major histocompatibility complex enables the immune system to differentiate between cells of the host and foreign cells. It is responsible for the rejection of grafts, for instance. But none of these mechanisms is able to explain all experimental facts. From a physical point a view a 'perfect' discrimination principle is hard to believe. Furthermore, we know a number of cases where self-recognition occurs. The most dramatic cases concern auto-immune diseases such as multiple sclerosis or chronic active hepatitis, where myelin or liver cells are the targets of attacks by the immune system. Even healthy individuals do have Ab directed against their own cells.

A network approach was proposed by Jerne [2] to deal with such problems. The basic idea is that antibodies secreted by the immune system itself can also be considered as antigens by other antibodies, called anti-idiotypic antibodies. The reaction of the anti-idiotypic antibodies against the primary antibodies is a possible mechanism to control their expression (which means their actual production by the immune system). Of course, anti-idiotypic antibodies can themselves be the target of other antibodies which control their own expression. We are then in the presence of a network of interacting chemical species and cells and one should be interested in its dynamical properties. In fact, very little is known about the actual mechanisms of control of the Ab expression and a simple neural net modelling is consistent with the amount of available information. We shall first explain the results of a number of experiments done at the Weizman Institute of Science by Cohen and coworkers [3] and then present a simple dynamical interpretation in terms of a Jerne net modelled by a neural net.

The experiments of Cohen and coworkers were done on experimental auto-immune encephalomyelitis (abbreviated as EAE), a disease of the rat which 'models' human multiple sclerosis. In EAE the basic protein (BP) of myelin is the target of attacks by T lymphocytes (killer cells), which results in paralysis and then death of the animal. The following set of experiments has to be taken into account in any theoretical model.

(*a*) Auto-immune carrier state. Healthy rats can harbour potentially virulent T lymphocytes, as shown by transfer experiments of anti-BP lymphocytes of vaccinated to naive rats.

(*b*) Different types of T cells. Among the different cell types directed against BP, one named A2b induces the disease but cannot protect against it by vaccination at normal doses. Another type, A2c, does not transfer the disease but induces protection against it. The protection mechanism is inefficient *in vitro* and only observed *in vivo*. This is an indication that A2c induces *in vivo* the proliferation of suppressor T8 cells which suppress the activity of the killer cells directed against BP. Dilution experiments, which select only one cell type per tissue culture, allow the determination of the different cell types that are present in the lymph nodes of infected rats. The presence of both T8 suppressor cells and T4 helpers is detected in these cultures. T4 cells induce the action of killer cells while T8 cells suppress it.

(*c*) Features of the protection against EAE. Transfer of A2c or of small amounts of A2b vaccinates rats against EAE. Even rats that have contracted the disease can be cured by administration of A2c.

A simple immune network with five cell types is represented in figure 1. The binary state of each threshold automaton represents the concentration of the corresponding

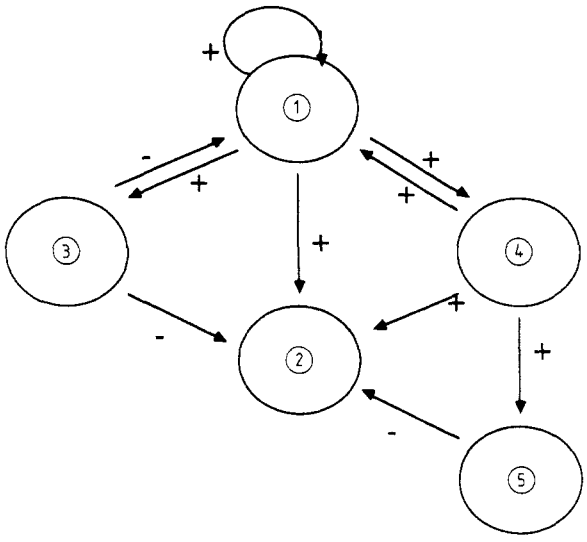

Figure 1. A simple immune network.

cell type: 0 corresponds to small concentrations, 1 to high concentrations. Automaton 1 represents killer cells in a resting state, 2 represents killers activated by the presence of the antigen, 3 and 5 show suppressor cells and 4 is a helper cell. The arrows represent 'synaptic connections', of either sign. All amplitudes of synaptic connections are taken equal to 1. A more elaborate model would play on these amplitudes. Selective processes with mutations could be taken into account by varying them. The thresholds are positive and less than 1. The iteration process involves parallel updating of the automata.

Such a net can be in any of the 32 configurations corresponding to different concentrations of the 5 cell types. The dynamical evolution from any initial set of concentrations can be followed on the iteration graph (figure 2).

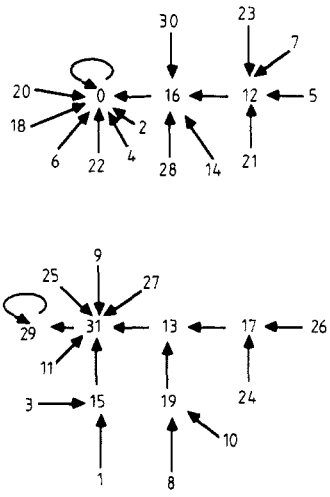

Figure 2. Iteration graph of the simple immune network.

The configurations are noted using their decimal representation with the following coding: the most significant bit is the state of automaton 5, and significance decreases with the number of the automaton. Configuration 29, for instance, has binary representation 11101 which indicates a small concentration of activated killers and a large concentration of all other cell types. Two attraction basins with stable attractors are seen on the iteration graph. Attractor 0 can be interpreted as a virgin state corresponding to the absence of any cell type specific to the antigen. Attractor 29 corresponds to a healthy carrier state. It is preceded by configuration 31 with active killer cells. If the patient can survive this critical period he reaches attractor 29, the vaccinated carrier state.

This crude modelling fully uses the available experimental data. It exemplifies the importance of configurations of cell concentrations as opposed to theories based on the presence or absence of only one cell type to account for the different immunological conditions of a patient. As far as we know it is one of the first implementations of the Jerne network in terms of neural nets.

We had stimulating discussions with F Jacquemart of the Pasteur Institute and I Cohen of the Weizman Institute of Science. This work was partly supported by INSERM grant 87/9002.

Part of this letter had been presented to the Dusseldorf Meeting on Neural Networks, September, 1987.

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