An introduction to the immune network

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Abstract

In this paper, after a telegraphic introduction to modern immunology, we present a simple model for the idiotypic network among antibodies and we study its relevance for the maintenance of immunological memory. We also consider the problem of computing the memory capacity of such a model.

1 Introduction

The aim of this talk is to give to the audience some feelings on the research that has been done in these recent years on the field of the immune network. Although I will concentrate my attention mainly on the theoretical aspects, it is necessary to recall some of the basic properties of the immune system, especially since I speaking to an audience of physicists[1]. This task is no simple: immunology is a very much developed science: 20.000 articles appear every year[2].

In presenting this introduction, for simplicity I will do sharp statements that often should be better qualified. At the contrary of physics, in biology every law, included this one, has exceptions.

2 Immunisation

The most important function of the immune system, which everybody knows, is immunisation. As one finds in the books, the introduction of a given amount of antigen (most of the antigens are proteins, e. g. tetanus toxoid or bovine albumin) inside a mammal[3] stimulates the production of antibodies directed against that given antigen.

We could just write the equation:

$$Antigen \ = \ new\ protein. \tag{1}$$

[1] A nice introduction to immunology is Hood et al. 1984.

[2] Here I will provide only a very short reference list, quoting only those papers which may be easier to read.

[3] The immune system is present in all chordates (vertebrates), with some difference among the different classes. For simplicity I will refers only to mammals.

Antibodies are soluble proteins secreted by the lymphocytes, which have a high affinity toward the antigen (in this context high affinity means an equilibrium constant K equal 10^5 or more).

The precise number of chemically different antibodies, that an organism (e.g. a mouse) is able to produce at a given moment (i.e. the repertoire), is of order $10^6 - 10^7$. The number of antibodies is so high that the repertoire of possible responses is complete, i.e. the immune system is able to react against any possible protein.

After the introduction of the antigen, only those lymphocytes (B lymphocytes), which have a high affinity with the antigen, are stimulated and they expand exponentially. This clonal expansion is crucial to direct the antibodies production against the antigen. The typical time, that is needed to reach the maximum of antibodies production, is of the order of one week.

3 Some complications

Things are no so simple as it may seem. The situation is complicated by the phenomenon of hypersomatic mutation. We have seen that after the introduction of the antigen there is competitive selection among different clones. However mutations may happen; in this way new clones are created and they are further selected. Normally the mutation rate of a usual cell is very low (of the order 10^{-9} per base per division), however in this case we have a much higher mutation rate (of the order 10^{-3}). This process leads to variation of the immune response with time. Its study is an interesting problem in population dynamics. It is usually believe the hypersomatic mutation is present to further increase the affinity of the antigens (Berek & Milstein 1988).

One should also say that the interaction with T lymphocytes is crucial in the dynamics of the system. These lymphocytes control the activity of the B lymphocytes and they may have an excitatory or a suppressor role. Also other cells (dendritic cells or macrophages), which present antigens to B cells, are crucial for the correct functioning of the system. We are going to neglect all these important details (and the tens of different kinds of receptors on the surface of the immune system cells) that would make this talk quite long.

4 Tolerance

A crucial effect of all these complicated interactions is that the response to the external antigen has a bell shaped form. To be more precise let us consider the following experiment.

We inject a dose x of antigen at time zero (priming) and at time t (e.g. 1 month later) we measure the production of antibody directed against the antigen shortly after the second shot. The response has function of x has a bell shaped form. We can distinguish four regions:

- a) Very low x: no effect.
- b) Low x: a decrease (not an increase!) of the antibody production, i.e. low dose tolerance.
- c) Medium x: an increase of the antibody production, which is the naively expected result.
- d) High x: a decrease (which may be very strong) of the antibody production, i.e. high dose tolerance. In other words a too strong stimulation leads to anergy.

Summarizing, for both small and high dose of the antigen the responce after priming smaller than without priming (tolerance). Only for medium dose of the antigen the responce is higher. The range of values for which a positive responce is obtained depends on the antigen. It is usually wide a few orders of magnitudo.

These unexpected features of the response are related to a very important phenomenon, i.e. tolerance. In the nutshell it is crucial that the immune system does not react against the self, i.e. it does not produce antibodies against his own proteins. If this happens, severe illnesses (e.g. *diabetus mellitus*) may arise.

As a consequence during the ontogenesis[4] the immune system learns not to produce antibodies against the self.

Generally speaking we can conclude that when the immune system is stimulated, two pathways are open: tolerance or immunity; the choice of the pathway is crucial and depends on many factors.

A mechanism which contributes to the establishment of tolerance is the following. In order to be stimulated by B cells, T cells needs two signal, one is antigen specific and the other one is not specific[5]. It was proved that in presence of only the fist signal and in absence of the second signal, T cells are not stimulated and they are lead to anergy (Shwartz 1990).

5 The idiotypic network

An antibody which starts to be produced at a certain moment in large quantities is (at the all practical effects) a new protein for the organism. This new antibody (which we call Ab1) stimulates the formation of a second wave of antibodies (Ab2) which are directed against Ab1. This fact is not only reasonable for a theoretically point of view, but it is experimentally well proved (Oudin & Mitchel 1963).

In the same way it is reasonable to assume that Ab2 stimulates the formation of a third wave of antibodies Ab3 which are directed against Ab2. Not too much ingenuity is needed to assume that Ab3 stimulates the production of Ab4 which stimulates....

In other words the production of a given antibody influence the production of other antibodies and we can thus speak of a network of antibodies (the so called idiotypic network, proposed by Jerne 1967, 1974, 1984).

A crucial property of the network is a symmetry of the interaction: if Ab1 stimulates Ab2, Ab2 stimulates Ab1. As a consequence Ab3 is not too different from Ab1 and a large fraction of Ab3 binds to Ab2 and to the antigen. Indeed most of Ab2 looks (at the binding site) like the antigen.

The origin of this symmetry is not surprising. Protein - protein interaction is dominated by weak short range non covalent forces which depends on the geometry (dipole dipole interaction), on the charge distribution and on hydrophilic - hydrophobic effects. In this situation is clear that a strong interaction is present only if the geometries of the two proteins are complementary (and there is match of the charge distributions and of the hydrophobicity).

While there are no doubts on the existence of the idiotypic network, its physiological relevance has been much debated (Cohn 1986, Holberg et al. 1986, Hoffmann et al. 1988,

[4]There is a large body of experimental evidence that the immune system is genetically able to produce antibodies against the self. The learning happens during the ontogenesis and it has not happened during the phylogenesis.

[5]This is the famous two signal theory (of Bretcher and Cohn) and I am particularly proud to have been the first to point out an experimental proof of its correctness (Parisi 1988).

Rossi et al. 1989). It is been often suggest that it may be important for memory and this will be discussed in the next section.

6 Memory

As it should be clear from the previous discussion there are two kinds of memories:

- a) a positive one which is connected to immunisation.
- b) a negative one, which is connected to tolerance, especially self tole- rance, i.e. the absence of antibodies directed against the self[6].

The memory lasts for a very long time (practically infinite). If we concentrate our attention on the positive memory, the explanations for this phenomenon are of two different types.

- **Static explanations**

  In this kind of explanations the dynamics and the idiotypic network play no role. Let me quote two of them:

  - a) Antibodies producing cells and their descendants have very long mean life.
  - b) The antigen remains for very long time in the organism on the surface of APC (antigen presenting cells, i.e. dendritic cells, macrophages).

  The mathematical equation describing situation (a) (in absence of the antigen) would be given in a first approximation by

  $$\frac{dx_i}{dt} = 0, \tag{2}$$

  where x_i is the concentration of the i-th antigen. The index i runs from 0 to N, where N is a large number (of the order of 10^8). The solution of this equation is an easy task.

- **Dynamic explanations**

  A typical explanation is the following. The network has two stable state: in the first the antibody Ab1 is not produced and in the second the antibody Ab1 is produced. The effect of the antigen is to induce the transition of the network from the first state to the second one. After the transition the antigen may disappear and memory lasts forever.

  It is clear in this kind of explanation the number of stable states should be extremely large, i.e. at least of the order of all possible combination of antibodies which can be simultaneously produced (Parisi1989).

[6]The precise definition of the self is a little ambigous: if antibodies belong to the self, Ab2 is an antibody directed against the self (Coutinho 1989). It should also be stressed the total amount of antibody is constant as function of time and does not depend on immunisation (Varela et al. 1991). Also in absence of external antigens there is a large production of natural antibodies. Their physiological role is not completely clear.

The mathematical equations describing this situation (in absence of the antigen) would be given in a first approximation by

$$\frac{dx_i}{dt} = -x_i + s_i[x], \tag{3}$$

where the functions $s_i[x]$, (which depends explicitly on the index i and represent the stimulatory effects of the other antibodies) are functions of all the antibodies concentrations of the systems.

The stable states are the solutions of the equations:

$$x_i = s_i[x], \tag{4}$$

which has only the trivial solution ($x_i = 0$) if we neglect the functions s_i.

As we have already remarked the functions si should be such that the equations 4 must have an exponentially large number of solutions.

If we do an analogy with electronics, the static explanation corresponds to dynamic memory chips: a capacitor is charged and it remains active for a very long time (a few milliseconds which is small on the human scale but is large if measured in nanoseconds.)

On the contrary the dynamic explanation corresponds to static memory chips: learning correspond to changing the state of a flip flop. Here the memory has an infinite mean life, i.e. it lasts as far as electric power is on.

Unfortunately there is no consensus among immunologists on which kind of explanation should be correct. One can present arguments in different direction and no conclusive experiment has been done. It is likely that in order to achieve further progresses it is necessary do present a detailed model and to compare the predictions of the model with the experimental data (Weisbuch et al. 1990, Seiden & Celada, 1992 Bern et al. 1993).

7 Models

A large literature exists on the construction of models of the immune system. If we consider all the complications of the immune system, a realistic model cannot be simple.

Here due to limits of time I will consider a very simple model (Parisi 1990), which should hopefully capture most of the qualitative features of the immune system and it has some points in common with the Hopfield model (Hopfield 1982).

We introduce a matrix $J_{i,k}$, which codes the effect of the k-th antibody on the ith antibody. The stimulatory effect of the network on the i-th antibody is given by

$$h_i = \sum_k J_{i,k} x_k. \tag{5}$$

The equation of motion (in presence of the antigen concentration a_i) are

$$\frac{dx_i}{dt} = f(x_i, h_i + a_i) \tag{6}$$

where f is given function.

If the matrix J is symmetric[7], the equations are of gradient type[8] and the time evolution is such to bring the system toward a fixed point of eq. 6, i.e. no chaotic behaviour is possible[9].

Different models depends on the choice of the function f and of the matrix J. We can consider two different class of model, depending on the connectivity of the network (Perelson 1988 and Stewart & Varela 1989).

- a) Localised models: here the effect of a perturbation (i.e. a variation of a_i) is localised only on a few values of k. This may be realised if for given i there is a small number of kUs for which $J_{i,k}$ is large and the perturbation does not spread.
- b) Percolating models: here the effect of a perturbation influences the whole system. There is a large number (e.g. proportional to $N^{1/2}$) of k's which are strongly affected by a perturbation at i. This may be realised if for given i there is a large number of values of k's for which $J_{i,k}$ is large or if there is a small number of values of k's for which $J_{i,k}$ is large, but the perturbation does spread.

Both kinds of models can be constructed in such a way that the number of stable states is exponentially large (i.e. proportional to $\exp(AN)$, with positive A). An analytic computation of the number of fixed point can be done using the replica tecnique (Mézard et al. 1987) in the case of randomly chosen J. Learning however will be quite model depending and we cannot discuss it in details (Lefevre & Parisi 1992).

8 Conclusions

The organisation of the immunological system as a network is not a isolated phenomenon in biology (Cattaneo 1991). In many other cases networks of interacting substances are present (e.g. intracellular signaling, hormones in an organism). The crucial problem is to understand which functions of the immune system crucially depend on the network. At the present moment there are many important problems in the immune system that are not well understood (e.g. the very existence and structure of suppressor T cells). The construction of a realistic model is very difficult due to these incertitudes.

New experimental data must be collected in order to test the network hypothesis. For example the experimental study of the time dependence of the level of natural antibodies (i.e. antibodies produced in absence of external antigens) show the presence of oscillations and chaotic behaviour. These oscillations strongly suggest the presence of underlying non linear evolution equations (Varela et al. 1992).

A particular field in which a better understanding of the network would be extremely useful is related to tolerance. It is rather difficult to break tolerance or to induce tolerance. If tolerance could be induced at our will, we could cure autoimmune diseases (like *diabetus mellitus*) or perform organs transplantation without rejection. If tolerance is (at least partly) under the control of the network, a better understanding of the network may strongly improve our ability in dealing with those problems.

[7] The symmetry of the interaction has been suggested in Cooper Willis & Hoffman (1983) and Rajewsky (1983).

[8] We also need $J_{i,i} = 0$.

[9] We have neglected the possibility the matrix J is time dependent. This may arise from the variation (as function of time) in the populations of produced antibody, e.g. as an effect of hypersomatic mutation. The relevance of a possible time dependence in J is difficult to estimate.

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