Proc. Natl. Acad. Sci. USA
Vol. 87, pp. 429–433, January 1990
Immunology

A simple model for the immune network

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Communicated by Nicola Cabibbo, April 19, 1989

ABSTRACT **In this note I present a simple model for the idiotypic network among antibodies and study its relevance for the maintenance of immunological memory; in particular, the memory capacity of such a model is studied. Some of the similarities with the spin glass model and with neural networks are discussed.**

Comparison of the brain and the immune system has been quite fruitful in the past (1, 2). Stimulated by the analogy with the brain and by the discovery of the idiotypy (3), Jerne has proposed a network theory for the immune system. Roughly speaking, the production of a given antibody elicits (or suppresses) the production of other antibodies that elicit (or suppress) the production of other antibodies and so on. This is reminiscent of the way in which a firing neuron may induce (or inhibit) the firing of other neurons.

In this note I study a specific model that demonstrates that a functional network of antibodies may be possible. I concentrate on modeling the behavior of the immune system in absence of any driving force of external antigens in order to study the maintenance of the immunologic memory. The aim is not to produce a detailed model of the system, which could be used for quantitative comparison with the experimental data, but rather to provide a simple theoretical framework in which different questions may be discussed. For this reason the construction of the model is simplified as much as possible, in the same spirit as the construction of formal neurons (4) and of a symmetric neural network (5). If the model is sufficiently simple, as the one presented here, some results may be derived analytically, without recourse to simulations, and many results obtained in statistical mechanics become available. The use of statistical techniques is inescapable, if we want to understand the behavior of a system in which $>10^6$ different kinds of molecules interact.

It is well established that antiidiotypic antibodies (i.e., antibodies against antibodies) are normally generated in the process of the response to an external antigen [especially by repeated vaccination (6)]. Such antiidiotypic antibodies also exist in unprimed animals (7). Although one of the main assumptions of the network theory is satisfied, the functional role of the network is not fully understood and a spectrum of different conclusions can be found in the literature. Moreover, if we accept that the network is not a pure accident (8) and that it has a precise functional role, its properties are not clear. There are some crucial points on which there is no general agreement and various options are available.

(*i*) It is not established whether the autoantibodies, which arise in response to a given antibody and have a functional role, are produced by a small set of high responder clones or by a large set of low responder clones.

(*ii*) A related question concerns the effect of a new antigen on the behavior of the network: Does it modify the whole network of antibodies or does the perturbation remain localized within a given set? Does the network remain a whole indivisible unit, or can it be decomposed into a large number of nearly independent regulatory subnetworks (each subnetwork being composed by a small set of antibodies) (9, 10)? Sometimes these two options are summarized by saying that the network is open or closed. In the second case the network would be the union of many independent circuits of low complexity; in the first case the network would look more like a real brain.

(*iii*) If we assume that the available states of the network are determined by the properties of internal dynamics (11), how then does the network learn, as it does upon vaccination? In other words if the immune system is an "organism centered, self referential" (11) system, how is it possible that its behavior may be easily modified in the desired direction as it happens by vaccination?

(*iv*) How large is the memory of the immune system—i.e., against how many antigens can a mammal be vaccinated (or be actively tolerant)? Does this number coincide with the number of different clones, or is it smaller?

In this note I try to construct a model for the immune network based on the most extreme hypothesis: I assume that autoantibodies to a given antibody are a very large set of low responder clones, the connectivity of the network is very high [i.e., $O(10^6)$], and consequently the network cannot be decomposed into independent networks. I further assume that the network is fully functional and the immunological memory is a property of the network. Some of these assumptions are not fully realistic. However it is interesting to consider the features of this extreme case. Indeed, I will prove that it is possible to construct such a network, which can memorize a very high [$O(10^6)$] number of external antigens.

Before entering into the discussion of the model let me sketch some well-established results on the immune system.

Some Known Facts

The precise number of different antibodies that an organism (e.g., a mouse) is able to produce at a given moment (i.e., the available repertoire) is of the order of 10^6–10^7 and the number of antibodies that are actually produced (the actual repertoire) is likely to be smaller by a factor of 10 (12, 13). The very high number of different antibodies in the available repertoire is usually referred to by saying that the repertoire is complete (if we neglect holes)—i.e., the immune system can react against any possible protein (14).

When the immune system is stimulated by an external antigen two pathways are open: tolerance or immunity; the choice of the pathway is crucial and depends on many factors, most notably the amount of antigen and the way it enters the organism (15). (It is quite likely that the time dependence of the antigen concentration plays a crucial role: unfortunately practically no data are available on this point.) Low doses of antigen normally induce tolerance, whereas medium doses induce immunity (high doses too induce tolerance, but the mechanism is not the same as for low doses). The low dose tolerance and the immunity are related to the proliferation of T cells, which act as suppressors in the first

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case and helpers in the second case and have a negative or a positive effect on the proliferation of antigen-producing B cells.

Summarizing, when the antigen is presented to the organism, the immune system decides which pathway should be taken (suppression or immunity) and it remembers the choice for a very long time, even after the disappearance of the antigen. It is crucial that the organism does not react (at least not too much) against some of its own proteins. Some cells of the immune system are able to produce antibodies directed against the organism (i.e., the self); these antibodies are not produced (neglecting pathologies) in sizable amount. Therefore during ontogenesis the immune system learns which antibodies it should not produce and it remembers this decision for its entire life. These two kinds of phenomena are what we call immunological memory.

Another effect, idiotypy (3), is at the basis of network theories (1) of the immune system. The antibodies (called Ab1) elicited directly by the antigen are a new protein for all practical purposes; they elicit the production of new antigens (Ab2), which induce Ab3, which induce Ab4, which induce Ab5, and so on . . ..

This phenomenon, the idiotypic cascade, can be studied experimentally in the following way. The different waves (Ab1, Ab2, Ab3 . . .) are separated in time by a delay of 1 week (or less). The first antibodies, produced by the mouse after stimulation, are Ab1. These antibodies may be injected in a genetically identical mouse and in this way one obtains Ab2. Ab3, Ab4, etc., are obtained in a similar way. Sometimes Ab3 is like Ab1 and it binds to the same antigen of Ab1 (16, 17).

It is natural to assume that a similar idiotypic cascade takes place inside the same organism and it plays a crucial role in the regulatory phenomena. However, one must be very careful with these identifications for many reasons:

(*i*) The concentration of antibodies produced by the same organism increases relatively slowly, whereas the concentration jumps instantaneously when the antibody is injected into another organism: the differences in the protocol may be responsible for the transition from tolerance to immunity.

(*ii*) It is possible to transfer the antibodies that have been produced (Ab2), but it is not possible to study those antibodies that are no longer produced as a consequence of the increase in the Ab1 concentration.

(*iii*) Genetically identical mice may have a different idiotypic environment and this may account for different behavior to the same antigen in genetically identical, but different mice.

The Model

My main interest in this note is the study of a network that may be functionally useful as far as memory is concerned (obviously the network may be relevant in other contexts).

I formulate a model for the immune system, in the absence of an antigen, and try to keep it as simple as possible. Although it is clear from the previous discussions that the numbers of B and T lymphocytes of a given specificity play a crucial role, the actors of this model will be the antibody concentrations, it being understood that their interactions are mediated by lymphocytes. This choice is made in order to simplify the model to the maximum. It would be definitely interesting to include B cells, T cells (helpers and suppressors), and the elusive T-cell suppressor factors in more refined versions of the model.

The concentration $c_i(t)$ of a given antibody (i) is assumed, in absence of external antigen, to have only two values that conventionally we take 0 or 1 (t is the time). (In the presence of antigen it is natural to assume that the concentration c_i becomes much greater than 1.) The status of the immune system at a given time is determined by the values of all c_i for all possible antibodies (i.e., $i = 1, \ldots N$, where N is of order 10^7).

We assume a simple dynamical process where the time is discretized (the time step τ is the time needed to mount the immune response—i.e., about 1 week). In the absence of external antigen the following equations are satisfied:

$$h_i(t) = S + \sum_{k=1,N} J_{i,k} c_k(t) \qquad (J_{i,i} = 0)$$

$$c_i(t + \tau) = \theta[h_i(t)], \qquad [1]$$

where the function $\theta(x)$ is zero for negative x and 1 for positive x; $J_{i,k}$ represents the influence of antibody k on antibody i. If $J_{i,k}$ is positive, antibody k elicits the production of antibody i, whereas if $J_{i,k}$ is negative, antibody k suppresses the production of antibody i. The absolute value of $J_{i,k}$ represents the efficiency of the control of antibody k on antibody i.

The variable h_i represents the total stimulatory (or inhibitory) effect of the network on the ith antibody. It is positive when the excitatory effect of the other antibodies is greater than the suppressive effect and then c_i is one. Otherwise h_i is negative and c_i is zero. The quantity S regulates the dynamics when the J terms are very small. Here, for simplicity we take S equal to zero.

If the concentrations of antibodies are time independent, Eq. **1** simplifies and we get

$$h_i = S + \sum_{k=1,N} J_{i,k} c_k \qquad (J_{i,i} = 0)$$

$$c_i = \theta(h_i), \qquad [2]$$

which is just Eq. **1**, where we have erased the time dependence of the antibodies concentrations (S is still zero).

Many other models of the idiotypic network have already appeared in the literature (18–20). The model presented here has the advantage of being simpler and easier to analyze.

The phenomenon of low-dose tolerance (and more generally the dependence of the pathway, tolerance or immunity, on the amount of antigen) may suggest that the concentration of a given antibody is crucial in determining the sign of its effects on the other antibodies. The simplification to two levels of concentration (0 or 1) bypasses the problem of the choice of the pathway (immunity or tolerance). I implicitly assume that the protocol in which antibodies are produced by the organism is such as to induce a given pathway. Although in a realistic model the concentrations must eventually become continuous variables, I propose to investigate first whether a simplified functional idiotypic network with only two levels of concentration can be set up. If this hypothesis fails, the precise values of the antibody concentrations will have to be relevant variables and more complex nonlinear differential equations for the time evolutions will have to be written (the c terms should be continuous variables) and the analytic study of the system would become more difficult.

In the current model the antibodies with positive c_i are actually produced by the system and the others are suppressed. The suppression due to clonal abortion is neglected and I consider only the active suppression that selects which cells of the available repertoire are transferred into the actual repertoire. I am not interested here in the physiological level at which the interactions between the different antibodies take place. The aim is to obtain a global functional description of the immune network.

More Details of the Model

The whole memory of the system (immune states and suppressed states) is encoded in the network in the sense that the knowledge of the concentrations of all antibodies different from a given one completely determines the concentration of that given antibody.

Now we must make some hypotheses on the J terms, assuming that:

(a) the diagonal terms $J_{i,i}$ are zero—i.e.,

$$J_{i,i} = 0 \qquad \forall_i, \qquad [3]$$

(b) there are J terms of both sign,

(c) the J terms are symmetric—i.e.,

$$J_{i,k} = J_{k,i}, \qquad [4]$$

(d) the J terms are random and they are equidistributed in the interval -1, 1.

The assumption of setting $J_{i,i}$ to zero is the most extreme one. It implies that a given antibody is produced only because of the excitatory effects of the other antibodies. The other extreme situation is when off diagonal terms (i.e., $J_{i,k}$ for $i \neq k$) are equal to zero and positive diagonal terms. In this case, Eqs. **1** and **2** would have a trivial implication: the antibody concentrations would be always time independent. In other words Eq. **3** implies that memory (i.e., vaccination) can only be realized by modifying the state of the whole network.

The last assumption (d) is clearly an oversimplification. It would be more reasonable that $\ln|J_{i,k}|$ (which should be related to the chemical affinities) is equidistributed. Moreover the antibodies are not random proteins. If the connectivity of the ith antibody is defined to be the number of antibodies for which $J_{i,k}$ is significantly different from zero, assumption d implies that the connectivity of every antibody is equal to the total number of antibodies. The concentration of any given antibody depends on the concentration of all other antibodies. Hence, the network is open and cannot be broken into smaller independent subnetworks.

Despite the fact that different antibodies have quite different connectivity, it is interesting however to study how the network may work in this limiting case of assumption d. The probability distribution of the J terms can be modified in later refinement of the model, without changing the qualitative predictions of the models as long as one remains with very large connectivity. I will proceed with assumption d for simplicity.

Next I discuss the physiological feasibility of assumptions b and c.

Assumption b implies that there should be antibodies that suppress the production of other antibodies. This effect is well known (21–23). It is also possible that some antibodies elicit the production of other antibodies at low dose and they suppress the production of other antibodies at medium dose (24–26); however a more careful discussion of this point is needed (27).

Moreover, if all J terms are positive, the only solution of Eq. **1** is that the concentrations of all antibodies are equal to 1. Hence in this model inhibition plays a crucial role in regulating the immune network.

The most crucial and most controversial point is assumption c. If both J terms are positive, there is some experimental evidence to the effect that symmetry holds (18, 28, 29). If one of the J terms is negative, the situation is less clear; however I shall assume for simplicity that assumption c is strictly satisfied. I will later discuss the consequences of the removal of this assumption.

Different sets of hypotheses can also be entertained. For example, one could keep assumptions a, c, and b, assume that all J terms are negative, and assume that S is different from zero and positive. This model would become a simplified version of the one of ref. 30.

The discussion presented here is very short and does not take into account many of the features of the immune system. For example, I have overlooked the fact that Ab2 antibodies may be functionally classified into four major categories (26, 31–33).

The Memory Capacity

Having defined the model, one can now analyze it. The intuitive way in which the model should explain immunological memory is rather simple. After the production of Ab1 starts as an effect of the antigen, the environment of B and T cells is modified by the presence of Ab2 in such a way that the life-span of Ab1-producing B cells is increased and also the population of helper T cells, specific for Ab1, is increased. Ab3 must have a strong component that coincides with Ab1 or is functionally equivalent to Ab1. In other words, we suppose that the internal image of the antigen (Ab2) remains after the antigen has disappeared and its presence induces the survival of memory B cells directed against the antigen.

Moreover, the symmetry of the J terms implies that Ab3 should be rather similar to Ab1. However this should not be true in a transfer experiment where monoclonal Ab2 is used. Indeed, different effects of monoclonal and polyclonal Ab2 have been observed. For example, it has been shown that sometimes monoclonal Ab2 does not elicit Ab1-like molecules, but rather a heterogeneous response similar to the heterogeneous response to monoclonal Ab1 (6, 34).

If the J terms are symmetric, this model coincides with a very familiar and widely investigated model for spin glasses (35).

It is well known (36) that the behavior of the solution of Eq. **1**, after a long time, would be a stable situation satisfying Eq. **2** or a limit cycle of period 2τ. It is quite possible that the oscillating behavior for a symmetric model is an artifact of the choice that we have made for the dynamics. Some other choices lead only to the stable solutions described by Eq. **2**. For simplicity, let us consider only the time-independent solutions, keeping in mind that a periodic behavior is also possible.

We now face a difficulty: the possible equilibrium configurations of the network (i.e., solutions of Eq. **2**) are genetically fixed, while we would like the network to learn which antibodies should be produced. How can this take place?

It is natural to assume that only a tiny fraction of all of the antibodies have a physiological relevance: there are $M = \alpha N$ antibodies that should have a preassigned concentration, some of them should have a zero concentration, others a non-zero concentration. Therefore, the value of M is likely to be much less than N—i.e., $\alpha < 1$.

In other words, if one considers a healthy mouse, one could write two lists. The first contains the antibodies that should not be produced (to avoid autoimmune illnesses); the second contains the antibodies that must be produced. In the network theory, the state of the system cannot be preassigned completely, because the production of the antibodies is controlled by the other antibodies—i.e., the state of the network must satisfy Eq. **2**. The total number of antibodies (M) in the two lists cannot be equal to N (the size of the repertoire) but must be much smaller.

The natural question is the following: For a given N, which is the value of M such that there exists one (or more) equilibrium state of the network with preassigned values of the M concentrations? Equivalently, which is the maximum size of the two lists of antibodies that must (or those that must

not) be produced? This value of M is what I call the memory capacity of the model.

It is not known what is the value for the storage capacity of a mammal—i.e., maximum number of the number of antibodies that have been actually learned by the immune system (antibodies that are produced in sizable amount, or antibodies whose production is suppressed). This number is certainly high. A storage capacity independent of N (e.g., the maximum size of the list is seven) would put the model at serious variance with experimental data. After all we are vaccinated against an extremely large set of antigens.

We now proceed to compute the storage capacity of the model network. Eq. 2 is well known in the theory of spin glasses and it has been proved that the number of its solutions is very high: it increases exponentially with N (35, 37, 38). In fact, it is proportional to $2^{\lambda N}$ with $\lambda \approx 0.3$.

The existence of a stable state with M preassigned antibody concentrations depends on M. When N is very large, such a state exists for $\alpha < \alpha_c$ (i.e., $M < \alpha_c N$), where

$$\alpha_c = \lambda. \qquad [5]$$

The proof of Eq. 5 is rather simple. The number of possible states of the network with M preassigned antibody concentrations is 2^{N-M}. The probability that a given random state is a solution of Eq. 2 is $2^{-(1-\lambda)N}$. Therefore, the average number of solutions of Eq. 2 with αN preassigned antibodies is $2^{(\lambda-\alpha)N}$, which is greater than one when $\alpha < \lambda$.

A detailed computation, which parallels the original evaluation of λ (35, 37, 38), shows that the above argument is sound. (Technically speaking we have to prove that $2^{(\lambda-\alpha)N}$, which is the average number of solutions, is also the most likely number.)

Eq. 5 can be easily understood from an information-theoretical viewpoint. Indeed, we need M bits of information in order to specify M antibodies (on or off) and we need λN bits to identify one of the $2^{\lambda N}$ equilibrium states of the network. No equilibrium state can be found when $M > \lambda N$.

Summarizing, the storage capacity ($M_c = \alpha_c N$) is the total number of antibodies whose concentration may be assigned in a way compatible with Eq. 2. The simplicity of the model allows an analytic computation of the storage capacity.

If one compares this idiotypic model with neural models (5, 35), one sees that the J terms play the same role of the synaptic strengths of the neural network. However, in the immune system they cannot be modified. This point is similar to the one expressed by Toulouse *et al.* (39) in a different context. The randomness of the antibody–antibody interactions implies the existence of a large number of equilibrium states and the pressure from the antigen selects the needed equilibrium state. The Darwinian selectionist (as opposed to the instructionist) point of view is satisfied not only at the level of the single antibody but also at the level of the immune system as a whole entity.

If the J terms are not symmetric the situation is more complex. This is a most interesting case for neural networks and the behavior of such a system has been investigated (40–42). Although some of the phenomena present in the symmetric case persist, new features appear.

The main results are summarized here. If the J terms are completely asymmetric—i.e., $J_{i,k}$ is not correlated to $J_{k,i}$—the time behavior of the system is chaotic. This cannot be a good description of the immune system because the production of antibodies of a given specificity would start and stop at random.

The intermediate situation, in which the J terms have both a symmetric and an asymmetric component, is more realistic but cannot be studied in a simple way. If one sticks to Eq. 1, the concentrations of some antibodies will remain time independent, whereas concentrations of other antibodies may show an irregular behavior. The clearest results are obtained if we restrict ourselves to the time-independent solutions of Eq. 1 (i.e., to the solutions of Eq. 2). In this case one still finds (40–42) that there is an exponentially large number of solutions of Eq. 2 (proportional to $2^{\lambda N}$, and consequently the memory capacity increases linearly with N). This intermediate solution seems to be a quite promising case and its behavior should be investigated in greater detail.

Conclusions

In this paper I have constructed a simple model of the immune network and have used it to study immunological memory. I have found that the maximum memory capacity of the system—i.e., the number of antibodies that may be selected (expressed or suppressed)—is very high—i.e., proportional to the number of antibodies in the repertoire.

However, in this note I have not studied the very interesting phenomenon of learning—i.e., how the network moves from one equilibrium state to another equilibrium state. One should also make a distinction between the learning of the self, during the early ontogenesis, and the learning of antigens later in life. In the first case learning is a massive parallel phenomenon. An extremely large number of different antibodies are suppressed at the same time by an immature immune system. It is also likely that the network receives a strong maternal influence. In the second case learning may be sequential (or parallel)—i.e., few new antigens are memorized at a given time by a mature immune system.

I have neglected the role that somatic hypermutation plays in producing new antibodies and consequently modifying the J terms. It is usually believed that somatic hypermutation is crucial in producing antibodies with higher affinities with the antigen, and it is not relevant from the point of view of the network. Somatic hypermutation may be a crucial (unfortunately neglected) element of the immune network (it could be quite useful during learning), because it may generate new antibodies with a higher value of h_i, as defined in Eq. 2. The renewal of the repertoire due to the expression of new clones of B cells in the bone marrow may play a similar role as reservoir of diversity, as stressed in ref. 20.

In this case somatic hypermutation would play an analogous role to synaptic plasticity in the neural network (where learning is produced by a small change in many synapses). At the present stage I do not have solid support for this hypothesis.

The way in which learning happens should be investigated more carefully. As already stated, the values of the concentrations are 0 or 1, only in the absence of the antigen. It is reasonable that in the presence of the antigen the concentrations become much higher. Then the idiotypic cascade starts and the concentrations of many antibodies are changed. When the external pressure is removed we find ourselves in a new equilibrium state.

A more detailed model with some continuously changing concentrations is needed to investigate properly the way in which learning may happen; however there are two main features that should be model independent:

(*i*) Each time the immune system learns something, we modify the concentration of some of the antibodies and therefore we forget something else (30, 32). The antibodies, which are most easily forgotten, are those having a small h_i in Eq. 1. The total memory capacity of antibodies that will not be forgotten easily depends on the details of the learning process but it will be certainly much smaller than the maximal one.

(*ii*) Repeated exposure to the antigen is quite likely to increase the value of h_i and therefore to strengthen the memory. It is satisfactory that one apparent characteristic of

autoantiidiotypic antibodies is that they are produced most effectively by means of repeated immunization (6).

At present it would be a wild speculation to answer why this kind of network is used by the immune system. A possible answer is that the immunological memory is much more robust, if it is distributed in many clones, and the decrease in the total storage capacity is a reasonable price to pay for this increased robustness.

It is a pleasure to thank C. Brezin, A. Coutinho, and M. Virasoro for interesting discussions and useful suggestions. I am also grateful to M. Mezard for help in computing the storage capacity of the network and to D. Amit for a careful reading of the manuscript.

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