PART TWO

THEORETICAL IMMUNOLOGY

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Cognitive Networks: Immune, Neural, and Otherwise

1. COGNITIVE NETWORKS: THE CONTEXT

1.1 GOALS OF THIS PAPER

There is a strong intuitive sense in which immune systems are *cognitive*: they recognize molecular shapes, remember the history of encounters of an individual organism, define the boundaries of a molecular "self," and make inferences about molecular species likely to be encountered. By and large immunology has left these admittedly cognitive terms undefined or at a metaphorical level and has concentrated, instead, on the molecular details of immune components.

The first intention of this paper is to argue that by so doing one is leaving unexamined and shrouded in a fog of mystery the most interesting domain of phenomena the immune system affords to animals: their cognitive abilities. To advance in this direction, one must be willing to embark on an explicit examination of the cognitive *mechanisms* proper to the immune system.

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This task is timely, for in cognitive science[1] there has been an explosive realization that biological networks afford the model *par excellence* to account with great simplicity for uniquely cognitive capacities such as fast discrimination and memory. By and large, such cognitive networks are taken as analogs of *neural* networks. A second intention of this paper is to further clarify for cognitive scientists how immune systems can provide a distinctly different class of network architecture also capable of sophisticated cognitive performances. Immune nets merit to be examined on their own as a separate large class next to neural networks.

In the remainder of this section, we provide some minimal context for the recent development in cognitive networks which allows us to phrase immune events in a sharper focus. In Section 2, the substance of the paper, we propose what immune networks are, including their most relevant dynamics in the form of a model. Finally, we derive some conclusions in Section 3.

1.2 FROM SYMBOLS TO NETWORKS

The study of biological and artificial cognitive mechanisms was heavily marked by the tradition that considered any form of knowledge as necessarily linked to symbols and rules, in the tradition of logic. This gave rise to the *symbolic*[2] paradigm, where cognition is identified with information processing: rule-based manipulation of symbols. After many years of work with this symbolic paradigm, especially in neuroscience and artificial intelligence, it has become clear that such mechanisms are far too brittle, too inflexible to approach living expertise.

The alternative view revived recently from initial ideas dating back to the 1950's, is usually referred to as *connectionism*. Basically, the idea is to leave symbols aside and to start any analysis (or construction) from simple computing elements, each one carrying some value of activation which is calculated on the basis of the other elements in the network through a dynamical rule. In a typical connectionist model, the weight of the influences between the elements varies. Thus, the network's performance is embodied in a distributed form over the connections, whence the designation.[3] We will argue here that immune networks share with connectionist ideas the distributed dynamical base, but that their mode of change is fundamentally different.

A key idea in a network perspective is that the on-going activity of units, together with constraints from the system's surroundings, constantly produces *emerging* global patterns over the entire network which constitutes its performance. The network itself decides how to tune its component elements in mutual relationships that gives the entire system a capacity (recognition, memory, etc), which is not

[1] We use this term to designate the federation of neuroscience, artificial intelligence, linguistics, and cognitive psychology, which since the later 70's is associated with the scientific study of cognitive processes in animals and machines.

[2] Depending on preferences, the symbolic paradism is also called the cognitivist or computational paradigm. For an introductory discussion, see H. Gardner, 1984.

[3] For a full discussion of connectionism, see Rummelhart and McClelland, 1987.

available to the components in isolation. These emergent properties are the great attractive feature of the network approach, and one that needs to be explored more explicitly for immune networks.

For our purposes here, it is important to remark that, although the connectionist (dynamical network) approach is usually seen as close to the brain and neural networks, this is not necessarily the best understanding of them. Most of the time, the relation with detailed neural systems is suggestive rather than precise. In contrast, what is important is that they are not symbolic machines in the traditional sense, and they operate on the basis of many components with local interactions. This is, of course, also the case for immune networks. It is at this level that immune networks should be studied, offering insights into the way biological networks can achieve cognitive capacities with enormous adaptability, a performance unknown to neural networks.

That is the direction of analysis we will follow here. We now turn to consider in detail the composition and dynamics of immune networks.

2. IMMUNE NETWORKS

2.1 IMMUNE EVENTS AND SHAPE SPACE

The immune system's "knowledge" (whatever that might mean in more precise terms), is about molecular shapes and profiles. Since it has access to nearly every corner in a vertebrate organism, it encounters nearly all available molecular species of the individual. These are either (a) produced by the organism itself, or (b) have penetrated the organism normally through mucosal surfaces, by the food eaten or the air breathed.

The stuff the Immune System (IS) is made of is heterogeneous, in terms of cells and molecules. All structures in the body interact with immunocompetent cells. Many of these are produced by other cells, and lymphocytes themselves produce all sort of molecules regulating gene expression and the activity of other non-immune cells. However, out of this whole array of components, we shall sharply distinguish lymphocytes on the basis of their diversity of variable regions (V-regions). We, thus, take the structural and functional basis of these immune abilities as derived from: (a) the vast diversity of lymphocyte receptors and free antibodies, and (b) the nature of their interactions with their ligands. The scale of this diversity should not be underestimated. In a mouse, currently one estimates 10^4–10^5 the number of protein-encoding genes, while the size of the potential immune repertoire is set at about 10^9–10^{10}. In what follows, we let f_i and b_i denote the concentration of free antibodies and cell-bound antibodies (respectively) of the i-th kind, with $i = 1, \ldots, N \approx 10^9$.

A consequence of the above choice is that it is appropriate to consider all immune events as occurring in a *shape space*, S: a low-dimensional metric space, where each axis stands for a physico-chemical measure characterizing a molecular

shape. Typical examples of such parameters would be: electric charge, hydrophobicity, amino acid sequence, and so on (Perelson and Oster, 1979). We will assume that some 5–7 of such measurements suffice to characterize a molecular configuration (belonging to the IS or not) as a point $s \in S$. In particular, in our previous notation, the subscript $i = 1, \ldots, N$ denotes a location within S. Every pair (i, j) of molecular components will relate to each other within this shape space through the affinity m_{ij} of their interactions, which reflects the probability of remaining associated.

2.2 DOMAINS OF INFLUENCE

The weak, non-covalent forces that define immune interactions allow for reversibility and some degeneracy in the detail of reactive surfaces. It follows from all these combined factors that the IS is characterized by an enormous degeneracy and redundancy. Thus, for example, it is not surprising that the requirement for sufficient diversity and repertoire completeness is met by a tadpole with 10^4 or so clonal components as much as by a mouse IS containing 10^8–10^9. Obviously, however, the tadpole IS is less precise on molecular details, since its completeness owes more to degeneracy than to diversity.

This tells, then, that each IS component located at i will have within shape space a distributed *domain of influence*, defined as the distribution of affinity over S. For the finite set of locations occupied by the components of the IS, $j = 1, \ldots, N$, we write the value of the domain of influence of the i-th species as a row of the interaction matrix m_{ij}. Experimentally the values of this matrix are the measured affinity between a given antibody and any other component (free or bound). It is on the basis of their mutual domains of influence that two components will interact to some degree or not. Immune crossreactions keep two species together, neutralized from other interactions for a given period of time. The number of complexed $(i-j)$ pairs at any point in time is, thus, related to the product of their affinity and their molar concentrations; that is a quadratic term of the form: $m_{ij} f_i f_j$.

2.3 DYNAMICS

Clearly, free molecules cannot do much: their action requires some form of binding. Thus, the relevant events in the IS are not the molecules by themselves, but rather their interactions. This is significant, since by centering on interactions of immune components, one is *ipso facto* considering the IS *dynamics*: the active range of changes of immune components as a result of their mutual constraints and reciprocal actions.

It is well known, of course, that immune components are not static. In extreme conditions, a given antibody can vary up to a million fold in concentration. We will propose some specific dynamical rules for the IS in what follows, but before embarking on the analysis of details of immune dynamics, it is important to examine the overall capacities emerging from such an IS network.

2.4 COGNITIVE CAPACITIES

In our view, the IS *asserts a molecular self* during ontogeny, and for the entire lifetime of the individual, it keeps a memory of what this molecular self is. Fundamentally, the IS is an *identity mechanism* in shape space, much as the nervous system is an identity mechanism in the physical three-dimensional space. The IS dynamics is the mechanism that makes the establishment of such a molecular identity possible.

It is as a result of this assertive molecular identity that an individual who had measles in childhood is different from what he would have been had he not been in contact with the virus, or how an IS changes if the person switched from an omnivorous to a vegetarian diet. The IS keeps track of all this history, while defining and maintaining a sensorial-like interface at the molecular level. It must be stressed that the self is in no way a well-defined (neither pre-defined) repertoire, a list of authorized molecules, but rather a set of viable states, of mutually compatible groupings, of dynamical patterns. In effect, a molecule is neither self nor anti-self, as a musical note does not belong more to a composer than to another one. The self is not just a static border in the shape space, delineating friend from foe. Moreover, the self is not a genetic constant. It bears the genetic make-up of the individual and of its past history, while shaping itself along an unforeseen path.

2.5 METADYNAMICS

A unique quality of the IS identity is its adaptability. In fact, any possible new element in shape space, even if newly synthesized (and, hence, with no evolutionary history), can interact with a functioning IS. This quality of "completeness" (Coutinho, 1980) or better: open-endedness (Jerne, 1985) is not the result of learning, but of an intrinsic feature of the way the molecular identity is established while at the same time allowed to change. We refer to this as the *metadynamics* of the IS: the continuous production of new variables, of novel molecular alternatives, most of which never enter into the dynamics of the IS itself, but very rapidly decay and disappear.

The IS metadynamics is based on the unique non-conservatism of V-regions, genetically specified through 4 to 6 distinct gene segments, drawn from a large polygenic pool. Furthermore, the mechanisms leading to the production of mature genes by the rearrangement of those gene segments are error-prone and lack precision in the sites of recombination, giving rise to yet new combinations not to be found in germ-lines. These novelties are further amplified by the activity of an enzyme that randomly adds nucleotides at the sites of recombination, without copying them from a template (Tonegawa, 1983). Hence, it is biologically evident that such mechanisms have been introduced in this system through evolution, but as a result of their presence, the V-regions generated in the organism are not evolutionary selected.

This enormous reservoir of possibilities is the key to the open-ended quality for novelty, both resulting from the system itself, and from unrelated environmental changes.

2.6 IMMUNE DYNAMICS AS NETWORK

The dynamics of the IS was clearly brought to the fore by Jerne's network hypothesis, based on the diversity and degeneracy of variable V-regions (Jerne, 1974). The original postulate is fundamentally correct: normal individuals *do* contain a set of lymphocyte receptors and free antibodies which mutually interact with varying frequencies (Holmberg et al., 1984; Kearny and Meenal, 1986). In this paper, we interpret the admittedly fragmentary evidence, as implying that V-region connectivity is a key property from which the IS asserts a molecular identity, and not a mere epiphenomenon of diversity/degeneracy (see for discussion Urbain, 1986).

It is important, however, to stress the participation in the network of both free and bound receptors. Although the free V-region sub-network is by far dominant in quantity, the sub-network of bound components acts as regulator of the entire network. This is discussed in further detail below, but constitutes a key to the IS's capacity for stability and regulation.

At any given time, the network of free and bound components defines a surface of potential coupling in shape space, which is simply the superposition of the domains of influence of all participating components. Conversely, every point s in shape space will be accessible to the IS to the extent that there are components with some degree of affinity at that point and in a non-negligible concentration. Formally, this can be expressed as

$$\sigma_s = \sum_j m_{sj} f_j. \qquad s \in S,\ j = 1, \ldots, N \tag{1}$$

We shall refer to the coupling surface defined in (1) as the IS's *cognitive domain*, since it represents the limits (or boundaries in S) of the molecular self. For each s, σ_s, also named *sensivity* at s, may be viewed as the degree of engagement of s in the network, for it corresponds to the probability of meeting any other species.

2.7 THE COGNITIVE DOMAIN OF THE IS

Although Jerne's idiotypic network is well know among immunologists, it is less often discussed how immune connectivity extends beyond the "web of variable domains" to include all other molecules in the organism which bind to V-regions, that is, that can be coupled with the IS's cognitive domain.

Needless to say, immune components do not individually "know" about anything; they simply bind or do not bind to molecular surfaces. But in keeping with the style of analysis of networks in general, it is the entire ensemble of components which endows the system with a cognitive capacity which is not located anywhere

in particular, but embodied in the entire system. More precisely, since molecular complementarities create classes (if A binds to B, and A binds to C, then B and C are equivalent under A), the immune system will necessarily carry molecular complementarities or mimicries to all molecules which the cognitive domain of the IS is open to (can couple with). This on-going internal set of images coincides with what the specific constituents of the molecular self are.

Clearly, one can define "self" from a biochemical or genetic or even *a priori* basis. But from our vantage point, the only valid sense of *immunological self* is the one defined by the dynamics of the network itself. What does not enter into its cognitive domain is ignored (i.e., it is non-sense). This is in clear contrast to the traditional notion that IS sets a boundary between self in contradistinction to a supposed non-self. From our perspective, there is only self and its slight variations. That which is foreign is only so because it is similar to (or only slightly different from) self: the *Unheimlich* of that considered as foreign can only come from this proximity (as Freud pointed out long ago).

This foreignness-as-almost-self is dealt with by the system's metadynamics: the continuous production of novel V-regions with random diverse shapes, which, more often than not, makes little sense for the existing self as they do not interact significantly with existing molecular shapes in the network. For the system to become responsive to a "new" molecular species, it is necessary that what at the beginning are rather isolated new V-regions become selected and incorporated into the network itself by expansion or reinforcement of the cognitive domain into that region. This might never happen; often secondary contacts with non-self molecules evoke "immune responses" which are indistinguishable from "primary responses": no memory was generated in the first contact because the network was not engaged, and, thus, there is nothing to recognize.

It is very likely that many situations will be less clear cut than the above discussion suggests. Some aspects of antigens will fall in varying degrees into the cognitive domain of the network—otherwise, they could not be said to be antigens! Other species may certainly evoke a transient response of disconnected V-regions. Multideterminant antigens, therefore, provide missing connections and generate novel interactions of previously isolated V-regions within the network. Alternatively, the concentration of the novel V-regions hyper-expressed in the immune response will reach significant levels as a self molecule and, consequently, integrate the immune network. In either case, the IS will undergo adaptive compensation through its dynamics and changes in its cognitive domain through metadynamical innovations. Thus, at any point in the life of an organism, the self of an individual is unique and covers a limited domain of shape space.

2.8 LYMPHOCYTE PRODUCTION AND ACTIVATION

Whatever the variability in the production of possible V-regions, it is clear that, ultimately, there is a single V-region in each lymphocyte: they are clonal. Thus, the upper limit for the size of an IS's repertoire is equal to the number of lymphocytes

in the individual, and the production of new V-regions requires the production of new cells.

Hence, for the on-going network change, it is key to understand the manner in which a newly produced lymphocyte, advertising a V-region on its surface, can be selected and incorporated in the on-going IS dynamics.

A large number of lymphocytes are produced throughout life in the central lymphoid organs (bone marrow and thymus). But, while B lymphocyte production in bone marrow continues at high rates until death, the generation of T lymphocyte in thymus is considerably slowed in adulthood. Roughly 20% of the total number B cells in an organism is renewed daily from the bone marrow. The large number of these decay rapidly, with mean survival times of a few hours or days, so that the total lymphocyte volume remains roughly constant. Some lymphocytes which migrate to peripheral lymphoid organs are selected for persistence or long life-span, from a few weeks to some months. Up to 10% of the newly formed cells enter this pool. The turnover rates in this compartment are some tenfold lower than in the short-lived pool (Freitas et al., 1986)[4]

Thus, it is clear that there is an enormous production of novelty in newly produced lymphocytes which will never be used, and what is used depends on the configuration of the existing network.

In contrast with many other cells in the organism, lymphocytes are produced as resting cells with no effective actions (effector functions). B cells can produce and secrete antibodies; T cells can help or suppress B cells and even destroy other cells. Yet to do any of this, lymphocytes must be activated from their initial resting state. In our description of the IS, we deal only with activated lymphocytes, and thus, the transition from rest to activity is central to understanding immune phenomena.

In nearly all cases, lymphocyte activation results from V-region interaction with other ligands. These can vary in details; while B cells bind whole, free molecules to their surface receptors, T cells appear to interact with short linear fragments of molecules previously associated with a specific set of self molecules: the product of the MHC genes (Schwartz et al., 1985). There are far too many fragmentary details to cover here. Suffice it to say that, although T cells appear to be activated by some appropriate molecular profiles (Larsson et al., 1984), B lymphocytes fail to do so (Coutinho et al., 1984b). Interactions of B lymphocyte receptors with ligands only induce the resting cell to a stage of higher susceptibility to be activated by a T helper lymphocyte.

Activation of lymphocytes may result in mitosis, with both cells expressing the same V-region. Clearly, the proliferative potential of a lymphocyte is considerable: a single cell can produce thousands of descendents. But the contribution of cell division to clonal amplification in the normal operation of the IS is still unclear. At any rate, activation leads to the acquisition of effector functions: synthesizing antibodies at a rate of several thousand molecules per second (in contrast to one

[4]The population of T lymphocyte is somewhat different and less well studied. Many T cells are produced daily, but fail to be exported to the peripheral IS (about 1/30 of a total of about 30×10^6/day). A good many of these appear to persist in the periphery for long periods of time.

molecule/sec in resting cells). Thus, a unique V-region species on a resting lymphocyte represents some 10^5 molecules in the whole system, while an activated B cell in its 2–3 day life-cycle can produce up to 10^9 molecules of free antibody with the same V-region (Melchers et al, 1974; Jerne, 1984). Thus, network dynamics with regard to B cells is primarily one of activation-dependent changes in the rates of antibody production per cell, rather than cell multiplication. What then regulates B cell activation?

Activation always requires the participation of T cells. The two cooperating lymphocytes must engage in direct cell-to-cell contact for a period of time, before "non-specific" factors can come into play. This contact requires complementarity above a critical threshold, involving V-regions on both receptor types. There are at least three types of activation mechanisms one can envisage. In the first, B and T display complementary V-regions activating each other. It is plausible that this mechanism accounts for a good part of all immune activity in normal individuals (Tite et al., 1986; Bandeira et al., 1987). Such a mechanism is based on V-repertoires, and is independent of the rest of molecular self.

Two other mechanisms are known to exist, both involving V-regions and other self molecules. Resting B cells binding a molecule to surface antibody receptors can present it (or parts thereof) on their surface, and thus, become targets for selective interactions with competent T cells displaying the appropriate complementarities. This is the classical "antigen-bridge" model for T-B collaboration (for discussion, see Coutinho, 1984). There is little information about the frequency of this mechanism in immune dynamics, but believed to be common.

Finally, another type of B-T collaboration has been elucidated. Ligand binding to resting B cells (whether those ligands be somatic self molecules or free antibodies) induces the cell into a state of hyperactivity with regard to possible interactions with T helper cells, primarily because of the hyper-expression of surface molecules required for interaction with T lymphocytes—the MHC gene products (Monroe and Cambier, 1983). In the presence of T helper cells of self-related specificity, such hyperactive B lymphocytes engage in productive collaboration. This type of mechanism does not require that both cooperating cells display complementarities to the same molecule, and most importantly, it does not seem to require a strict receptor specificity from the cooperating T cell altogether. Since B cells cannot know which molecules bind to their receptor, this kind of mechanism strongly favors the activation of B cells that are very connected to the existing network. From recent experiments, we believe this mechanism plays a major role in the activation of normal individuals (Pereira et al., 1986b and to be published; Bandeira et al., 1987).

Thus, B cell activation also falls within the domain of influence of the immune network, and another loop is closed. Once activated, B cells produce large amounts of free antibodies with the same binding preferences as the receptors that had been selected for activation; it follows that these free components will bind and neutralize the very same molecules that led to their activation. Thus, while interactions between circulating antibodies and cell bound receptors are stimulatory, those between circulating antibodies in the immune network are inhibitory for

the activation of the B lymphocyte which can produce them (independently of the nature of the activation mechanism summarized above). The clonality of V-region expression finds in these stabilizing dynamical loops its most clear relevance.

Although we have not analyzed the mechanism of T cell activation and T cell repertoires, we have assumed that a network of B cells and antibodies *does* require T cell participation. In the present version of the IS, we simply assume that appropriate T helper cells are available in normal individuals, as supported from recent evidence (Pereira et al., 1985, 1986b). Also, we will not explicitly discuss here the role of T suppression, but assume that similar mechanisms as those discussed for T helper cells will apply (Pereira et al., 1985). Figure 1 summarizes a view of IS dynamics in a schematic way.

2.9 EQUATIONS FOR IS

The foregoing ideas on the IS dynamics, stabilizing factors, and change, can be summarized in the following generic set of equations:

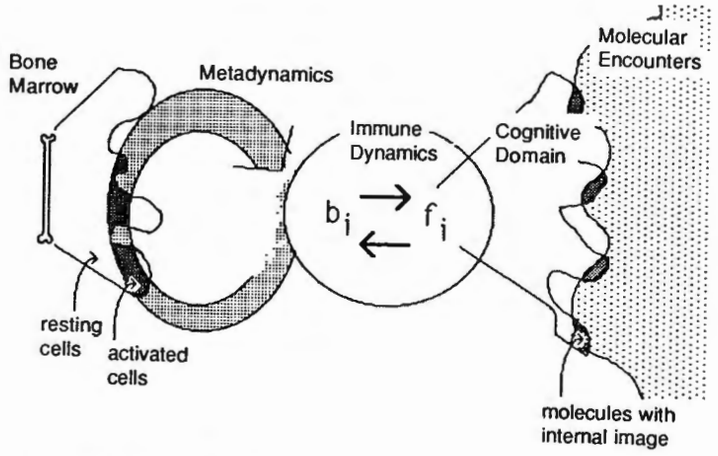

FIGURE 1 Schematic view of IS dynamics.

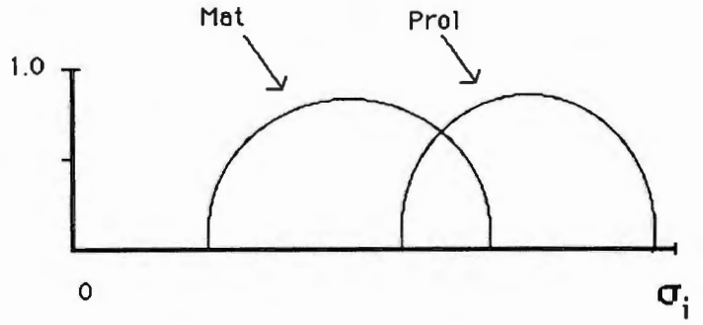

FIGURE 2 Distributed control of the (2a) dynamics under the influence of the antibodies species present, showing up as a proliferation function *Prol*, similar in shape to *Mat*.

$$\frac{df_i}{dt} = -\sigma_i f_i + Mat(\sigma_i) b_i \tag{2a}$$

$$\frac{db_i}{dt} = -b_i + Prol(\sigma_i)\, b_i + Meta(i) \tag{2b}$$

$$i \longleftarrow Meta(i), \qquad i = 1, \ldots, N. \tag{2c}$$

where σ_i denotes the sensitivity at i [see Eq. (1) in 2.6]. (Scaling constants have been omitted for clarity.)

Eq. (2a) describes the main dynamics of the IS through changing concentrations of V-regions: the species located at i in shape space will increase in concentration according to the level of activated B cells capable of producing it, scaled by a maturation function *Mat*, embodying both B cell activation through network contacts and T cell regulation (Figure 2). The f_i's will tend to be decreased in proportion to the network's sensitivity at i, being unable to bind to other ligands. Eq. (2b) represents the distributed control of the previous dynamics Eq. (2a), but itself under the influence of the antibodies species present, showing up as a proliferation function *Prol*, similar in shape to *Mat* (Figure 2).

Spontaneous cell death will reduce b_i's numbers. This pair of linked equations represent both the dynamics of the IS components and the way in which B cell are activated by the state of the network constantly specifying a cognitive domain through which the IS can couple.

The term in Eq. (2c) is not properly an equation, but a metadynamical *algorithm*: it represents the probability that a given species i will be produced by the bone marrow, and thus, a corresponding term with index i will play a role at all in the above dynamics. Formally, it indicates that the variable vector active in Eq. (2a-b) will not be a fixed one, as in a classical differential equation, but will change continuously (Farmer et al., 1986). This probability function is different for each

individual according to their specific V-gene endowment, but fixed over life, like a steady generator. Whether an i-th species will be incorporated into the network, proliferate, or mature, is a function of the entire IS's dynamics Eq. (2a-b).

2.10 SOME RESULTS AND OPEN POSSIBILITIES

Our intention in this article is not to make an exhaustive analysis of the model proposed above, but rather to indicate its general characteristics, their interest in immunology, and their relationship with neural networks. A more detailed analysis of the simulation results and their applications will appear elsewhere (Varela, Coutinho, and Dupire, in preparation).

The first item to remark is that the *qualitative* behavior of this family of equations is relatively stable within a broad range of parameters, while at the same time quite varied in the behavior of individual components. This is required if one is to come moderately near the intricacies of biological immune dynamics. The basis of this qualitative behavior is, of course, the non-linearity of the laws we have chosen. Other possible simpler variants do not give satisfactory results. For example, if both *Prol* and *Mat* are constants, Eq. (2) turns out to have unstable behavior, with all the f_i either imploding or exploding. Thus, Eq. (2) embodies a carefully selected and realistic set of local rules of immune networks which seem to be over the minimal threshold of complexity required to begin to be useful in the context of biological observations.

The richness of the dynamics can be appreciated through two examples. First, simulations reveal that Eq. (2) exhibits oscillations for many of the variables. That is precisely the kind of behavior one gets in measuring antibody concentration over a period of several months (Lundqvist et al., 1987). A purely cellular analysis of this fact is bound to fail, since it is an network phenomenon, spontaneously produced by the local rules.

A second interesting emergent property is the fact that, although the system undergoes constant metadynamical change, and can be subjected to a history of interactions with independent antigenic sources, there is a large core of species which stay remarkably regular. The source of this memory of the system resides in the strength of the subsets of variables which act as buffer to one another against change, in complex topological patterns in shape space. In other words, the memory capacity of an immune network is revealed here as a property of topological self-organization in the shape space proper to the non-linear equations.

Histories of antigenic interactions are easily accommodated within this framework, as it should be obvious by now. In fact, it is enough to add to Eq. (2a) a term of the form

$$\sum_j m_{ij} f_j a_j \qquad j = 1, \ldots, M \tag{3}$$

where a_j are the amounts of antigens the IS encounters in a unit of time. Obviously, these encounters will cause a shift in the relative concentrations within the network. But, in contrast to the view most currently adopted, we have left this term for last, to emphasize that in our perspective the IS is not antigen-driven, but self-referential. That is, by far the most interesting dynamics to study is proper to the immune components themselves (Vaz and Varela, 1978; Coutinho et al., 1984a).

That this is biologically sensible is directly seen by considering experiments with "antigen free" mice. These are germ-free animals maintained for a few generations on chemically defined, low-molecular-weight diets and, of course, on filtered air. Therefore, they do not contain or come in contact with antigens that are foreign to their own body. Such mice maintain, nevertheless, levels of immune activity in the spleen that are comparable to those of normal infected mice eating antigenic diets. Both the numbers of activated and "effector" lymphocytes and their turnover, as well as the levels of circulating IgM antibodies are the same in antigen-free and conventional mice (Hooijkaas et al., 1984; Pereira et al., 1986b). This self-centered activity engenders a cognitive domain which *defines* antigenicity, and for which external encounters provide boundary conditions, but not directive inputs.

These results are admittedly only suggestive. The point is to outline a way of doing research on immune networks. Every one of the qualitative results mentioned here needs to be properly studied and quantified. But our approach is meant to provide also a tool for research which constitutes its own validation. For this purpose, the optimal implementation of the model should be on real-time calculation displaying on a computer the updated state of the IS as a cloud of its sensitivities in the context of the self molecules present as constraints. The IS would then become readily visible as an active unity, relating to itself and its environment, and where the user could actively interact by adding or subtracting species, or altering dynamical parameters. In such a more advanced implementation, immune networks become a tool for research capable of explaining known results and suggests future ones.

3. CONCLUSIONS

3.1 NEURAL VS. IMMUNE

The immune and the neural systems have been compared often since they represent the most potent forms of biological cognition known throughout the animal realm. From our perspective, this comparison can be done in detail, given the explicit form of the IS we have put forward. In what follows, we outline what we see as some fundamental *differences* in the mechanism embodied by both cognitive networks.

This comparison is easier to carry out by considering an equivalent set of equations typical of neural network models, say

$$\frac{df_i}{dt} = \sum_j m_{ij} G\{f_j\} - f_i \tag{4a}$$

$$\frac{dm_{ij}}{dt} = F\{f_i, f_j\} \tag{4b}$$

where G is a sigmoid threshold function of the voltages, f_i, the source of the non-linearities in the neural network, and F is a quadratic in terms of both variables as in Hebb's rule.[5] We have written Eq. (4) to emphasize the contrast with Eq. (2) along some main directions:

- First, in immune nets connectivity depends on probabilistic encounters, required by a network made up of components which diffuse in a large volume, in contrast to neural connectivity based on a fixed anatomy over axo-dendritic extensions. This is the basis of the different sources of non-linearities in both systems.
- Secondly, the relevant variables in Eq. (2a) are under the controlling influence of the B cells that produce them. In Eq. (4) instead, it is the connectivity matrix itself which is the controlling factor, as a function of the network's state, as defined by Eq. (4b).
- Third, the algorithmic term Eq. (2c) has no analog in neural networks: this is the source of the rich adaptability immune dynamics exhibit and accounts for a continuously changing topology. This would correspond to a brain where many neurons vanish while others pop up from nowhere.

These points make explicit our initial suggestion that IS seem to provide a radically *different* kind of biological network capable of (at least a few) basic cognitive performances. The full extent of these differences (or their possible equivalence) remains to be investigated in detail.

[5]This family of equations is broadly used in neural modelling; for example, recently by Hopfield and Tank (1985). Many variants do, of course, exist, but they are not our concern here. For a related set of equations and an extensive discussion, see Grossberg (1984).

3.2 ENACTING VS. REPRESENTING

One of the most interesting aspects of the cognitive mechanism present in immune networks is that they operate in the domain of molecular shapes which are not inhabited by man's habitual objects of perception: objects, 3-D space, and other people. This provides an occasion to see how knowledge operates without the anthropomorphic weight of our ordinary perceptual world.

In this sense, the immune networks reveal how biological cognition is a matter of action, or better, of *enaction*: in its very operation the system specifies a domain of relevance (or significance), which becomes a "world" for the animal to act and live with. In fact, the shape space is, without an immune system that lives in it, completely neutral and void of any sense of signification and distinctions of any sort. But as soon as an immune network appears, its own self-assertion creates a clear demarcation of a cognitive domain, and hence, an entire series of discriminations between self and non-sense, proper and inadequate, friendly and foe.

This kind of enactive cognition, so clearly seen in immune networks, has to be contrasted with our usual view of cognition as being a more or less accurate representation of a world already full of signification, and where the system picks up information to solve a given problem, posed in advance (Varela, 1979, 1987). This is the understanding of immune cognition for the antigen-driven clonal selection view of the immune system, where adequate operation means optimal defense of invaders as out-there. This understanding of the IS has also been the base of recent models similar in scope to ours (Farmer et al., 1986).

To be sure, there are some constraints under which the IS must operate, including a clear discrimination of some small number of bacterial shapes which must be kept at bay. But this is not a great cognitive task. The more difficult and creative one is, instead, the operational assertion of a molecular identity which makes vertebrate life possible, which is a positive task and not a defensive one. Immune cognition shows that this world of molecular shapes can be addressed in a vast (infinite?) number of ways, all of them complete, provided that they are consistent enough. The molecular world we inhabit, thus, is not pre-given, and then inhabited *post facto* by our immune systems through some optimal adaptation. It is rather laid down as we walk in it, it is a world brought forth.

This clear demonstration of knowledge as enactive, is another unique contribution of immunology to the yet poorly explored realm of biological cognitive networks and their mechanisms.

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