The Immune System : Emergent Self-assertion in an Autonomous Network.

John STEWART, CNRS.

Mailing address:
Department of Immunobiology, Pasteur Institute,
25 rue Dr Roux, 75724 Paris Cedex 15, France.

Abstract.

This paper presents a model of the immune system as a network of lymphocyte clones which interact via immunoglobulin molecules and hence mutually activate each other. The dynamics of the model is represented by two differential equations governing the production and elimination of free and cell-bound immunoglobulins. In addition, the composition of the activated clones which constitute the network is continually renewed by the elimination of certain clones and the recruitment of new clones from the pool of resting lymphocytes freshly produced by the bone-marrow; this second-order process is termed metadynamics. The dialectical interplay between the dynamical and metadynamical aspects is a highly characteristic feature of the immune network. Computer simulations illustrate the way in which this interplay renders the system as a whole autonomous, so that its functioning gives rise to an emergent self-identity in the domain of a molecular ecology.

Introduction.

The immune system of vertebrate animals is composed essentially of a special class of cells, the lymphocytes, which produce protein molecules known as immunoglobulins. The immunoglobulins produced by any given clone of lymphocytes are all identical, but from one clone to another the immunoglobulins are astonishingly diverse. This diversity, generated by a remarkable process of somatic DNA rearrangement (which as far as is known occurs only in lymphocytes) is so great that no two clones produce identical immunoglobulins. Moreover, the diversity is such that in a population of 10^8 cells (the number of lymphocytes in a mouse) there exists at least one immunoglobulin which will interact specifically with any molecular shape whatsoever of the appropriate size. Immunologists describe this phenomenon by saying that the "repertoire" of the immune system is "complete" (Coutinho *et al.*, 1984).

Immunoglobulins exist in two forms, either as free molecules secreted into the body fluids, or bound in the cell-membranes of the lymphocytes where they function as receptors for the activation of the cell. According to the theory of classical immunology, lymphocyte clones are activated independantly of each other through their interaction with external antigens, giving rise to an "immune response". In recent years, however, immunological theory has been enriched by a new approach to understanding the organization of the system. The initial impetus was given by Jerne (1974), who pointed out that if the immune repertoire is indeed complete, then since immunoglobulins are themselves molecular shapes, the immunoglobulin receptors of one clone should interact with the immunoglobulins produced by certain other clones. This has led to a concept of the immune system as an autonomous, self-activating network.

A model of the immune network.

In order to gain some idea as to how such a network might work, Varela et al (1988) have built a mathematical model consisting of n clones of lymphocytes (denoted by i=1,2,.....n). The dynamics of the system are defined by the equations:

$$df_i/dt = -k_1 f_i h_i + k_2 b_i \mathrm{Mat}(h_i) \qquad \text{Equation [1]}$$

$$db_i/dt = -k_3 b_i + k_4 b_i \mathrm{Prol}(h_i) \qquad \text{Equation [2]}$$

(where f_i and b_i are the concentrations of free and cell-bound immunoglobulins of clone i, and k_1, k_2, k_3 and k_4 are constant parameters. The "field" h_i , representing the total effect of all the clones $j=1...n$ on clone i, is given by $h_i = \Sigma\, m_{ij} \cdot f_j$, each m_{ij} being the "affinity" or interaction strength between clones i and j. The "maturation" and "proliferation" functions Mat(h) and Prol(h), describing the activation of cells to immunoglobulin secretion and cell division respectively, are log-normal bell-shaped curves with maxima at intermediate values of the field h and tending to zero at either very low or very high field values.)

In addition to the purely dynamic aspects, modelled by the differential equations [1] and [2], the list of clones i=1....n constituting the system at any one point in time is not fixed, but is continually renewed by the elimination of certain clones and the recruitment of new clones from the pool of resting lymphocytes freshly produced by the bone-marrow. The rate of bone-marrow production is such that the entire system could be reconstituted in less than a week; at any one point in time, the pool of potentially recruitable cells comprises fully 80% of all lymphocytes, whereas only 20% are actually incorporated in the network of activated cells. This process of renewal is thus quantitatively important, and we have coined the term *meta-dynamics* to signify that the dynamics of the system is embedded in a second-order process which is potentially of great biological significance.

The relationship between the dynamics and the meta-dynamics of the system is complex. On the one hand, the dynamics is largely determined by the connectivity matrix m_{ij} , which in turn depends on the composition of the clones i=1...n resulting from the meta-dynamics. On the other hand, the meta-dynamical processes governing the effective recruitment and elimination of clones from the population of activated cells themselves depend on the dynamics of the clones concerned (Bersini 1992). This dialectical interplay between the dynamics and the meta-dynamics constitutes one of the most characteristic features of the immune network.

Computer simulations.

This model of the immune system is based on current knowledge of the biological reality of the immune system (Varela et al 1988). Even though the model voluntarily represents a drastic simplification of that reality, it is still a highly non-linear dynamic system of great complexity. We have therefore performed computer simulations to investigate its behaviour (Stewart & Varela 1989, 1990, 1991; Detours 1992). In order to get our conceptual bearings, we will look first at a simplified version of the metadynamics; we will then examine more closely the dynamics resulting from equations [1] and [2]; finally, we will briefly examine the possible results of combining the dynamics and metadynamics.

Elementary metadynamics.

In order to permit graphic visualisation of the results of the metadynamical process, we have adopted a modified version of the "shapespace" concept originally proposed by Segel & Perelson (1989). More precisely, each point in a 2-dimensional shape-space corresponds to a pair of complementary shapes, distinguished as "black" and "white", so that neighbouring points of opposite colour have a high affinity m_{ij} between them. Candidate clones for recruitment into the network are then generated as random black or white points in shapespace. (It should be noted that this represents a strong constraint on the connectivity structure of the total set of all possible clones). The rule governing the metadynamical process is the following: if the field h_i experienced by a clone i lies within a "window" between a lower and an upper threshold, the clone is maintained/recruited into the network; if the field is outside this window, the clone is eliminated/not recruited. On this basis, a simulation proceeds as illustrated in Figures 1a and 1b. During an initial phase, the available shapespace is populated by clones in a rather disorganized fashion (Figure 1a). During this phase, it often happens that the recruitment of a new (white/black) clone, due to the field created by neighbouring (black/white) clones, raises the field for these (black/white) clones above the upper threshold so that they are eliminated, which in turn leads to the elimination of the (white/black) clone. In other words, the process displays a form of self-organized criticality with local avalanches. The initial phase comes to an end when this perpetual reorganization leads to the emergence of quasi-stable configurations, with the formation of "chains" of black clones running parallel to chains of white clones (Figure 1b). To summarize, purely local rules give rise to clearly discernible global patterns, a process that we have termed "morphogenesis in shapespace" (Stewart & Varela 1991).

Dynamics.

As we have already remarked, the dynamic behaviour of the system defined by equations [1] and [2] obviously depends on the form of the connectivity matrix m_{ij}. It is useful to analyse these dynamics with reference to a certain number of "reference" connectivity structures.

(i) A single clone with self-affinity possesses a fixed point attractor with a field on the declining portion of the bell-shaped Mat and Prol functions (as can be seen mathematically by putting the time-derivatives in [1] and [2] equal to zero). This result can be extended to a collection of fully connected clones which behave collectively in the same manner (Bersini 1992).

(ii) A system composed of two clones connected to each other (in general, the matrix m_{ij} is symmetric), but with no self-affinity, does not appear to posses a fixed-

point attractor (but see de Boer et al 1992 for a fuller discussion of this point in the context of more complex models). However, for suitable values of the four parameters k_{1-4} , this sytem does possess a cyclic attractor in which the two clones oscillate 180° out of phase with each other (Stewart & Varela 1990). This result can be extended to a set of n clones connected in a "chain": 1 with 2, 2 with 3, ... i with (i+1)....., (n-1) with n. In this case, the odd-numbered clones form one group whose members fluctuate synchronously; the even-numbered clones form a second such group; and the two *groups* oscillate alternately in the same way as two single clones (Figure 2).

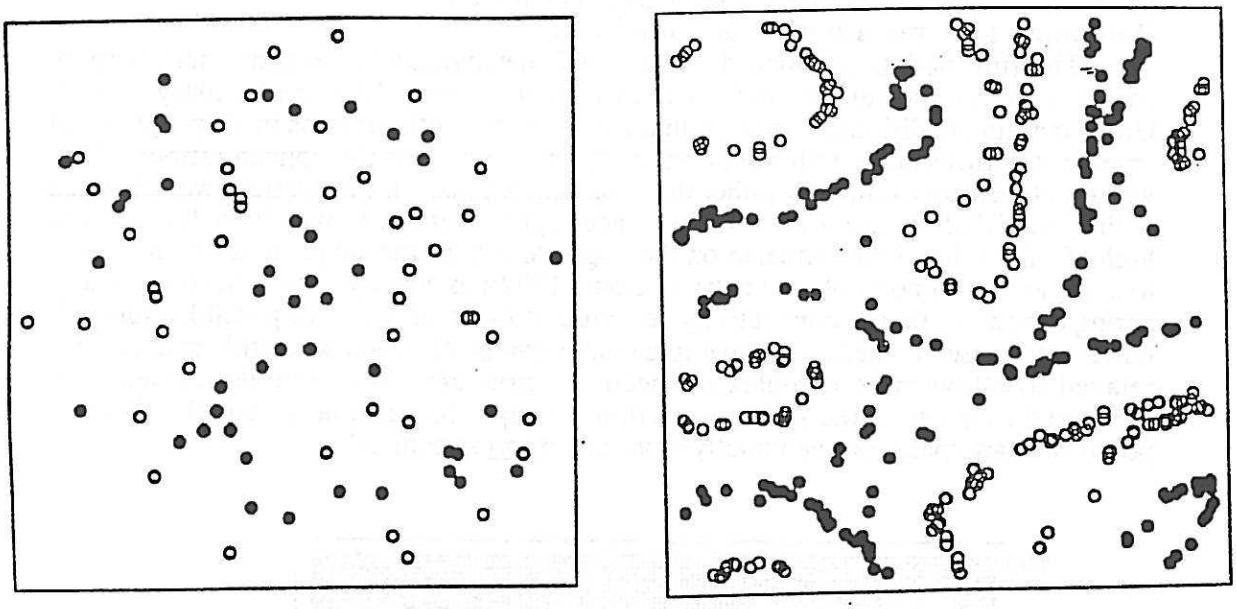

Figure 1. Morphogenesis in shapespace, resulting from the metadynamical process. (a) Left : Initial phase, during which the shapespace is populated in a rather disorganized fashion. Self-organized criticality gives rise to local avalanches. (b) Right : The autonomous reorganization of phase (a) leads to the emergence of characteristic patterns with parallel chains of "black" and "white" clones. From Stewart & Varela (1991).

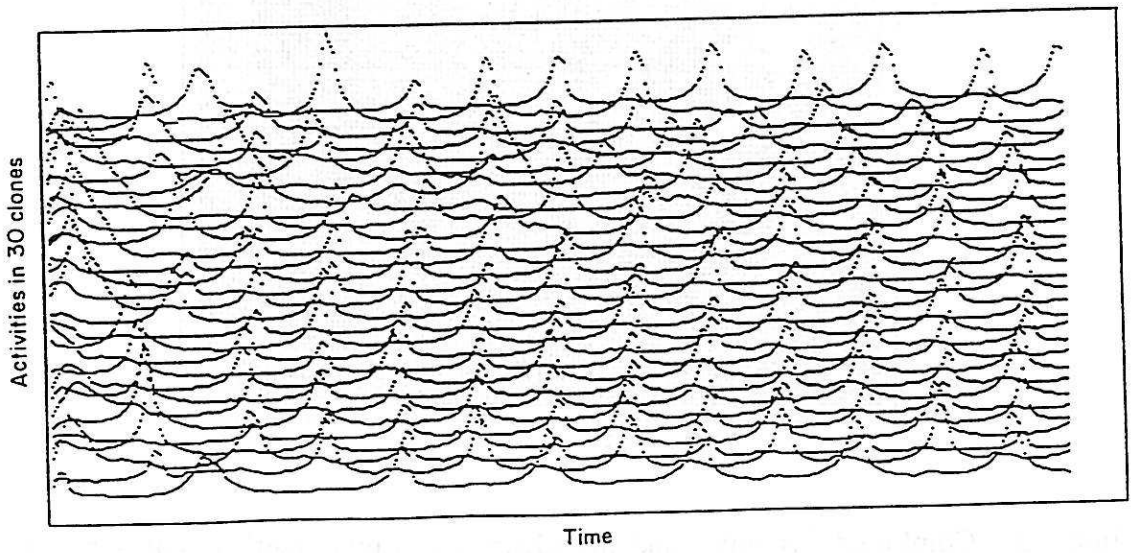

Figure 2. The dynamics of a linearly connected chain of lymphocyte clones. Odd-numbered clones form a group of clones which oscillate in phase with each other; even-numbered clones form a second group of this sort; the two groups oscillate out of phase with each other. From Stewart & Varela (1990).

(iii) As might be expected from the above, an additional connection between clones 1 and n (forming a closed loop) creates a complex situation if n is odd. The reason is that without this last connection, the two clones would be oscillating *in* phase with each other; the connection, however, requires them to oscillate *out* of phase. This prediction is fulfilled: closed loops of 3, 5 and 7 clones show quasi-chaotic dynamics (Bersini & Calenbuhr, personal communication). In fact, there is a tendency for one clone (at random) to be eliminated, which restores the "open chain" connectivity structure of (ii), and thus permits the regular pattern of oscillations to establish itself. However, the resurgence of the "excluded" clone pushes another clone out of the "dance", so that the overall result is highly irregular.

Dynamics and metadynamics combined.

The full model, in which dynamics and metadynamics are combined, is more complex than either alone, and for the moment we only have preliminary results. Under certain conditions, it appears that quasi-stable configurations in shapespace can emerge, the difference with the previous results being that the concentrations of the various clones are oscillatory rather than constant (Figure 3). This pattern was obtained with a modified version of the shape-space representation, in which each clone has high affinity with clones situated on the opposite side of the shape-space with respect to a single central point of symmetry (Detours 1992); as already noted, this represents a strong constraint on the connectivity structure of the total set of all possible clones. It remains to be seen whether comparable results can be obtained when this constraint is relaxed to allow more complex connectivity structures (for example, closed odd-numbered loops as in the previous section, multiple connections to widely different points in shapespace, or even totally random a priori structures).

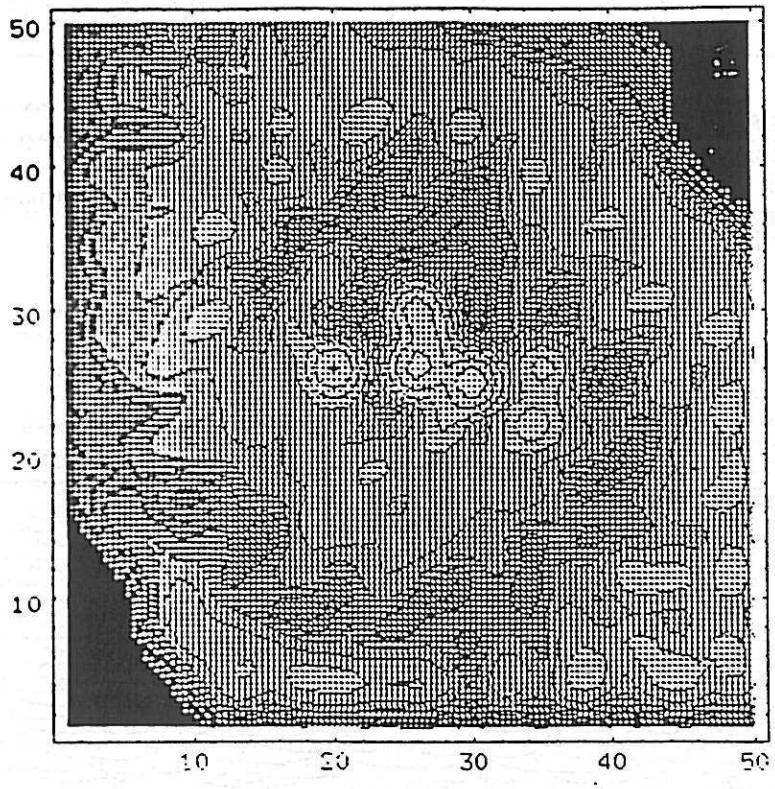

Figure 3. Combined dynamics and metadynamics. Light shading represents clones of high concentration, dark shading representing low concentrations. This Figure illustrates the emergence of a quasi-stable spiral configuration in shapespace, the difference with Figure 1 being that the concentrations of the various clones are oscillatory rather than constant. From Detours (1992).

Discussion.

As we have already noted, a highly characteristic feature of the immune network as we have modelled it is the dialectical interplay between its dynamics and metadynamics. The composition of the system is determined by a selective process in which only certain clones are recruited and maintained as active members of the network. It is important to emphasize that the instance responsible for this selection is not external to the system, as it is in classical neo-Darwinian population genetics, or indeed in classical immunological theory where clones are selected by an external antigen. Here, by contrast, it is the system itself which does the selecting; for this reason, we may consider that the network is truly *autonomous*. The results presented here, although still preliminary in many respects, strongly suggest that the result of such a process is not just random "white noise": the process appears to be morphogenetic, giving rise to discernible regularities and generic patterns. However, for an external observer, the *particular* form of these patterns is largely unpredictable, so that the process is more akin to natural drift than to some well-defined optimalization. Nevertheless, since the component elements of the system mutually select each other, we are justified in saying that the system as a whole is *coherent* ; and we may speak of the emergent object of this coherence as a *self-identity*. Thus, the work presented here represents a validation and partial concretization of the original intuitions of Vaz and Varela (1978) and Coutinho et al (1984), according to which the function of the immune network is one of *self-assertion.*

The full biological significance of such a mode of functioning is largely a matter for future research. 80% of the B-lymphocytes in a normal mouse are small resting cells which are not functionally connected, either to each other or to the network. When activated by external antigens, such lymphocytes will give rise to an immune response which, by the classical mechanism of clonal selection, will be relatively specific for the antigen and will trigger its destruction. But what is the function of the network? One obvious possibility is that, by incorporating "self-antigens" (i.e. the molecules of the body of the organism) into its regulatory dynamics, the network protects the organism from autoimmunity, i.e. an inflammatory immune response against self-antigens. Another possibility is that the incorporation of self-antigens (which correspond to particular points in shapespace) into the emergent patterns in shapespace (Stewart & Varela 1991) might have the effect that the various molecular events occurring in the body will no longer be independant and unrelated to each other, but will rather be integrated as elements in an overall "molecular ecology" (Varela et al 1992). These effects may be particularly marked in the case of "messenger" molecules such as hormones and neurotransmitters, and may provide a partial explanation for psychosomatic phenomena. If these speculations should turn out to be substantiated, it might be justified to speak of the immune network as a "central" system (Varela & Coutinho 1991), in analogy with the brain which, as a "central" nervous system, not only integrates otherwise unrelated peripheral events, but in the process also gives rise to an emergent self-identity characterized by its autonomy. It is even conceivable that immunoglobulins originally arose in evolution in the context of a "central" function of this ort, and that the deployment of the "peripheral" part of the system to trigger defence reactions was a later development (Stewart 1992).

Acknowledgements.

The work described in this paper was carried out in collaboration with Francisco Varela and Antonio Coutinho, and would not have been possible without their intellectual stimulation, friendship and support.

References.

Bersini H. (1992). The Interplay between Dynamics and Metadynamics of the Immune Network. Artificial Life III Workshop, Santa Fe, 15-19 June 1992.

Coutinho A. Forni L., Holmberg D., Ivars F. & Vaz N. (1984). From an antigen-centered, clonal perspective of immune responses to an organism-centered, network perspective of autonomous activity in a self-referential immune system. *Immunol. Revs.* **79**, 151-169.

De Boer R.J., Kevrekedis I.G. & Perelson A.S. (1992). Immune Network Behaviour. I. From stationary states to limit cycle oscillation. II. From oscillations to chaos and stationary states. Bull Math. Biol., in press.

Detours V. (1992). Simulation du développement du système immunitaire. Mémoire de D.E.A., Université de Paris 6/E.H.E.S.S.

Jerne N.K. (1974). Towards a network theory of the immune system. Ann. Immunol. (Paris) **125C**, 373-389.

Segel L. & Perelson A.S. (1989). Shapespace analysis of immune networks. In: *Cell to cell signalling: from Experiments to Theoretical Models* (Goldbeter A. ed.), pp 273-283. New York: Academic Press.

Stewart J. & Varela F.J. (1989). Exploring the meaning of connectivity in the immune network. Immunol. Revs. **110**, 37-61.

Stewart J. & Varela F.J. (1990) Dynamics of a class of immune networks. II. Oscillatory activity of cellular and humoral components. J. Theoret. Biol. **144**, 103-115.

Stewart J. & Varela F.J. (1991) Morphogenesis in Shape-space. J. Theoret. Biol. **153**, 477-498.

Stewart J. (1992). Immunoglobulins did not arise in evolution to fight infection. Immunology Today **13**, 396-399.

Varela F., Coutinho A., Dupire B. & Vaz N.M. (1988). Cognitive networks: immune, neural and otherwise. In: *Theoretical Immunology*. A.S.Perelson Ed., Addison-Wesley, New York. Vol II pp. 359-374.

Varela F., Coutinho A. & Stewart J. (1992). What is the immune network for? In: W. Stein & F. Varela (Eds), *Thinking about biology: an invitation to current theoretical biology*. Addison Wesley (SFI Series on Complexity), New Jersey.

Varela F.J. & Coutinho A. (1991). Second generation immune networks. Immunology Today **12**, 159-166.