

Network Description of the Immune System: Dormant B Cells Stabilize Cycles

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The role of dormant B cells and cycles is analyzed in the context of a Lotka–Volterra network. It is shown that dormant B cells stabilize a cycle and that in this way both cooperate to preserve the internal image (memory) of an antigen. The network is embedded in a hierarchical scheme which allows adaptation, learning, and innovation by biased and random mutation.

KEY WORDS: Immune system; dormant B cells; cycles; Jerne theory; memory; nonlinear phenomena; stability.

1. INTRODUCTION

The immune system, as a result of biological evolution, protects higher organisms against a multitude of possible invaders. To do this, it develops remarkable abilities³ during the lifetime of an individual. It can identify a wide range of foreign materials. The reaction to them depends on the individual history of the organism. Each individual starts, in a sense, from zero. Early impressions are especially deep and lasting. The system is able to learn and to memorize. It recognizes even fuzzy stimuli and responds in a way appropriate to the context. Thus, the immune system shares an astonishing number of properties with the central nervous system, which is the subject of intense study (under the heading of neural networks). Both systems are built from a macroscopic number of functionally connected constituents.

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³ See ref. 1 for an excellent introduction (in German). See ref. 2 for a broad overview of recent developments.

Apart from these striking similarities at the system level, there are important differences at the microscopic level. The cells of the immune system move more or less freely and have a finite lifetime. During the whole existence of the organism there is the production of new cells, and mutation and selection play an important role. In contrast to the central nervous system, it is easier to isolate parts of the immune system and to study their functioning separately. It is even possible to construct and exploit artificial subsystems (e.g., monoclonal antibodies).

We now explain some major key terms and give a brief and simplified description of the constituents of the immune system and how they interact.

Antibodies are Y-shaped macromolecules which identify foreign material (antigens) and tag them for further treatment. A total of 10^5 identical antibodies are attached on the surface of one *B lymphocyte*. Typically there exist 10^8 different types of antibodies in the organism. They are distinguished by three-dimensional structures, *paratopes* and *epitopes*, whose function can be visualized as keys and locks. The paratopes fit as keys on locks provided by an antigen or the epitopes of other antibodies (see below). The set of all epitopes characterizing an antibody of a given type is called the *idiotope*.

A B lymphocyte is *stimulated* to proliferate (cloning) and to secrete free antibodies if paratopes of its surface antibodies recognize a complementary structure. Capable of serving as such is the epitope (or even the paratope) of a different antibody or a corresponding three-dimensional structure on the surface of an antigen, also called an epitope. The strength of the reaction increases with the *matching* between the complementary structures. The paratopes of free antibodies dock at the corresponding epitopes of the antigens and thus mark them, e.g., for eating by macrophages. On the other hand, a B lymphocyte is *inhibited* if its epitopes are recognized by a complementary structure. The amplifying of the production of useful antibodies is called *clonal selection*.⁽⁸⁾

Since the paratope of a given antibody reacts not only with the epitopes of foreign material (antigens), but also with the epitopes of antibodies of a different type, there exists a complicated network of interactions between the antibodies in one organism, the *idiotopic network*.⁽³⁾ Typical patterns in this network are (Fig. 1):

(i) *Idiotopic cascades*. An antigen with epitope e_0 stimulates the production of antibodies with complementary paratope p_1 . Their idiotope i_1 eventually stimulates the production of antibodies with complementary (anti-idiotoxic) paratope p_2 and so on. This dynamical pattern is driven by the presence of the antigen.

(ii) *Cycles*. If in the above-described wave an idiotope i_n is by chance

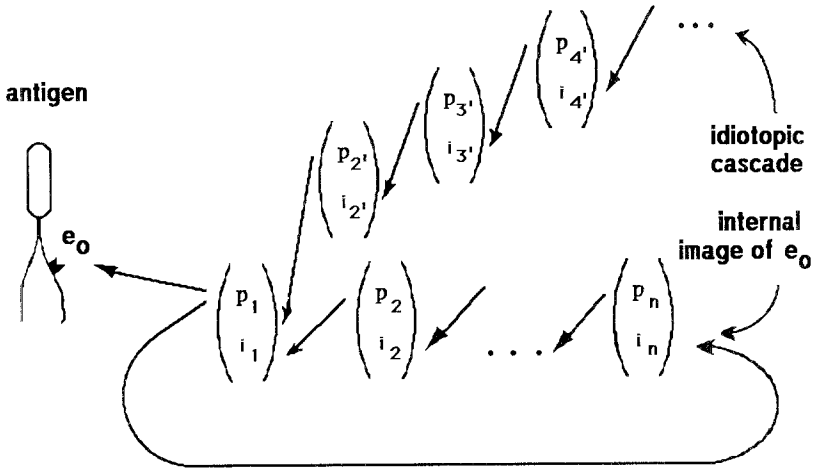


Fig. 1. Typical patterns of the idiomatic network: idiomatic cascade and cycle. An antibody of type k is represented by its paratope and idiotope (p_k, i_k) . The arrows indicate a nonzero matching between paratope p_k and idiotope i_{k-1} . In the cycle, the paratope p_1 recognizes both the antigen e_0 and the idiotope i_n , the internal image (memory) of e_0 .

complementary to the paratope p_1 , the chain is closed to form a cycle and the production of antibodies of type 1 is triggered even in the absence of the antigen. The idiotope i_n acts within this stationary pattern as an *internal image* of e_0 (memory).

It should be mentioned that there is a second mechanism for memory: If a B lymphocyte is stimulated to proliferate, a few cells of the next generation go into a *dormant* state. The lifetime of these dormant B cells is several orders of magnitude larger than usual.

There are two ways to introduce new types of antibodies. About 5% of the B lymphocytes are replaced per day by new ones generated in the bone marrow. The new antibodies are built through a process of combining genes from a relatively small library of V, D, J, and C genes.⁽⁹⁾ Furthermore, stimulated B lymphocytes reproduce themselves with a mutation rate which is five orders of magnitude larger than usual.⁽¹⁰⁾ It has been argued that higher-order control mechanisms exist which cause some nonrandomness in the mutation.

This picture is of course a crude simplification of reality. For instance, a whole class of cells, the T lymphocytes, which are known to play an important role in the distinction between self and non-self, is neglected as well as many other details.

The paper is organized as follows. In the next section we introduce a

system of Lotka–Volterra equations which describe a given set of constituents of the idiotopic network including dormant B cells. In Section 3 it is shown, for a representative class of examples, that the two mechanisms for memory, dormant B cells and cycles, cooperate in the sense that the former stabilize the latter. In the absence of dormant B cells, cycles are unstable. If a formation of stable cycles is possible, inhibition dominates stimulation, and as a consequence the system cannot explode. In Section 4 the Lotka–Volterra network is embedded in a hierarchical scheme which governs the generation of new types of antibodies (innovation), the dynamics of the parameters (adaptation), as well as the appearance of dormant B cells.

2. LOTKA–VOLTERRA EQUATIONS FOR THE IDIOTOPIC NETWORK

In this section we derive equations of motion which describe the interactions between a *given set* of constituents of the idiotopic network.⁴ Naturally, this leads to equations which are familiar from a different context, e.g., from the kinetics of autocatalytic reactions, the so-called Lotka–Volterra equations.^(11,12)

For simplicity we do not distinguish between free and surface antibodies and denote their number by x_i , where $i = 1, \dots, N$ labels the type, characterized by only a single epitope e_i and paratope p_i . (The B lymphocytes are thus only implicitly dealt with.) The number of antigens characterized by the epitope e_j , where $j = N + 1, \dots, N + R$, is denoted by y_j .

In a simple mean-field approach the probability of a collision between two of them is proportional to the respective products $x_i x_j$ and $x_i y_j$. The strength of the reaction is proportional to the matching m_{ij} between the paratope p_i and the epitope e_j . Then the stimulation of an antibody x_i is proportional to $m_{ij} x_i x_j$ and $m_{ij} x_i y_j$. The inhibition is proportional to $-\kappa m_{ji} x_i x_j$, where κ allows for an asymmetry between stimulation and inhibition. A further important parameter is γ , the inverse lifetime of the antibodies in the absence of stimuli.

The effect of dormant B cells is to ensure the production of antibodies of type i if there is a nonzero matching m_{ij} with the epitopes of the stimuli x_j , respectively y_j , even in the absence of x_i . This is included by adding a term $m_{ij} d_i x_j$, respectively $m_{ij} d_i y_j$, where d_i is a source strength mimicking the presence of dormant B cells of type i .

⁴ Several models of mathematical immunology are reviewed in ref. 13; see also refs. 5–7 and 14–21.

In this way, introducing the shorthand $M_{ij} = m_{ij} - \kappa m_{ji}$, we arrive at

$$\dot{x}_i = x_i \left(\sum_{j=1}^N M_{ij} x_j - \gamma \right) + d_i \sum_{j=1}^N m_{ij} x_j + (d_i + x_i) \sum_{j=N+1}^{N+R} m_{ij} y_j, \quad i = 1, \dots, N \tag{1}$$

Here \dot{x} denotes a differentiation with respect to time. A similar set of equations holds for the antigens,

$$\dot{y}_i = y_i \left(\alpha - \sum_{j=1}^N m_{ji} x_j \right), \quad i = N + 1, \dots, N + R \tag{2}$$

where α is the difference between a proliferation rate and an inverse lifetime. For relevant antigens, α is positive. Equations (1) and (2) are of a generalized Lotka–Volterra type. Setting $d_i \equiv 0$ in (1), we recover the model proposed by Farmer *et al.*⁽¹⁶⁾

The matching m_{ij} measures how well the complementary structures of paratope p_i and epitope e_j (key and lock) fit together. The m_{ij} enter the Lotka–Volterra equations as parameters which could be obtained, for example, in the following way. The underlying three-dimensional structures can, as any information, be encoded by binary strings, i.e., sequences of 0 and 1. Then, similar to the calculation of the Hamming distance (cf., e.g., ref. 11), the number of complementary bits v is counted. If v is below a certain threshold v_{th} , the matching is zero (no reaction). Above the threshold the matching linearly increases with $v - v_{th}$. This is the simplest version. The procedure can be refined allowing different lengths of the binary strings and all possible alignments.

3. MEMORY AS CYCLES IN A LOTKA–VOLTERRA NETWORK

We now investigate the existence and the stability of simple stationary solutions (fixed points) of the above Lotka–Volterra equations in the absence of antigens ($y_i \equiv 0$) to check the possibility of a memory provided by cycles⁽³⁾ in the idiotopic network.

We first consider (1) without taking into account the effects of dormant B cells ($d_i \equiv 0$), as originally proposed in ref. 16. From

$$\dot{x}_i = x_i \sum_{j=1}^N (M_{ij} x_j - \gamma) \tag{3}$$

we obtain the equation of motion for $s = \sum_{k=1}^N x_k$,

$$\dot{s} + \gamma s = \sum_{j,k=1}^N x_j M_{jk} x_k = (1 - \kappa) \sum_{j,k=1}^N x_j m_{jk} x_k \tag{4}$$

It shows (the x_i and m_{ij} are positive) that for $\kappa \geq 1$ the zero fixed point $s = 0$, i.e., $\mathbf{x}^s = \mathbf{0}$, is globally stable. A nonzero fixed point $\mathbf{x}^s = \mathbf{a}$, which is determined by $M\mathbf{a} = \gamma\mathbf{1}$, can exist only for $\kappa < 1$. Here $\mathbf{1}$ is the vector consisting of ones only.

The local stability of a fixed point \mathbf{x}^s of a system of differential equations $\dot{\mathbf{x}} = \mathbf{F}(\mathbf{x})$ is determined by considering the dynamics of a small deviation $\boldsymbol{\varepsilon} = \mathbf{x} - \mathbf{x}^s$, which is governed by

$$\dot{\boldsymbol{\varepsilon}} = \left(\frac{\partial \mathbf{F}}{\partial \mathbf{x}} \right)_{\mathbf{x}=\mathbf{x}^s} \boldsymbol{\varepsilon} = \mathbf{F}'(\mathbf{x}^s) \boldsymbol{\varepsilon} \tag{5}$$

\mathbf{x}^s is locally stable if $\boldsymbol{\varepsilon}$ dies out, i.e., if the matrix $\mathbf{F}'(\mathbf{x}^s)$ has only eigenvalues with negative real part.

For the system (3) we find

$$\mathbf{F}'(\mathbf{x}^s)_{ij} = \delta_{ij} \left(\sum_{k=1}^N M_{ik} x_k^s - \gamma \right) + x_i^s M_{ij} = \begin{cases} -\gamma \delta_{ij} & \text{if } \mathbf{x}^s = \mathbf{0} \\ a_i M_{ij} & \text{if } \mathbf{x}^s = \mathbf{a} \end{cases} \tag{6}$$

which shows that $\mathbf{x}^s = \mathbf{0}$ is locally stable for all κ .

As an example for a nontrivial fixed point we consider the simplest possible cycle of two antibodies x_1 and x_2 characterized by the mutual matching m_{12} and m_{21} as shown in Fig. 2. All the other x_i and m_{ij} , including m_{11} and m_{22} in (3), are put to zero. Then the nonzero fixed point,

$$\mathbf{a} = \gamma \{ 1/M_{21}, 1/M_{12} \} \tag{7}$$

is in the positive cone if $\kappa < \kappa^0 = \min \{ m_{12}/m_{21}, m_{21}/m_{12} \} \leq 1$.

However, since the matrix

$$\mathbf{F}'(\mathbf{a}) = \gamma \begin{pmatrix} 0 & M_{12}/M_{21} \\ M_{21}/M_{12} & 0 \end{pmatrix} \tag{8}$$

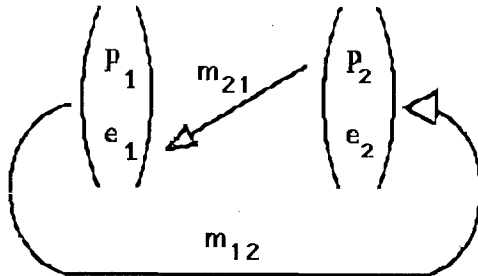


Fig. 2. Simplest possible cycle, consisting of two antibodies x_1 and x_2 . The production of x_1 is stimulated since its paratope recognizes the epitope of x_2 and is at the same time inhibited since its epitope is recognized by the paratope of x_2 . This competition allows a stationary state, i.e., a cycle.

has the eigenvalues $\pm\gamma$, the 2-cycle corresponds to a saddle point and is locally unstable (Fig. 3).

We now turn to the higher-dimensional case. We first treat the n -cycle characterized by $m_{i,i+1} = m$ with $m_{n,n+1} = m_{n,1}$ and the other matrix elements vanishing, and show that it is unstable. The components of the corresponding fixed point \mathbf{a} are $\gamma/[(1-\kappa)m]$ and they are positive provided $\kappa < 1$. Due to (6), we need only investigate the spectrum of the matrix M so as to determine the stability of \mathbf{a} . The eigenvalue equation $M\mathbf{z} = \Lambda\mathbf{z}$ gives

$$z_{k+1} = \lambda z_k + \kappa z_{k-1}, \quad k = 1, \dots, n \tag{9}$$

with $\lambda = \Lambda/m$ and boundary conditions $z_0 = z_n$ and $z_1 = z_{n+1}$. The general solution of (9) is⁽²²⁾

$$z_k = Xz_+^k + Yz_-^k \tag{10}$$

where z_{\pm} are the roots of the equation $z^2 = \lambda z + \kappa$. The boundary conditions lead to

$$\begin{pmatrix} z_+^n - 1 & z_-^n - 1 \\ z_+(z_+^n - 1) & z_-(z_-^n - 1) \end{pmatrix} \begin{pmatrix} X \\ Y \end{pmatrix} = 0 \tag{11}$$

which allows a nontrivial solution only if $z_+^n = 1$ or $z_-^n = 1$. This determines λ . Writing $z_{\pm} = \exp(i\phi)$, we obtain

$$\lambda = (1 - \kappa) \cos \phi + i(1 + \kappa) \sin \phi, \quad \phi = 2\pi l/n, \quad l = 0, \dots, n - 1 \tag{12}$$

Whatever κ , the spectrum contains eigenvalues with positive real part. This proves the assertion that the cycle is unstable. [In fact, this also follows

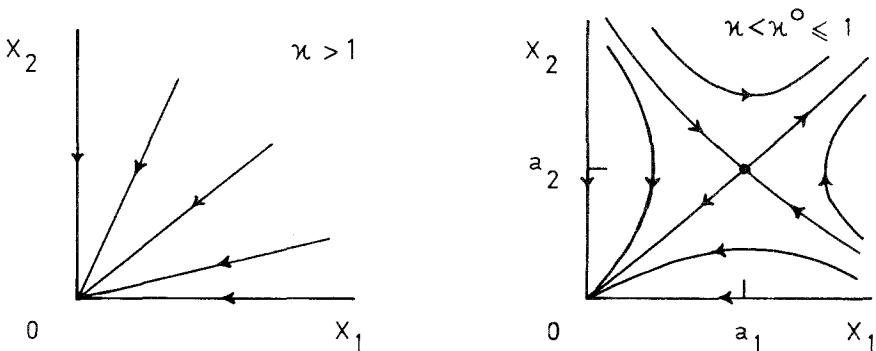


Fig. 3. Schematic flow diagrams for the case of two antibodies in the model (3), without dormant B cells. For $\kappa > 1$, zero is the only (globally stable) fixed point. A nonzero fixed point exists for $\kappa < 1$ and lies in the positive cone for $\kappa < \kappa^0$. It is unstable, however.

from $\text{Tr } \mathbf{F}'(\mathbf{a})=0$.] Since the eigenvalues depend continuously on the matrix elements, there is an open neighborhood of matrices whose cycles are unstable as well.

As a further example, complementary to the previous one, we consider the case where the matrix m is symmetric and assume that it allows a fixed point of Eq. (3) with *positive* components. Let us denote by A the diagonal matrix with elements a_i . The spectrum of AM , which occurs in (6), equals that of $A^{1/2}MA^{1/2}$ and by the law of inertia⁽²³⁾ the number of positive eigenvalues of the latter agrees with that of $M=(1-\kappa)m$. The fixed point has a chance of being stable only if $\kappa < 1$. (Otherwise zero is globally stable.) It then suffices to study m , which has nonnegative matrix elements only. By the theorem of Perron and Frobenius,⁽²³⁾ an indecomposable matrix with nonnegative elements has a strictly positive (maximal) eigenvalue. Since a general symmetric matrix can be written as a direct sum of indecomposable blocks,⁽²³⁾ we have shown that also in the symmetric case a fixed point is unstable.

In view of the above case studies and the fact that $\text{Tr } \mathbf{F}'(\mathbf{a})=0$, we conjecture that no memory due to stable fixed points exists in the dynamics associated with (3).

The stability of zero and the instability of cycles make the results of a numerical simulation qualitatively reported in refs. 15 and 16 plausible. There, the Lotka–Volterra equations without dormant cells were integrated numerically. After a characteristic time, the system was examined and all constituents below a minimal concentration were removed by hand. The removed antibodies were replaced by ones which were generated from the old ones by applying genetic operators or using a random sequence generator. Even in the absence of antigens no steady state of the network was observed, but only a dynamic behavior: “something like a weather pattern.”

We now turn to our model, which takes into account dormant B cells. In the absence of antigens, (1) reads

$$\dot{x}_i = x_i \sum_{j=1}^N (M_{ij}x_j - \gamma) + d_i \sum_{j=1}^N m_{ij}x_j \quad (13)$$

It is intuitively clear—and will be confirmed shortly—that the presence of the source term in the right-hand side of (13) destabilizes the zero fixed point and favors the formation of stable cycles. The stability matrix $\mathbf{F}'(\mathbf{x}^s)$ for this model differs from (6) by an additional term $d_i m_{ij}$ on the right-hand side,

$$\mathbf{F}'(\mathbf{x}^s)_{ij} = \delta_{ij} \left(\sum_{k=1}^N M_{ik}x_k^s - \gamma \right) + x_i^s M_{ij} + d_i m_{ij} \quad (14)$$

We first investigate the 2-cycle shown in Fig. 2. Besides $\mathbf{x}^s = \mathbf{0}$, we find the nonzero fixed point

$$\mathbf{a} = (\gamma^2 - d_1 d_2 m_{12} m_{21}) \{ (\gamma M_{21} + d_2 m_{21} M_{12})^{-1}, (\gamma M_{12} + d_1 m_{12} M_{21})^{-1} \} \tag{15}$$

and the corresponding stability matrices

$$\mathbf{F}'(\mathbf{0}) = \begin{pmatrix} -\gamma & d_1 m_{12} \\ d_2 m_{21} & -\gamma \end{pmatrix}, \quad \mathbf{F}'(\mathbf{a}) = \begin{pmatrix} -d_1 m_{12} q & \gamma/q \\ \gamma q & -d_2 m_{21}/q \end{pmatrix} \tag{16}$$

where $q = a_2/a_1$. The analysis of the (always real) eigenvalues yields that for $\gamma < \gamma^0 = (d_1 d_2 m_{12} m_{21})^{1/2}$ the 2-cycle is locally stable and the zero fixed point is unstable. For $\gamma > \gamma^0$ the opposite is true (Fig. 4). The conditions that \mathbf{a} lies in the positive cone are $\kappa > \kappa_s^0 = \max\{\kappa_{12}, \kappa_{21}\}$ and $\kappa < \kappa_u^0 = \min\{\kappa_{12}, \kappa_{21}\}$ for the stable and the unstable cycle, respectively. Here $\kappa_{ij} = (\gamma m_{ij} + d_i m_{ij} m_{ji}) (\gamma m_{ji} + d_i m_{ij}^2)^{-1}$. For $m_{12} = m_{21}$, we have $\kappa_s^0 = \kappa_u^0 = 1$.

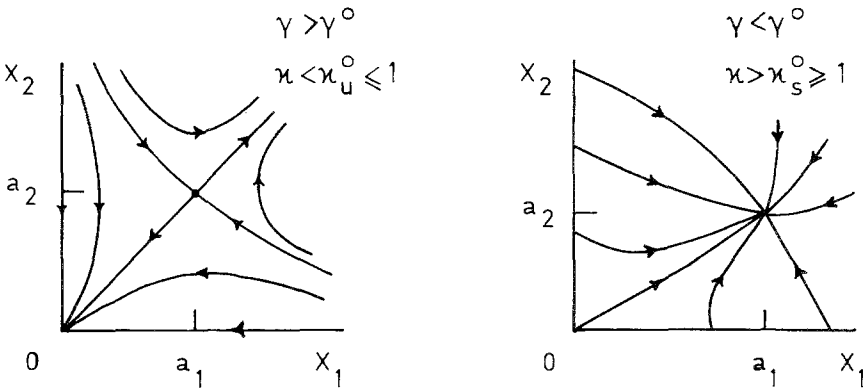


Fig. 4. Schematic flow diagrams for the case of two antibodies in the model (13), which includes dormant B cells. There exists a nonzero fixed point which changes its stability at $\gamma = \gamma^0$. For $\kappa_u^0 < \kappa < \kappa_s^0$ the fixed point is not in the positive cone. A *stable* cycle (right picture) can serve as a memory.

The second case we study is the n -cycle in the presence of dormant cells. We now assume $m_{i,i+1} = m$ and $d_i = d$. The components of the fixed point \mathbf{a} all equal $(\gamma - md)/[(1 - \kappa)m] = a$. The corresponding stability matrix is

$$\mathbf{F}'(a) = m \begin{pmatrix} -d & d+a & & & -\kappa a \\ -\kappa a & & & & \\ & & \ddots & & \\ & & & 0 & \\ & & & \ddots & \\ & & & & 0 & \\ & & & & & d+a \\ & & & & & -\kappa a & -d \end{pmatrix} \tag{17}$$

and by a similar analysis to the one used previously we find that the eigenvalues λ are

$$\lambda = \gamma \cos \phi - dm + im[d + (1 + \kappa)a] \sin \phi, \quad \phi = 2\pi l/n, \quad l = 0, \dots, n-1 \quad (18)$$

The real part of λ is always negative if $\gamma - dm < 0$. The fixed point \mathbf{a} then has positive components if $\kappa > 1$, i.e., inhibition dominates. This condition has the additional advantage of inhibiting the system's escape to infinity—as is most easily seen by generalizing (4) to the case of nonzero d .

We now present an intuitive argument which extends the previous one and supports the idea that the presence of dormant cells stabilizes nonzero fixed points and destabilizes zero. Combining (13) and (14), one easily finds that the stability matrix at a nonzero fixed point \mathbf{a} may be written

$$\mathbf{F}'(\mathbf{a})_{ij} = d_i \left(m_{ij} - \delta_{ij} \sum_{k=1}^N m_{ik} \frac{a_k}{a_i} \right) + a_i M_{ij} \quad (19)$$

If $a_k/a_i \approx 1$, as in the previous case, the first matrix on the right-hand side has eigenvalues with negative real parts, by Gershgorin's theorem.⁽²³⁾ Hence we might expect that the spectrum of the whole expression is shifted to the left.

Whatever the matching matrix m , zero is always destabilized for large enough d_i . To see this, we note that the stability matrix for the zero fixed point is

$$\mathbf{F}'(\mathbf{0})_{ij} = -\gamma \delta_{ij} + d_i m_{ij} \quad (20)$$

By the Perron–Frobenius theorem and its extensions,⁽²³⁾ the maximal (positive) eigenvalue λ_{\max} of the matrix $d_i m_{ij}$ is a strictly increasing function of its elements. Hence, the maximal eigenvalue $\lambda_{\max} - \gamma$ of (20) becomes positive for d_i large enough.

In summary, we have seen that only in the presence of dormant B cells does a parameter region exist in which the simple fixed points are stable. Stable fixed points provide a reservoir of antibodies which do not die out: They are memorized. Antigens with an epitope similar to the epitopes of the involved antibodies are immediately attacked. The matching need not be perfect and, as we will see in the next section, the memory is associative.

We would like to add a final remark on the destabilization of the zero fixed point. We have just studied the role of dormant B cells. However, zero also loses its stability by the mere presence of antigens. For example,

suppose a fixed dose y_3 of an antigen matching a single antibody of type 1 is injected. Then, as follows from (1), the stability matrix of zero is

$$\mathbf{F}'(\mathbf{0})_{11} = -\gamma + m_{13}y_3 \quad \text{and} \quad \mathbf{F}'(\mathbf{0})_{ij} = -\gamma\delta_{ij} \quad \text{for } i \neq 1 \quad (21)$$

so that zero is destabilized if the matching or the concentration is large enough. In a similar vein one can show that a stable cycle $\mathbf{a} = (a_1, a_2, \dots, a_N)$, with an antigen matching x_1 , loses its stability if $\alpha - m_{1,N+1}a_1 \geq 0$; cf. Eq. (2). That is, if the antigen is too virulent, the matching is too small, or simply not enough a_1 is available. The new cycle is also stable, but the organism exhibits a "chronic" disease.

4. INNOVATION, ADAPTIVE LEARNING, AND MEMORY IN A HIERARCHICAL SCHEME

In the previous sections we have analyzed the Lotka-Volterra equations describing a *given* set of constituents of the idiotopic network. We know, however, as briefly described in Section 1, that the list of variables and parameters of these equations is dynamic. Therefore, the Lotka-Volterra equations have to be embedded into a hierarchical scheme which governs the generation of new variables and the dynamics of the parameters. This scheme consists essentially of the following.

(i) To describe the renewal of B lymphocytes from the bone marrow, we inject at randomly chosen instants new antibodies whose paratopes and epitopes are generated at random or through genetic operators which describe typical mechanisms of mutation, e.g., inversion, point mutation, and crossover. These new antibodies replace those antibodies which are not stimulated (*innovation*) and die out after a characteristic lifetime γ^{-1} .

The proliferation of B lymphocytes of type i is stimulated if its paratopes p_i recognize with nonzero matching m_{ij} a complementary epitope e_j (cloning). The cells of the new generations may differentiate into those which release free antibodies and into dormant cells with a considerably longer lifetime.

(ii) To describe the enhanced mutation during the cloning of stimulated B cells of sort i , we inject new antibodies whose paratopes are mutations of p_i , at a rate which increases with the respective magnitudes of $m_{ij}x_ix_j$ and $m_{ij}x_iy_j$. Thus, we generate new antibodies centered about the stimulated type. It is likely that the matching with the stimulating epitope could be improved in this way. However, this mechanism is equivalent to a random walk on the corners of a high-dimensional hypercube. The time which the system needs to attain a specific point increases

exponentially with the dimension. It therefore seems desirable to look for a faster alternative.

A possible, higher-order, control mechanism can be simulated through a Monte Carlo dynamics of the paratopes: A mutation $p_i \rightarrow p_k$ is accepted only if the matching with the stimulating epitope e_j increases. Thus, the rule

$$H(e_j) = - \sum_{k=1}^N m_{kj}^2 = \text{minimal} \quad (22)$$

acts as a “teleological principle” which ensures an adaptation of the paratopes to the stimulating epitope and implies adaptive learning. Whatever the prescription to calculate the matching between epitope and paratope, the notation $m_{ij} = \langle p_i | e_j \rangle$ elucidates the similarity with the description of neural networks. Here, however, we deal with a dynamics of the patterns. More details will be published elsewhere.

(iii) To describe the appearance of dormant cells of the stimulated type i , we insert a nonzero d_i into the Lotka–Volterra equations if $m_{ij}x_i x_j$ or $m_{ij}x_i y_j$ exceeds some threshold. Above the threshold, the formation of stable cycles is allowed. Below the threshold, the corresponding species may die out (we only mention that this effect could also be achieved by introducing higher-order nonlinearities). Starting from the virgin state (where all d_i vanish), the organism acquires in the course of its life a set of nonzero $\{d_i\}$ which reflects the individual history (*memory*). In other words: Due to the nonzero $\{d_i\}$, there is some symmetry breaking of the virgin state.

Taking into account that also the dormant cells have a longer but finite lifetime, we conclude that only the formation of cycles (which needs some fortune) makes the information unforgettable. For instance, to ensure the formation of a stable cycle, one repeats a vaccination. We therefore think that the two memory mechanisms, dormant B cells and stable cycles, do not act independently, but rather cooperatively.

In this paper, we have concentrated on “small” subsystems. A full, preferentially analytic, understanding of this type of system seems to be indispensable for extending both theory and simulation to large-scale networks. In future work we will analyze the reaction of the virgin state to the exposure of an antigen, the stimulation of complementary antibodies, the appearance of dormant cells, and the formation of specific cycles.

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