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# Memory to Antigenic Challenge of the Immune System: Synergy of Idiotypic Interactions and Memory B Cells

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Memory to antigenic challenge of the immune system is described as a synergy of two components: cycles of interacting B cells in a dynamic equilibrium which store an internal image of an antigen, and long-lived memory B cells which stabilize the cycle that generates them. Small cycles are most relevant to the immune system's memory. The network is globally stable and supports Jerne's idea that suppression is important. Our model allows for exponential increase of antigens during the initial stage of infection. It has a number of stable fixed points, *viz* the virgin state, the healthy immunized state, and a state of chronic infection, the last occurring if the antigen is virulent enough. Numerical simulations show a difference between primary and secondary response and exhibit both predator–prey and intracycle oscillations. In the case of a chronic infection, the simulations suggest a specific stimulation therapy triggered by repeatedly injecting the antigens, thus making the infection acute. An optimal therapy is indicated.

## 1. Introduction

During its existence, the immune system exhibits a remarkably good memory of its previous experience—remarkable in view of both its complexity and the finite lifetime of its constituents which is typically one or two orders of magnitude less than its memory span. In this paper we present extensive simulations based on a network theory that incorporates three key ideas:

(i) A memory is stored in a *cycle* which consists of elements (antibodies) that mutually stimulate and inhibit each other so as to preserve a dynamic equilibrium. One of the antibodies in the cycle functions as an internal image of the antigen.

(ii) The equilibrium is stabilized by *memory* (*dormant*) B cells, whose lifetime exceeds the one of their associated antibodies by about an order of magnitude (though still finite!).

(iii) The whole structure is embedded in a network that is globally *inhibitory* (repressive) as advocated by Jerne (1974)§ and hence globally stable.

Memory to antigenic challenge in the immune system is somewhat paradoxical. On the one hand, an immunized organism "remembers" previous illness since the antigen that initiates it is eliminated subclinically soon after the infection. On the

§Cf. the motto of this paper: "The essence of society is repression of the individual".

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other hand, antibodies, even memory (or dormant) B cells, have a *finite* lifetime that may be, and in general is, orders of magnitude *less* than the time elapsed before the next infection occurs. (For the current understanding of memory B cells, see, for example, Gray & Skarvall, 1988; Schittek & Rajewski, 1990; McHeyzer-Williams *et al.*, 1991; Vitetta *et al.*, 1991.) This then gives rise to the paradox that the elementary constituents of the immune system do not live long enough to store the memory. In spite of that, antigenic challenge leads to immunity.

It is widely believed that antigen-driven immune response is performed by non-interacting clones. The dynamics of each B-cell clone is governed by an intricate interaction of cells with distinct immunoregulatory functions. An idiotypic regulation is considered unimportant. In this paper we treat the intraclonal regulation only implicitly and concentrate on the interclonal idiotypic interactions. We propose that the idiotypic interactions of the B-cell clones provide a dynamic memory, as is explained in detail below, and thus resolve the paradox we alluded to. We do not exclude that a repeated stimulation of functionally disconnected B-cell clones by persistent antigen can also lead to a memory.

In addition to the antigen-driven response, the immune system exhibits a somatic (antigen-independent) memory associated with an intrinsic dynamics (Lundqvist *et al.*, 1989; Varela *et al.*, 1991) that has been the subject of recent theories (Stewart & Varela, 1990; Varela & Stewart, 1990; de Boer *et al.*, 1992) based on idiotypic interactions. Though we concentrate here on the antigen-driven response, our model can describe the intrinsic dynamics as well.

In section 2 we formulate a reaction kinetics model that is based on Jerne's network theory (Jerne, 1973, 1974, 1976, 1984, 1985; Jerne *et al.*, 1982; for recent reviews see, for example, Perelson, 1989; Varela & Coutinho, 1991; for experimental support see, for example, Lundkvist *et al.*, 1989) and explain the ensuring memory mechanism: memory is stored in a cycle whose constituents mutually stimulate and inhibit each other and in so doing generate memory B cells that stabilize the cycle locally (Behn & van Hemmen, 1989*a*, *b*). More specifically, an $n$-cycle is a sequence of antibodies $i$ with $1 \leq i \leq n$ so that $i$ is inhibited since its epitope is recognized by the paratope of $i+1$ ($n+1 \equiv 1$) and stimulated since its paratope recognizes the epitope of $i-1$ ($0 \equiv n$). Furthermore, the paratope of $i = 1$, say, fits into both the epitope of a specific antigen and the epitope of $i = n$. So $n$ carries‖ the "internal image" of the antigen's epitope and in this way is a constituent of the immune system's memory. The simulation of each of the antibodies in the cycle guarantees its reproduction over a period far beyond its individual lifetime. Hence, the paradox is resolved. It turns out, though (Behn & van Hemmen, 1989*a*, *b*), that the cycle, a symbiotic equilibrium, is unstable by itself and that it is stabilized by the memory B cells which correspond to the active B lymphocytes in the cycle.

The concentration of antibodies which recognize a specific antigen is relatively low, so steric hindrance does not occur (yet) and it is realistic to describe the symbiotic dynamics by equations of a simple reaction kinetics or, in physical terms, "mean-field" type. Owing to a global repression, the escape to infinity is blocked and

‖ Frequently, immunologists use a different numbering and say Ab2 carries the image.

global stability is guaranteed. It is shown that in this context repression is a surprisingly powerful notion.

In section 3 we present the simulation results and harvest the corollaries of our theory, an explanation of oscillatory behavior of the number of antigens and antibodies (the Weigle phenomenon) as it also occurs in experiments (see, for example, Weigle, 1975; Hiernaux *et al.*, 1982), and a specific stimulation therapy for a chronic infection through periodic injection of a small dose of antigen.

In section 4 we sketch the rudiments of an *Aufbauprinzip*, the construction of a "true" network out of various parts such as cascades and cycles. Section 5 is a discussion.

Before turning to our model, it may be interesting to compare previous literature with the present approach. As to modeling, there are three categories: (i) models with continuous time and continuous variables describing the antigen and antibodies, usually of the Lotka–Volterra type; (ii) models with discrete time, not to be discussed here; and (iii) models where both time and state variables are discrete (cellular automata). Our model belongs to the first category and is a true network theory, in contrast to the work of Bell (1973) and Marchuk (1983). Richter (1975) has studied cascades and cycles of idiotypically interacting antibodies, emphasizing tolerance effects. In rejecting, however, *(f)actual* suppression as a stabilizing factor of the immune system, Richter deviates from one of Jerne's seminal ideas that is fundamental to our work. Hoffmann's theory (1975) for idiotypically connected pairs, in a sense similar to Richter's, includes T cells. Hoffmann was the first to stress the importance of symmetric interactions. Both authors initiated a mathematical network theory of the immune system to account for the immune system's memory since, after elimination of the antigens, there are no external constituents stimulating the corresponding B lymphocytes. Hiernaux (1977) has analyzed numerically the stability of Richter's (1975) cycles. The interactions in a cycle are taken to be asymmetric. An interaction is symmetric, if $i$ and $i+1$ suppress *each other*, whereas it is asymmetric if the inhibition is unidirectional. Hiernaux finds odd–even effects: for $n$ even, the cycle relaxes to a stationary state with alternatingly low and high concentrations, whereas for $n$ odd it asymptotically approaches a limit cycle. Though topologically identical, our cycles will be shown not to exhibit any of these effects. The reason is simply that they crucially depend on a source term $S$ providing suitable B lymphocytes from the bone marrow and that we do not assume the cycle to operate under a bell-shaped curve. We would like to stress that our model is not restricted in any way to cyclic or asymmetric structures. We will comment on Hiernaux's (1977) work as we go on.

The work of Farmer *et al.* (1986, 1987) is closest to our's in spirit, contains quite an interesting ansatz for the antibody–antibody interaction, but does not include memory B cells and, hence, cannot provide a stable memory. As we already noted, the concentrations involved in storing memory are relatively low and the reaction kinetics proposed by these authors (mass action) therefore seems realistic. It is adopted throughout what follows.

De Boer & Hogeweg (1989) and, in a similar way, Weisbuch (1990) have introduced a model which employs a function with a single maximum, for example, a log-

bell-shaped curve to describe response of a B-cell clone to its anti-idiotypic stimulus. This model has been investigated thoroughly (Weisbuch *et al.*, 1990; Neumann & Weisbuch, 1992) and extended to capture more details (de Boer *et al.*, 1990; Segel & Perelson, 1991). It operates with globally stimulatory idiotypic interactions in contrast to our global suppression. It, therefore, need not incorporate memory B cells.

In the context of a shape space approach, Segel & Perelson (1989) have examined the size of long-lived memory cell clones in a network environment depending on their death rate. It was argued by Perelson (1989) that "memory may be carried by both static and dynamic means". To the best of our knowledge, our model (Behn & van Hemmen, 1989*a*, *b*) is the first that establishes a synergy between both possibilities and recognizes the crucial role of memory cells to stabilize the dynamic equilibrium of a cycle.

Cellular automata introduced by Kaufman *et al.* (1985) and by Weisbuch & Atlan (1988) were analyzed in detail and have since experienced several sophistications (Kaufman & Thomas, 1987; Dayan *et al.*, 1988; Kürten, 1988; Atlan, 1989; Neumann, 1989; Pandey, 1989, 1990; Pandey & Stauffer, 1989; Chowdhury & Chakrabarti, 1990; Chowdhury *et al.*, 1990; Stauffer, 1990, 1991). Though easy to simulate, both this type of model and Parisi's Ising-spin version (Parisi, 1988, 1989, 1990) are not close to biological reality because the state variables are taken to be discrete (0 and 1) and do not allow any gradual response. More realistic is, however, the recent work of Celada & Seiden (1992) and Seiden & Celada (1991). A combined discrete and continuous approach was proposed by Kaufman (1988). The references mentioned so far are concerned with the dynamics of elementary constituents of the immune system, for example, antibodies and antigens, which form a *functional* network. Ikegami (1988, 1989), however, is interested in steric structures, *spatial* networks, allows aggregates of arbitrary complexity, and studies their statistics.

For recent accounts, see also Perelson (1988), Atlan & Cohen (1989), and Perelson & Weisbuch (1992).

## 2. Description of the Model

### 2.1. FUNDAMENTAL EQUATIONS

In this section we consider a *given* set of constituents of the idiotypic network. For the sake of simplicity, we do not distinguish free antibodies from those which are on the surface of a B lymphocyte (surface antibodies). The analysis of a more sophisticated model without this simplification (see Appendix A) gives qualitatively the same results.

The number of free and surface antibodies per unit volume is denoted by $x_i$ where $i = 1, 2, \ldots, N$ labels the type characterized by only a single epitope $e_i$ and paratope $p_i$. The number of antigens per unit volume characterized by the epitope $e_j$, $j = N+1, \ldots, N+R$, is denoted by $y_j$.

In a simple "mean-field" approach, the probability of a collision between two of

the constituents 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 the parameter $\kappa$ allows for an asymmetry between stimulation and inhibition. The terms $x_i x_j$ and $x_i y_j$ are *bilinear* in the variables $x_i$ and $x_j$ or $y_j$. Additional evidence in favor of this bilinear interaction is given in Appendix A.

Another important parameter is $\gamma$, the inverse lifetime of the antibodies in the absence of stimuli. The memory B cells ensure the production of antibodies of type $i$ if there is a non-zero 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 memory B cells of type $i$.

Introducing the shorthand $M_{ij} = m_{ij} - \kappa m_{ji}$, we thus obtain (Behn & van Hemmen, 1989*a*, *b*)

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

Here, and in the remainder, $\dot{x}$ denotes a differentiation of $x$ with respect to time.

A few remarks are in order. After a primary response, memory B cells appear once normal B cells are stimulated sufficiently. Little is known about the lifetime of unstimulated memory B cells but it is reasonable to assume that it is one or two orders of magnitude larger than that of ordinary B cells. Upon division (stimulated) memory cells produce a high percentage (30–40%) of new memory cells (Celada, 1991, private communication), thus providing an efficient reproduction mechanism. In this paper we describe the dynamics of memory B cells—as a first approximation—in a very rudimental way: we insert a non-zero $d_i$ into (1), if the total stimulus per antibody $i$, *viz* $(\sum_j m_{ij} x_j + \sum_k m_{ik} y_k)$, exceeds some threshold $\mu$. (The existence of a threshold is explained in Appendix A.) Once they have been inserted we treat the $d_i$ as constant. So we assume that the surplus in the production compensates the loss owing to a finite lifetime. Models including a more sophisticated dynamics of memory B cells are at present under investigation. The suspicious reader might argue that a term $-\kappa d_i \sum_j m_{ij} x_j$ is missing in eqn (1). This is not the case, however, since (1) describes the dynamics of $x_i$, not $d_i$. In passing, we note that it would have been straightforward to add a small source term $S$ to the right-hand side of (1) so as to include the new cells produced by the bone marrow. These provide a reservoir of antibodies apt to react against an intruding antigen during a primary response. Once a cycle is established the concentration of its antibodies is so high that $S$ can be neglected. We have dropped $S$ because its inclusion clutters the formulae below but does not alter our conclusions.

As to the matchings $m_{ij}$ Hoffmann (1975) has stressed the importance of symmetric interactions ($m_{ij} = m_{ji}$). Our model includes this situation as a special case, i.e. paratope and epitope may, but need not, be identical.

Finally, since we are mainly interested in memory and, therefore, in cases where

the input signals are (nearly always) rather weak, we have refrained from composing the input signal with a bell-shape function that takes into account steric hindrance and saturation.

For the antigens, a set of equations similar to (1) holds,

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

where $\alpha$ is the difference between a proliferation rate and an inverse lifetime. For most antigens, $\alpha$ is positive. In general, the dynamics described by (1) and (2) may be very complicated. The simplest qualitative statements which can be made are about the stationary states (fixed points) and their stability.

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

$$\dot{\varepsilon} = \left(\frac{\partial F}{\partial z}\right)_{z=z^s} \varepsilon = F'(z^s)\varepsilon. \tag{3}$$

The fixed point $z^s$ is locally stable if $\varepsilon$ dies out, i.e. if the matrix $F'(z^s)$ has only eigenvalues with negative real part.

In the *virgin state* ($d_i = 0$) and in the absence of antigens, the trivial fixed point $x^s = 0$ is *globally stable* for $\kappa \geq 1$ (in the subspace spanned by the $x_i$) as can be seen by writing the equation of motion for

$$s = \sum_{k=1}^{N} x_k,$$

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

but obviously $x^s = 0$ is unstable against antigens since we have from (2)

$$\dot{y}_i = y_i \alpha \geq 0. \tag{5}$$

From (4) it is clear that in the virgin state a non-trivial fixed point $x^s = a$ can exist only for $\kappa < 1$. However, it is *locally unstable* since the trace of $F'(a)$ is positive,

$$Tr\, F'(a) = \sum_{i=1}^{N} \lambda_i = \sum_{i=1}^{N} a_i(1-\kappa)m_{ii} \geq 0 \tag{6}$$

since $m_{ii} \geq 0$. The $\lambda_i$ are the eigenvalues of $F'(a)$. So in the virgin state the only stable fixed point is the trivial one ($x = 0$). No memory exists.

Formally speaking, a non-zero $d_i$ mimicking the presence of memory B cells may destabilize the zero fixed point and allow the formation of stable non-trivial fixed points, for example cycles (Behn & van Hemmen, 1989*a*, *b*), provided $d_i$ is large enough and $\kappa > 1$.

To elucidate this, we give a qualitative argument in addition to those already

presented elsewhere (Behn & van Hemmen, 1989*a*, *b*). We write the equation of motion for

$$s = \sum_{k=1}^{N} x_k,$$

$$\dot{s} + \gamma s = (1 - \kappa) \sum_{j,k=1}^{N} x_j m_{jk} x_k + \sum_{j,k=1}^{N} d_j m_{jk} x_k, \tag{7}$$

and suppose that *all* $x_i$ are of the *same order of magnitude*. Then for small $x_i$ the second (linear) term in the right-hand side of (7) dominates—irrespective of $\kappa$—and for $d_j m_{jk}$ large enough, the zero fixed point is destabilized. On the other hand, for large $x_i$ the first (bilinear) term becomes essential but, *if repression* dominates, i.e. $\kappa > 1$, the system cannot explode.

These formal arguments support in a natural way Jerne's idea that "the essence of the immune system is the repression of its lymphocytes" (Jerne, 1974: 382); see also Appendix B.

The result of the competition between the instability of $x = 0$ and the repression at infinity will be a non-zero *finite* solution—for instance, a non-zero stable fixed point. This solution then provides a reservoir of antibodies which do not die out. Thus, starting from the virgin state (where all $d_i$ vanish), the organism acquires in the course of its life (owing to encounters with antigens or owing to the interactions between antibodies) a set of non-zero $\{d_i\}$. In short, there is a symmetry breaking of the virgin state.

### 2.2. DYNAMIC NATURE OF THE COUPLINGS

In the previous subsection 2.1 we have described the dynamics of a *given set* of constituents of the idiotypic network. There is, however, a continuous production of new types of B lymphocytes. In other words, the list of variables and parameters itself is dynamic. Therefore, eqns (1) and (2) have to be embedded in a hierarchical scheme which governs the generation of new variables and the dynamics of the parameters (see, for example, Farmer *et al.*, 1986; Behn & van Hemmen, 1989*a*, *b*; de Boer & Perelson, 1990; Stewart & Varela, 1990; Varela & Stewart, 1990). New types of antibodies are generated in two ways. First, about 20% of the B lymphocytes are replaced each day by new ones generated in the bone marrow (see, for example, Jerne, 1984). This is a mechanism of *innovation*. Furthermore, *stimulated* B lymphocytes reproduce themselves with a mutation rate which is five orders of magnitude higher than usual in cell division (see, for example, Köhler, 1987). The antibodies generated this way are centered about the stimulated type. It is likely that the matching between them and the stimulating epitope is improved and that an *adaptation* to the stimulus occurs. Both innovation and adaptation can be described in a shape space context (Segel & Perelson, 1988). New antibodies are built through a process of combining genes from a relative small library of $V$, $D$, $J$ and $C$ genes (see, for example, Tonegawa, 1985). There exist well-formalized schemes to describe

typical mechanisms of mutation (see, for example, Holland, 1986; Ikegami & Kaneko, 1990).

A description of the dynamics of a "living" network should include three factors: (i) innovation through the injection of new antibodies with a given rate to describe the innovation from the bone marrow, (ii) adaptation through the injection of new antibodies centered about the stimulated one with a rate depending on the degree of stimulation and, as already mentioned in 2.1, (iii) appearance of *memory* cells if the stimulation exceeds some threshold.

The present paper is the second in a series that aims at realizing the above program and exploring its novel aspects, in particular in treating the immune system as a globally repressive network and stressing the role of memory B cells in stabilizing the cycles and, hence, the memory to antigenic challenge in this network.

## 3. Memory Mechanism: Co-operation of Memory B Cells and Cycles

### 3.1. QUALITATIVE ANALYSIS

In section 2.1 we have established the fundamental equations describing a given set of constituents of the idiotypic network and showed that in the working regime repression should dominate ($\kappa > 1$). Then, in the *virgin state* (no memory cells) the zero fixed point is, in the absence of antigens, globally stable. We have shown that the *appearance of memory cells* may destabilize the zero fixed point and supplied arguments that the formation of a non-trivial, bounded, solution is favored, which provides a reservoir of useful antibodies (memory).

In this subsection, we analytically investigate the simplest case, a symmetric two-cycle interacting with an antigen, and show in a more explicit way the synergism of the two mechanisms for memory, *viz* a cycle and the associated memory B cells which stabilize it.

The equations of motion describing two types of antibody $x_1$ and $x_2$ with mutual matching $m_{12} = m_{21} = m$ and an antigen $y$ which stimulates $x_1$ with matching $\bar{m}$ *in the presence of memory cells* $d_1$ and $d_2$ are

$$\dot{x}_1 = x_1[(1-\kappa)mx_2 - \gamma] + d_1 mx_2 + (d_1 + x_1)\bar{m}y, \tag{8}$$

$$\dot{x}_2 = x_2[(1-\kappa)mx_1 - \gamma] + d_2 mx_1, \tag{9}$$

$$\dot{y} = y(\alpha - \bar{m}x_1). \tag{10}$$

This system, which is of the form $\dot{z} = F(z)$, has three fixed points

$$z_1^s = (0, 0, 0), \tag{11}$$

$$z_2^s = \left(\frac{\gamma^2 - m^2 d_1 d_2}{m(1-\kappa)(\gamma + md_2)}, \frac{\gamma^2 - m^2 d_1 d_2}{m(1-\kappa)(\gamma + md_1)}, 0\right) \tag{12}$$

$$z_3^s = (a_1, a_2, b) = \left\{\alpha/\bar{m}, \frac{d_2}{\kappa - 1 + \gamma\bar{m}/(\alpha m)}, \frac{\gamma(a_1 - a_2) + m(d_2 a_1 - d_1 a_2)}{\bar{m}d_1 + \alpha}\right\}. \tag{13}$$

A fixed point is *relevant* if its components are non-negative. Correspondingly, there exist four parameter regions where either only the trivial fixed point $z_1^s$, or $z_1^s$ and $z_2^s$, or $z_1^s$ and $z_3^s$, or all three fixed points lie in the positive cone. In the various parameter regions, the fixed points may change its stability. [A fixed point is locally stable if $F'(z^s)$—cf. (3)—has only eigenvalues with negative real part.]

In Fig. 1 the schematic flow diagrams resulting from the linear stability analysis in three parameter regions are shown. For the sake of convenience we have taken $d_1 = d_2 = d$. Then $z_2^s$ takes the simple form $(a, a, 0)$, where $a = (d - \gamma/m)/(\kappa - 1)$.

In the *virgin state* [Fig. 1(a)] only the trivial fixed point $z_1^s$ is relevant. The eigenvalues of $F'(z_1^s)$ are $\lambda_{1/2} = -\gamma \pm md$ and $\lambda = \alpha$. Thus, $z_1^s$ is stable in the $(x_1, x_2)$ plane as long as not too many memory B cells are present, i.e. $d < \gamma/m$. It is, however, unstable in the $y$-direction as long as $\alpha > 0$; the virgin state may become infected.

If there are enough memory B cells, i.e. $d > \gamma/m$, the non-trivial stable fixed point $z_2^s$ which describes a two-cycle enters the positive cone and $z_1^s = 0$ loses its stability in the $(x_1, x_2)$ direction [Fig. 1(b)]. The two-cycle provides a reservoir of antibodies $x_1$ even in the absence of the stimulating antigen $y$ *since the antibodies* $x_2$ *act as an internal image of* $y$. The eigenvalues of $F'(z_2^s)$ are $\lambda_{1/2} = -md \pm \gamma$ and $\lambda_3 = \alpha - \bar{m}a$, [$a$ is defined in (12)]. Thus, $z_2^s$ is stable in the $(x_1, x_2)$ plane and as long as the antigen is not too virulent, i.e. $\alpha < \bar{m}a$, it is stable in the $y$-direction. The system is in an *immunized state*, and an infection is spontaneously cured.

If the antigen $y$ becomes too virulent (or the matching is too small, or not enough antibodies are provided by the cycle), i.e. $\alpha > \bar{m}a$, the new fixed point $z_3^s$ emerges from $z_2^s$ which loses its stability in the $y$-direction [Fig. 1(c)]. A straightforward but lengthy application of the Hurwitz criterion shows that $z_3^s$ is stable for all $\alpha > \bar{m}a$. The antibodies are not able to eliminate the virulent antigen, the system lives with a *chronic infection*. Using similar arguments one can verify that, if $a < 0$, the fixed point $z_3^s$ is relevant and stable for $\alpha > 0$.

If one relaxes the condition $d_1 = d_2 = d$ and allows $d_1 > 0$ and $d_2 = 0$, then the system relaxes to the attractive fixed point $z_3^s$ which is now in the $x_1, y$-plane. For $d_1 = d_2 = 0$ it becomes marginally stable. If $b$ is low, this state can be interpreted as a dynamic memory established by a "cycle" consisting of the antibody $x_1$ and the antigen itself. For large values of $b$ it is better to call it a chronic disease. [The same remarks apply to the chronic infection shown in Fig. 1(c).] The above analytical treatment can be extended straightforwardly to an $n$-cycle ($n > 2$); cf. Behn & van Hemmen (1989*b*).

## 3.2. SIMULATION

### 3.2.1. *Phenomenological parameters*

In the description of the idiotypic network on a phenomenological level, a number of phenomenological parameters appear. For the purpose of a numerical simulation we have to choose a reasonable parameter setting.

The *time scale* is fixed by choosing a value for $1/\gamma$, the *lifetime of antibodies*, which is of the order of 1–3 weeks. In the simulations we took $\gamma = 0{\cdot}01$ and $0{\cdot}002$. In all

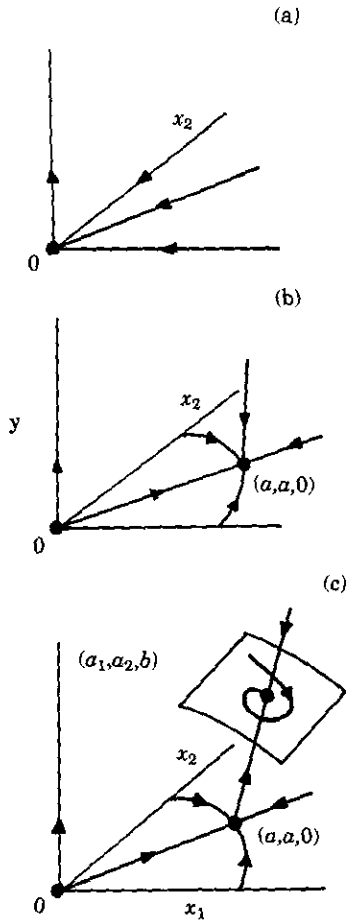


FIG. 1. Schematic flow diagrams for the case of two sorts of antibody $x_1$ and $x_2$ with mutual matching $m$. The antigens $y$ are recognized by antibodies $x_1$ with matching $\tilde{m}$. (a) Virgin state. The amount of memory B cells is so small ($d < \gamma/m$) that $x = 0$ is stable in the $(x_1, x_2)$ plane: antibodies $x_{1/2}$ will die out without stimulation by an antigen. However, $x = 0$ is unstable in the $y$-direction so that the virgin state may become infected. (b) Immunized state. The amount of memory B cells is large enough ($d > \gamma/m$) so that a non-zero stable fixed point $(a, a, 0)$, a two-cycle, exists. This two-cycle provides a non-zero number of antibodies $x_1$ even in the absence of the stimulating antigen. Antibodies of type $x_2$ can be considered as internal image of the stimulating antigen $y$ (*memory*). The two-cycle is stable in the $y$-direction as long as $\alpha < a\tilde{m}$, i.e. an infection ends in a healthy state if the antigen is not too virulent. (c) Chronic infection. If the antigen $y$ becomes too virulent ($\alpha > a\tilde{m}$), the two-cycle $(a, a, 0)$ loses its stability and a new stable fixed point $(a_1, a_2, b)$ with a non-zero number of antigens $b > 0$ emerges. The antibodies are not able to extinguish the invading antigen, there is a chronic infection. For the example shown here the system relaxes to the new fixed point in an oscillatory manner.

figures the time is measured in days assuming a lifetime for antibodies of about 10 days.

The *virulence* $\alpha$ is taken to be 0·05, 0·1 and 1, i.e. in the absence of antibodies the number of antigens is doubled in $\ln 2/\alpha \approx 0{\cdot}7/\alpha$, which ranges from about 1 hr to 1–2

days. For the other parameters we have only few or no information from experimental data.

From our analysis of the global stability of the system [cf. eqn (7)] we know that $\kappa > 1$ or, in other words, that repression should dominate stimulation. We parenthetically note that these arguments, made on a purely formal level, strongly support Jerne's philosophy (Jerne, 1974). Except for Fig. 8, we have chosen $\kappa = 1{\cdot}1$ throughout. As a general rule, one can assume that the system becomes stiffer the larger $\kappa$ is and that it is more sensitive the closer $\kappa$ is to 1.

For the absolute value of the *matching parameters* $m_{ij}$ we do not have any experimental hint. We note, however, that a replacement $m_{ij} \to \lambda m_{ij}$ only means a *rescaling* of the units in which the number of constituents is counted. So the equations remain invariant under the substitution $x_i \to x_i/\lambda$, $d_i \to d_i/\lambda$, $y_i \to y_i/\lambda$. Thus, both the matching and the number of constituents per unit volume are measured in arbitrary units. For numerical convenience we have taken $m_{ij}$ between $10^{-2}$ and $5 \times 10^{-2}$.

It remains to fix the number of memory B cells $d_i$ and the threshold $\mu$ above which they are generated. We have taken $d_i = d$ for all $i$ and used values for $d$ between $10^{-2}$ and $50 \times 10^{-2}$ so that $md > \gamma$ and, in a stable symmetric cycle, $x^s \equiv a = (a, a, \ldots)$, the fraction $a/d$ is between 5 and 50. The threshold $\mu$, which does not appear in the equations explicitly, is *always* taken to be 0·5.

In the simulations we have analyzed the behavior of small subsystems of antibodies which, through the mutual matching, are able to form $n$-cycles ($n = 2, 3, 4, 7$). The matchings $m_{ij}$ are defined through $m_{ii+1} = m$ for $1 \leq i \leq n-1$ and $m_{n1} = m$. All other $m_{ij}$ vanish. We are particularly interested in the dynamics of the response owing to an infection with antigens in the three cases we distinguished in 3.1, *viz* the virgin state, the immunized state and the chronic infection. In this context we consider a method to cure a chronic infection by provoking it to become acute.

### 3.2.2. *Relaxation to a healthy immunized state*

Whatever their mutual matching in the *virgin state*, the antibodies, in the absence of antigens, die out and the zero fixed point is globally stable in the subspace of antibodies.

First, we consider (Fig. 2) two types of antibody, in short, two antibodies $x_1$ and $x_2$, with mutual matching $m$, and infect (vaccinate) the system with an antigen $y$ which stimulates $x_1$ owing to a matching $\bar{m}$. If the stimulation is strong enough, i.e. if $mx_2 + \bar{m}y$ exceeds some threshold $\mu$, then memory B cells appear. After elimination of the antigens, the system does not relax to the virgin state but to a *healthy immunized state*: in the two-cycle the antibody $x_1$, which has proved to be useful, is memorized. In the case of a second infection with $y$ it is immediately available, the *secondary response* is much more effective than the primary one.

In Fig. 3 it is shown how the stimulation owing to an antigen $y$ coupling with $\bar{m}$ to $x_1$ propagates through a symmetric seven-cycle and induces *internal* oscillations. During the response to an antigen, the antibodies oscillate around its steady-state

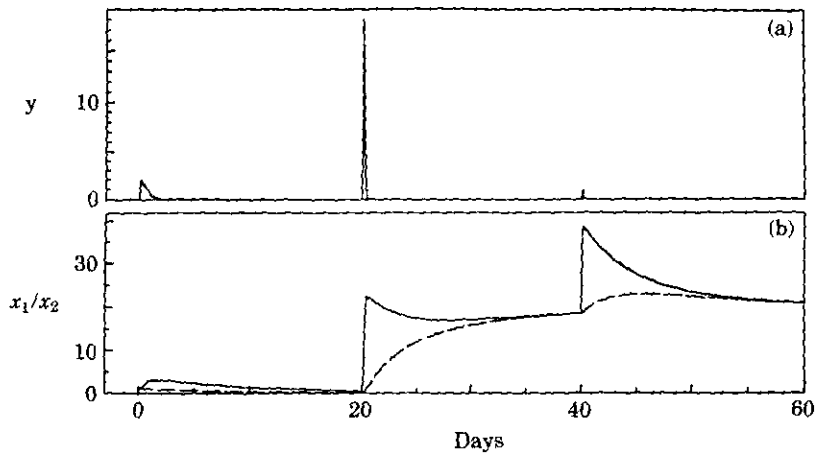


FIG. 2. Response of a two-cycle ($x_1$, solid line; $x_2$, dashed line) to an antigen $y$ coupling to $x_1$. The system starts in the virgin state ($d = 0$), is infected at $t = 0$ with a *subclinical* dose $y_{in} = 2$ and relaxes back to the virgin state. At $t = 200$ it is infected again with a dose $y_{in} = 20$ strong enough to initiate the appearance of memory B cells ($d = 0{\cdot}4$) which leads to the formation of a stable two-cycle (*primary response*). At $t = 400$ the system is infected again with the *same* dose $y_{in}$. Owing to the existence of a stable cycle the response is much more efficient (*secondary response*). The parameters are $\alpha = 0{\cdot}05$, $\gamma = 0{\cdot}01$, $\kappa = 1{\cdot}1$, $m = 0{\cdot}05$, $\bar{m} = 0{\cdot}03$, so that $a/d = 5$.

value, which is for a symmetric $n$-cycle $a = (d - \gamma/m)/(\kappa - 1)$ (Behn & van Hemmen, 1989*b*). An oscillating response is also observed in experiments (see, for example, Weigle, 1975; Hiernaux *et al.*, 1982). In passing, we note that as $t \to \infty$, the system always approaches a *homogeneous* state, which is to be contrasted with the even–odd behavior found by Hiernaux (1977). Both the alternating maxima and minima ($n$ even) and the limit cycle ($n$ odd) found by him hinge on an effective negative bell-shaped curve and a suitably chosen source term $S$. Since we do not work with bell-shaped curves it is not surprising that we obtain neither of these effects—despite the fact that both theories stress inhibition. The oscillations which we observe in Fig. 3 are inherent to cycles of length $n \geq 3$. The underlying mechanism is that antibody $i$ stimulates antibody $i-1$ and inhibits antibody $i+1$. Stimulation and inhibition propagate through the cycle in opposite directions and equilibrate each other as $t \to \infty$. In a two-cycle, however, we get a direct compensation of both effects since here $i - 1 = i + 1 \pmod 2$.

### 3.2.3. *Chronic infection*

We now turn to the situation that the antigens $y$ are so virulent that the antibodies $x_1$ are not able to eliminate them: the system relaxes to a chronic infection, showing typical *predator–prey* oscillations. In Fig. 4 the response of a three-cycle is shown. Note that just after the infection the antigen is much below its final value and apparently near to becoming extinct. Superposed on these predator–prey oscillations we have faster intra-cycle oscillations which have been discussed in subsection (ii).

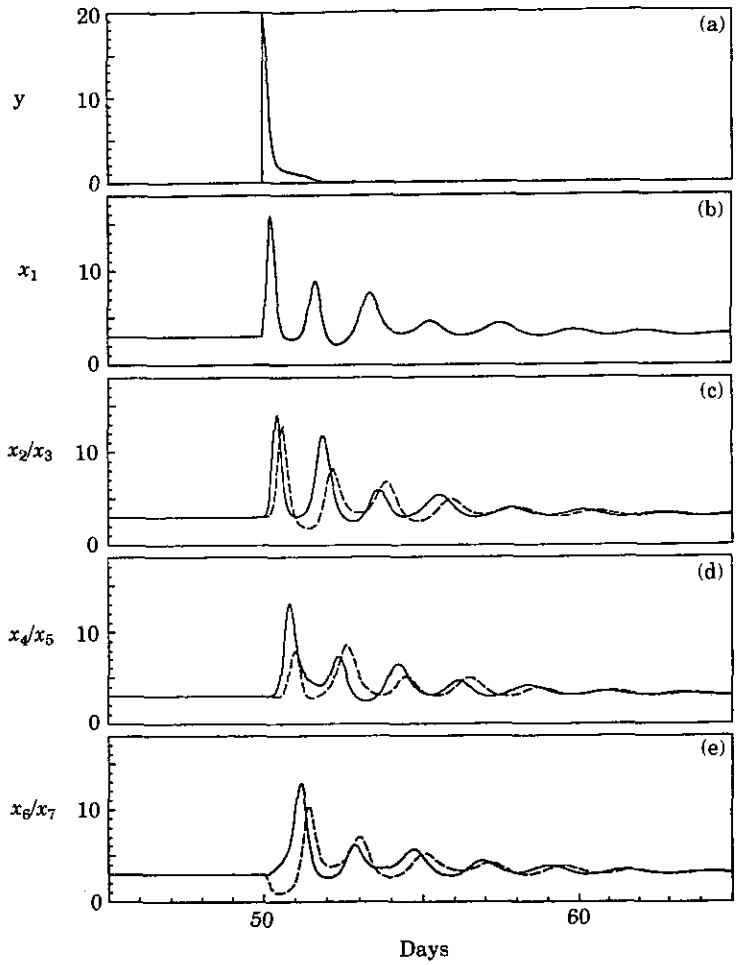


FIG. 3. Response of a seven-cycle $(x_1, \ldots, x_7)$ which is *stable* against an antigen $y$ that stimulates $x_1$. The system relaxes to a healthy immunized state. In the cycle, $x_1$ stimulates $x_2$ (solid line), $x_2$ stimulates $x_3$ (dashed line), and so on. In this way, stimulation propagates through the cycle and induces an *internal oscillation*, which is seen both following a single track and by pursuing the wave fronts (hills) from top $(x_1)$ to bottom $(x_7)$. The parameters are $\alpha = 0{\cdot}05$, $\gamma = 0{\cdot}01$, $\kappa = 1{\cdot}1$, $m = \bar{m} = 0{\cdot}05$, $d = 0{\cdot}5$, so that $a/d = 6$.

### 3.2.4. *Therapy for a chronic infection*

We consider again a two-cycle which is now *un*stable against a virulent antigen. After a primary infection the system will relax to a chronic infectious disease.

Our key idea, which we expound below, is to induce a second infection *for the purpose of therapy*. To this end, we inject the same dose $y_{in}$ of antigen repeatedly, *viz* $I$ times. The injections drive the system out of the stable fixed point of the chronic infection towards a new one which exists as long as the antigen input lasts and is characterized by an extremely high value of antibody $x_1$, the one inhibiting the antigen $y$ (phase 1). Once the injections are stopped the system moves "free" along

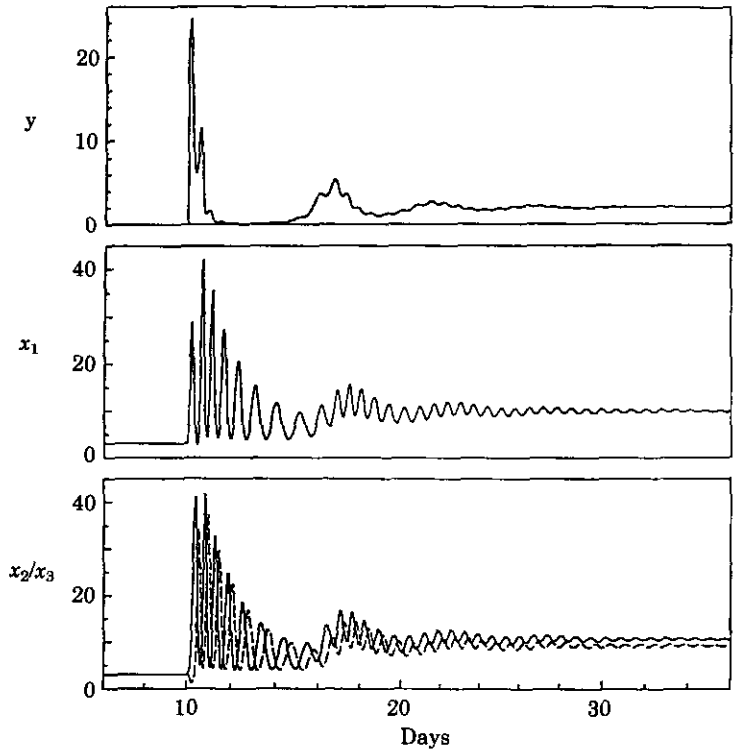


FIG. 4. Response of a three-cycle ($x_1$, $x_2$, solid line; $x_3$, dashed line) which is *unstable* against the instantaneously applied antigen $y$ ($y_{in} = 20$) stimulating $x_1$. There are two different oscillations: (i) of the predator–prey type which is dominant (cf. Fig. 3), and (ii) the internal oscillations of the cycle which relax much faster. The parameters are $\alpha = 0{\cdot}1$, $\gamma = 0{\cdot}002$, $\kappa = 1{\cdot}1$, $m = \bar{m} = 0{\cdot}01$, $d = 0{\cdot}5$, so that $a/d = 6$.

trajectories governed by (8–10). The "surplus" antibodies attack the antigen, whose number now decreases exponentially to a very small value (phase 2). During this process $x_1$ relaxes to its normal value, which is of the order one. The antigen seems extinct but it need not be and, if it is not, it returns to a value of order one after a time we call the *recurrence time* $R$ (phase 3). If the infection has reappeared the treatment can be repeated.

As shown in Fig. 5, the recurrence time $R$ increases with $I$. It becomes infinite once the antigen is extinct. In passing, we note that the *numerically* determined recurrence time loses its biological relevance as soon as $y$ becomes so small that the antigen can be considered extinct; cf. Fig. 6. We now explain the three phases in more detail. The equations describing the two-cycle ($x_1$, $x_2$) and the antigen $y$ interacting with $x_1$ are (8), (9) and

$$\dot{y} = y(\alpha - \bar{m}x_1) + y_{in}/\Delta\tau \tag{14}$$

which replaces (10). Here, we introduced an extra simplification. In our simulations we have assumed discrete injections through $[y_{in} \sum_{n=1}^{I} \delta(t - n\Delta\tau)]$. In (14), however,

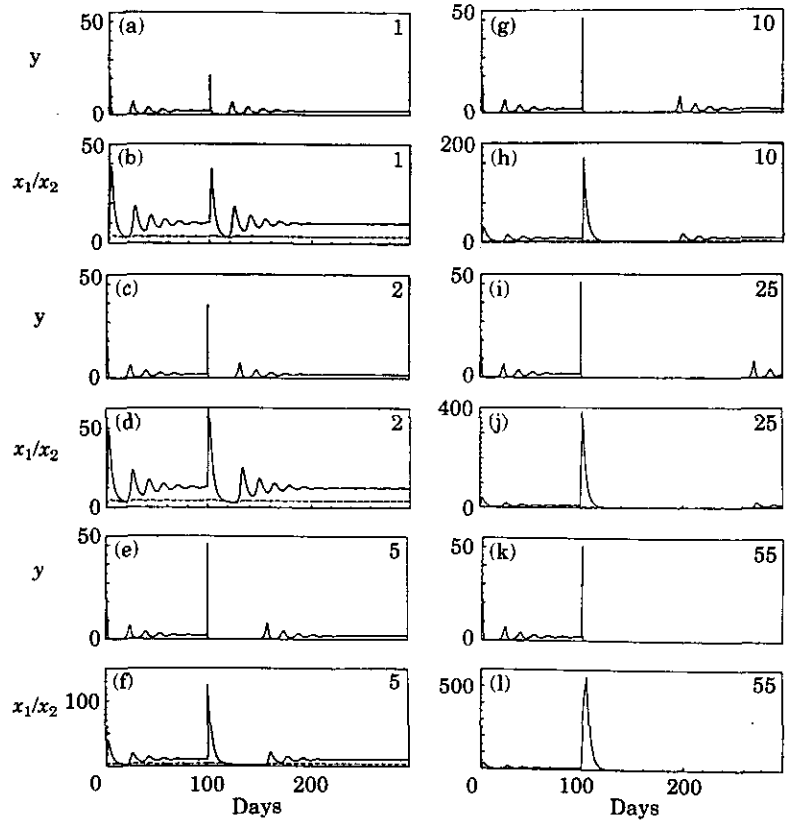


FIG. 5. Specific stimulation therapy for a chronic infection. We show the response of a two-cycle ($x_1$, solid line; $x_2$, dotted line) which is unstable against a virulent antigen $y$ stimulating $x_1$. All parts of the figure have the first infection at $t = 0$ in common, after which the system relaxes to a chronic infection (note the different scales at the ordinate). Then, at $t = 100$ (days), an additional dose of antigen $y_{in} = 20$ is repeatedly injected each time unit over different periods of time $I$ ($I = 1, \ldots, 55$, as indicated in the right upper corners) for the purpose of therapy. After this, the antigen appears nearly extinct before it reappears (latent period). The duration of the recurrence time increases in a non-linear way with increasing $I$. The parameters are $\alpha = 0{\cdot}1$, $\gamma = 0{\cdot}01$, $\kappa = 1{\cdot}1$, $m = 0{\cdot}05$, $\bar{m} = 0{\cdot}03$, $d = 0{\cdot}4$.

we have a source term $y_{in}/\Delta\tau = \text{const.}$ which produces the same amount of antigen but is continuous. This approximation is excellent as long as $\Delta\tau$ is small compared with characteristic times of the system and greatly simplifies the ensuing arguments. (In the remainder we put $\Delta\tau = 1$.)

In all three phases, the value of $x_2$ hardly changes and equals $d/(\kappa - 1)$ to good approximation as $x_1$ is large. During phase 1, the variable $x_1$ approaches asymptotically, as $I$ increases, a new quasi-stationary value which usually exceeds the "chronic" value $\alpha/m$ by two orders of magnitude. So it does not make any sense to augment $I$ without bound.

Once the injections are stopped, phase 2 begins and the huge reservoir of $x_1$ reduces $y$ at an *exponential* rate. This is clearly seen in Fig. 6 where we have used a

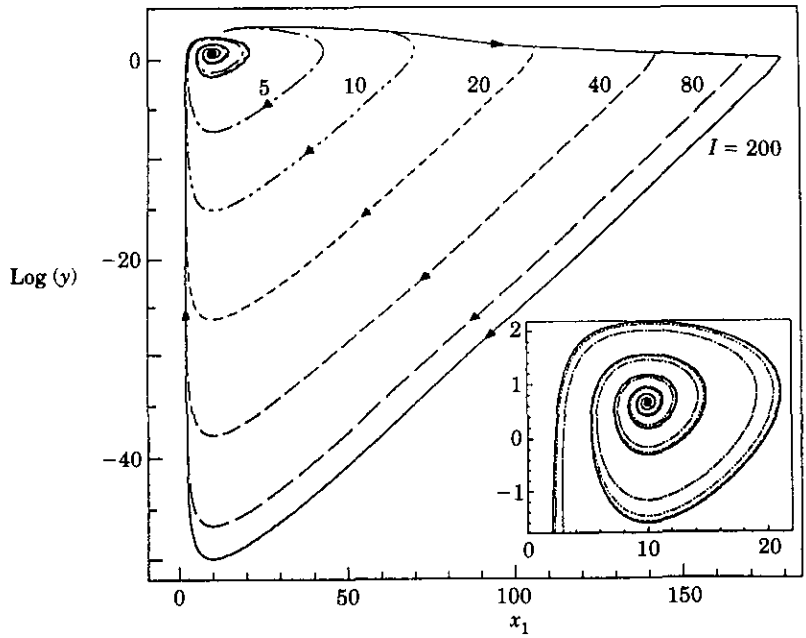


FIG. 6. Flow diagram for the specific stimulation therapy as in Fig. 5. Since $x_2$ is nearly constant (cf. Fig. 5, dotted line) we restrict ourselves to the projection on the $x_1 - \ln(y)$ plane and show trajectories for increasing $I$. After these injections (which drive the system out of the stable fixed point of the chronic infection) the number of antigens decreases exponentially. For $y$ smaller than a given threshold the antigens can be considered as extinct. (Formerly, however, the trajectories always return to the stable fixed point as shown in the figure, see also insertion.) The parameters are the same as in Fig. 5 with the exception of $m = 0{\cdot}01$ and $y_{in} = 5{\cdot}0$.

logarithmic scale for $y$ and a linear one for $x_1$. From (8) and (9) we have

$$\frac{d\ln(y)}{dx_1} = (\alpha - \bar{m}x_1)/\{x_1[(1-\kappa)mx_2 - \gamma] + dmx_2 + (d+x_1)\bar{m}y\} \approx \bar{m}/(\gamma + md) \quad (15)$$

and the linear dependence of $\ln(y)$ upon $x_1$ follows. During this process, $x_1$ is also reduced to normal values where the above approximation breaks down. Then, finally, phase 3 starts, if $y$ is not extinct yet.

The therapy described so far has two parameters, the dose $y_{in}$ of a single injection and the time $I$ during which the antigen is given. With increasing time $I$ the system reaches asymptotically the new, quasi-stationary, fixed point corresponding to $y_{in}$ (phase 1). The free trajectory through this new fixed point is the *marginal* trajectory. It may be impossible, however, to treat the patient with arbitrarily high total doses of antigen $y_{total} = y_{in} I$. We have therefore also investigated the case where a *fixed* total dose $y_{total}$ is partitioned into momentary doses $y_{in} = y_{total}/I$ applied over period $I$. A relevant quantity to measure the success of the therapy is the *recurrence time* $R$ which we have defined as the time span between the last injection of the antigen and the first maximum of antigen population thereafter; cf. Fig. 5. It approximately coincides with the time span during which the antigen is nearly extinct. Given a fixed total

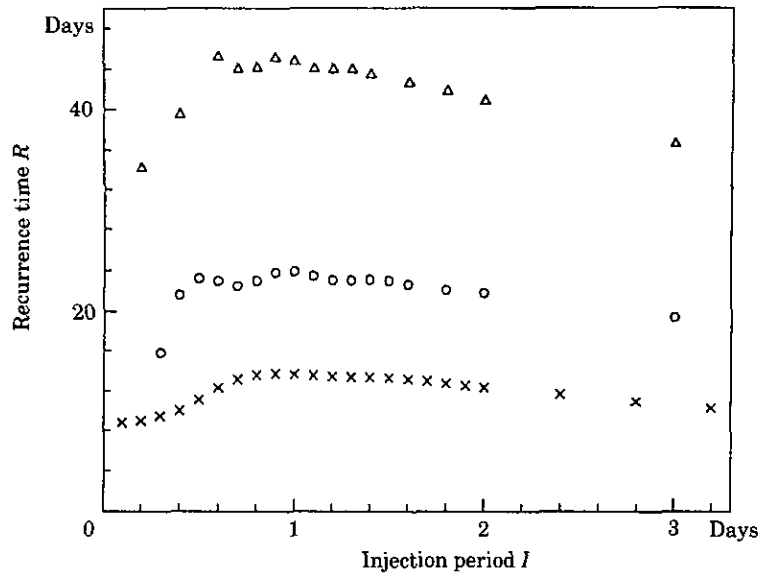


FIG. 7. Optimal therapy. Dependence of recurrence time $R$ upon injection period $I$ for *fixed* total dose $y_{total}$. For a set-up similar to that of Fig. 6, we have measured the recurrence time $R$ as a function of the injection time $I$. The injection period $I$ and the momentary dose $y_{in}$ are chosen so that the integrated dose $y_{total} = y_{in}\, I$ over the whole injection period is a constant: $y_{total} = 20$ (×), 75 (○) or 200 (△). The graphs clearly exhibit a maximum for injection periods of intermediate length ($I \approx 30$–$50$) and indicate that it may be advantageous to spread the total dose of antigen over an extended period of time. The results are obtained for a four-cycle where antibody $x_1$ is stimulated by antigen $y$. The parameter values are $\alpha = 0{\cdot}1$, $\gamma = 0{\cdot}002$, $\kappa = 1{\cdot}1$, $m = \tilde{m} = 0{\cdot}01$ and $d = 0{\cdot}5$.

dose $y_{total}$, one can determine the recurrence time $R$ as a function of the injection time $I$. This has been done in Fig. 7 for different total doses $y_{total}$. The recurrence time has a smooth maximum for an injection period of approximately 40 units of time where it is considerably larger than for a single injection ($I = 1$) of the same integrated dose $y_{total}$. For still larger injection periods the recurrence time decreases slightly. The global shape of the curves does not depend on the total dose. The data indicate that it can be more favorable to dispense repeatedly a small dose of antigen than injecting a large dose once. (We have also found, however, cases where the recurrence time decreases monotonically with the injection time.)

Obviously, it is not necessary to inject the antigen with its full virulence which might be suspected to be hazardous. The same effect could be reached by injection of a weakened antigen with a smaller virulence $\alpha' \ll \alpha$ or with a substitute with similar matching that does not reproduce itself at all. The only aim is to provoke a production of the useful antibodies $x_1$ *above the value of the steady state* of the chronic infection.

The method to cure a chronic infection by provoking it to become acute (specific stimulation therapy) is well known in medicine. For instance, it was applied to tuberculosis before the era of chemotherapy and antibiotics (see, for example, Alexander-Crespera, 1951). In theoretical immunology there exist models which

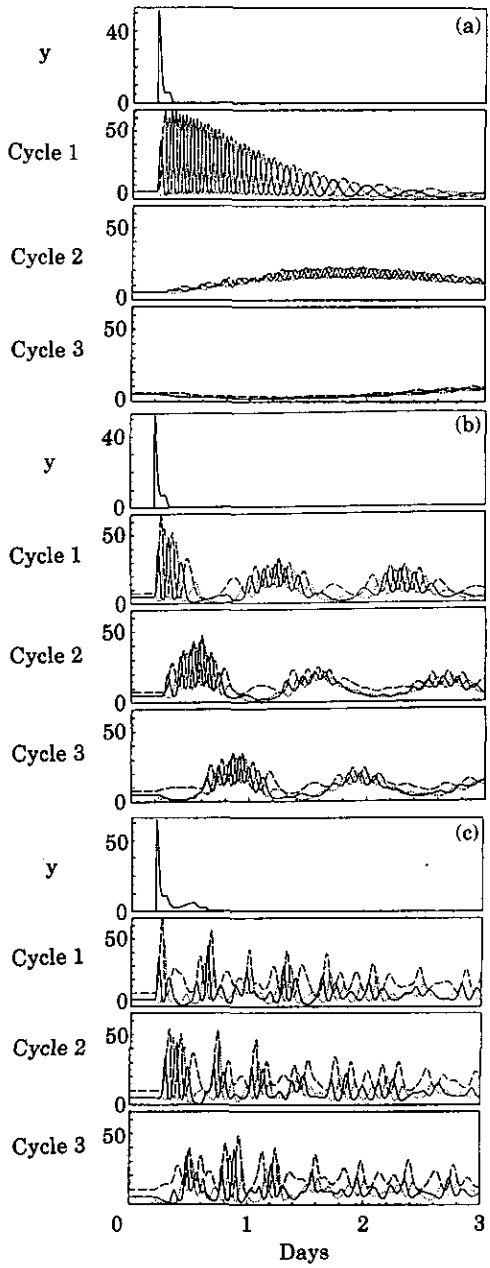


FIG. 8. Aufbauprinzip. We consider three three-cycles with intracycle matching $m = 0{\cdot}2$ for different strengths of the intercycle coupling $\tilde{m}$ [$\tilde{m}/m = 0{\cdot}02$ (a), $0{\cdot}1$ (b) and 1 (c)]. $x_1$ in cycle 1 matches with $\tilde{m} = 0{\cdot}2$ to the antigen $y$. For small intercycle coupling (a) the cycles 2 and 3 show only a very modest response on a longer time scale. (This is the most probable case, cf. section 2.3.) With increasing strength of the intercycle coupling, the time scale of the response becomes faster, the strength of the response increases, one observes predator–prey oscillations superposed to internal oscillations. If $\tilde{m}/m = 1$ (c) one observes a complex multifrequent response, it does not seem justified to separate the whole system into subsystems.

describe the method of unspecific stimulation (Marchuk, 1983). Our approach, however, is, to the best of our knowledge, the first attempt to explain a stimulation therapy in the framework of a network theory. It furthermore could help to understand the rationale behind a homeopathic therapy. We finally note that a desensibilization therapy for allergic diseases could be explained in a similar vein.

## 4. Aufbauprinzip

An *Aufbauprinzip* is a rule, or a set of rules, that governs the composition of a network out of its basic constituents—here the immune system, as it is composed of its basic components, cycles and other complexes. The underlying idea of the present work is that cycles, or whatever basic complexes, can be put together through matching without destroying the memory storage that is performed by each individual cycle. Now that we have studied the constituents carefully, we turn to analyzing a network.

Suppose we have a collection of cycles $\Gamma_k$ with $1 \leq k \leq K$. By assumption, the intracycle matchings are rather strong, but we still have to decide about the strength $\tilde{m}_{kk'}$ of the intercycle interaction. According to a recent proposal of Varela & Coutinho (1991), about one-fifth of an adult's immune system constitutes a network, whereas the remaining four-fifths which the authors hold responsible for the defense against invaders, is made up of functionally *disconnected* units. If this picture is correct, then it implies a very weak intercycle coupling $\tilde{m}_{kk'}$. In this paper, however, we have taken the $\tilde{m}_{kk'}$ rather strong so as to vindicate our approach.

Figure 8 shows the response of three three-cycles ($K = 3$) with *intra*cycle coupling $m$ for different values of intercycle coupling $\tilde{m}$. We assume that antibody 3 of the cycle $k$ is inhibited by antibody 1 of cycle $(k+1)$ and that antibody 1 of cycle 1 matches with the antigen. A glance at Fig. 8(a) suffices to conclude that for small intercycle coupling $\tilde{m} = m/100$, the response of cycle 1 upon insertion of the antigen is dominant and that the other cycles react with a considerable delay. The response of cycles 2 and 3 becomes (i) faster, (ii) more pronounced, and (iii) more "chaotic" as the intercycle matching is increased. This behavior confirms our *a priori* expectation. A weak interaction between the cycles does not destroy the basic features of each of them, individual memory is preserved, and the response of the cycle which matches the antigen is by far more pronounced than that of the rest of the network.

In the spirit of the work of Varela & Coutinho, which we have already referred to, we now propose another model, which is analytically tractable. The network is modeled as a system of $K$ quasi-independent antibodies which interact via a matching $m/K$. Here, one may also include a noise term. In addition to the network, we take a single cycle that we couple either to one of the network's constituents or to the whole network. The network then either functions as background noise or

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(This case is highly unprobable; cf. section 2.3.) Note that in the latter case the system is not too efficient in fighting against the antigen. A total dose of antigen $y_{in} = 50$ is injected at $t = 2$. The other parameters are $\alpha = 1{\cdot}0$, $\gamma = 0{\cdot}01$, $\kappa = 1{\cdot}01$ and $d = 0{\cdot}1$. (In all cycles: $x_1$, solid line; $x_2$, dashed line; $x_3$, dotted line.)

"swallows" the cycle. Details of analytical and numerical work are deferred to a future publication.

## 5. Discussion

Though significant differences exist between memory storage in the immune system and in the brain—for example, neurons live much longer than any of the constituents of the immune system—there is also a striking similarity. Memory in the brain has been modeled either as storage *in specific neurons*, each reacting to a specific stimulus only (grandmother neurons), or in a distributive manner through a tuning of the couplings (synapses) *between* the neurons. Memory to an antigenic challenge of the immune system can be modeled either as an "excited" state of "grandmother cells", for example, B cells (Weisbuch, 1990; Weisbuch *et al.*, 1990), or in a distributive manner through the matchings *between* different cells—as has been done in the present paper. In the spirit of Jerne (1974), we suppose that memory is stored "in the symbiotic equilibrium of a cycle that contains an image" of an antigen and produces dormant (memory) B cells, which stabilize the cycle. We have established a synergy between both dynamic memory (cycles) and static memory (memory B cells). Also, in agreement with Jerne (1974), we assume the interaction to be such that it is globally suppressive. Our model allows an exponential growth of the number of antigens as it occurs during the initial stage of an infection.

A cycle may, but need not, be embedded in a network. The matching is not required to be symmetric or uniform nor do we assume a cellular automaton approximation. In most cases, memory storage is realized at concentrations which are so low that the saturation and steric hindrance do not occur (yet). If one includes these effects in the dynamics through, say, a bell-shaped response function, a straightforward explanation of high-zone tolerance results. Another extension of the present model is by combining it with, for example, a dynamics in shape space (Segel & Perelson, 1988) so as to take care of the interplay between mutation and B-cell dynamics. Finally, most immune responses also include T cells and the memory associated with them. However, once basics are understood, a more realistic description of idiotypic memory is within reach.

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## APPENDIX A

### Separate Treatment of B Lymphocytes and Antibodies

In the main part of this paper no distinction was made between free antibodies and those on the surface of B lymphocytes, i.e. the dynamics of B cells were only implicitly dealt with. Here, we drop this simplification and establish the equations which separately describe B cells (carrying about $10^5$ antibodies on its surface), free antibodies and antigens. We denote the number of B cells of type $i$ by $X_i$, $i = 1 \ldots N$, the number of corresponding *free* antibodies by $x_i$, and the number of antigens of type $i$ by $y_i$, $i = N+1 \ldots N+R$. Then the equations of motion read

$$\dot{X}_i = X_i\left(\sum_{j=1}^{N} M_{ij}x_j - \gamma_1\right) + d_i \sum_{j=1}^{N} m_{ij}x_j + (d_i + X_i)\sum_{i=N+1}^{N+R} m_{ij}y_j, \tag{A.1}$$

$$\dot{x}_i = -\gamma_2 x_i + \delta X_i\left(\sum_{j=1}^{N} m_{ij}x_j + \sum_{j=N+1}^{N+R} m_{ij}y_j\right) - \varepsilon_1 x_i\left[\sum_{j=1}^{N} m_{ij}(X_j + d_j) + \sum_{j=N+1}^{N+R} m_{ij}y_j\right] - \varepsilon_2 x_i \sum_{j=1}^{N}(m_{ij} + m_{ji})x_j. \tag{A.2}$$

$$\dot{y}_i = y_i\left\{\alpha - \sum_{j=1}^{N} m_{ij}[\varepsilon_1 x_j + \varepsilon_3(d_j + X_j)]\right\}. \tag{A.3}$$

The *bilinear* term $X_i M_{ij} x_j$ is to be explained as follows.

A B lymphocyte is stimulated only if it carries a minimal number $n$ antibodies or antigens; $n$ depends on $i$ and $j$. At first sight this might suggest a term proportional to $X_i M_{ij} x_j^n$ corresponding to a *simultaneous* occurrence of at least $n$ antibodies (antigens) on a B lymphocyte of type $i$. This is not the case, however, because there is an antibody–antibody (–antigen) *binding* so that they can arrive one after the other and are bound for a certain time. If their number exceeds $n$, a reaction takes place. In the present paper we do not take into account the corresponding delay and therefore describe the production/elimination term simply by $X_i M_{ij} x_j$. Of course, the sojourn time of antibodies (antigens) $j$ on the surface of a lymphocyte $i$ is finite. Hence, it is more appropriate to speak about the *mean* number of antibodies $j$ on $i$ at a given time $t$. If this number remains less than $n$, there is no response of the lymphocyte $i$. This directly leads to a threshold $\mu$ as it appears in 2.1 and, hence, to a *low-zone tolerance*. The very same threshold could have been included in (1) at the cost of making the analytical work much harder—without altering the essentials, though.

Equation (A.2) deserves an additional explanation: the second term on the right-hand side describes the *production* of free antibodies by B cells which are stimulated

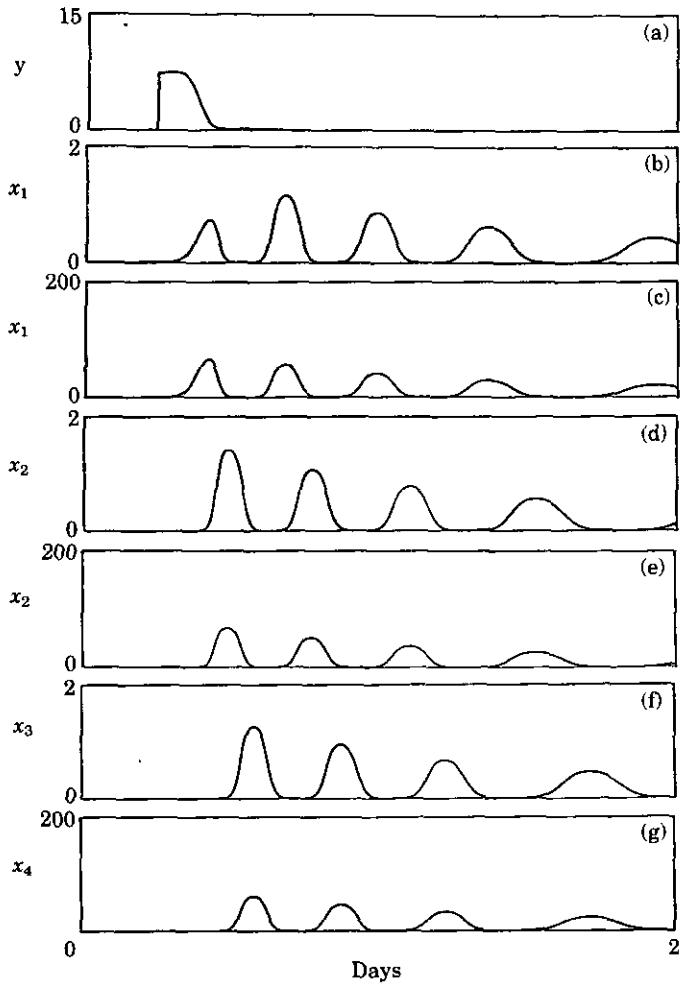


FIG. 9. Response of a three-cycle which is stable against the instantaneously applied antigen $y$ ($y_{in} = 20$). We distinguish between B cells ($X_1$, $X_2$, $X_3$) and free antibodies ($x_1$, $x_2$, $x_3$). The trajectories of B cells (surface antibodies) and free antibodies have a similar qualitative behavior. The parameters are $\alpha = 0{\cdot}05$, $\gamma_1 = 0{\cdot}03$, $\gamma_2 = 0{\cdot}009$, $\kappa = 1{\cdot}1$, $m = 0{\cdot}1$, $\bar{m} = 0{\cdot}5$, $d = 0{\cdot}001$, $\varepsilon_1 = 0{\cdot}1$, $\varepsilon_2 = 1{\cdot}0$, $\varepsilon_3 = 0{\cdot}1$ and $\delta = 200$.

by antibodies or antigens. The third and fourth terms describe the *loss* of free antibodies owing to the binding of free antibodies by B cells and antigens, or by free (anti-idiotypic) antibodies, respectively. Equation (A.3) is built as eqn (3) in section 2.1 with the only difference that we now distinguish the loss of antigens owing to interactions with free *antigens*, memory B cells and B cells.

The $\delta$, $\varepsilon_1$, $\varepsilon_2$ and $\varepsilon_3$ are the corresponding new phenomenological constants. Furthermore, $\gamma_1$ and $\gamma_2$ denote the inverse lifetimes of B cells and free antibodies in the absence of stimuli, respectively, while $m_{ij}$, $M_{ij}$ and $d_i$ keep their previous meaning.

The numerical simulation of the dynamics described by (A.1–A.3) for small

systems, as two- and three-cycles interacting with an antigen, shows that the trajectories of B cells and free antibodies closely follow each other (cf. Fig. 9). This justifies not to distinguish between them.

It is, however, just natural that the behavior may as well become more complex as more details are included; see, for example, Perelson (1989) and de Boer *et al.* (1990).

## APPENDIX B

### Global Stability

From (7) it follows that it is impossible that two antibodies, say $x_k$ and $x_1$, connected by a non-zero mutual matching diverge at the same time. In this case, the left-hand side of (7) would diverge to $\infty$, whereas for $\kappa > 1$, the right-hand side diverges to $-\infty$, which is a contradiction.

Is it possible that only a *single* antibody diverges? To answer this question we take a finite $x_i$ interacting with $x_1$ owing to a non-zero $M_{i1}$, suppose that $x_1$ diverges to infinity, and write

$$\dot{x}_i + \gamma x_i = (x_i M_{i1} + d_i m_{i1}) x_1 + x_i \sum_{j \neq i,1} M_{ij} x_j + \text{rest}, \tag{B.1}$$

where the "rest" denotes all the terms not containing $x_i$ and $x_1$ and therefore staying finite.

If $M_{i1} > 0$ ($x_1$ stimulates $x_i$), the right-hand side of (B.1) diverges to $\infty$ and so does $x_i$, in contrast to our assumption.

If $M_{i1} < 0$ ($x_1$ suppresses $x_i$), we first assume that $x_i(t \to \infty)$ converges to a limit $a_i$ so that $\dot{x}_i \to 0$. Then the prefactor of $x_1$ in (B.1) should vanish which implies $a_i = -d_i m_{i1}/M_{i1}$. In the case that $x_i(t)$ is oscillating, we consider the local extrema of the trajectory which occur at the times $t = \tau_n$ for which $\dot{x}_i(\tau_n) = 0$. From (B.1) we then have

$$\gamma x_i(\tau_n) = [x_i(\tau_n) M_{i1} + d_i m_{i1}] x_1(\tau_n) + x_i(\tau_n) \sum_{j \neq i,1} M_{ij} x_j(\tau_n) + \text{rest}. \tag{B.2}$$

Since $x_1$ increases without bound the sequence $x_i(\tau_n)$ converges to $a_i$ for the same reason as in the previous case.

That it is, indeed, possible that a single antibody completely dominates can already be seen for the example of a two-cycle (Behn & van Hemmen, 1989*a*, *b*). Its fixed point is

$$a = (\gamma^2 - d_1 d_2 m_{12} m_{21}) \{(\gamma M_{21} + d_2 m_{21} M_{12})^{-1}, (\gamma M_{12} + d_1 m_{12} M_{21})^{-1}\} \tag{B.3}$$

which is stable for $\gamma^2 < d_1 d_2 m_{12} m_{21}$. The positivity of the components leads to a condition on $\kappa$, namely, $\kappa > \kappa_s^\circ = \max\{\kappa_{12}, \kappa_{21}\}$ where $\kappa_{ij} = m_{ij}(\gamma + d_i m_{ij})/(\gamma m_{ji} + d_i m_{ij}^2)$. So $\kappa > \kappa_{ij}$ ensures that $a_j$ is positive. Therefore, as $\kappa \to \kappa_s^\circ + 0$ the larger component of $a$, say $a_1$, diverges to infinity and the other stays finite, $a_i = -d_i m_{i1}/M_{i1} > 0$. To avoid this we have again to make sure that $\kappa$ is large enough, i.e. *repression should dominate*—as advertised.