Memory in the Immune System : Synergy of Different Strategies

Ulrich Behn, Karen Lippert, and Christine Möller[1]
Leo van Hemmen and Bernhard Sulzer[2]

[1]Institut für Theoretische Physik, Universität Leipzig, Augustusplatz 10
O-7010 Leipzig, Germany
e-mail: behn@fkt.physik.uni-leipzig.dbp.de

[2]Physik-Department, TU München, James-Franck-Straße
W-8046 Garching, Germany

Abstract

Memory stored in the idiotypic network within a cycle that contains an internal image of an antigen is stabilized by long-lived memory cells. The dynamics of small cycles relaxes to fixed points describing the virgin state, a healthy immunized state and a chronic infection. Considering explicitly the delay in the appearance of antibodies after the stimulation of B lymphocytes we additionally observe limit cycles, period doubling, and chaos including periodic windows. We extend our model by dynamic equations for memory B cells which allows learning from experience at marginal stability.

1. Introduction

In this paper we report on a model (Behn and van Hemmen, 1989a,b; Behn et al., 1992, 1993a,b) which is based on the concept of idiotypic networks formed by B lymphocytes (Jerne, 1974, 1984). For recent reviews see, e.g., Perelson (1988, 1989), and Varela and Coutinho (1991). We extend our previous work including the delay in the appearance of antibodies after the stimulation of a B cell and the dynamics of long-lived memory cells.

The model describes a synergy of two mechanisms for memory. The first mechanism is – as proposed by Jerne (1974) – that memory is stored "in the symbiotic equilibrium of a cycle that contains an image". The simplest cycle consists of two sorts of antibodies, say Ab_1 and Ab_2, where the 'useful' Ab_1 recognizes the antigen Ag and *is* recognized by the 'anti-antibody' Ab_2. The cycle is closed if Ab_1 also recognizes Ab_2 which then act as an *internal image* of the antigen. Since the production of a sort of antibody is stimulated if its paratope recognizes a complementary structure (which may be the epitope of other antibodies or an antigen) and inhibited if its epitope *is* recognized by a complementary structure, the interaction may result in a dynamical equilibrium which provides a reservoir of useful antibodies Ab_1 even in the absence of the antigen Ag – a memory. The second mechanism is that, after a sufficiently strong primary response against Ag, there appear memory B cells (Vitetta et al., 1991) which have (if not stimulated) a life-time orders of magnitudes longer than 'normal' B cells and which can become activated in a new encounter with Ag. This finally results in a production of antibodies Ab_1. In the framework of our model the above mentioned cycles are *unstable* unless the corresponding memory cells are present, or, in other words: memory cells stabilize cycles (Behn and van Hemmen, 1989a,b).

Independently, it was argued by Perelson (1989) that "memory may be carried by both static and dynamic means". Our results give some evidence that there is a synergy of both possibilities.

To concentrate on essential mechanisms our model contains a number of simplifications. We do not distinguish between antibodies on the surface of a lymphocyte and those secreted by plasma cells. To describe the dynamics of the antibodies we adopt a bilinear form of the interaction (Farmer et al., 1986) which is familiar from the kinetics of chemical reactions.

A lymphocyte which is sufficiently strong stimulated replicates identically n times ($n \approx 10$). The majority in this clone of identical lymphocytes transforms then into plasma cells which secrete antibodies whereas a minor part transforms into memory cells. The time elapsed during the cloning process is the characteristic delay τ between stimulation and response and is typically in the order of several days.

Delay seems to us beeing an *intrinsic* property in biological systems in the following sense. Those systems are organized in a hierarchy of substructures. If we describe the system at a given level, say cells, the constituents themselves have a complex structure, e.g., at the level of chemical reactions, which we do not include explicitly. The delay is the typical time needed to organize the reaction of, e.g., the cells at the molecular level. A time lag between stimulation and response would result of course also by including *explicitly* the subordinate

level(s) of the hierarchy but at the expense of making the description much more complicated, and possibly intractable. In Behn et al. (1993b) we extended our previous work including a delay explicitly.

The model is formulated in the next Section. In Section 3 we analyze stability and dynamics of a 2-cycle interacting with an antigen. If the delay is not too long the system relaxes to one of three relevant states as for the case without delay. Beyond critical values of the delay, however, the corresponding fixed points change their stability properties and the solution oscillates, is chaotic, or explodes. The dynamics of memory cells which is treated in Section 3 only in a rudimental way is the subject of Section 4. We propose a dynamic equation which describes a mechanism for maintaining the pool of memory cells and allows a learning from experience at marginal stability. Finally, in Section 5, we comment on learning in dynamical systems. Forthcoming problems and extensions of our model are shortly discussed.

2. The Idiotypic Network

We consider a *given set* of constituents of the idiotypic network and describe the dynamics of the number x_i of antibodies of sort i, $i = 1, \ldots, N$, per unit volume interacting with other antibodies and with antigens. Here y_j denotes the number of antigens of sort j per unit volume. By x_i^τ, y_i^τ, and d_i^τ we denote the values of $x_i(t-\tau)$, $y_i(t-\tau)$, and $d_i(t-\tau)$ where τ (assumed as a constant) is the delay mentioned above. In a simple 'mean-field' approach the interaction is bilinear in x_i and y_j (of Lotka-Volterra form) and we obtain

$$\dot{x}_i = -\gamma x_i + \sum_{j=1}^{N} (m_{ij} x_i^\tau x_j^\tau - \kappa m_{ji} x_i x_j) + d_i^\tau \sum_{j=1}^{N} m_{ij} x_j^\tau + (d_i^\tau + x_i^\tau) \sum_{j=N+1}^{N+R} m_{ij} y_j^\tau \quad , (1)$$

where γ is the inverse life time of noninteracting antibodies and m_{ij} measures the matching between paratope of antibody i with a complementary structure j (on antibody j or antigen j). There is a *stimulation* if paratope i matches a complementary structure and an *inhibition* if epitope i is recognized by a complementary structure. The parameter κ allows for an asymmetry between stimulation and inhibition.

Since the lifetime of memory cells d_i is orders of magnitude longer than that of antibodies and the delay we describe the dynamics of antibodies and memory cells d_i – as a first approximation – in a very rudimental way: The system starts in the virgin state where all $d_i \equiv 0$. Memory cells d_i are inserted after a sufficiently strong stimulation (namely if the total stimulus per antibody i, $\sum_j m_{ij} x_j + \sum_k m_{ik} y_k$, exceeds some threshold), and we assume that their number stays constant in time once they appeared. A more sophisticated dynamics of memory cells is sketched in Section 4.

The dynamics of the antigens y_i, $i = N+1, \ldots, N+R$, is described by

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

where α, the virulence, is the difference between proliferation rate and the inverse life time. For most relevant antigens α is positive. Eq. (2) allows an exponential growth of antigen during the initial stage of an infection.

Eqs. (1,2) are invariant against a scaling of the matching parameters $\{m_{ij}\}$ by ζ if $\{x_i\}$, $\{y_i\}$, and $\{d_i\}$ are scaled by ζ^{-1}. Thus matching and number of constituents per unit volume are measured in arbitrary units choosen for numerical convenience. The time scale is fixed by choosing a value for the life-time of the antibodies which is of the order of 10...20 days. The matching m_{ij} is treated here as a parameter.

The model (1,2) without delay was extensively studied in a series of papers (Behn and van Hemmen, 1989a,b; Behn et al., 1992, 1993a). There it was shown that without antigens and without memory cells the only stable fixed point is the virgin state, i.e., all $x_i \equiv 0$ (nontrivial fixed points are unstable). With memory cells one finds stable nontrivial fixed points provided suppression dominates, $\kappa > 1$. This naturally supports Jernes idea (1974) that "the essence of the immune system is the repression of its lymphocytes". The organism acquires in the course of its life (due to encounters with antigen or due to interaction between antibodies) a set of nonzero $\{d_j\}$ which means a 'symmetry breaking' of the virgin state. In well defined parameter regions the dynamics of small subsystems relaxes to the virgin state, to a healthy immunized state, or to a state of chronic infection.

Differential-delay equations have infinitely many degrees of freedom since the state of the system corresponds to a function given over the time span of the delay. The formal identity $x(t-\tau) = exp(-\tau\partial/\partial t)x(t)$ elucidates that a differential-delay equation is indeed of infinite order. Therefore one should expect that the behaviour of the model with delay becomes richer compared to the case without delay. In a real system the delay is obviously not a constant but will depend on several details, e.g., the strength of the stimulation of the lymphocytes. Furthermore the number of replications in the cloning process before differentiation is randomly distributed. However, we do not expect substantial alterations in the qualitative behaviour. This is supported by our experience with models differing from (1) in that the stimulation by antigens is not delayed, respectively only the terms including memory-cells are delayed.

Lotka-Volterra systems with time lags have been considered also in different biological context (Goel et al., 1971). For the immune system a different model including delay was recently proposed (Fujita and Aihara, 1989).

3. Behaviour of 2-Cycles with Delay

Since the space of possible paratopes and its complementary structures is high dimensional a good matching between two randomly selected paratopes and epitopes has a very small probability. The formation of a fully connected network is a sort of percolation problem (Perelson, 1989). Here we assume to work in a parameter regime where small subsystems connected by good matching are most probable.

The smallest subsystem is a 2-cycle of two sorts of antibodies, x_1 and x_2, with mutual matching $m_{12} = m_{21} = m$. Antigens y stimulate x_1 with matching

$\overline{m}$. In the presence of memory cells d_1 and d_2 Eqs. (1,2) simplify to

$$\dot{x}_1 = -\gamma x_1 + m x_1^\tau x_2^\tau - \kappa m x_1 x_2 + d_1^\tau m x_2^\tau + (d_1^\tau + x_1^\tau)\overline{m} y^\tau \ , \tag{3}$$

$$\dot{x}_2 = -\gamma x_2 + m x_1^\tau x_2^\tau - \kappa m x_1 x_2 + d_2^\tau m x_1^\tau \ , \tag{4}$$

$$\dot{y} \ = y(\alpha - \overline{m} x_1) \ . \tag{5}$$

Independent on the delay Eqs. (3-5) have three fixed points $z^s = (x_1^s, x_2^s, y^s)$ which are relevant if their components are nonnegative,

$$z_1^s = \ (0,0,0) \ , \tag{6}$$

$$z_2^s = (a_1, a_2, 0) = \ \frac{m^2 d_1 d_2 - \gamma^2}{(\kappa - 1)m} \left(\frac{1}{m d_2 + \gamma} \, , \ \frac{1}{m d_1 + \gamma} \, , \ 0 \right) \ , \tag{7}$$

$$z_3^s = (b_1, b_2, b_3) = \left(\frac{\alpha}{\overline{m}} \, , \ \frac{d_2}{\kappa - 1 + \gamma\overline{m}/(\alpha m)} \, , \ \frac{\gamma(b_1 - b_2) + m(d_2 b_1 - d_1 b_2)}{\overline{m} d_1 + \alpha} \right) \tag{8}$$

Stability. We start discussing the stability for zero delay. Without antigen, $y \equiv 0$, and without memory cells, $d_{1/2} \equiv 0$, the system is in the *virgin state*. Eqs. (3,4) describe relaxation towards $x_1 = x_2 = 0$.

The virgin state, however, may become infected which leads to an increase of antigens and antibodies. If the reaction was strong memory cells appear. If there are enough memory cells, $d_1 d_2 > (\gamma/m)^2$. the system of Eqs. (3,5) has besides the unstable fixed point z_1^s the stable fixed point z_2^s describing a *healthy immunized state* (Fig. 1a). The production of useful antibodies x_1 is triggered even in the absence of antigens by antibodies x_2, the internal image of the antigen. z_2^s is stable as long as the antigen is not too virulent ($\alpha < \overline{m} a_1$); an infection is spontaneously cured.

For a virulent antigen (or poor matching, or not enough antibodies) we have $\alpha > \overline{m} a_1$ and z_2^s looses the stability. The fixed point z_3^s becomes relevant and stable describing the state of *chronic infection* – a 'remis' in the competition between antigen and antibodies (Fig. 1b). For $d_1 d_2 < (\gamma/m)^2$ the fixed point z_2^s is not relevant since $a_1, a_2 < 0$ (Fig. 1c).

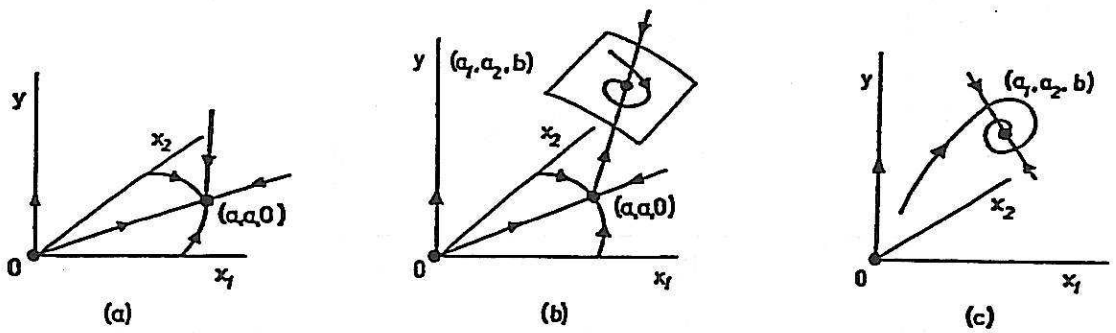

Fig. 1. Fixed points and schematic flows for a 2-cycle of two sorts of antibodies x_1 and x_2 with mutual matching m without delay. The antigens y are recognized by antibodies x_1 with matching $\overline{m}$. In the immunized state (a) an infection is cured. If the antigen is too virulent the immunized state looses its stability and a new stable fixed point describing a chronic infection emerges (b). For weak coupling the immunized state becomes irrelevant (c).

In passing we note that for $d_1 > 0$ and $d_2 = 0$ the Ab_2 die out, see Eq. (4), and 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 the antigen concentration is low this state can be interpreted as *memory* established by a 'cycle' of antibody x_1 and the antigen y itself. Otherwise it is better to call it chronic infection. There is experimental evidence that the production of Ab_1 may be triggered by Ag retained in follicular dendritic cells found in secondary lymphoid tissues (Tew et al., 1990). This can be considered as a third – independent – strategy for preserving memory.

We now turn to the case of nonzero delay (Behn et al., 1993b). For small delay the stability of the fixed points is not changed. For the sake of convenience we assume $d_1 = d_2 = d \neq 0$ which means no qualitative restriction. With increasing delay, however, a fixed point may loose its stability. The linear stability analysis leads to quasipolynomial eigenvalue equations. There exist well elaborated methods to determine the critical delay for which a complex eigenvalue enters the right complex half plane (Bellman and Cooke, 1963; El'sgol'ts, 1966; Cooke and Grossman, 1982; MacDonald, 1989).

We first consider the case of chronic infection where both z_2^s and z_3^s are relevant. The fixed point z_2^s is unstable independent on the delay: the characteristic quasipolynomial has a positive eigenvalue $\lambda = \alpha - \overline{m}a_1$. Without delay the fixed point z_3^s is stable.

The critical delay τ_c for which z_3^s looses the stability determines a first threshold. It is calculated numerically using a method which can be found, e.g., in MacDonald (1989). Beyond this threshold there is no stable fixed point in the space of states to which the system could relax. The system can only explode or – if its motion remains bounded – it could converge to a limit cycle or a chaotic attractor.

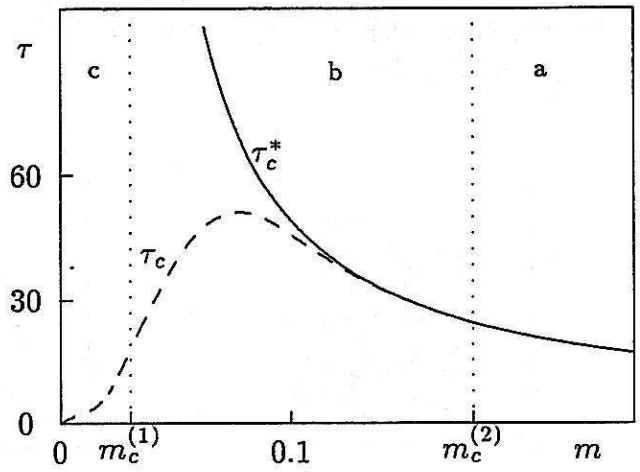

Fig. 2. Critical delays τ_c and τ_c^* for a 2-cycle with antigen. We display the dependence on the intracycle matching m for $\alpha = 0.1$, $\gamma = 0.012$, $\kappa = 1.1$, $\overline{m} = 0.03$, $d_1 = d_2 = 0.4$. For small delay the system qualitatively behaves as for zero delay relaxing to a stable fixed point (regions a, b, c correspond to Figs. 1a-c). For $\tau_c < \tau < \tau_c^*$ the systems motion is oscillatory or chaotic. For $\tau_c^* < \tau$ the system explodes in the x_1, x_2 plane.

The second critical delay τ_c^* is determined by the condition that the second-largest eigenvalue of the (unstable) fixed point z_2^s enters the right half plane. This leads to

$$\tau_c^* = \left[(dm)^2 - \gamma^2\right]^{-1/2} \arccos(-\gamma/dm). \tag{9}$$

It can be rigorously shown by introducing new coordinates $x_1 - x_2$ and $x_1 + x_2$ that the system explodes in the x_1, x_2-plane for delays $\tau > \tau_c^*$. In Figure 2 the thus determined thresholds τ_c and τ_c^* are displayed as functions of the intracycle matching m. For the parameters used in the numerical calculations both thresholds may be in the biological relevant time interval of several days.

For small matching ($m < m_c^{(1)} = \gamma/d$, i.e., $a < 0$) the fixed point z_2^s is not relevant. For large matching ($m > m_c^{(2)} = \gamma/[d - (\kappa - 1)\alpha/\overline{m}\ ]$, i.e., $b < 0$) only z_2^s is relevant. The eigenvalue $\lambda = \alpha - \overline{m}a < 0$ which is independent on τ, is now negativ.

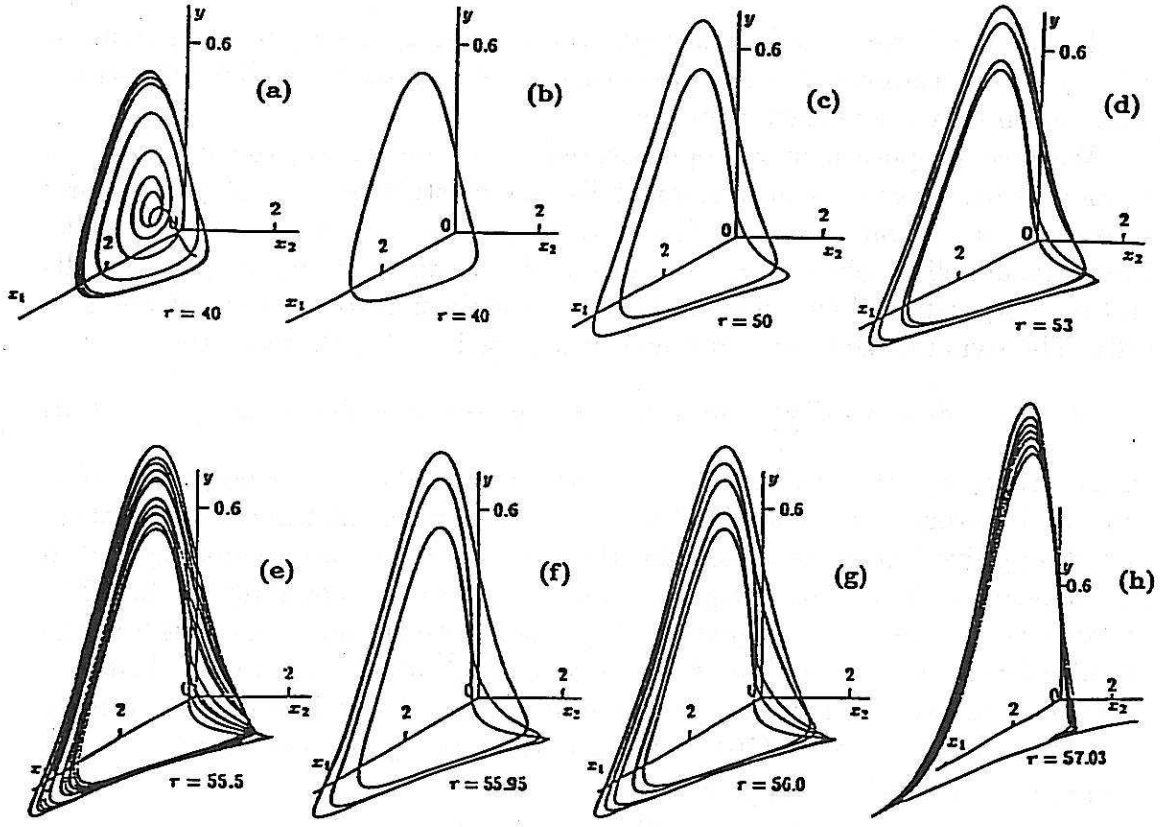

Fig. 3. Trajectories for the 2-cycle of antibodies x_1 and x_2 interacting with an antigen y for different delays ($m = 0.04$, other parameters as in Fig. 2). After a transient phase (shown only in (a)) the system reaches the attractor. With increasing delay τ we observe starting from a limit cycle of period $T \approx 303$ (b) a series of period doublings (the first two are shown in (c) and (d)) ending in a chaotic state (e). Within the chaotic region there are windows characterized by odd periods, see (f) and (g). Increasing τ further we observe a transient chaotic behaviour before the system explodes (h).

Dynamics. We investigated the dynamics of 2-cycles described by Eqs. (3-5) for delays $\tau_c < \tau < \tau_c^*$. In this region there are no relevant stable fixed points. We found that for τ just above τ_c the motion converges to a limit cycle (Fig. 3a). Oscillating behaviour in the number of antibodies and antigens is known from experiment (Weigle, 1975; Hiernaux et al., 1982). With increasing delay a sequence of period doublings occurs (Figs. 3c,d) ending in a chaotic state (Fig. 3e). Within the chaotic region of τ there are small periodic windows characterized by odd periods (Figs. 3f,g). To check whether the system behaves chaotic we calculated the largest Lyapunov exponent averaged along the trajectory modifying a scheme given by Farmer (1982). It is positive and of order $10^{-3}...10^{-2}$. Increasing τ further the system spends a considerable time in a (transient) chaotic state before it finally explodes. A more detailed analysis of the scenario which leads to chaos and of the chaotic state itself will be given elsewhere.

4. Dynamics of Memory B-Cells

In Section 2 we took into account the dynamics of long-lived memory B cells in a very rudimental way: Once they appeared after a sufficiently strong stimulation they stay constant in time.

We now propose a more sophisticated model describing the dynamics of memory cells. Once present, memory cells may be stimulated by Ab_2 or Ag and transform to normal cells, i.e. they disappear from the pool of memory cells. The normal cells replicate several times and transform then into plasma cells and memory cells, which means a *delayed* contribution to the pool of memory cells. The dynamic equation for memory cells d_1 in a 2-cycle reads then

$$\dot{d}_1 = -\gamma_d d_1 + \Lambda m d_1^\tau x_2^\tau - m d_1 x_2 + \overline{m}(d_1^\tau y^\tau - d_1 y) + f(t, x_1, x_2, y), \qquad (10)$$

where $f(t, x_1, x_2, y)$ describes, e.g., the *first* appearance of memory cells after sufficiently strong stimulation and $\gamma_d \ll \gamma$ is the inverse lifetime of the unstimulated long-lived memory cells. (For the sake of brevity we assume $\gamma_d = 0$ in the following). In a similar equation for d_2 there is no coupling to Ag. The dynamics of x_1, x_2 and y is given by Eqs. (3-5). We suppose that $f \equiv 0$ in the initial interval $(0, \tau)$ as well as for $t \to \infty$ and $\int_0^\infty dt f$ beeing finite. Without excitation, the system is at marginal stability if $\Lambda = 1$ which implies that every $d_1 = const.$ is a solution of (10) provided both x_2 and y approach for $t \to \infty$ the fixed point values $x_2^{(\infty)}$ and $y^{(\infty)}$.

Starting in a fixed point $d_1^{(0)}, x_2^{(0)}$, ... a perturbation $f(t, x_1, x_2, y)$ drives the system to a new fixed point where

$$d_1^{(\infty)} = \frac{d_1^{(0)}(1 + m x_2^{(0)}\tau + \overline{m} y^{(0)}\tau) + \int_0^\infty dt f}{1 + m x_2^{(\infty)}\tau + \overline{m} y^{(\infty)}\tau} \qquad (11)$$

which manifestly depends on the history. Note that Eq. (11) is an implicit equation since both $x_2^{(\infty)}$ and $y^{(\infty)}$ depend on $d_1^{(\infty)}$, cf. Eqs. (7,8).

Our new system has fixed points which hold the same meaning as before (virgin state, healthy immunized state, and chronic infection). The memory

cells d_1 and d_2 are no longer parameters but obey dynamic equations. Because of the marginal stability any perturbation or change in the initial conditions may shift the fixed points in the space of states. For example, starting in a state of chronic infection the system can be driven by injections of Ag or Ab_2 into a state where $d_1^{(\infty)}, d_2^{(\infty)}$ are so large that the system is healthy.

A shift of the (stable or unstable) fixed point happens if the 'scalar product' of the initial function with the eigenfunction corresponding to the eigenvalue zero of the linearized problem is nonvanishing. With increasing delay a pair of complex eigenvalues, λ and λ^*, enters the right half plane, the only stable fixed point looses its stability, and a limit cycle with a period near the threshold of $T \approx 1/Im(\lambda)$ establishes. With increasing distance from the threshold the period and the amplitudes of the limit cycle enlarge. The dynamics of memory cells stabilizes the system in the following sense: We found no explosion for delays much larger than the critical delay τ_c^* in Section 3. More details about the complex behaviour of models of this type will be reported elsewhere.

5. Concluding Remarks

We shortly comment on learning described by dynamical systems. There are – at least – three categories of models: (i) For a given parameter setting the system has a number of attractors, e.g. fixed points, corresponding to the (preconditioned) states of memory. External perturbations push the system across the boundaries of the basins of attraction. (ii) Parameters of the system are changed 'by hand' if the variables cross some thresholds mimicking a dynamics beyond the level of description of the given model, e.g. at the intracellular level. This leads to a change in the configuration of attractors. (iii) Learning at marginal stability. In both initial and final state the system is at marginal stability. A perturbation (experience) drives the system out of equilibrium and moves a limited number of fixed points with a given meaning into different regions of the space of states so that appropriate fixed points become relevant. The model with rudimental dynamics of memory cells belongs to category (ii) whereas the sophisticated version is a member of (iii).

We found that already the smallest subsystems of the idiotypic network exhibit a complex dynamic behaviour. A weak (global) coupling between several chaotic or oscillating systems may lead to an interesting new and – in a sense – universal behaviour as is known from different context (Kook et al., 1991; Kaneko, 1992; Niebuhr et al., 1991). This could be essential in describing the internal activity of the immune system.

Furthermore, it is of interest to include stochastic perturbations opening the field for noise induced phenomena (Longtin, 1991; Leung, 1991).

We have seen that the model exhibits quite a reasonable behaviour – in spite of its crude simplifications. So we could think about $\{x_i\}$ and $\{y_i\}$ as a sort of 'lumped' variables describing the gross behaviour of subsystems the details of which we do not know respectively we are not interested in, or which are not important. In a living organism the list of variables is of course dynamic itself. New sorts of antibodies (lymphocytes) are introduced from the bone marrow (innovation) and there is an enhanced mutation during the process of

clonal selection (adaptation). We think, however, that the understanding of the dynamics of a given set of constituents is indespensable for extending both theory and simulation to large scale 'living' networks.

Acknowledgment

One of us (U. B.) acknowledges encouraging discussions with Alan Perelson and George Bell and thanks the Center for Nonlinear Studies (Los Alamos National Laboratories) for hospitality. Thanks is also due to Frank Moss and Arthur Wightman for valuable discussions about delayed systems.

References

Behn, U. and van Hemmen, J. L. 1989a. On the theory of networks for the immune system. In: *Dynamical Networks* , eds. Ebeling, W. and Peschel, M., Akademie Verlag, Berlin, 162-172.

Behn, U. and van Hemmen, J. L. 1989b. Network description of the immune system: dormant B cells stabilize cycles. *J. Stat. Phys.* **56**, 533-545.

Behn, U., van Hemmen, J. L. and Sulzer, B. 1992. Memory B cells stabilize cycles in a repressive network. In: *Theoretical and Experimental Insight into Immunology*, eds. Perelson, A. S., Weisbuch, G. and Coutinho, A., NATO ASI Series H **66**, Springer, Heidelberg, 249-260.

Behn, U., van Hemmen, J. L. and Sulzer, B. 1993a. Memory in the immune system: Network theory including dormant B cells. *J. theor. Biol.*, to appear.

Behn, U., Lippert, K., Möller, C., van Hemmen, J. L., and Sulzer, B. 1993b. Memory in the immune system: Network theory including memory B cells and delay. In: *Phase Transitions: Physics, Mathematics, Biology* , ed. Kotecky, R., World Scientific, Singapore, in print.

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

Jerne, N. K. 1984. Idiotopic networks and other preconceived ideas. *Immunol. Rev.* **79**, 5-24.

Perelson, A. S. (ed.) 1988. *Theoretical Immunology, Parts I and II,* In: *Santa Fe Institute Studies in the Science of Complexity, Vol II and III*, Addison-Wesley, Redwood City.

Perelson, A. S. 1989. Immune network theory. *Immunol. Rev.* **110**, 5-36.

Varela, F. J. and Coutinho, A. 1991. Second generation immune networks. *Immunol. Today* **12**, 159-166.

Vitetta, E. S., Berton, M. T., Burger, C., Kepron, M., Lee, W. T., and Yin, X.-M. 1991. Memory B and T cells. *Ann. Rev. Immunol.* **9**, 193-217.

Farmer, J. D., Packard, N. H., and Perelson, A. S. 1986. The immune system, adaption and machine learning. *Physica* **22D**, 187-204.

Farmer, J. D. 1982. Chaotic attractors of an infinite-dimensional dynamical system. *Physica* **4D**, 366-393.

Bellman, R. and Cooke, K. L. 1963. *Differential-difference equations.* Academic Press, New York.

El'sgol'ts, L.E. 1966. *Introduction to the Theory of Differential Equations with Deviating Arguments.* San Francisco, Holden-Day.

Cooke, K. L. and Grossman, Z. 1992. Discrete delay, distributed delay and stability switches. *J. Math. Anal. Appl.* **86**, 592-627.

MacDonald, N. 1989. *Biological delay systems: Linear Stability Theory.* University Press, Cambridge.

Goel, N. S., Maitra, S. C., and Montroll, E. W. 1971. On the Volterra and other nonlinear models of interacting populations. *Rev. Mod. Phys.* **43**, 231-276.

Fujita, H. and Aihara, K. 1989. Application of the PDP model with a logistic activation function to immune networks. *Transact. IEICE* **E72**, 416-421.

Tew, J. G., Kosco, M. H, Burton, G. F., and Szakal, A. K. 1990. Follicular dendritic cells as accessory cells. *Immunol. Rev.* **117**, 185-211.

Weigle, W. O. 1975. Cyclical production of antibody as a regulatory mechanism in the immune response. In: *Advances in Immunology* **21**, eds. Dickson, F. J. and Kunckel, A. B., Academic Press, New York, San Francisco, London, 87-111.

Hiernaux, J. R., Baker, P. J., Delisi, C., and Rudbach, J. A. 1982. Modulation of the immune response to Lipopolysaccharide. *J. Immunol.* **128**, 1054-1058.

Kook, H., Ling, F. H.. and Schmidt, G. 1991. Universal behaviour of coupled nonlinear systems. *Phys. Rev. A* **43**, 2700-2708.

Kaneko, K. 1992. Mean field fluctuations of a network of chaotic elements. *Physica* **55D**, 368.

Niebuhr, E., Schuster, H. G., and Kammen, D. M. 1991. Collective frequencies and metastability in networks on limit-cycle oscillators with time delay. *Phys. Rev. Lett.* **67**, 2753-2756.

Longtin, A. 1991. Noise-induced transitions at a Hopf bifurcation in a first-order delay equation. *Phys. Rev. A* **44**, 4801-4813.

Leung, H. K. 1992. Noise-induced metastability in a dynamic system. *Phys. Rev. A* **46**, 6217-6221.