Immune Networks Modeled by Replicator Equations

By

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Abstract

In order to evaluate the role of idiotypic networks in the operation of the immune system a number of mathematical models have been formulated. Here we examine a class of B-cell models in which cell proliferation is governed by a non-negative, unimodal, symmetric response function $f(h)$, where the field h summarizes the effect of the network on a single clone. We show that by transforming into relative concentrations, the B-cell network equations can be brought into a form that closely resembles the replicator equation. We then show that when the total number of clones in a network is conserved, the dynamics of the network can be represented by the dynamics of a replicator equation. The number of equilibria and their stability are then characterized using methods developed for the study of second-order replicator equations. Analogies with standard Lotka-Volterra equations are also indicated. A particularly interesting result of our analysis is the fact that even though the immune network equations are not second-order, the number and stability of their equilibria can be obtained by a superposition of second-order replicator systems. As a consequence, the problem of finding all of the equilibrium points of the nonlinear network equations can be reduced to solving linear equations.

Key Words

B-cells – immune system – mutation – replicator equations

1. Introduction

Jerne (1974) suggested that the immune system is organized as a network of lymphocytes and antibody molecules that interact via specific or idiotypic interactions. In order to evaluate the role of idiotypic networks in the operation of the immune system a number of mathematical models have been developed (see Perelson, 1988, 1989, 1992; Varela & Coutinho, 1991; and De Boer *et al.*, 1993a for recent reviews). Within the last five years a considerable body of work has arisen around a model that we have termed the B-cell model (*cf.*, De Boer, 1988; De Boer & Hogeweg, 1989; De Boer *et al.*, 1990; Weisbuch *et al.*, 1990; Perelson & Weisbuch, 1992; De Boer *et al.*, 1993a,b,c). This model, which includes only B cells, attempts to describe the population dynamics of a set of n distinguishable B-cell clones that interact in a network. The B-cell model has been thoroughly studied for the case of two B-cell clones ($n = 2$), but when a large number of clones are present fundamental questions, such the number of steady states and their stability, remain largely unanswered. Boutet de Monvel & Martin (1994) examine the number of steady states in B-cell network models with random connection matrices. Weisbuch & Oprea (1994) examine related questions for networks whose topology is generated by matching random digit strings. Here we show how the question of the number of steady states and their stability can be attacked for a special case in which the B-cell model can be transformed into a set of replicator equations (Schuster & Sigmund, 1983; Hofbauer & Sigmund, 1988). This approach is particularly relevant to cases where biological mechanisms exist to control the total number of clones in a network.

To proceed, we first introduce the B-cell model and show that by transforming from cell concentrations to relative concentrations we obtain a model closely related to the replicator equation model. We then review replicator equations and their relationship to Lotka-Volterra and B-cell model equations. Once these preliminaries are out of the way we show how one can compute the number of steady states and characterize their stability.

2. B-Cell Model

2.1. General Considerations

Let y_k denote the concentration of B-cells in clone $k = 1, \ldots, n$, and denote by c the total concentration of B cells,

$$c = \sum_{k=1}^{n} y_k. \tag{2.1}$$

The relative concentrations of B cells will be denoted by

$$x_k = y_k / c. \tag{2.2}$$

When stimulated by interactions with other clones, a clone will proliferate. We summarize the effects of all other clones by a variable called the field. The *field* of clone k (De Boer & Perelson, 1991; Perelson & Weisbuch, 1992) is given by

$$h_k(y) = \sum_{j=1}^{n} \tilde{J}_{kj} y_j = c \sum_{j=1}^{n} \tilde{J}_{kj} x_j = c\, h_k(x). \tag{2.3}$$

The coefficients $\tilde{J}_{ij}$ describe the topology of the B-cell network.

In the B-cell model, the population dynamics of B-cells is described by

$$\dot{y}_k = y_k \left[p\tilde{f}(h_k(y)) - \tilde{d}_k \right] + \tilde{s}_k, \tag{2.4}$$

where p is the proliferation rate, $\tilde{f}$ is a response function determining the fraction of cells proliferating, $\tilde{d}_k$ is the death-rate of cells in clone k, and $\tilde{s}_k$ is the (constant) influx of cells into clone k from the bone marrow. The influx rates are typically small. We shall take them to be identically zero and then show how they can be reintroduced as perturbations of the simplified dynamical system with $\tilde{s}_k = 0$ that we study in the main part of this paper. Further, we assume that the death-rates for all cells are equal, i.e., $\tilde{d}_k = \tilde{d}$. Hence we arrive at the following differential equation

$$\dot{y}_k = y_k \left[p\tilde{f}(h_k(y)) - \tilde{d} \right] . \tag{2.5}$$

By the chain rule, $\dot{y}_k = c\dot{x}_k + \dot{c}x_k$. Hence, in terms of relative concentrations the corresponding dynamics are

$$\dot{x}_k = x_k \left[p\tilde{f}(c \cdot h_k(x)) - \Phi(x) \right] , \tag{2.6a}$$

$$\Phi(x) = p \sum_{k=1}^{n} x_k \tilde{f}(c \cdot h_k(x)) , \tag{2.6b}$$

$$\dot{c} = c \left(\Phi(x) - \tilde{d} \right) . \tag{2.6c}$$

The structure of the model in equation (2.6) suggests that it might be worthwhile to consider a larger class of models in which the dynamics of the relative concentrations is still described by equations (2.6a) and (2.6b) but the dynamics of the total concentration c given by the third equation (2.6c) is relaxed. In particular, we will pursue the case in which $\dot{c} = 0$, i.e., where the total concentration of cells is conserved. Note that in this case $\Phi(x) = \tilde{d}$ and equations (2.5) and (2.6) become equivalent as long as c is bounded away from 0.

2.2. Example: The Two B-cell Model

As an example we examine the two B-cell model studied extensively by De Boer *et al.* (1993b). Here $n = 2$, and $\tilde{J}$ is chosen symmetric with the only interaction being being clone 1 and 2, i.e., $\tilde{J}_{11} = \tilde{J}_{22} = 0$, $\tilde{J}_{12} = \tilde{J}_{21} = 1$. Hence (2.5) becomes

$$\dot{y}_1 = y_1 \left[p\tilde{f}(y_2) - \tilde{d} \right] , \tag{2.7a}$$

$$\dot{y}_2 = y_2 \left[p\tilde{f}(y_1) - \tilde{d} \right] , \tag{2.7b}$$

with $c = y_1 + y_2$. In terms of relative concentrations these equations become

$$\dot{x}_1 = x_1 \left[p\tilde{f}(cx_2) - \Phi(x) \right] \ , \tag{2.8a}$$

$$\dot{x}_2 = x_2 \left[p\tilde{f}(cx_1) - \Phi(x) \right] \ , \tag{2.8b}$$

where

$$\Phi = p \left[x_1 \tilde{f}(cx_2) + x_2 \tilde{f}(cx_1) \right] \ . \tag{2.8c}$$

Choosing $\Phi = \tilde{d}$, so that the total concentration of cells is conserved, equations (2.8) become

$$\begin{aligned} \dot{x}_1 &= x_1 \left[p\tilde{f}(cx_2) - px_1\tilde{f}(cx_2) - px_2\tilde{f}(cx_1) \right] \ , \\ \dot{x}_2 &= x_2 \left[p\tilde{f}(cx_1) - px_1\tilde{f}(cx_2) - px_2\tilde{f}(cx_1) \right] \ , \end{aligned} \tag{2.9}$$

which as we shall see below is of replicator form. Since $x_1 + x_2 = 1$, this equation can be rewritten in the simplified form

$$\dot{x}_1 = px_1x_2 \left[\tilde{f}(cx_2) - \tilde{f}(cx_1) \right] = -\dot{x}_2 \ . \tag{2.10}$$

We immediately see there exist steady state solutions with $(x_1, x_2) = (0, 1)$ and $(1, 0)$. These solutions we shall call "corner equilibria" since they occur on the corners of the 2-simplex. In addition, there are "interior equilibria" where $\tilde{f}(cx_2) = \tilde{f}(cx_1)$. One such equilibria is at (0.5,0.5). In addition, if f is unimodal there may be an additional equilibrium point with x_1 and x_2 on opposite sides of the maximum of f. For example, if f were symmetric about a maximum at $1/2$, then with $c = 1$, (0.25,0.75) would be the second interior equilibrium. We shall show in section (4.3) that there are at most 2^{n-1} isolated interior equilibria in a system with n clones. In section 4, we shall rescale f so as to take advantage of symmetry.

3. Replicator Equations and Lotka-Volterra Equations

The term replicator equation was coined about ten years ago (Schuster & Sigmund, 1983) for a whole series of ordinary differential equations (ODEs) of the form

$$\dot{x}_k = x_k \left[F_k(x) - \sum_{j=1}^{n} x_j \, F_j(x) \right] \qquad k = 1, ..., n\,. \tag{3.1}$$

with variables normalized to one. The physically meaningful domain of the state space is thus confined to the unit simplex

$$\mathbf{S}_n \ = \ \left\{ x \in \mathbb{R}^n \middle| x_i \geq 0, \sum_{i=1}^{n} x_i = 1 \right\} \ . \tag{3.2}$$

These equations arise in a broad variety of different and seemingly unrelated fields. In sociobiology it occurs as the game dynamical equation modeling the evolution of behavioral phenotypes (Hofbauer & Sigmund, 1988). It describes autocatalytic networks in molecular evolution (Schuster and Sigmund, 1983). In population genetics, the continuous version of Fisher's selection equation (Fisher, 1930) is of the form (3.1). Disguised as Lotka-Volterra equations, they play the dominant role in mathematical ecology. The common denominator is Dawkin's notion of *replicators*, that is entities which get copied and whose inherited properties effect the copying (Dawkins, 1976). Replicators, as abstract units of selections, may have different biological realizations: macromolecules, genes, entire organisms, or behavioral strategies. The mere fact that they are copied and inherit the properties crucial for the copying process implies a dynamics of the form (3.1).

The functions $F(x)$ in (3.1) are often represented as polynomials. The special case of second order replicator equations, $F_k(x) = (Ax)_k$,

$$\dot{x}_k = x_k \left[(Ax)_k - (xAx) \right] \tag{3.3}$$

(where A is an $n \times n$ matrix, $(Ax)_k = \sum_j A_{kj} x_j$, and $(xAx) = \sum_{ij} A_{ij} x_i x_j$) is of particular interest. (For a review see, e.g., Hofbauer & Sigmund, 1988). Equation (3.3) is up to a transformation of the time axis dynamically equivalent to the classical Lotka-Volterra equation of dimension $n-1$ (Hofbauer, 1981)

$$\dot{y}_k = y_k [r_k + (By)_k] \qquad k = 1, \ldots, n-1\,, \tag{3.4}$$

and as has been shown by Smale (1976) any dynamics can be mimicked faithfully by replicator dynamics of some dimension m.

In the following we shall assume that the effective growth rates of individual species are all equal in the Lotka-Volterra equation: $r_k = r$. Then the n-dimensional counterpart of equation (3.4) becomes in terms of relative concentrations

$$\begin{aligned} \dot{x}_k &= \dot{y}_k / c - y_k / c \cdot \dot{c} / c = \\ &= x_k [r + (By)_k] - x_k \sum_{j=1}^{n} x_j [r + (By)_j] = \\ &= x_k r - x_k r \sum_{j=1}^{n} x_j + x_k \left[(By)_k - \sum_{j=1}^{n} x_j (By)_j \right] = \\ &= c \cdot x_k [(Bx)_k - (xBx)] \end{aligned} \tag{3.5}$$

The interesting part of the dynamics of the Lotka-Volterra equation (3.4), that is, the relations between among species as opposed to the overall size of the system, is then faithfully represented by the dynamics of the second order replicator equation (3.3) in relative concentrations, as long as c is bounded away from zero, in other words, as long as at least a single species survives in the system. Since the system size c is variable, both the replicator and the Lotka Volterra equation describe n species; the state space of the replicator equation, however, is only $n-1$ dimensional.

The dynamics of second order replicator equation (3.3) is determined by the properties of the matrix A. Special examples are Fisher's selection equation (Fisher, 1930) where A is symmetric and all trajectories converge to fixed points, or the elementary hypercycle equation (Eigen & Schuster, 1978a) where A is cyclic and has only one positive off-diagonal entry per row ($A_{ij} = a\,\delta_{i,j+1}$), and which sustains a stable limit cycle for $n \geq 5$ (Hofbauer *et al.*, 1991). General replicator equations may lead to various kinds of complex dynamics including deterministic chaos for $n \geq 4$ (Schnabl *et al.*, 1991).

In replicator systems the simplex $\mathbf{S}_n$ and all its faces are invariant. Vanishing concentrations do not change the general form of the ODE (3.1) and hence the dynamics on each face follows some lower dimensional replicator equation. The problem of determining the rest points of (3.1) thus boils down to finding all interior rest points of the simplex and all subsystems. We quote a lemma from Hofbauer & Sigmund (1988):

Lemma 1. *Let $\hat{x}$ be a rest point of the replicator equation (3.1) that is on the boundary of the unit simplex $\mathbf{S}_n$. Then $\hat{x}$ has eigenvalues*

$$\lambda_k(\hat{x}) = F_k(\hat{x}) - \sum_{j=1}^{n} \hat{x}_j F_j(\hat{x}) \tag{3.6}$$

for all k for which $\hat{x}_k = 0$. The corresponding eigenvectors point towards the corners $\mathbf{e}_k = (0, \ldots, 0, x_k = 1, 0, \ldots, 0)$ of the simplex.

These eigenvalues are called transversal. A rest point $\hat{x}$ is called saturated if all its transversal eigenvalues are non-positive. By definition an interior rest point does not have transversal eigenvalues, and is considered saturated by definition.

The stability analysis of replicator equations is complicated by the fact that only $n-1$ of the n eigenvalues of the Jacobian describe the dynamics on the simplex. The remaining n-th eigenvalue,

$$\lambda_n \;=\; -\Phi(\hat{x}) \;=\; -\sum_{j=1}^{n} \hat{x}_j \, F_j(\hat{x}) \;, \tag{3.7}$$

has no meaning for the dynamics on the simplex, $\Phi(x)$ being a nonspecific dilution flux. It describes the stability of the simplex $\mathbf{S}_n$ embedded in $\mathbb{R}^n$.

4. Analysis of the B-Cell Model

4.1. The Response Function

The rate of proliferation of B-cells in response to the field that they experience is determined by the response function $\tilde{f}(h)$. The response of B-cells to a ligand such as antigen that interacts in a specific manner with the receptors on the cell's surface is typically unimodal (*cf.* Celada, 1971; Dintzis *et al.*, 1982; Dintzis & Dintzis, 1988). That is small concentrations of ligand give little or no response, there is an optimal concentration that gives a maximal response, and higher concentrations give a diminished response. Weisbuch *et al.*, (1990) compared network behavior using a piecewise linear "tent shaped" response function and a "log-bell" shaped function, i.e., a function which is bell shaped when plotted versus $\log(h)$. Both functions gave similar qualitative behavior. Most subsequent work has utilized a log-bell shaped function that is symmetric around its maximum (*cf.*, De Boer & Perelson, 1991; Perelson & Weisbuch, 1992; De Boer *et al.*, 1992, 1993a,b,c) since such functions arise naturally from the physical chemistry of receptor cross-linking by bivalent ligands (Perelson & DeLisi, 1990). However, not all ligands are bivalent, and more than cross-linking is involved in activating lymphocytes into proliferation. Many other functions may underlie lymphocyte behavior. Here we shall not specify a particular function but rather examine the model for a class of functions which have the properties described below.

Definition. The response function $\tilde{f}$ fulfills:

(A1) $\tilde{f}$ is non-negative and has a unique maximum h_0.

(A2) $\tilde{f}$ is strictly monotonic on both sides of the maximum.

(B) $\tilde{f}(h_0 + h) = \tilde{f}(h_0 - h)$.

(T1) $\tilde{f}$ is continuous.

(T2) $\tilde{f}$ is differentiable wherever it is positive.

Conditions (A1) is generic for all B-cell models discussed above. Condition (A2) is generally true but in some models (*cf.*, Weisbuch *et al.*, 1990) $\tilde{f}$ is zero outside a window of values. The technical conditions (T1) and (T2) will be used in subsequent derivation. We consider them as quite natural regularity assumptions. Condition (B) ensures that the response functions that we examine are symmetric about their maximum. For technical reasons we do not consider response functions that are symmetric on a logarithmic scale.

4.2. Scaling of Variables

Before we proceed we rescale the response function $\tilde{f}$ such that it has its maximum at 0 and its range is the interval $[0, 1]$. We define

$$f(q) = \tilde{f}(h_0 + cq)/\tilde{f}(h_0)\,, \qquad q = (h - h_0)/c. \tag{4.1}$$

The new variable q is the rescaled field; with $\sum_i x_i = 1$ we obtain

$$q_k = \frac{1}{c}(h_k - h_0) = \sum_{j=1}^{n} \tilde{J}_{kj} x_j - h_0/c = \sum_{j=1}^{n} J_{kj} x_j\,, \tag{4.2}$$

with the rescaled coupling coefficients

$$J_{kj} = \tilde{J}_{kj} - h_0/c. \tag{4.3}$$

Note that the rescaled coupling coefficients depend not only on the topology of the network but also on the position of the maximum of the response function, h_0, relative to the total concentration of clones, c. Thus, systems with the same topology but different response functions may generate different rescaled systems.

Equation (2.6) can now be written in the form of a replicator equation

$$\dot{x}_k = x_k \left[f([Jx]_k) - \sum_{j=1}^{n} x_j f([Jx]_j) \right] \tag{4.4}$$

after a rescaling of the time axis by the factor $1/p$. An immediate consequence of the definition of the response function is the following

Lemma 2. *Suppose the conditions (A1), (A2), (T1), and (T2) hold. Then there exist differentiable functions*

$$\begin{aligned}\varphi_+ &: [0,1] \to [0,+\infty) \\ \varphi_- &: [0,1] \to (-\infty,0]\end{aligned} \tag{4.5}$$

such that $q = \varphi_\pm(f(q))$ for all q. We will refer to $\varphi_\pm$ as the "positive" and "negative" inverse of f, respectively.

In the reminder of this paper we will assume that the symmetry condition (B) is valid. In terms of the rescaled variables condition (B) becomes $f(q) = f(-q)$. The inverse functions thus fulfill $\varphi_-(f) = -\varphi_+(f)$. Because of this simple relation we can always use the positive inverse in our derivations. In order to simplify notion we will drop the subscript + in the following. Furthermore, we will use

$$\Phi(x) = \sum_{j=1}^{n} x_j f([Jx]_j) \tag{4.6}$$

for the nonspecific dilution flux.

4.3. Equilibria

Despite the (non-removable) *nonlinearity* of the growth rates $f(q_k)$ the problem of finding all rest points can be reduced to simple *linear* algebra.

We will frequently make use of the auxiliary vectors η_ℓ defined as follows: For $0 \le \ell < 2^n$, let η_ℓ be the n-dimensional sign vector that has the entry -1 in position j whenever the binary representation of ℓ contains 2^{j-1}, and entry $+1$ otherwise. For example, $\eta_0 = \mathbf{1}$ and $\eta_1 = (-1, 1, \ldots, 1)$.

Theorem 1. *Suppose f fulfills (A1), (A2), (B), (T1), and (T2). Then the isolated interior rest-points $\hat{x}$ of equation (4.4) are the points fulfilling the following three conditions for all $k = 1, \ldots, n$ and some $\ell = 0, \ldots, 2^n - 1$.*

(i) $\hat{x}_k = \dfrac{[\text{adj } J \cdot \eta_\ell]_k}{(\mathbf{1}, \text{adj } J \cdot \eta_\ell)}$.

(ii) $\hat{x}_k > 0$.

(iii) $(\eta_\ell)_k \cdot [J\hat{x}]_k \geq 0$.

Proof. Suppose $\hat{x}$ is an interior rest point of equation (4.4). Then for all k the components of $\hat{x}$ satisfy $f([J\hat{x}]_k) = \Phi(\hat{x})$. Applying the positive inverse φ of f to this equation we obtain

$$[J\hat{x}]_k = \begin{cases} \varphi(\Phi(\hat{x})) & \text{for} \quad [J\hat{x}]_k \geq 0 \\ -\varphi(\Phi(\hat{x})) & \text{for} \quad [J\hat{x}]_k < 0 \end{cases} \tag{4.7}$$

We can calculate the set of candidate rest points by the following procedure. Set $\phi = \varphi(\Phi(\hat{x}))$. Then any rest point has to fulfill $J \cdot \hat{x} = \phi \cdot \eta_\ell$ for some ℓ. Since ϕ is non-negative by definition, we have $(\eta_\ell)_k \cdot (J\hat{x})_k \geq 0$, i.e., condition (iii). Suppose that J is an invertible matrix (which is generically true). Then $\hat{x}_\ell$ is explicitly given by $\hat{x}_\ell = \phi \cdot J^{-1}\eta_\ell$. Since $\hat{x}$ has to fulfill $(\mathbf{1}, \hat{x}) = 1$, we find $\phi = (\mathbf{1}, J^{-1}\eta_\ell)^{-1}$. Using the well-known formula $A^{-1} = \text{adj}A/\det$ A, we obtain finally

$$\hat{x}_\ell = \frac{\text{adj}J \cdot \eta_\ell}{(\mathbf{1}, \text{adj}J \cdot \eta_\ell)}, \tag{4.8}$$

for each candidate point, i.e., condition (i). If J is not invertible, we have either no rest points or linear manifolds of rest points, contradicting the requirement that $\hat{x}$ is isolated (Hofbauer & Sigmund, 1988). Condition (ii) ensures that we take into account only rest points with non-negative concentrations. ∎

Corollary. Suppose J is a non-negative matrix. Then $\eta = \mathbf{1}$ for all rest points, i.e., the equilibria of (4.4) are the same as the equilibria of the second order replicator equation (3.3) with the same matrix of coefficient. In this case equation (4.8) coincides with the explicit representation of the rest points of the second order replicator equation (3.3), see Voigt (1989).

Corollary. Equation (4.4) has at most 2^{n-1} isolated interior equilibria. There may be one interior equilibrium for each choice of the sign vector η. Replacing η by $-\eta$, however, does not change $\hat{x}$, as is obvious from equation (4.8).

4.4. Stability of Equilibria

For corner-equilibria there is a very simple stability result:

Theorem 2. *A regular corner rest point* $\mathbf{e}_p$ *of equation (4.4) is stable if and only if* $|J_{kp}| > |J_{pp}|$ *for all* $k \neq p$.

Proof. All eigenvalues of a corner equilibrium are transversal, hence lemma 1 in section 3 immediately yields $\lambda_k(\mathbf{e}_p) = f(J_{kp}) - f(J_{pp})$. The proposition then follows from $f(z) = f(-z)$ and the fact that $f(z_1) > f(z_2)$ if and only if $|z_1| < |z_2|$. ∎

Remark. Recall that the rescaled coupling constants J_{ij} depend on h_0/c. For the 2-B cell network discussed in section (2.2), $\tilde{J}_{11} = \tilde{J}_{22} = 0$ and $\tilde{J}_{12} = \tilde{J}_{21}$. Thus, $J_{12} = 1 - h_0/c$ and $J_{11} = h_0/c$. Hence, assuming h_0 is positive, as one would expect for an immunological response function, the corner equilibria e_1 and e_2 are stable if and only if $0 \leq h_0/c < 0.5$.

It is interesting to notice that the question of the stability of equilibria reduces to simple linear algebra. We may restrict attention to the analysis of interior equilibria since the transversal eigenvalues are available explicitly as discussed in the previous section.

In order to reduce the number of variables to the actual dimension of our dynamical system, following Hofbauer (1981) we introduce the auxiliary variables

$$z_k = \frac{x_k}{x_n} \quad \text{for } x \in \operatorname{int} \mathbf{S}_n. \tag{4.9}$$

Instead of transforming equation (4.4) completely to the new variables z we will use a mixed form that is particularly convenient for investigating the stability of equilibria (see also Stadler & Stadler, 1991):

$$\dot{z}_k = z_k \Big[f([Jx(z)]_k) - f([Jx(z)]_n) \Big] \tag{4.10}$$

where $x(z)$ is given by the inverse of Hofbauer's transformation (4.9), i.e.,

$$x_j(z) = \frac{z_j}{\sum_{i=1}^n z_i} \quad \text{and} \quad z_n = 1. \tag{4.11}$$

In the following we will need

Lemma 3. *For $\ell \neq n$,*

$$\frac{\partial x_j}{\partial z_\ell} = x_n \cdot (\delta_{j\ell} - x_j) \tag{4.12}$$

for all $x \in S_n$ with $x_n \neq 0$ and $z \in I\!R_+^{n-1}$.

Proof. By differentiating equation (4.11) with respect to z_ℓ we find

$$\frac{\partial x_j}{\partial z_\ell} = \frac{1}{\sum_i z_i}\delta_{j\ell} - \frac{z_j}{(\sum_i z_i)^2} \cdot \sum_{i=1}^n \frac{\partial z_i}{z_\ell} = \frac{1}{\sum_i z_i} \cdot (\delta_{j\ell} - \frac{z_j}{\sum_i z_i}).$$

Using equation (4.11) again completes the proof. ∎

Theorem 3. *Let $\hat{x}$ be a rest point of equation (4.4) corresponding to the sign vector η. Let $\Delta(\hat{x})$ be the $(n-1) \times (n-1)$ matrix defined by*

$$\Delta_{kl}(\hat{x}) = -\hat{x}(\eta_k J_{kl} - \eta_n J_{nl}) \tag{4.13}$$

Then the stability of $\hat{x}_\eta$ is determined by the eigenvalues of $\Delta(\eta)$.

Proof. We have shown in the proof of theorem 1 that for an interior rest point $[J\hat{x}]_j = \eta_k \cdot \phi$, with some non negative constant ϕ. An immediate consequence of the fact that the response function is even is that

$$f([J\hat{x}]_j) = f(\phi) \quad \text{and} \quad f'([J\hat{x}]_j]) = \eta_j f'(\phi). \tag{4.14}$$

The fact that f has maximum implies $f'(\phi) \leq 0$. The Jacobian of the equivalent system (4.12) at the position $\hat{z}$ corresponding to $\hat{x}$ is thus given by

$$\frac{\partial z_k}{\partial z_\ell} = \hat{z}_k \Big[f'([J\hat{x}]_k) \sum_{j=1}^{n} J_{kj} \hat{x}_n (\delta_{j\ell} - \hat{x}_j) - f'([J\hat{x}]_n) \sum_{j=1}^{n} J_{nj} \hat{x}_n (\delta_{j\ell} - \hat{x}_j) \Big] =$$
$$= \hat{z}_k \hat{x}_n f'(\phi) \cdot \big[\eta_k (J_{k\ell} - \eta_k \phi) - \eta_n (J_{n\ell} - \eta_n \phi) \big] =$$
$$= \hat{f}'(\phi) \cdot \hat{x}_k \cdot (\eta_k J_{k\ell} - \eta_n J_{n\ell})$$

Using $f'(\phi) \leq 0$ completes the proof. ∎

Theorem 3 is a generalization of the following result for replicator equations of type (3.3) with a monotonically increasing response function g.

Lemma 4. *Let $g : [0,1] \to [0,1]$ be continuous and strictly monotonically increasing. Then the differential equations*

$$\dot{x}_k = x_k \big[g([Ax]_k) - \sum_{j=1}^{n} x_j g([Ax]_j) \big] \tag{4.15}$$

and the second order replicator equation (3.3) with the same matrix of coefficients A have the same rest-points. Furthermore the rest points have the same stability properties provided they are hyperbolic, otherwise they are non-hyperbolic in both models.

Proof. See Voigt (1989). Lemma 4 follows from the theorems 1 and 2 by noticing that $\eta = \mathbf{1}$ for all rest points and that $g'(\phi)$ is always positive. (A decreasing response function g instead of an increasing one would invert the stability properties.) ∎

Theorem 4. [Superposition Principle] *Suppose (A1), (A2), (B), (T1), and (T2) hold. Then we have independent of the actual choice of the response function f:*

(i) *The set of rest points of equation (4.4) is the union of the sets of equilibria of second order replicator equations (3.3) with matrices of coefficients $A_\eta = -\mathrm{diag}\,\eta \cdot J$.*

(ii) *The local stability of an isolated interior rest point coincides with the stability of the interior rest point of a second order replicator equation with coefficients A_η or $-A_\eta$, if $(A_\eta \hat{x})_k > 0$, or $(-A_\eta \hat{x})_k > 0$, respectively.*

(iii) *The stability result (ii) carries over to the non-transversal interior rest points of all subsystems. The stability of the transversal directions depends on the choice of f.*

Proof. This is an immediate consequence of Theorems 1 and 3, and the corresponding results for second order replicator equations (see, e.g., Hofbauer & Sigmund, 1988). ∎

4.5. Example 1: J is the identity matrix

In this and the next two sections we give examples of the use of the general results derived in sections (4.3) and (4.4). The examples we consider have not been chosen for their immunological relevance but rather because the second order replicator models with the corresponding interaction matrices J have been well studied. In the example given below, we let $J = I$, the $n \times n$ unit matrix. While this represents the simplest replicator system, and would appear to correspond to a set of n independent clones, recall that because of rescaling the corresponding B-cell model has a topology with $\tilde{J}_{ij}$ given by (4.3). Hence for $h_0/c \neq 0$, all clones interact at some base level and clones interact with themselves at a somewhat higher level. Thus, in this model interactions of clones with themselves dominate. Such interactions have been observed experimentally and antibodies that bind themselves have been called autobodies (Kang & Kohler, 1986).

The first corollary to theorem 1 implies $\eta = \mathbf{1}$ for all equilibria. Let $\hat{x}$ be an equilibrium with m surviving clones, $1 \leq m \leq n$. Then $\hat{x}_k = 0$ or $\hat{x}_k = \frac{1}{m}$, since $I\hat{x} = \phi$ implies that the concentrations of the surviving clones must be equal. In each m-clone subsystem the equilibrium is unique.

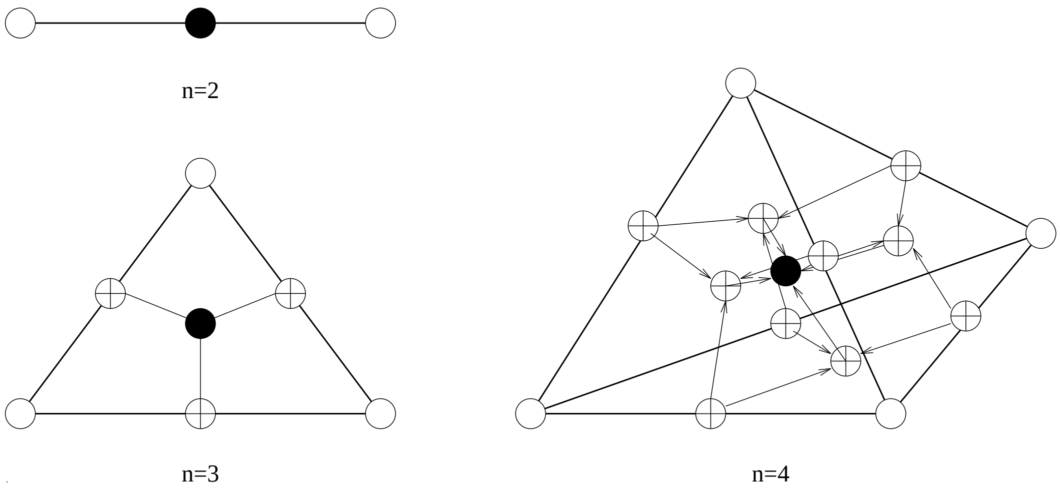

Figure 1: Example 1. The phase portrait looks like the time reversion of the Schlögl model (Schlögl, 1971, 1972). Sinks, saddles, and sources are denoted by $\bullet$, $\oplus$, and $\circ$, respectively.

Let us rename the clones such that the survivors are numbered 1 through m. The transversal eigenvalues, equation (3.6), become then

$$\lambda_k = f(0) - \sum_{j=1}^{m} \frac{1}{m} f(\frac{1}{m}) = 1 - f(\frac{1}{m}) > 0 \quad \text{for } m < k \leq n, \tag{4.16}$$

i.e., all transversal directions are unstable. Now consider the subsystem of the m surviving clones. It has the unique interior rest point $\hat{x} = \frac{1}{m}\mathbf{1} \in S_m$. A short calculation shows that the matrix $\Delta(\hat{x})$ responsible for the stability of $\hat{x}$ is given by $\Delta = -\frac{1}{m} \cdot I$, i.e., all its eigenvalues are negative. Hence the only stable rest point in the system is the interior rest point of the full system, since it has no transversal directions. All corners are sources, since they have only transversal eigenvalues. All other rest points are saddles, with the number of stable directions given by the number of non-vanishing clones. The total number of rest points in this system is $\sum_{m=1}^{n} \binom{n}{m} = 2^n - 1$, since there is exactly one equilibrium in each subsystem, and there are $\binom{n}{m}$ subsystems with m clones.

4.6. Example 2: Cyclic Network

Let $J_{ij} = \delta_{i,j+1}$, where $j+1$ is chosen modulo n. This is the analogue of the hypercycle (see Eigen & Schuster, 1977, 1978a,b, 1979). In immunology cyclic networks have been studied by Hiernaux (1977), but again some caution is needed in translating the results below into an immunological setting because of the difference between J_{ij} and $\tilde{J}_{ij}$. As a consequence of the first corollary of theorem 1 there are only rest points corresponding to the sign vector $\eta = \mathbf{1}$, i.e., the rest points of this B-cell model are the same as those of the hypercycle equation.

There are two types of edges in the model, "flowing" edges which do not contain rest points in their interior, and "non-flowing" edges which consist entirely of rest points (Schuster *et al.*, 1978; Stadler & Schuster, 1992). The flowing edges are exactly those that are consecutive along the cycle. The flow along the edge $(\mathbf{e}_k\text{-}\mathbf{e}_{k+1})$ runs towards $\mathbf{e}_k$ since the transversal eigenvalue $\lambda_{k+1}(\mathbf{e}_k) = f(1) - f(0) < 0$. The system hence behaves like a time-inverted hypercycle equation. For details see Aulbach & Flockerzi (1989).

4.7. Example 3

Let us consider the following toy model for $n = 3$ species.

$$J = \begin{pmatrix} 0 & \varepsilon & 1 \\ 1 & 0 & \varepsilon \\ \varepsilon & 1 & 0 \end{pmatrix} \tag{4.17}$$

For $\varepsilon = 0$ we recover the hypercycle type dynamics discussed in example 2. For second order replicator equations with $\varepsilon < 0$ we have a globally stable interior rest point, as in the hypercycle equation. This behavior is robust, i.e., it does not change under small perturbations of the interaction matrix J. In the B-cell model (4.4) the situation is different. The (time-reversed) hypercycle occurs for $\varepsilon = 0$, the phase portrait changes qualitatively, however, with an arbitrary small perturbation of ε (see Figure 2). Frequently, immune networks are modeled with a symmetric connection matrix. Thus, the case $\epsilon = 1$ is particularly relevant.

According to theorem 4 the dynamics can be viewed as a superposition of the second order replicator equations with interaction matrices J, $-J$,

$$J_{(-++)} = \begin{pmatrix} 0 & -\varepsilon & -1 \\ 1 & 0 & \varepsilon \\ \varepsilon & 1 & 0 \end{pmatrix} \tag{4.18}$$

the two permutations $J_{(+-+)}$ and $J_{(++-)}$ of $J_{(-++)}$, and the corresponding matrices $-J_{(-++)}$, $-J_{(+-+)}$, and $-J_{(++-)}$. See Figure 2 for details.

The characteristic parameters for the second order replicator equations with interaction matrices $-J_{(+++)}$ and $-J_{(-++)}$ are shown in the table below. See Stadler & Schuster (1990) for details.

Bifurcations occur for the following parameter values:

$$\begin{array}{rclc} \varepsilon_1 & = & 0 & J_{ij}J_{ji} = 0 \\ \varepsilon_2 & = & \frac{1-\sqrt{5}}{2} & \omega_2 = 0 \\ \varepsilon_3 & = & \frac{-1-\sqrt{5}}{2} & \omega_3 = 0 \\ \varepsilon_4 & = & -1 & \Delta = 0 \end{array} \tag{4.19}$$

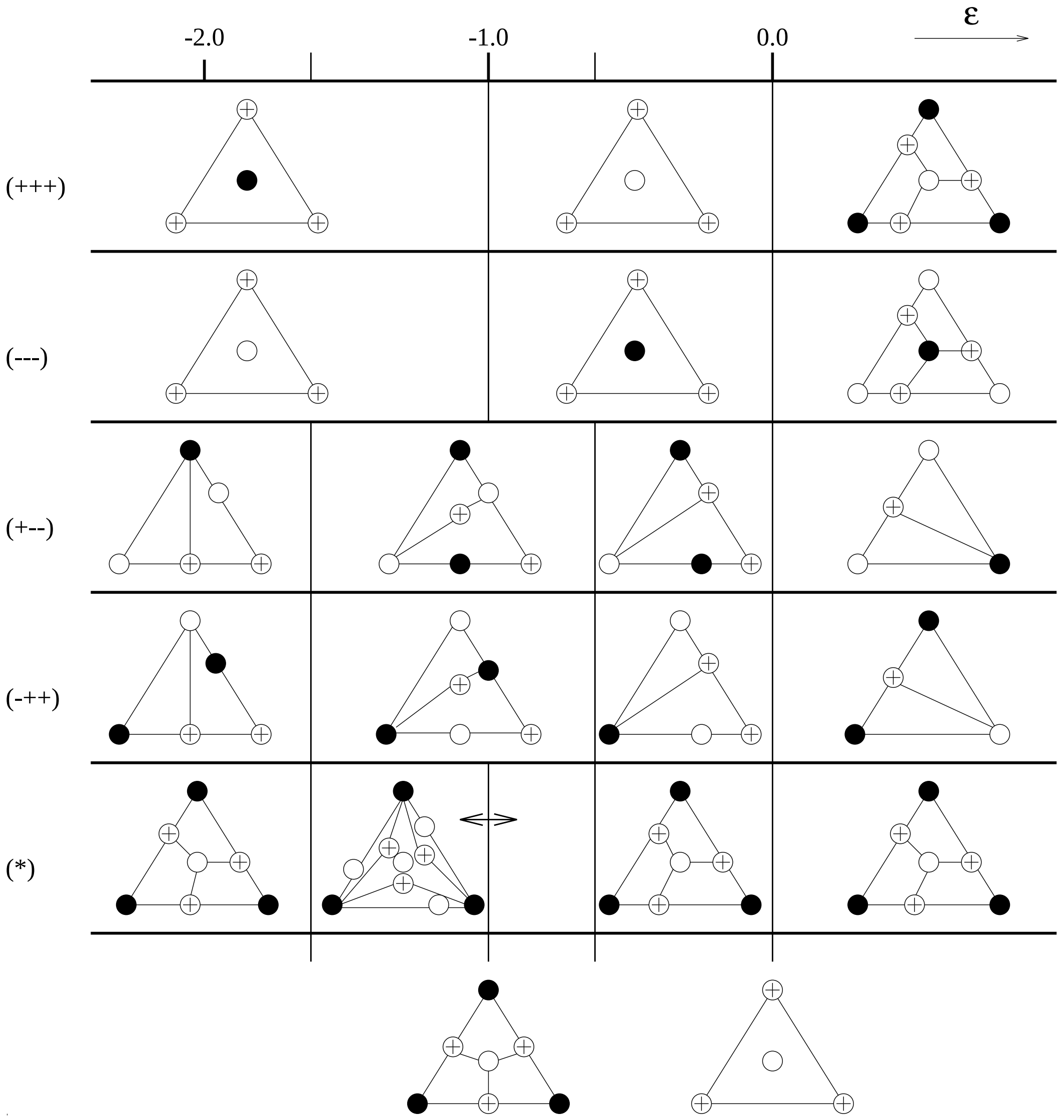

Figure 2: Phase Portraits (PP) of example 3, equation (4.17), and the corresponding second order replicator equations. The sign pattern η is indicated in each row. Whether a rest point has the stability given by the PP for η or $-\eta$ is decided by condition (iii) in theorem 3. Rows 3 and 4 gives only one of the three cases with sign pattern η=$(+--)$ and η=$(-++)$, since the missing cases are obtained by rotation. The last row shows the PP of equation (4.4). The PPs at the bifurcation points ε=0 and ε=-1 are indicated below the last row. Sinks, saddles, and sources are denoted by $\bullet$, $\oplus$, and $\circ$, respectively.

Table 1: Characteristic parameters of example 3. The dynamics of a three species second order replicator equation (3.3) can be completely understood in terms of the signs of the products $(a_{kj} - a_{jj})(a_{jk} - a_{kk})$, $k \neq j$, and the characteristic parameters $\Delta = \det A$ and ω_i, $i = 1, 2, 3$. For the details of the stability analysis see Stadler & Schuster (1990).

Parameter	$J_{(+++)}$	$J_{(-++)}$
ω_1	$\varepsilon^2 - \varepsilon + 1$	$-\varepsilon^2 - \varepsilon - 1$
ω_2	$\varepsilon^2 - \varepsilon + 1$	$\varepsilon^2 + \varepsilon - 1$
ω_3	$\varepsilon^2 - \varepsilon + 1$	$-\varepsilon^2 + \varepsilon - 1$
Δ	$\varepsilon^3 + 1$	$-\varepsilon^3 - 1$

Remark. The parameters ω_k are defined as $\omega_k = a'_{ki}a'_{ij} + a'_{kj}a'_{ji} - a'_{ij}a'_{ji}$ with k,j,i pairwise distinct and $a'_{ij} = a_{ij} - a_{jj}$. They are related to the transversal eigenvalues of rest points on edges as well as the coordinates of the interior rest point. An interior rest point, for example, exists if and only if all ω_k have the same sign. The parameters ω_k remain unchanged if J is replaced by -J. The interior rest point is a saddle if and only if the ω_k's are all negative. If they are positive, then the parameter Δ defines whether it is a source or a sink. Of course Δ changes its sign when A is replaced by $-A$.

At ε_1 rest points on the edges enter or leave the simplex. At ε_2 and ε_3 interior rest points enter or leave the simplex. At ε_4 the stability of interior equilibria changes.

The number of rest points in this example varies from 4 in the degenerate case of the hypercyclic coupling, $\varepsilon = -1$, to 10 for $\frac{-1-\sqrt{5}}{2} < \varepsilon < \frac{1-\sqrt{5}}{2}$ and $\varepsilon \neq -1$. For all other parameter values there are 7 rest points. We find at most three stable equilibria, and at most four sources.

5. Comparison with the Lotka-Volterra Type Model

We briefly review the properties of the Lotka-Volterra type model

$$\dot{y}_k = y_k(f(h_k(y) - h_0) - d) \tag{5.1}$$

The constant h_0 is the position of the maximum of the unscaled response function $\tilde{f}$. Here f is the scaled response function and thus has its maximum at 0.

The *virgin state* 0 is always a rest point. This is the major difference between the replicator and the Lotka-Volterra approach: in the replicator model the population size is constant, hence the virgin state cannot even be represented in the model. This not a serious disadvantage, however. The virgin state is stable only if $f(-h_0) = f(h_0) < d$. Otherwise the virgin state is repelling in all directions, since all transversal eigenvalues are equal. Said biologically, if the proliferation rate is greater than the death rate, all clones expand. In this unstable case the total concentration of B-cells is uniformly bounded from below, i.e., there is a positive constant m such that the total concentration of clones $c(t) > m$ for t large enough.

Let $\hat{y}$ be an interior rest point of the model (5.1), i.e., $\hat{y}_k > 0$ for all k. Then

$$\begin{aligned} d &= f\left(\sum_{j=1}^{n} J_{kj}\hat{y}_j - h_0\right) \\ \varphi(d) &= \eta_k \cdot [(J\hat{y})_k - h_0] \\ (J\hat{y})_k &= \eta_k\varphi(d) + h_0 \end{aligned} \tag{5.2}$$

In principle there may be equilibria for each sign vector η and hence there are at most 2^n interior rest points in a network of n clones. Note that for $h_0 = 0$ we recover essentially the results for the replicator model, since $\hat{y} = J^{-1}\eta_k\varphi(d)$ and by tranforming to relative concentrations we recover equation (4.8).

The stability of an equilibrium is given by the Jacobian

$$\frac{\partial \dot{y}_k}{\partial y_l}\Big|_{\hat{y}} = \hat{y}_k f'(h_k(\hat{y}) - h_0)J_{kl}\,. \tag{5.3}$$

Observing that $h_k(\hat{y}) - h_0 = \eta_k\varphi(d)$ this reduces to

$$\frac{\partial \dot{y}_k}{\partial y_l}\Big|_{\hat{y}} = f'(\varphi(d))\hat{y}_k\eta_k J_{kl}\,, \tag{5.4}$$

where we have used that the derivative f' of the even function f is odd. Observing that $f'(\varphi(d)) < 0$ since $\varphi(d) > 0$ by definition, we find that the stability of an interior equilibrium of (5.1) is completely described by the matrix

$$\Delta_{kl}(\hat{y}) = -\hat{y}_k \eta_k J_{kl} \,. \tag{5.5}$$

A superposition principle anlogous to theorem 4 holds for the Lotka-Volterra type system. Let

$$\begin{aligned} B_\eta &= -\mathrm{diag}(\eta) \cdot J \,, \\ r_\eta &= -h_0 \mathbf{1} - \varphi(d)\eta \,. \end{aligned} \tag{5.6}$$

Then the set of equilibria of (5.1) is the union of the set of equilibria of Lotka-Volterra equations (3.4) with the parameters defined by equation (5.6) for all sign vectors η. As for the replicator case in the previous chapter, all non-transversal eigenvectors of rest points of equation (5.1) are given by the non-transversal eigenvectors of these Lotka-Volterra equations as well. The main difference between both models is that the vector r_η (corresponding to the independent growth rates in a conventional Lotka-Volterra equation) depends on the actual form of the response function f (via the inverse φ of f).

6. Perturbation Analysis

Two other effects which have to be accounted for in realistic models of idiotypic networks are (i) the production of B-cells from the bone marrow and (ii) somatic mutations during maturation of the immune response (Kepler & Perelson, 1993).

Let us consider an ODE of the form

$$\dot{x}_k = x_k \left[F_k(x) - \sum_{j=1}^{n} x_j F_j(x) \right] + \varepsilon\, G_k(x) \,. \tag{6.1}$$

where F and G are continously differentiable on the simplex and both these functions and their derivatives are uniformly bounded on the simples. Furthermore, we require that $\sum_{k=1}^{n} G_k(x) = 0$ in order to ensure $\sum_k x_k = 1$ for all times.

Theorem 5. [Rest point migration]. *Suppose $G_k(x) > 0$ whenever $x_k = 0$, i.e., the vector field G is transversal to the boundary of the simplex and points inwards everywhere. Let $\hat{x}$ be a regular rest point of the unperturbed replicator equation ($\varepsilon = 0$). Then, for sufficiently small $\varepsilon > 0$,*

(i) *There is a neighborhood $U(\hat{x})$ of $\hat{x}$ such that there is a unique rest point $\hat{x}_\varepsilon \in U(\hat{x})$ of equation (6.1). For $\varepsilon \to 0$ we have $\hat{x}_\varepsilon \to \hat{x}$. $\hat{x}$ and $\hat{x}_\varepsilon$ have the same stability properties.*

(ii) *There are no other rest points of equation (6.1).*

(iii) *$\hat{x}_\varepsilon$ is in the interior of the simplex if and only of $\hat{x}$ is saturated, i.e., if all transversal eigenvalues of $\hat{x}$ are negative.*

Proof. See Stadler and Schuster (1992). ∎

We remark that an analogous result holds for limit cycle on the boundary: those with no unstable transversal eigenvalues move into the interior, all other limit cycles leave the state space, for sufficiently small $\varepsilon > 0$.

It is obvious that source terms in the B-cell model give rise to perturbations of the above form.

Mutations are described be means of a stochastic matrices Q: Q_{ij} is the frequency of mutation from species j to species i, and hence we have $\sum_i Q_{ij} = 1$. Including mutation terms explicitly in equation (4.4) we find

$$\dot{x}_k = \sum_{j=1}^{n} Q_{kj} f(q_j) x_j - x_k \cdot \Phi(x) , \qquad q_j = \sum_{i=1}^{n} J_{ji} x_i , \tag{6.2}$$

where the flow function $\Phi(x)$ is chosen such that $\sum x_i = 1$. We may rewrite this as

$$\dot{x}_k = x_k \big[f(q_k) - \sum_{j=1}^{n} f(q_j) x_j \big] + \sum_{j=1}^{n} \big[Q_{kj} f(q_j) x_j - Q_{jk} x_k f(q_k) \big] . \tag{6.3}$$

The first contribution corresponds to correct replication whereas the second contribution contains the mutations. Provided the matrix of mutation probabilities Q is irreducible the second term fulfills the conditions on the vector field G in the rest point migration theorem 5 (Stadler & Schuster, 1992).

7. Numerical Experiments

7.1. Random Networks

The structure of immune networks, specified by the matrix J, is difficult and maybe even impossible to determine experimentally. Various modeling approaches have been undertaken (reviewed in Perelson, 1992). One popular approach has been to assume that the network connections are random. Typically the strengths of the connections have been chosen to be 0 or 1 (*cf.*, Weisbuch *et al.*, 1990) or have a limited number of values between 0 and 1, e.g., 0, 0.1 and 1.0 (De Boer & Perelson, 1991). Here we shall take the connection strengths to be uniformly distributed random variables. For convenience we take these values between -1 and $+1$ but by appropriate scaling of the response function f, see section 4.2, we could also chose them between 0 and 1, as is more typical in the analysis of B-cell models.

Thus we shall consider the replicator model (4.4) with random matrices with entries being independent random variables

$$J_{ij} = U[-1;+1] + a_0 = U[-1+a_0;+1+a_0] \tag{7.1}$$

and a response function

$$f(q) = \exp(-q^2). \tag{7.2}$$

This response function is chosen as a typical example that fulfills postulates (A1), (A2), (B), (T1), and (T2).

Because we are studying the replicator form of the B-cell model rather than the B-cell model directly, the restriction that $\sum_j x_j = 1$, is significant.

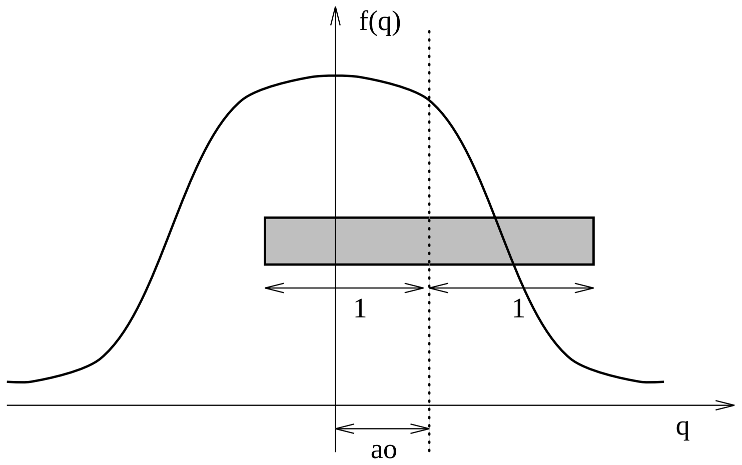

Figure 3: Range of the field and response function. The parameter a_0 measures the offset of the average connection matrix entry from the maximum of the response function. Choosing J_{ij} from a uniform distribution of width 2 implies that $|q(x)-a_0|\leq 1$ for all x. Hence the maximum of the response function f is in the accessible range only for $|a_0|\leq 1$.

In particular, field strengths will be limited since relative clone concentrations are less than or equal to 1 (see Figure 3). Thus, a point of interest is to determine how restrictions on typical field values effect the behavior of the system. In particular we shall examine the effect on the number of equilibria and their stability. Note that if we restrict the field values so that say only the positive part of f is sampled, then this analysis becomes equivalent to studying the number of rest points in system with monotonic response functions. Also, if the field mainly samples the positive part, then one might view this as being applicable to systems with nonsymmetric response functions, with say a long tail to the right as would be found when the log-bell response function is presented on a linear scale.

7.2. Number of Equilibria

Let us denote the expected number of equilibria in an n-clone system with parameter a_0 by $r(n; a_0)$. Symmetry of f ensures that $r(n; a_0) =$

$r(n; -a_0)$. Any model with $n-1$ clones is a subsystem of an n-clone model. The n-clone system hence contains all rest points of the subsystem and at least the equilibrium consisting only of the additional clone. Hence we have $r(n; a_0) \geq r(n-1; a_0) + 1$.

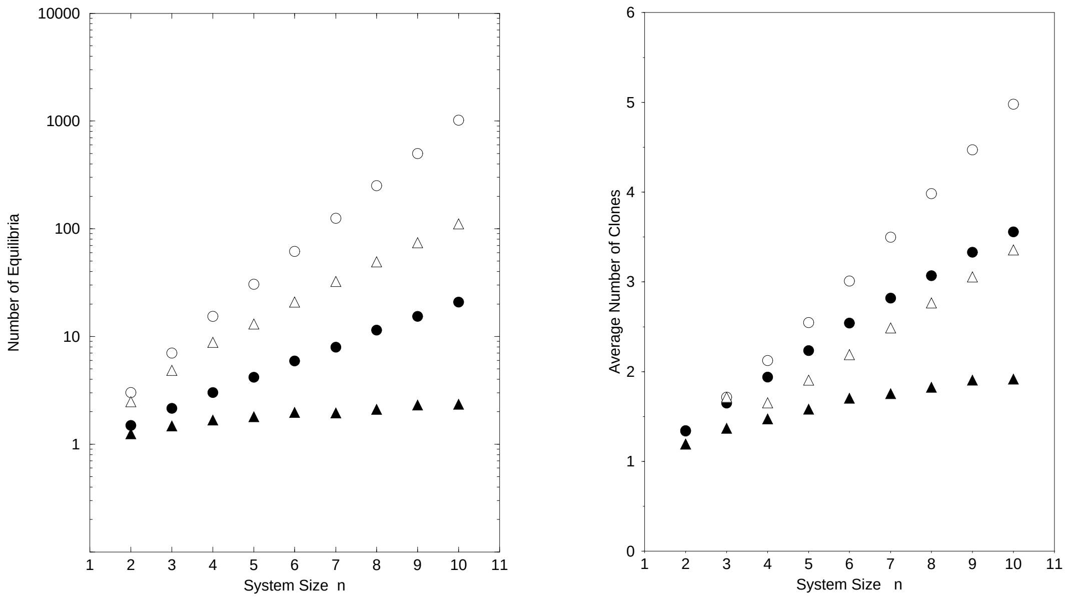

Figure 4: a) Number of equilibria (open symbols) and stable equilibria (filled symbols) for a_0=0, ○, and a_0=2, △.
b) Average number of clones in equilibrium states.

For $a_0 = 0$ we have the following naive estimate for the number of rest points $r(n; 0)$. There are $\binom{n}{m}$ faces of the n-simplex with m nonzero coordinates, for each of them there are 2^{m-1} choices of the sign vector η. The chance to find an interior rest point of a second order replicator equation with m species is $1/2^{m-1}$, since it is equivalent to a Lotka-Volterra equation with $m-1$ species for which there is a chance of $1/2$ for each coordinate being positive (see Stadler & Happel, 1993). Thus we should find on average 1 rest point per face and $\sum_{m=1}^{n} \binom{n}{m} = 2^n - 1$ rest points for the entire system. This is not a rigorous derivation, since we have assumed that the equilibria are

Table 2: Empirical number of rest points. All data are obtained by averaging over 1000 systems. $a_0 = 0$ means that the distribution of coupling constants J_{kl} is centered at the maximum of the response function, while $a_0 = 2$ implies that in the accessible range the response function is monotonic.

n	$r(n;a_0)$	$s(n;a_0)$
$a_0 = 0$		
2	3.016	1.495
3	7.013	2.157
4	15.390	3.016
5	30.511	4.172
6	61.774	5.918
7	124.920	7.947
8	251.475	11.445
9	497.979	15.398
10	1017.859	20.860
$a_0 = 2$		
2	2.480	1.246
3	4.839	1.475
4	8.080	1.676
5	13.043	1.797
6	20.853	1.967
7	32.398	1.951
8	49.157	2.101
9	74.291	2.306
10	110.718	2.354

mutually independent, which, of course is not strictly true. The numerical data,

$$r(n;0) \sim 2^n - 1, \tag{7.3}$$

are consistent with the above estimate even for very small $n = 2, 3$.

We expect fewer rest points as $|a_0|$ increases. In fact, as $a_0 > 1$ for all $x \in \mathbf{S}_n$ we have $[Jx]_k > 0$. Thus equation (4.4) becomes *de facto* a replicator equation with monotonous growth function, and we expect the number of equilibria to become independent of a_0. Again the numerical data,

$$r(n;a_0) \sim 1.54^{n-1}, \qquad |a_0| > 1\,, \tag{7.4}$$

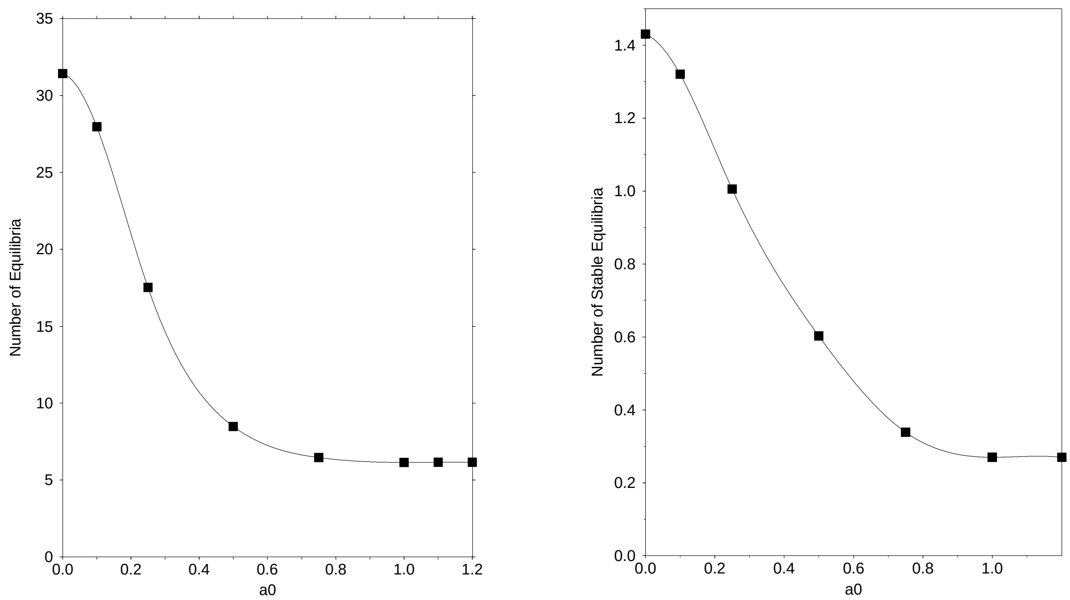

Figure 5: Number of all equilibria (left) and stable equlibria (right) as a function of a_0 for n=8. The solid lines are spline fits to the numeric data.

with a correlation coefficient $\rho = 0.9996$ from the data for $n = 5 \ldots 10$, are consistent with such a behaviour.

Denote the number of stable equilibria by $s(n; a_0)$. From our numerical experiments this number seems to scale exponentially for $a_0 = 0$,

$$s(n; 0) \sim 0.8 \cdot 1.390^n \tag{7.5}$$

for $n = 2 \ldots 10$ with a correlation coefficient $\rho = 0.9997$. For $|a_0| \leq 1$, however, it grows even slower than linear and may even saturate at $\mathcal{O}(1)$.

7.3. Number of Clones in an Equilibrium

Trivially, there are exactly n single-clone-equilibria in each network, since the corners of the simplex are invariant. We find numerically that for $a_0 = 0$ there is on average 1.0 stable corner, i.e., a stable state consisting of only single clone. This result is independent of the system size n.

In the more conventional models (Weisbuch *et al.*, 1990) it is assumed that $\tilde{J}_{ij} \geq 0$, and that the self-interations vanish, i.e., $\tilde{J}_{ii} = 0$, instead of being chosen randomly as in our numerical experiments. Single clone equilibria do not exist in this case. In fact, the smallest equilibria consist then of pairs of interacting clones, with one clone providing the field for the other member of the pair. In the replicator model with random matrices, J_{ij}, as given by equation (7.1), this corresponds to setting $J_{ii} = a_0 - 1$, which is the smallest possible value. If $a_0 = 0$, it follows immediately from theorem 2 that all transversal eigenvalues are non-negative, since $|J_{kp}| \leq 1$ is always true. Hence by theorem 5 an arbitrarily small influx term drives these rest points into the unphysical exterior of the simplex. When a_0 increases some transversal eigenvalues become stable. Still influx or mutation will move such an equilibrium out of the simplex as long as there is at least one unstable direction. If $a_0 > 1$, however, theorem 2 ensures that all transversal eigenvalues are negative, and the rest points in the corners are stable. In this case influx or mutation terms push them into the interior of the simplex.

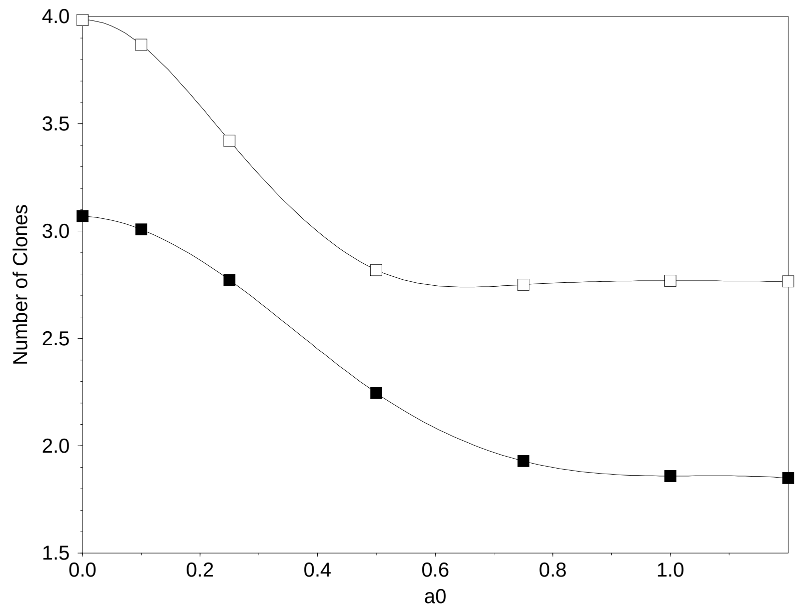

Figure 6: Average number of clones in all equilibria (open symbol) and stable equlibria (filled symbol). The solid lines are spline fits to the numerical data.

The number of interior equilibria, i.e., of rest points with all clones present, decreases slowly from 1 to about 0.55 when n increases from 2 to 10 for $a_0 = 0$. For $|a_0| \geq 1$ their number decreases roughly as $1/2^{n-1}$ as expected for second order replicator equations (Stadler & Happel, 1993).

The average number of clones in equilibrium states seems to rapidly approach $n/2$, i.e., on average half of the clones of the initial network are present, the other 50% vanish. If one considers stable equilibria only, the number of clones in equlibrium is smaller, but still seems to approach a constant proportion of the original network. The data shown in Figure 4b indicate that roughly one third of the original clones survives on average for $a_0 = 0$. For the extreme case of a monotonic response function in the accessible range, i.e., for $|a_0| > 1$, however, the number of clones in stable equilibria may well saturate at a constant of the order of 2.0.

8. Conclusions

Analyzing the behavior of large networks is a difficult task. Here we have shown how one can exploit a relationship between B-cell network models and second degree replicator equations to take advantage of many existing mathematical techniques and results. Replicator equations differ from the usual network models studied in immunology in that they require that the total concentration of clones in the network be held constant. This is equivalent to requiring that the total number of B cells involved in network activity be constant. Experiments in germ-free mice have shown that a relatively constant proportion of B cells remain activated, and thus it is plausible that mechanisms exist which control the number of B cells involved in network activity. Coutinho (1989) in fact has suggested that the immune system is composed of two parts, a central immune system in which network activity is localized and a peripheral immune system. Estimates have suggested that about 20% of the immune system may be in the central part. If this is in fact the case, then models in which the total size of the network compartment is constrained may be relevant to immunology. In addition to incorporating the constaint of network size, the replicator formulation brings to bear powerful mathematical machinery. We have shown that the dynamics of B-cell networks can — to a certain extent — be understood as the superposition of a large number (2^n) of second order replicator equations.

One feature that distinguishes immune network models from neural network models is that the response function, $f(h)$, which determines the fraction of lymphocytes that proliferate in response to a given field, h, is unimodal, having a single maximum, rather than being monotonically increasing. We have studied the case in which f is not only unimodal but also symmetric. For technical reasons, we have restricted our attention to the case in which this symmetry is seen when f is expressed as a function of h rather than $\log h$. In many models (cf. De Boer & Perelson, 1991; De Boer et al., 1993a,b,c) f is chosen to be symmetric on a log scale, but as has been shown by Weisbuch et al. (1990) symmetry in h or $\log h$ gives rise to similar dynamical behavior.

Using the replicator approach, we have shown when the response function f is unimodal in the range of possible fields, the network has a large variety of stable equilibrium states. Typically, in such a stable state a substantial fraction, about one third, of the total number of clones in the network will be non-zero. As the maximum of the response function f is shifted away from the typical values for the fields of most clones, the network looses its robustness and the majority of clones will be extinct.

The above results have been obtained by performing a complete analysis of all rest points for a replicator equation with an even response function connecting the field and the growth rate of a clone. For such a model we have shown that the problem of finding all the rest points of the non-linear system reduces to solving linear equations. Simulation of the dynamical systems by integrating the differential equations could not provide the data presented above because the number of stable equilibria can be very large even in moderate size systems.

Studying the number of equilibria and their stability is of considerable importance in understanding the role of networks in the immune system. As in Hopfield type neural networks (cf. Hopfield, 1982; Hertz et al., 1990), it has been proposed that state states of networks could encode memories of past encounters with antigen (cf. Weisbuch et al., 1990; Weisbuch & Opera, 1994). Thus the number of stable steady states that a network possess places a contraint on the memory capacity of a network. Alternatively, as proposed by Coutinho, networks may not be involved in immune responses. If the memory capacity of a network is small then it most likely would not be useful for storing information about past encounters with antigen, it might however still be useful in self–nonself discrimination and in regulating serum antibody levels, number of lymphocytes, completeness of the repertoire, etc. De Boer & Perelson (1991) show how networks that operate in a non-steady state manner can explain many of the observed global properties of immune systems. Rose & Perelson (1993) show how networks operating in an oscillatory regime may play a role in antigen elimination and short-term memory. These various studies, as well as the one presented here, help define the potential role of networks in immunology.

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References

- Aulbach, B. and D. Flockerzi. 1989. The past in short hypercycles. *J. Math. Biol.* **27**, 223–231.
- Boutet de Monvel, J. H. and O. C. Martin. 1994. Memory capacity in large idiotypic networks. *Bull. Math. Biol.* (submitted).
- Celada, F. 1971. The cellular basis of immunological memory. *Prog. Allergy* **15**, 223–267.
- Coutinho, A. 1989. Beyond clonal selection and network. *Immunol. Rev.* **110**, 63–87.
- Dawkins R. 1976. *The Selfish Gene.* Oxford University Press, Oxford UK.
- De Boer, R.J. 1988. Symmetric idiotypic networks: connectance and switching, stability, and suppression. In *Theoretical Immunology*, Part Two, SFI Studies in the Science of Complexity, Vol. III. A.S. Perelson (Ed.), pp. 265–289. Redwood City CA: Addison-Wesley.
- De Boer, R.J. and P. Hogeweg. 1989. Memory but no suppression in low-dimensional symmetric idiotypic networks. *Bull. Math. Biol.* **51**, 223–246.
- De Boer, R.J. and A.S. Perelson. 1991. Size and connectivity as emergent properties of a developing immune network. *J. Theor. Biol.* **149**, 381–424.

- De Boer, R.J., L.A. Segel and A.S. Perelson. 1992. Pattern formation in one and two dimensional shape space models of the immune system. *J. Theor. Biol.* **155**, 295–333.
- De Boer, R.J., A.U. Neumann, A.S. Perelson, L.A. Segel and G. Weisbuch. 1993a. Recent approaches to immune networks. In *Mathematics Applied to Biology and Medicine*. J. Demongeot and V. Capasso (Eds). Winnipeg, Canada: Wuerz (in press).
- De Boer, R.J., A.S. Perelson and I.G. Kevrekidis. 1993b. Immune network behavior I. From stationary states to limit cycle oscillations. *Bull. Math. Biol.* **55**, 745–780.
- De Boer, R.J., A.S. Perelson and I.G. Kevrekidis. 1993c. Immune network behavior I. From oscillations to chaos and stationary states. *Bull. Math. Biol.* **55**, 781–816.
- Dintzis, R.Z., B. Vogelstein and H.M. Dintzis. 1982. Specific cellular stimulation in the primary immune response: Experimental test of a quantized model. *Proc. Natl. Acad. Sci. USA* **79**, 884–888.
- Dintzis, H.M. and R.Z. Dintzis. 1988. A molecular basis for immune regulation: The immunon hypothesis. In *Theoretical Immunology, Part One*. A.S. Perelson, ed. Reading, MA: Addison-Wesley, pp. 83–103.
- Eigen, M. and P. Schuster. 1977. The hypercycle: A principle of natural selforganisation. Part A: Emergence of the hypercycle. *Naturwissenschaften* **64**, 541–565.
- Eigen, M. and P. Schuster. 1978a. The hypercycle: A principle of natural selforganisation. Part B: The abstract hypercycle. *Naturwissenschaften* **65**, 7–41.
- Eigen, M. and P. Schuster. 1978b. The hypercycle: A principle of natural selforganisation. Part C: The realistic hypercycle. *Naturwissenschaften* **65**, 341–369.

- Eigen, M. and P. Schuster. 1979. *The Hypercycle.* Berlin: Springer-Verlag.
- Fisher, R.A. 1930. *The Genetical Theory of Natural Selection.* Oxford: Claredon Press.
- Hertz, J., A. Krogh, and R.G. Palmer. 1990. *Introduction to the Theory of Neural Computation*, Addison-Wesley, Redwood City, CA.
- Hiernaux, J. 1977. Some remarks on the stability of the idiotype network. *Immunochem.* **14**, 733–739.
- Hofbauer, J. 1981. On the occurrence of limit cycles in Lotka Volterra equations. *Nonlin. Analysis* **5**, 1003–1007.
- Hofbauer, J. and K. Sigmund. 1988. *The Theory of Evolution and Dynamical Systems.* Cambridge: Cambridge University Press.
- Hofbauer, J., J. Mallet-Paret and H.L. Smith. 1991. Stable periodic solutions for the hypercycle system. *J. Dynamics Diff. Eqns.* **3**, 423–436.
- Hopfield, J. J. 1982. Neural networks and physical systems with emergent collective computational abilities. *Proc. Natl. Acad. Sci. USA* **79**, 2554–2558.
- Jerne, N.K. 1974. Towards a network theory of the immune system. *Ann. Immunol. (Inst. Pasteur)* **125C**, 373–389.
- Kang, C.-Y. & H. Köhler. 1986. Immunoglobulin with complementary paratope and idiotope *J. Exp. Med.* **163**, 787–796.
- Kepler, T.B. and A.S. Perelson. 1993. Somatic hypermutation in B cells: An optimal control treatment. *J. Theor. Biol.* **164**, 37–64.
- Perelson, A.S. and C. DeLisi. 1980. Receptor clustering on a cell surface I. Theory of receptor cross-linking by ligands bearing two chemically identical functional groups. *Math. Biosc.* **48**, 71–110.
- Perelson, A.S. 1988. Toward a realistic model of the immune system. In *Theoretical Immunology, Part Two, SFI Studies in the Sciences of Complexity*, A.S. Perelson (Ed.), pp. 377-401. Reading, MA: Addison-Wesley.

- Perelson, A.S. 1989. Immune network theory. *Immunol. Rev.* **110**, 5–36.
- Perelson, A.S. 1992. Mathematical approaches to immunology. In *Theory and Control of Dynamical Systems: Applications to Systems in Biology*, S.I. Andersson, Å.E. Andersson, and U. Ottoson (Eds.), pp. 200–230. Singapore: World Scientific.
- Perelson, A.S. and G. Weisbuch. 1992. Modeling immune reactivity in secondary lymphoid organs. *Bull. Math. Biol.* **54**, 649–672.
- Rose, R. and Perelson, A. S. (1993). Immune networks and immune responses. In *Frontiers in Mathematical Biology*, S. Levin, ed., *Lect. Notes Biomath.* **100** (in press).
- Schlögl, F. 1971. On thermodynamics near steady states. *Z. Phys.* **248**, 446–458.
- Schlögl, F. 1972. Chemical reaction models for non-equilibrium phase transitions. *Z.Phys.* **253**, 147–161.
- Schnabl, W., P.F. Stadler, C. Forst and P. Schuster. 1991. Full characterization of a strange attractor. Chaotic dynamics on low-dimensional replicator systems. *Physica D* **48**, 65–90.
- Schuster, P., K. Sigmund and R. Wolff. 1978. Dynamical systems under constant organization I: Topological analysis of a family of non-linear differential equations – A model for catalytic hypercycles. *Bull. Math. Biol.* **40**, 743–769.
- Schuster, P. and K. Sigmund. 1983. Replicator dynamics. *J. Theor. Biol.* **100**, 533–538.
- Smale, S. 1976. On the differential equations of species competition. *J. Math. Biol.* **3**, 5–7.
- Stadler, P.F. and R. Happel. 1993. The probability of permanence. *Math. Biosc.* **113**, 25–50.

- Stadler, P.F. and P. Schuster. 1990. Dynamics of small autocatalytic reaction networks I. Bifurcations, permanence, and exclusion. *Bull. Math. Biol.* **52**, 485–508.
- Stadler, P.F. and P. Schuster. 1992. Mutation in autocatalytic reaction networks. *J. Math. Biol.* **30**, 597–631.
- Stadler, B.M.R. and P.F. Stadler. 1991. Small autocatalytic reaction networks III. Monotone growth functions. *Bull. Math. Biol.* **53**, 469–485.
- Varela, F.J. and A. Coutinho. 1991. Second generation immune networks. *Immunol. Today* **12**, 159–166.
- Voigt, H.M. 1989. *Evolution and Optimization.* Berlin: Akademie-Verlag.
- Weisbuch, G., R.J. DeBoer and A.S. Perelson. 1990. Localized memories in idiotypic networks. *J. Theor. Biol.* **146**, 483–499.
- Weisbuch, G. and M. Oprea. 1994. Capacity of a model immune network. *Bull. Math. Biol.* (submitted).