A Cayley Tree Immune Network Model
with Antibody Dynamics

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ABSTRACT

A Cayley tree model of idiotypic networks that includes both B cell and antibody dynamics is formulated and analyzed. As in models with B cells only, localized states exist in the network with limited numbers of activated clones surrounded by virgin or near-virgin clones. The existence and stability of these localized network states are explored as a function of model parameters. As in previous models that have included antibody, the stability of immune and tolerant localized states are shown to depend on the ratio of antibody to B cell lifetimes as well as the rate of antibody complex removal. As model parameters are varied, localized steady-states can break down via two routes: dynamically, into chaotic attractors, or structurally into percolation attractors. For a given set of parameters, percolation and chaotic attractors can coexist with localized attractors, and thus there do not exist clear cut boundaries in parameter space that separate regions of localized attractors from
regions of percolation and chaotic attractors. Stable limit cycles, which are frequent in the two-clone antibody B cell (AB) model, are only observed in highly connected networks. Also found in highly connected networks are localized chaotic attractors. As in experiments by Lundkvist et al. (1989), injection of $Ab_1$ antibodies into a system operating in the chaotic regime can cause a cessation of fluctuations of $Ab_1$ and $Ab_2$ antibodies, a phenomenon already observed in the two-clone AB model. Interestingly, chaotic fluctuations continue at higher levels of the tree, a phenomenon observed by Lundkvist et al. but not accounted for previously.
1. INTRODUCTION

Jerne (1974) postulated that the immune system functions as a network, where lymphocytes are stimulated or suppressed by “idiotypic” interactions with complementary antibodies and immunoglobulin receptors. Since then, experimental evidence of an active immune network has been found (Holmberg et al., 1984; Kearney and Vakil, 1986; Lundkvist et al., 1989). Several theories have been advanced for a biological function of this idiotypic network, among them is the idea that immunological memory is a dynamic consequence of network interactions (Hoffmann, 1975; Richter, 1975; Farmer et al., 1986; Weisbuch, 1990; Weisbuch et al., 1990; Behn et al., 1992). Under the “dynamic memory hypothesis” after initial antigen exposure, an expanded, neutralizing clonal population is sustained through network interactions with idiotypically related clones. Mathematical models have been formulated to make these ideas more precise (for reviews see Perelson, 1989; Varela and Coutinho, 1991; and De Boer et al., 1992a).

Immune network models can be classified by the degree of complexity with which they model (i) the structure of network connectivity and (ii) the dynamics of individual clonal species. Network structure has been modeled with varying degrees of realism.

The simplest model structure describes the dynamics of a pair of complementary B cell clones. We refer to this class as “two-clone models”. Variations of these models have been studied extensively (Perelson, 1989; De Boer et al., 1990; Stewart and Varela, 1990). (A rigorous dynamical analysis of two-clone models - under a variety of assumptions for clonal dynamics - is given by De Boer, Kevrekidis and Perelson (1993a,b).) Two-clone models have the advantage of mathematical tractability and shed light on the dynamics of clonal populations as a function of model assumptions and parameters. But, they are insufficient for investigations of the effects of network structure on dynamical behavior.

The next level of model complexity introduces network connectivity. This has been done in two ways. One method prescribes the network structure using static, a priori connectivity assumptions. For example, Cayley tree models assume a uniform connectivity structure (Weisbuch et al., 1990). Other models prescribe a network structure based on experimentally known interactions (Stewart and Varela, 1989).
or assume random connectivity matrices (Hoffmann, 1982; Spouge, 1986; De Boer, 1988). The second method allows network connectivity to develop from assumptions of affinity matching rules, which in turn, determine idiotypic interactions. This class of models includes bit-string models (Farmer et al., 1986; De Boer and Perelson, 1991; Celada and Seiden, 1992), as well as other shape-space models (Segel and Perelson, 1988, 1989; Weinand, 1990; Weisbuch, 1990; Stewart and Varela, 1991; De Boer et al., 1992b).

In this study, we analyze one type of prescribed network model: a homogeneous Cayley tree model. Previous models of this class modeled B cell populations but not their corresponding antibodies (Weisbuch et al., 1990; Neumann and Weisbuch, 1992a,b). It was shown that in certain parameter ranges, this model possesses localized steady-states, where a large population at one level could be sustained by idiotypic interactions with small or intermediate populations of clones at the next level, and neighboring clones in the network would remain virgin or near-virgin. For example, if antigen is assumed to only interact with the level 1 clone, then a localized state occurs when the second level populations are not high enough to stimulate proliferation of third level populations. These localized states were presented as models of immune network “memory” or “tolerance”, depending upon whether the field at level 1 was low or high.

In their analysis of two-clone models, De Boer et al. (1993a,b) show that when antibody dynamics are included, what would be stable system attractors in a simple B cell model may become oscillatory or chaotic, depending on parameter values. Here, we investigate the effect of antibody dynamics on the stability of states in a Cayley tree model. We call this model the “AB Tree model”, where AB stands for antibody and B cell dynamics, and Tree stands for the Cayley tree topology.

We show that the addition of antibody dynamics does not substantially alter the steady-states observed in the work of Weisbuch and colleagues and that isolated, non-oscillatory states are readily obtained. We derive conditions for the existence and stability of these localized states and perform bifurcation analyses on the model. As network connectivity is increased, localized steady-states disappear and only chaotic attractors and nonlocalized steady-states remain. Non-localized
steady-states are referred to as “percolation” attractors. They are states in which alternating levels of clones are activated throughout the network. As dynamical parameters (such as the ratio of the antibody death rate or complex removal rate to the B cell death rate) are decreased, stable localized steady-states lose stability and trajectories approach what appear to be chaotic attractors. These attractors, as is the case with percolation attractors, generally do not remain localized in the network, and signals eventually propagate through successive levels of the network. Information about initial conditions is generally lost in both of these attractors and there is no way to know which level was originally stimulated. However, we do find localized chaotic attractors and limit cycle behavior in parameter regimes characterized by high connectivity. Nevertheless, if real immune systems operate in parameter domains characterized by nonlocalized behavior, it would be difficult to see how they could account for dynamical memory. Finally, we will discuss other limitations of this approach toward understanding immune network behavior.

2. THE AB Tree MODEL

We consider individual B cell clones which are formed in the bone marrow, proliferate in response to stimulation, and die in the periphery. The corresponding antibodies are secreted by the B cells in response to stimulation, decay in the periphery, and are actively removed or inactivated by complex formation with other antibodies. Following previous work (Weisbuch et al., 1990; Varela and Coutinho, 1991; Perelson, 1989; De Boer and Perelson, 1991), we assume for each clone $i$, the total amount of idiotypic stimulation is a linear combination of the concentration of antibodies of all other clones $j$. The amount of stimulation detected by a clone $i$ is referred to as it’s field, $h_i$:

$$h_i = \sum_j J_{ij} a_j,$$  

where $J_{ij}$ is the affinity between clone $i$ and the antibodies of clones $j$ and $a_j$ is the concentration of antibody $j$. We assume $J_{ij} = 0$ (no interaction) or $J_{ij} = 1$ (maximum affinity). Without loss of generality one can make the maximum affinity any real positive number, $K$, rather than 1, however for reasons of simplicity we choose $K = 1$.

Network structure is determined by this affinity, or connectivity matrix.
Proliferation of B cell clones and antibody secretion rates are a function of their stimulation. In this model, we use a phenomenological biphasic activation function:

\[ f(h_i) = \frac{h_i}{(\theta_1 + h_i)} \frac{\theta_2}{(\theta_2 + h_i)} . \]  

(2.2)

where \( \theta_2 \gg \theta_1 \). The maximum activation level is close to 1 and occurs at the intermediate field strength, \( h = \sqrt{\theta_1 \theta_2} \). The use of this function has theoretical and experimental justification and has been used extensively in immune system models (Varela and Coutinho, 1991; Perelson, 1989; De Boer and Perelson, 1991; De Boer et al., 1992a,b, 1993a,b). Activation is thought to be proportional to the proportion of surface immunoglobulin that is crosslinked. Biophysical models of receptor crosslinking of bivalent ligands predict a symmetric, log bell-shaped crosslinking curve (Perelson and DeLisi, 1980); furthermore, antibody production follows a similar empirical dose-response curve (Celada, 1971).

We model the population change of clone \( i \) with a pair of differential equations representing the B cells \( b_i \) and the concentration of their antibodies \( a_i \):

\[ \frac{d b_i}{d t} = m + p f(h_i) b_i - d_B b_i , \]

\[ \frac{d a_i}{d t} = s f(h_i) b_i - d_A a_i - d_C a_i h_i , \]  

(2.3)

where \( f \) is the activation function, \( m \) is the bone marrow source rate, and \( d_B \) is the B cell death rate. The proliferation parameter, \( p \), must be such that when B cells are stimulated, their growth rate exceeds their death rate or else no clonal expansion would occur; thus,

\[ p > d_B . \]  

(2.4)

Parameters in the antibody equations are \( s \), the secretion rate, \( d_A \), the antibody decay rate, and \( d_C \), the rate of complex formation and removal. The parameter \( d_C \) is a combination of several physical parameters, e.g. \( d_C = \hat{d}_c v^2 K \), where \( \hat{d}_c \) is the rate of complex elimination by macrophages and phagocytic cells, \( v \) is the valence of the antibody, and \( K \) is the affinity of the idiotype for anti-idiotypic antibodies (De Boer et al., 1993a,b).

In two-clone models, the fields \( h_1 \) and \( h_2 \) are simply the complementary antibody populations \( a_2 \) and \( a_1 \), respectively. In the Cayley-tree model, the fields
incorporate a branching network structure where each clone is connected to \( z \) other clones (see Fig. 1). The parameter \( z \) is called the coordination number of the Cayley tree. The field for the root, or first level clone, is then

\[
h_1 = za_2 ,
\]

(2.5)
since the clone at level 1 interacts with \( z \) clones at level 2. If antigen is present, it is assumed to react only with the clone at level 1, and the field becomes

\[
h_1 = za_2 + Ag ,
\]

(2.6)
where \( Ag \) represents the effective antigen concentration (the actual antigen concentration, multiplied by it's valence and affinity). In fact, this property of antigen reactivity defines level 1. Note that in this model, all antibodies at a given level are treated equivalently. The state variables \( b_i \) and \( a_i \) thus represent a single B cell or antibody population, which is the same for all populations at a given level. All subsequent clones experience a field:

\[
h_i = a_{i-1} + (z - 1)a_{i+1} , \quad i > 1 , \quad z \geq 2 .
\]

(2.7)

### 2.1 Parameter Values

Previous modeling studies have provided estimates for the model parameters (Varela and Coutinho, 1991; De Boer and Perelson, 1991; De Boer et al., 1993a,b). Briefly, typical parameter estimates are as follows: Due to cell division at the pre-B cell stage, each clone will consist of approximately 10-20 cells when it is generated. Here, we assume that the bone marrow produces cells of clone \( i \) at a constant rate \( m \). Because the same clones are probably not produced every day, we use as an average production rate about one cell per clone per day, \( m \approx 1 \). B cells have a lifetime of about 2 days, \( d_B \approx 0.5 \, \text{d}^{-1} \). Activated cells divide about every 16 hours, \( p \approx 1 \, \text{d}^{-1} \). Antibodies may persist much longer, about 20 days; thus, \( d_A \approx 0.05 \, \text{d}^{-1} \). (Varela and Coutinho estimate \( d_A \approx 0.1 \, \text{d}^{-1} \).) A unit of antibody is the amount of antibody produced by a fully matured B cell in one day, thus, measured in units, \( s = 1 \, \text{d}^{-1} \). Antibody complexes are removed at a rate \( d_C \approx 10^{-2} \, \text{d}^{-1} \, \text{unit}^{-1} \), estimated in De Boer and Perelson (1991) where the notation \( d_C = d_cK \) was used. The threshold for proliferation is set at \( \theta_1 = 100 \). The onset of suppression, or the higher threshold
of the dose-response curve, is generally set several orders of magnitude higher, i.e. $\theta_2 = 10^4$. Throughout this paper, these estimated parameters will be referred to as the “standard” parameter set.

Connectivity can be defined and measured in a number of ways. In a young mouse, any given antibody will crossreact with as much as 23-28% of the other antibodies; in adult mice, this percentage reduces to about 1-2% (Holmberg et al., 1984; Kearney et al., 1987). However, affinities of IgM molecules in immature immune systems are relatively low and nonspecific. Using accessibility computations, Novotný et al., (1987) estimate that a immunoglobulin molecule has 40 distinct idiotypic determinants available for anti-idiotypic binding. Not all of these epitopes will necessarily result in an idiotypic response, while more than one antibody may bind to others. Thus, although 40 could serve as a reasonable estimate for $z$, for our standard parameter set, we choose a more conservative, intermediate value of $z = 10$.

3. STEADY-STATES

In the following analysis, we find the conditions for the existence of localized states for the AB Tree model. We derive estimates for the steady-state B cell populations and their corresponding antibodies at each level in the network. We then apply stability analysis to these steady-states to find the conditions for the stability of these localized states.

In previous analyses of models that contain only B cells (B models) and that employ a log bell-shaped activation function (Weisbuch et al., 1990; De Boer et al., 1990, 1992a), three possible equilibrium levels for each B cell population have been identified:

1.) a virgin, or unstimulated, level, $m/d_B$ ,

2.) a large population level corresponding to cells in an “immune” state, that experience a low activating field, $\frac{d_B}{(p-d_B)} \theta_1$ (see Eq. 3.7), and

3.) an intermediate population level corresponding to cells in a “suppressed” state, that experience a high suppressive field, $\frac{(p-d_B)}{d_B} \theta_2$ (see Eq. 3.5).
To a good approximation, localized network attractors consist of B cell populations at these various levels (Weisbuch et al., 1990). The purpose of this study is to investigate the behavior of the Cayley tree model when antibody dynamics are introduced; therefore, it is of interest to examine how the system attractors are affected by the introduction of dynamical equations for the antibodies.

When B cell populations are unstimulated, (i.e. \( f(h_i) = 0 \ \forall i \)), all B cell populations attain the virgin steady-state; while the corresponding antibody populations diminish to zero. This is an important, but dynamically uninteresting, system attractor corresponding to the resting state of a classical clonal selection immune response model. It would correspond to a completely decoupled immune network. In our network model, this state is not attainable if even one antibody population is non-zero at steady-state. As we shall see, however, a near-virgin steady-state is possible under some conditions.

Other system attractors likely to exist in this model are localized memory and percolation attractors. A localized memory state occurs when the clonal population at one level is high while all other levels remain suppressed or at near-virgin levels. For example, a localized memory at level 1 corresponds to a high, activated population of level 1 clones, sustained by an intermediate, suppressed population of level 2 clones. In order for this state to be considered localized, levels 3 and beyond must remain at low, or near-virgin levels. This attractor is called a localized memory because the antigen-reactive clone at level 1 is high and capable of quickly eliminating antigen as in a typical secondary immune response. (In a percolation attractor, by comparison, levels 3 and beyond would experience activating fields.)

The first localized state of interest is a special case. In this state level 1 is activated, level 2 suppressed, and all others near-virgin. Other localized states (where a level other than the first is activated) are a generalization of this result, since connectivity backward through the network must be taken into account. The conditions for localized memory will be shown to be only slightly more restrictive in the general case (see Section 5).

Estimates for the steady-state populations are greatly simplified using the following approximations: From Eq. (2.3), for small \( m \) (bone marrow source term),
approximate B cell equilibria are obtained at the intersections of the curve \( y = pf(h) \) with the line \( y = d_B \) (the B cell death rate), i.e. at

\[
pf(h_i) \approx d_B . \tag{3.1}
\]

Since we are seeking a steady-state with level 2 suppressed, we assume \( h_2 \gg \theta_1 \), thus \( f(h_i) \) can be approximated by the trailing edge of the activation curve:

\[
d_B = pf(h_2) \approx p \frac{\theta_2}{\theta_2 + h_2} , \tag{3.2}
\]

where

\[
h_2 = a_1 + (z - 1)a_3 . \tag{3.3}
\]

Level 3 is assumed to be in a virgin or near-virgin state. Thus \( a_3 \ll a_2 \). Since level 1 is activated and level 2 suppressed, \( a_2 < a_1 \); therefore, if \( z \) is not too large,

\[
h_2 \approx a_1 . \tag{3.4}
\]

To find the approximate steady-state values, we substitute Eq. (3.4) into (3.2). Solving for \( a_1 \), we find

\[
a_{1ss} \approx \frac{\theta_2(p - d_B)}{d_B} . \tag{3.5}
\]

Similarly, since level 1 is activated, \( h_1 \ll \theta_2 \), and

\[
d_B \approx pf(h_1) \approx p \frac{h_1}{h_1 + \theta_1} , \tag{3.6}
\]

where \( h_1 = za_2 \). Solving for \( a_2 \) yields

\[
a_{2ss} \approx \frac{d_B \theta_1}{z(p - d_B)} . \tag{3.7}
\]

Substituting \( a_{1ss} \) and \( a_{2ss} \) into the steady-state conditions, i.e. Eqs. (2.3) with \( da_1/dt = 0 \) and \( da_2/dt = 0 \), yields estimates for \( b_{1ss} \) and \( b_{2ss} \):

\[
b_{1ss} \approx \frac{\theta_2 p}{sd_B} \left[ \frac{(p - d_B)}{d_B} \right] d_A + d_C \theta_1 \] . \tag{3.8a}

\[
b_{2ss} \approx \frac{\theta_1}{sz} \left[ \frac{p}{(p - d_B)} \right] d_A + d_C \theta_2 \frac{p}{d_B} \] . \tag{3.8b}
The steady-state values for the antibody populations, Eqs. (3.5) and (3.7), turn out to be essentially the same as the estimated clone sizes in the corresponding localized memory state in the B cell Cayley tree model (Weisbuch et al., 1990). This was to be expected, since it is the field that determines clone size. In the case of the B model, the field consists of the B cell population levels; whereas, in the AB Tree model, the field consists of the antibody populations.

For the standard parameter set, the approximate steady-state values are \( b_{1ss} = 21,000, \ a_{1ss} = 10,000, \ b_{2ss} = 2,000, \ a_{2ss} = 10 \). The accuracy of these approximations was tested by numerical calculation of the exact steady-state values. The approximate values were found to be within 2% of the numerical values. Notice that in an immune state, the antibody population of the memory level, \( a_1 \), is \( z\theta_2/\theta_1 \) times larger than the antibody, \( a_2 \), of the sustaining, suppressed level. The B cell populations, however, differ by a factor approximately equal to \( z \). Thus, the clone size of the suppressed population for \( z = 2 \), for example, is only half the size of the activated population. In the case of the two-clone model (\( z = 1 \)), \( B_1 \) is only slightly larger than the \( B_2 \) in a stable immune state.

For the immune steady-state to remain localized, level 3 must not become activated, (i.e., \( pf(h_3) < d_B \) or \( h_3 < \theta_1 \frac{d_B}{p - d_B} \)). Also, level 4 is assumed to be near-virgin, so that

\[
  h_3 = a_2 + (z-1)a_4 \approx a_2 . \tag{3.9}
\]

Substituting the steady-state value for \( a_2 \) into Eq. (3.9) yields as a necessary condition for this localized state

\[
  z > 1 . \tag{3.10}
\]

Thus, for a localized memory to remain localized, there must be more clones in level 2 than in level 1. This is in agreement with the results of Weisbuch et al. (1990).

We now estimate the steady-state values for the level 3 populations. Note that, since \( b_3 \) is assumed to be near-virgin, \( m \) is not negligible in this case. Approximating \( f(h_3) \approx f(a_2) \) by its rising part, or

\[
  f(h_3) \approx \frac{a_2}{a_2 + \theta_1} . \tag{3.11}
\]
From Eq. (2.3), at steady-state

$$b_3 = \frac{m}{d_B - p \left( \frac{a_2}{a_2 + \theta_1} \right)} .$$  \hfill (3.12)

Substituting $a_{2ss}$ yields

$$b_{3ss} \approx \frac{m}{d_B} \frac{z}{(z - 1)} \left[ 1 + \frac{d_B}{z(p - d_B)} \right] .$$  \hfill (3.13)

The corresponding steady-state antibody concentration is given by

$$a_{3ss} = \frac{sf(h_3)b_{3ss}}{(d_A + d_Cb_{3ss})} .$$  \hfill (3.14)

Substituting Eqs. (3.7), (3.13) and (3.11) into (3.14) yields

$$a_{3ss} = \frac{sm(z/(z - 1))}{[d_Az(p - d_B) + d_Cd_B\theta_1]} .$$  \hfill (3.15)

Notice that

$$\lim_{z \to \infty} b_{3ss} = m/d_B ,$$  \hfill (3.16)

and for large $z$, $b_3$ is nearly virgin ($\frac{d_B}{(p - d_B)} = 1$ for our standard parameters), consistent with the condition for a localized state. However, as $z$ increases, $a_{2ss}$ decreases (see Eq. 3.7) and $a_{4ss}$ increases until the assumption of Eq. (3.9) becomes invalid. This will be shown explicitly in Section 6 using numerical methods, and is illustrated in Fig. 4. Again the accuracy of the approximate steady-state populations at level 3 were compared to their numerically determined values. For the standard parameter values, the estimated values, $b_{3ss}$ and $a_{3ss}$, were 68% and 62% of the numerical values. As $z$ is increased from 10, the standard value, this error increases significantly. For example, at $z = 15$, the approximate steady-state populations are only 34% and 31% of the numerical values. Thus, the estimated steady-state values for level 3 are only valid for relatively small values of $z$.

Initially, we had calculated the steady-state values for levels 1 and 2 assuming that

$$h_2 = a_1 + (z - 1)a_3 \approx a_1 .$$

In order for this assumption to hold, $a_{1ss} \gg (z - 1)a_{3ss}$, or
\[ \theta_2 \gg \frac{mszd_B}{(p - d_B)p[d_Az(p - d_B) + d_Cd_B\theta_1]} \]  \hspace{1cm} (3.17)

For our standard parameters, this condition is easily met. Thus, in certain parameter regimes the AB Tree model has localized steady-states. The analysis thus far, however, has not put any conditions on the stability of these states.

4. STABILITY ANALYSIS

We next find conditions under which the localized immune steady-state is stable. Stability analysis is greatly simplified if we continue to use the approximations
(i) \( h_1 \ll \theta_2 \),
(ii) \( h_2 \gg \theta_1 \), and
(iii) \( a_1 \gg (z - 1)a_3 \).

Using (i) and (ii), we can approximate the activation function for levels 1 and 2 by the rising and falling parts of \( f(h) \), respectively. Approximation (iii) allows us to ignore population dynamics beyond level 2. Thus, near the localized state, the model reduces to the following four-dimensional form:

\[
\begin{align*}
\frac{db_1}{dt} &= m + p \left( \frac{za_2}{za_2 + \theta_1} \right) b_1 - d_B b_1 \\
\frac{da_1}{dt} &= s \left( \frac{za_2}{za_2 + \theta_1} \right) b_1 - d_A a_1 - d_C a_1 z a_2 \\
\frac{db_2}{dt} &= m + p \left( \frac{\theta_2}{a_1 + \theta_2} \right) b_2 - d_B b_2 \\
\frac{da_2}{dt} &= s \left( \frac{\theta_2}{a_1 + \theta_2} \right) b_2 - d_A a_2 - d_C a_1 a_2 
\end{align*}
\]  \hspace{1cm} (4.1)

Since it assumes no level 3 interactions, this model consists of a single, first level clone and \( z \) clones at level 2. We shall refer to this reduced model as the “star” model.

To linearize these equations about the steady-state, we compute the Jacobian

\[
J = \begin{bmatrix}
\frac{\partial b_1}{\partial b_1} & \ldots & \frac{\partial b_1}{\partial a_2} \\
\vdots & \ddots & \vdots \\
\frac{\partial a_2}{\partial b_1} & \ldots & \frac{\partial a_2}{\partial a_2}
\end{bmatrix}
\]
and evaluate it for the localized steady-state values \((a_{1ss}, a_{2ss}, b_{1ss}, b_{2ss})\) given by Eqs (3.7) and (3.9)-(3.11). Notice that when these substitutions are made, two of the diagonal terms vanish:

\[
J = \begin{bmatrix}
\frac{pz_2 a_2}{za_2 + \theta_1} - d_B & 0 & 0 \\
-s\frac{za_2}{za_2 + \theta_1} & -d_A - d_C za_2 & 0 \\
0 & \frac{-p\theta_2 b_2}{(a_1 + \theta_2)^2} & \frac{\theta_2}{a_1 + \theta_2} - d_B \\
0 & \frac{-s\theta_2 b_2}{(a_1 + \theta_2)^2} - d_C a_2 & \frac{\theta_2}{a_1 + \theta_2} - d_A - d_C a_1
\end{bmatrix}
\]

(4.2)

The eigenvalues, \(\lambda\), of \(J\) can be found by solving the characteristic equation

\[
p = \text{det}[\lambda I - J] = 0 ,
\]

(4.4)

or,

\[
p = c_0 + c_1 \lambda + c_2 \lambda^2 + c_3 \lambda^3 + c_4 \lambda^4 = 0 ,
\]

(4.5)

where \(p\) is the characteristic polynomial and \(c_i\)'s are the coefficients of the characteristic equation. The coefficients are as follows:

\[
c_0 = d_B^2 (p - d_B)^2 (-d_A d_B + pd_A + d_B d_C \theta_1) [d_A d_B + (p - d_B) d_C \theta_2]
\]

(4.6)

\[
c_1 = p (p - d_B) \{-d_A d_B d_C \theta_1 (2d_B - p) + (p - d_B)^2 [2d_A^2 d_B \\
- d_A d_C \theta_2 (2d_B - 3p) + 2d_B d_C^2 \theta_1 \theta_2] \}
\]

(4.7)

\[
c_2 = d_A^2 d_B (p - d_B) (-2p^2 + 2pd_B - d_B^2) + d_A d_B^2 d_C \theta_1 (d_B^2 - d_B p + p^2) \\
+ d_A d_C \theta_2 (p - d_B)^2 (3p^2 - 3d_B p + d_B^2) + d_B d_C^2 \theta_1 \theta_2 (p - d_B)^3
\]

(4.8)

\[
c_3 = p^2 [-2d_A d_B (1 - p) + d_B^2 d_C \theta_1 + d_C \theta_2 (p - d_B)^2]
\]

(4.9)

\[
c_4 = p^2 d_B (p - d_B)
\]

(4.10)
Surprisingly, the characteristic equation is independent of the coordination number, $z$. (All $z$ terms of the characteristic polynomial are common factors.) This is still true when the exact Jacobian is used (that is, the Jacobian taken using the full $f(h)$ and not simply its rising and falling parts). What this implies is that stability is insensitive to the asymmetry in the model due to the fact that there is one level 1 clone and $z$ level 2 clones. Thus, if a localized memory state becomes unstable as $z$ is changed, it is due to the interactions with level 3 populations. This is explored further in Section 6.

If we set all parameters to constants and choose one parameter as a variable, the characteristic equation allows us to predict stability as a function of that variable. For example, if we vary the antibody death rate, $d_A$, leaving all other parameters at their standard values, we get the characteristic equation as a function of $d_A$ with the coefficients

$$
c_0 = 6.25 + 6.31d_A + 0.0625d_A^2 ,
$$

$$
c_1 = 25 + 50d_A + 0.25d_A^2 ,
$$

$$
c_2 = 25 + 175.75d_A + 1.25d_A^2 ,
$$

$$
c_3 = 101 + 2d_A .
$$

To find stability conditions in this case, it is not strictly necessary to find the eigenvalues; inspection of the coefficients of the characteristic polynomial is sufficient. The characteristic polynomial is stable if the following conditions are satisfied (Liénard-Chipart Theorem (Fortmann and Hitz, 1977)):

$$
c_i > 0 \forall \ i ,
$$

and

$$
c_3c_2c_1 > c_3^2c_0 + c_1^2 .
$$

Conditions (4.15) are always met in this example since $d_A > 0$. Condition (4.16) predicts that the localized state is stable for values of

$$
d_A > 0.0025 .
$$
If we repeat this analysis using the exact Jacobian, we find the slightly stronger condition

\[ d_A > 0.0047 . \]  

(4.18)

Our estimated value of \( d_A \) is 0.05, and thus with our standard parameters, the localized immune state is stable. Note, however, that if the antibody lifetime is too short, network interactions leading to localized memories cannot be sustained.

Similarly, conditions can be derived by varying other parameters. Setting \( d_A = 0.05 \) and freeing \( d_C \) yields

\[ c_0 = .00015625 + 31.5625d_C + 62500d_C^2, \]  

(4.19)

\[ c_1 = .00625 + 250000d_C + 250d_C^2, \]  

(4.20)

\[ c_2 = .003125 + 878.75d_C + 250000d_C^2, \]  

(4.21)

\[ c_3 = 10100 + 0.1d_C \]  

(4.22)

or

\[ d_C > 0.0060 . \]  

(4.23)

This condition remains essentially unchanged when the exact Jacobian is used. Again, with the estimated value, \( d_C = 0.01 \), our analysis predicts a stable localized immune state.

5. LOCALIZED STATES AT OTHER LEVELS

As previously noted, a localized state with level 1 high is a special case in that clones at lower levels need not be considered. Localized states at other levels are of interest as a generalization of the previous analysis as well as their potential biological relevance. For example, a localized state with level 2 high and level 1 low or intermediate has been referred to as a “tolerance attractor” (Weisbuch et al., 1990; Neumann and Weisbuch 1992a). A high level of \( Ab_2 \) suppresses the primary antibody response rendering the network unresponsive, or “tolerant”, to antigenic challenge.

To find the conditions for a localized state with a level other than level 1 high requires a similar analysis. Consider a state with \( a_i \) high (e.g. \( a_i \approx \theta_2 \)). Level \( i - 1 \),
experiencing a field of $a_{i-2} + (z-1)a_i$, will be far into the suppressive range of the dose-response curve; consequently, $a_{i-1}$ will be very low, perhaps near-virgin. Thus, the only assumption in section 3 that changes is the approximation for the level $i$ field

$$h_i = a_{i-1} + (z-1)a_{i+1} \approx (z-1)a_{i+1} .$$  \hfill (5.1)

The steady-state values are then given by

$$a_{iss} \approx \frac{\theta_2(p - d_B)}{d_B} \quad (5.2)$$

$$a_{(i+1)ss} \approx \frac{d_B \theta_1}{(z-1)(p - d_B)} \quad (5.3)$$

$$b_{iss} \approx \frac{\theta_2 p}{sd_B} \left[ (p - d_B) - d_A + d_C \theta_1 \right] \quad (5.4)$$

$$b_{(i+1)ss} \approx \frac{\theta_1 p}{s(z-1)(p - d_B)} \left[ d_A + d_C \theta_2 \frac{(p - d_B)}{d_B} \right] . \quad (5.5)$$

An example of a “tolerance” attractor (a localized steady-state at level 2, with a sustaining population at level 3) is shown in Fig. 2.

The necessary condition corresponding to Eq. (3.10) for this localized state is

$$z > 2 . \quad (5.6)$$

The unit increase in the condition on $z$ is a direct consequence of network structure. A similar condition has been found for more general structures (Neumann and Weisbuch 1992b). This condition is really the same as Eq. (3.14); that is, there must be more than one connected clone descending down the Cayley tree. Thus, the simplest structure which can support tolerance is a tree with coordination number $z = 3$ (see Fig. 1).

6. NUMERICAL BIFURCATION ANALYSIS

Having established some approximate conditions for stable, localized steady-state network behavior from the star model, we wish to know what happens to these
states as model parameters are changed and the stability conditions are violated. In this section, we analyze steady-state behavior of a more complete model of a Cayley tree model using a numerical bifurcation analysis software package, AUTO (Doedel, 1981; Taylor and Kevrekidis, 1990). The following numerical work was performed on a ten-level Cayley tree model (fields due to levels 11 and beyond are assumed to be zero). The result is a 20-dimensional system of equations (one equation for each B cell and antibody population at each level). In analyzing bifurcations that occur as \( z \) is varied, we treat \( z \) as a continuous variable. However, strictly speaking, Cayley trees are only defined for integer values of \( z \).

### 6.1 Nondimensional Model

First, we nondimensionalize the model equations to reduce the number of model parameters. For comparison, we have attempted to choose dimensionless units which are roughly equivalent to those in De Boer and Perelson’s (1993a,b) analysis of two-clone models. Accordingly, the time scale is based upon the B cell lifetime, i.e. \( T = t d_B \). We scale the antibody concentration by a factor, \( \alpha = \sqrt{\theta_1 \theta_2} \), which corresponds to the concentration of antibody which leads to maximum crosslinking (activation). We then scale the B cell population by a factor, \( \beta = (d_A \alpha)/s \), the concentration of B cells required to sustain a steady-state population of \( \alpha \) antibodies (at maximum activation and ignoring complex formation). The remaining quantities, \( h_i, \theta_1, \) and \( \theta_2 \) are scaled by \( \alpha \). The nondimensional dynamical equations become

\[
H_i = \sum_j J_{ij} A_j, \tag{6.1}
\]

\[
f(H_i) = \frac{H_i}{(\Theta_1 + H_i)} \frac{\Theta_2}{(\Theta_2 + H_i)}, \tag{6.2}
\]

where \( \Theta_1 = \theta_1/\alpha \), and \( \Theta_2 = \theta_2/\alpha \).

\[
\frac{dB_i}{dT} = \sigma + (\rho f(H_i) - 1)B_i, \tag{6.3}
\]

\[
\frac{dA_i}{dT} = \nu f(H_i)B_i - (\delta + \mu H_i)A_i,
\]

where

\[
A_i = a_i/\alpha, \quad B_i = b_i/\beta, \quad \delta = d_A/d_B, \quad \sigma = m/(\beta d_B), \quad \rho = p/d_B,
\]
\[ \nu = \beta s/(\alpha d_B), \quad \mu = (\alpha d_C)/d_B, \quad \alpha = \sqrt{\theta_1 \theta_2}, \quad \beta = (\alpha d_A)/s. \]

The corresponding standard, non-dimensional parameter values are \( \delta = 0.1, \sigma = 0.04, \rho = 2, \nu = 0.1, \mu = 20, \alpha = 1000, \) and \( \beta = 50. \)

### 6.2 Connectivity Dependence of Localized Steady States

The connectivity parameter \( z \) is the only new feature added to the basic two-clone AB model (De Boer et al., 1993a,b). We introduce a network structure to the two-clone model when \( z \geq 2 \). Thus, we first investigate the dependence of the localized steady-state on the connectivity parameter, \( z \). Figure 3 shows the \( z \)-dependence of two different localized steady-states, one with level 1 high (a localized immune state) and one with level 2 high (a localized tolerance attractor). With all other model parameters set to the standard values, conditions for stability of these states are \( 1 \leq z \leq 15 \) and \( 2 \leq z \leq 16 \), respectively. For \( z = 1 \), these steady-states correspond to the “HM” and “MH” states in the two-clone AB model (De Boer et al., 1993a,b). As discussed in Sections 3 and 4, the upper limits on \( z \) are imposed from interactions with level 3 populations. As \( z \) gets large, the approximation for the field at level 3, \( h_3 = a_2 + (z-1)a_4 \approx a_2 \), Eq. (3.9), breaks down. As the field at level 3 increases, it’s clonal population increases until it begins to stimulate higher-level clones.

Both of the localized states (with levels 1 and 2 non-virgin) exist as “isolated” solutions; that is, as \( z \) is varied the steady-states do not branch into other attractors, but rather loop back on themselves. In Fig. 3, the lower branches, indicated by the dashed lines, are unstable.

### 6.3 Extended Localization and Percolation Attractors

The stability of the localized immune state is independent of \( z \) in the two-level, star model; therefore, it is the interactions with deeper levels in the immune network which destroys the immune state. As \( z \) is increased, clone 3 begins to expand far enough above virgin levels to stimulate proliferation of level 4 clones. We refer to the loss of localization as structural, since system steady states are dynamically stable, while localized states are lost due to changes in the model structure (connectivity). As discussed above, the assumption that \( h_3 = a_2 + (z-1)a_4 \approx a_2 \), Eq. (3.9), only holds for small \( z \). In Fig. 4, the two components of the field experienced by level
3 clones is plotted against $z$. As $(z - 1)A_4$ becomes comparable $A_2$, the localized immune state is lost.

For high $z$, stable steady-states still exist, but these states correspond to “extended localization” (Neumann and Weisbuch 1992a) and “percolation” attractors, where many levels are maintained at high populations. Figure 5 shows the dynamical trajectory which results when the localized memory state is lost ($z = 16$). The initial system state was chosen to be the immune state for $z = 15$. At $t=0$, $z$ was increased to $z = 16$, and Eqs. (6.3) were integrated numerically. Since no localized immune steady-state now exists, the trajectory moves into a new basin of attraction (in this case an extended localization with B cells at levels 1 and 4 high, 3 and 5 intermediate, and deeper levels near-virgin). This state exists for a slightly larger range, $z \leq 19$ (Fig. 3). If we continue to increase $z$, activation cascades further down the network resulting in a percolation attractor.

Percolation attractors can coexist with localized steady-states in the AB Tree model. Notice in Fig. 3 that for $2 < z < 16$, the extended localized attractor coexists with a tolerance attractor. Thus, when the localized memory state disappears as $z$ is increased, it does not spawn a new attractor; trajectories simply approach other existing (immune, virgin, or one of the percolation) attractors - depending upon initial conditions.

6.4 Dependence of the Localized Steady State on Antibody Dynamics

The inclusion of antibody populations as state variables in the Cayley tree model introduces two important parameters, the antibody death rate, $d_A$, and the complex removal rate, $d_C$, i.e., dimensionless parameters $\delta$ and $\mu$, respectively. Varying these parameters can change steady-state behavior into chaotic behavior. The loss of localization in this case is dynamical, since nearly all stable steady state behaviors (including percolation attractors) are lost with changes in the dynamical variables.

The stability of the localized immune steady-state as a function of $\delta$ (the ratio of antibody/B cell death rates) is shown in Fig. 6. If $\delta$ is increased from its standard value of 0.1, the eigenvalues become increasingly negative, i.e. more stable (not shown). As $\delta$ is decreased from 0.1, a Hopf bifurcation occurs at $\delta \approx 0.0136$, and
the steady-state goes unstable. For the “standard” parameter value \( d_B = 0.5 \), this corresponds to the condition \( d_A = 0.0068 \), which is close to the estimate provided from linear stability analysis of the star model (Eq. (4.18) \( d_A > 0.0047 \)). The Hopf bifurcation branch consists of unstable limit cycles, while continuation of the primary branch follows an unstable steady-state. Most attractors in this region are chaotic, although some are steady-states with levels other than level 1 high.

Localized states can also lose stability if the complex formation parameter, \( \mu \), becomes too small. Figure 7 is a bifurcation diagram of the level 1 (immune) localized steady-state with \( \mu \) as the bifurcation parameter. Beginning with the standard value (\( \mu = 20 \)), the steady-state becomes unstable at the Hopf bifurcation as \( \mu \) drops below 12.45. For the standard parameter set, instability corresponds to the condition \( d_C < 0.00623 \). This, also, is in close agreement to the estimate of 0.0060 from linear stability analysis of the star model (Eq. (4.23)). Past the Hopf bifurcation, the steady-state is unstable with 2 complex eigenvalues, both having positive real parts. At the saddle-node bifurcation, an additional positive, real eigenvalue appears; thus, along the lower branch of the bifurcation curve the system has 3 eigenvalues with positive real part. At \( \mu = 12.1 \), the complex eigenvalues re-cross the imaginary axis, but the single unstable eigenvalue persists becoming increasingly unstable with increasing \( \mu \). The branches from the two Hopf bifurcations consist of unstable limit cycles. In the region past the first Hopf bifurcation, i.e. \( \mu < 12.45 \), system attractors, other than the virgin state, appear to be chaotic. For \( \mu > 12.45 \), the immune state is stable and surrounded by an unstable limit cycle. This unstable limit cycle, along with its stable manifold, define the basin of attraction of the stable immune state.

Figure 8 is a two-parameter continuation of the localized immune state. Assuming standard values for the other parameters, this diagram shows the combinations of \( \mu \) and \( \delta \) for which the localized immune state at level 1 exists, as well as whether it is stable. No localized immune steady-state exists below the saddle-node curve. The two broken lines indicate the boundaries for Hopf bifurcation curves (HB-1 and HB-2). The steady-state is stable only above the first Hopf bifurcation (HB-1). In the region between the saddle-node and Hopf bifurcation curves, only unstable steady-states exist. The one parameter continuations in Figs. 6 and 7 project onto
this diagram as a vertical line at $\mu = 20$ and a horizontal line at $\delta = 0.1$, respectively. This diagram qualitatively corresponds to Fig. 3 in Perelson and Weisbuch (1992) and De Boer et al. (1993a,b).

Figure 9 is a two-parameter continuation of the saddle-node and Hopf bifurcations of the localized steady-state at level 1 varying one dynamical parameter, $\mu$, and the connectivity parameter, $z$. As $\mu$ is lowered, the localized steady-state exists and is stable for a decreasing range of $z$. At approximately $\mu = 12.5$, the steady-state becomes unstable for all values of $z$, and remains unstable for all $\mu < 12.5$. The loss of stability occurs via a Hopf bifurcation. The limit cycles that appear are unstable. Again, network connectivity, $z$, mostly determines the existence of the localized state and the dynamical parameter primarily determines the stability of the steady-state. The one parameter continuations in Figs. 3 and 7 project onto this diagram as a vertical line at $z = 20$ and a horizontal line at $\mu = 20$, respectively.

6.5 Chaotic Attractors

As system parameters are varied past the Hopf bifurcations, the dynamics can become chaotic. To study the dynamics we use the dimensional equations (2.3). In Figs. 10a-h, a series of time plots and phase portraits are shown for $z = 10$ as $d_C$ is decreased past the critical value of 0.00623, and the localized steady-state becomes unstable. Beginning with the standard parameter set ($d_C = 0.01$), the localized memory state is asymptotically stable (Figs. 10a,b). As $d_C$ is lowered toward the Hopf bifurcation at $d_C \approx 0.00623$, the basin of attraction for the localized steady-state shrinks. Because the steady-state is surrounded by an unstable limit cycle, a large enough perturbation will cause trajectories to move away from the steady-state and approach another attractor. This is illustrated in Figs. 10c and d for $d_C = 0.0067$. Here a large perturbation was given and the trajectory slowly moves away from the steady-state, goes through a transient, and then approaches an apparently chaotic attractor. This attractor resembles the Lorenz attractor (Sparrow, 1982) in that the trajectory spirals around two stable states, one with $a_1$ high, the other with $a_2$ high. Just past the Hopf bifurcation ($d_C = 0.0060$), chaotic trajectories are also observed. In Figs. 10e and f it is seen that the trajectory often returns to the region in state space near the unstable steady-state. As $d_C$ is
reduced further, the attractor becomes increasingly dispersed in state space. This is illustrated in Figs. 10g and h for $d_C = 0.001$.

The time course of a typical chaotic attractor is shown in Fig. 11. At time $t=100$, a large dose ($10^5$) of $Ab_1$ is “injected” into the system. As can be seen, this causes $Ab_1$ and $Ab_2$ to stop fluctuating for about 50 days, while leaving $Ab_3$, $Ab_4$ and $Ab_5$ fluctuating (Fig. 11a). After 50 days, the system relaxes back into the fully chaotic state. Doses of injected antibody of order $10^4$ or less have little effect on network dynamics and the fluctuations continue unabated. For larger $z$, a larger dose is needed to disturb network dynamics due to the large number of connected clones at level 2 (Fig. 11b).

### 6.6 Localized Chaos and Limit Cycles

In the two-clone AB model, stable limit cycle attractors were found over a wide parameter range (De Boer et al., 1993a,b). With large amplitude oscillations in level 1 and 2 antibody populations, however, level 3 would be expected to be stimulated past the virgin threshold, leading to percolation or chaos. Indeed, when the system parameters were set to those of the oscillatory regime of the two-clone model (e.g. $\mu < 12.68$, dimensional value $d_C < .00634$), chaotic dynamics spread throughout the network, even for $z=2$. Moreover, even in the parameter regime in which the two-clone AB model exhibits limit cycle behavior ($\mu < 0.18$), the AB Tree model shows chaotic behavior for small $z$. Thus, the introduction of even the most minimal network structure, a linear chain, disrupted the limit cycle oscillations observed in the two-clone model.

The potential exists for localized oscillatory states if the oscillations of $a_2$ remain sufficiently small, i.e. below the threshold for activating level 3, such that the condition $a_{2max} < \frac{d_B}{(p-d_B)} \theta_1$ is fulfilled. On the other hand, the oscillations of $a_2$ must be smaller then the suppressive threshold in order to sustain oscillations at level 1, i.e. $h_{1max} = z a_{2max} = \frac{(p-d_B)}{d_B} \theta_2$. By combining the above two expressions we obtain a sufficient condition for localized oscillations,

$$z \geq \frac{\theta_2}{\theta_1}, \quad (6.4)$$
enough so that \( h_1 = za_2 \leq \frac{(p-d_B)}{d_B} \theta_2 \). For our standard parameter set, this condition is satisfied for \( z > 100 \).

Indeed, stable limit cycles have been found in high connectivity parameter regimes. One such attractor is shown in Fig. 12a,b. These limit cycles are only structurally stable when the bone marrow source term is extremely small so that virgin B cell clones are too small to be activated easily (\( m = .000025 \)). As \( d_C \) is increased, the limit cycle becomes unstable, and system dynamics are characterized by long-lived oscillatory transients which do not activate higher level clones (Fig. 12c,d). At even higher values of \( d_C \), a localized chaotic attractor appears (Fig. 12e,f), where chaotic oscillations at levels 1 and 2 do not substantially disturb the near-virgin populations deeper in the network.

7. DISCUSSION

7.1 More Complex Network Structures

We have studied the behavior of antibody–B cell immune networks that have the topology of a Cayley tree. A Cayley tree is a homogeneous network, without loops, in which every node is connected to precisely \( z \) others. The Cayley tree is clearly only an approximation to real immune network topology. While each clone in a network may be connected to \( z \) others (on average) it is unlikely that all clones would ever be connected to exactly \( z \) others. Natural IgM antibodies in neonatal mice, when tested in binding assays, exhibit highly variable reactivities (Holmberg et al., 1984; Holmberg, 1987). Many of the antibodies are found to be highly multireactive, while others are specific. Thus, at least in this example a homogeneous topology does not seem to exist. The effect of variable connectivities on system attractors has been studied for the B cell Cayley tree model (Neumann and Weisbuch 1992b) but not on the AB Tree model.

Further evidence of network structures that differ from the Cayley tree model comes from functional distinctions between classes of second level antibodies (Jerne, 1974; Jerne et al., 1982). Primary antibodies (\( Ab_1 \)'s) recognize epitopes of an antigen. Secondary antibodies (\( Ab_2 \)'s), can recognize either idiotopes or paratopes of \( Ab_1 \). If an \( Ab_2 \) recognizes an idiotope outside the binding site it is classified as an
$Ab_{2\alpha}$ antibody, while if it recognizes the paratope of $Ab_1$ it is referred to as an $Ab_{2\beta}$ or “internal image” antibody, since it mimics the shape of the original antigenic determinant. Internal images are not accounted for in a Cayley tree structure since, as we show below, they generate loops.

An internal image could be added to a network model. Consider network with coordination number $z$ and an external antigen as it’s root (see Fig. 13). An internal image would be indistinguishable from the antigen itself. If we allow a fraction $\mu$ of the second level antibodies to be internal images $Ab_{2\beta}$ of the antigen, the fields become:

$$h_1 = Ag + z[\mu a_{2\beta} + (1 - \mu)a_{2\alpha}] ,$$  \hspace{1cm} (7.1)

where $Ag$ is the effective antigen concentration. If we assume that the $Ab_1$’s represent the dominant idiotypic interactions for an internal image, the field for the internal images is

$$h_{2\beta} = za_1 ,$$  \hspace{1cm} (7.2)

(If one were to include further connectivity, a separate population of $Ab_{3\alpha}$’s would need to be added.) The $Ab_{2\alpha}$’s would retain a tree-like connectivity:

$$h_{2\alpha} = a_1 + (z - 1)a_3 .$$  \hspace{1cm} (7.3)

The inclusion of internal images violates the tree structure, and the dynamics of the $Ab_{2\alpha}$’s and $Ab_{2\beta}$’s must now be treated separately.

Köhler subdivides $Ab_2$ antibodies differently than Jerne et al. (1984) by defining a “network antigen” as an $Ab_2$ that can be used for vaccination (Köhler et al., 1989; Köhler, 1991). Network antigens do not necessarily meet the immunochemical criteria of internal images, but still are capable of inducing biologically beneficial immune responses. Network antigens and internal images have been used to prime an immune response without exposing an animal to the antigen itself (Köhler et al., 1986; Huang et al., 1988; Raychaudhuri et al., 1990; Bhattacharya-Chatterjee et al., 1990) and hence have obvious use as potential vaccines. Antibodies connected in loops may be used to model the connectivity of a network antigen (Fig. 13).

It is not only internal images and network antigens that generate loops, but as pointed out by Neumann and Weisbuch (1992b), any recognition scheme based
on complementary shapes implies a network with loops. For example, if $Ab_2$ and $Ab_4$ resemble each other, they may both interact with $Ab_3$ and $Ab_1$ forming a four-membered loop. In the case of B models, Neumann and Weisbuch (1992b) have used the window automata approximation (Neumann and Weisbuch, 1992a) to analyze the effects of simple loops on the existence and stability of localized states. Similar analyses remain to be done for AB models.

### 7.2 Oscillations and Immune Memory

Immune networks may be able to store memories in the form of dynamic steady-states (Farmer et al., 1986; Weisbuch, 1990; Weisbuch et al., 1990; Behn et al., 1992). Generally, when networks are used to explain memory to previous antigenic challenge the following implicit hypotheses are made (cf., Weisbuch et al., 1990):

(i) The immune system is antigen-driven; that is, prior to antigenic challenge, clones are in a stationary, virgin state.

(ii) Antigenic challenge can force clones from the virgin state into other states, such as those that correspond to immune and tolerant attractors.

(iii) If the new attractors that the system is driven to remain localized, the network will be capable of storing memories of many different antigens.

Some recent experimental data, however, do not support the hypothesis that the immune system is antigen-driven and that immunological memory is stored in stable, localized steady-states.

Measurements of naturally occurring antibody (NAb) concentrations in vivo at various times show complex dynamics. In the absence of external antigenic stimulation individual NAb concentrations fluctuate irregularly over time (Lundkvist et al., 1989; Varela et al., 1991). Based on Fourier spectra of rather limited time series, Lundkvist et al. argue that the fluctuations appear to be chaotic. However, because the data are so limited it is uncertain whether these fluctuations indicate the existence of a chaotic attractor, a high-dimensional limit cycle or are simply the result of noise and perturbations about a non-virgin steady-state. In germ-free mice the number of activated lymphocytes in the spleen and the serum level of IgM are similar to the values measured in conventionally raised animals (Hooykaas et al., 1984; Pereira et al., 1986). These data as well as the Lundkvist data indicate that the immune system is not in a rest state in the absence of external antigen.
Coutinho (1989) has argued that about 10-20% of the immune system is organized into an idio
typic network, or “central immune system” that is active in the absence of external antigen, and that the remaining 80-90% of clones are outside the network and constitute a “peripheral immune system” that is responsible for immune responses to foreign antigens. Thus, according to Coutinho, secondary responses and hence memory would be non-network derived. Whether a system in which clones and their anti-idiotypic clones were in localized states and relatively unresponsive to other activities in the network would correspond to the network or non-network parts of the system is unclear. Clones in the immune state could participate in rapid responses to antigen characteristic of secondary immune responses. However, while in the immune state they would be activated and subject to network interactions with their anti-idiotypic clone.

Lundkvist et al. (1989) did one additional experiment suggesting that the fluctuations in NAb populations are not due to noise. They showed that the fluctuations in the serum concentrations of natural antibodies with complementary idiotypes, which for notational simplicity, we call \( Ab_1 \) and \( Ab_2 \), could be eliminated for three months by injection of monoclonal antibodies with the idiotypes carried by either \( Ab_1 \) or \( Ab_2 \). Interestingly, the dynamics of serum antibodies with unrelated idiotypes remained relatively undisturbed and continued to fluctuate (Lundkvist et al., 1989). This might suggest that dynamical network activity remains localized in the immune network since dynamical behavior in only part of the immune system was noticeably changed.

We performed a similar experiment of injecting \( Ab_1 \) in our Cayley tree model when in a “chaotic” parameter regime. We found, as did De Boer et al. (1990, 1993b) for the two-clone AB model, that injection of high doses of \( Ab_1 \) could eliminate oscillations in \( Ab_1 \) and \( Ab_2 \) for a period of months (Fig. 11). However, low or moderate dose injections frequently would not lead to a loss of oscillations, the outcome depending on parameters values and the concentrations of antibodies present in the system at the time of the injection. Interesting, however, is that when oscillations at the \( Ab_1 \) and \( Ab_2 \) levels were eliminated, the higher levels \( Ab_3 \), \( Ab_4 \), and \( Ab_5 \) still oscillated (see Fig. 11). Thus in the AB Cayley tree model we can reproduce this second feature of the Lundkvist experiments that was not apparent.
in the previous two-clone AB models. Further, our model indicates that the continued fluctuations in higher levels of the tree, while fluctuations at levels 1 and 2 are eliminated, do not indicate that network activity is localized. In fact, this effect is seen in the model in the chaotic/percolating parameter regime. The explanation of this phenomenon in our model is that with high \( Ab_1 \), B cells at level 2 are suppressed and \( Ab_2 \) concentration levels are brought very low by a combination of complex formation with \( Ab_1 \) and lack of production by suppressed B cells. Since level 3 is influenced by both level 2 and level 4, it can continue to oscillate with \( Ab_2 \) very low as long as level 4 can stimulate it. In the chaotic regime, \( Ab_4 \) gets high enough to trigger level 3 and continue the percolation to higher levels.

The Lundkvist data suggests that if immune memory is stored in dynamical attractors they must be more complex than simple point attractors. It is difficult to envision memory storage in the global percolation and chaotic attractors found in the AB Tree model; however, the localized chaotic and limit cycle attractors found in section 6.6 could serve a localized memory role. Although these attractors were only found in very extreme parameter regions, in many other parameter regimes, transient oscillations around a steady-state may persist for as long as the lifetime of a mouse. For example, in Fig. 10c a large perturbation around a stable immune state produces slowly growing oscillations that last about 700 days.

Although the natural state of an immune network might be oscillatory, one would expect that if antigen drives the network then the \textit{time-averaged} \( Ab_1 \) population level would be much higher after antigenic challenge than before challenge. Indeed, the immune response to some antigens is oscillatory (Weigle, 1975; Romball and Weigle, 1982; Hiernaux et al., 1982) with the time-averaged antibody concentration remaining high for many weeks or months after antigenic challenge. The oscillations are usually damped and may reflect a slow return to a steady-state.

Thus, even if the immune system operates in an oscillatory or percolation regime it is still possible for memory to be stored dynamically. If responses stay localized it is easy to envision how both memory storage and memory recall would work. If responses do not stay localized it is much more difficult to see how the immune system could utilize dynamic memory. But this is not to say that it would be impossible. Neural networks of the Hopfield type store memory in a non-local
manner and this provides certain advantages if damage occurs to particular parts of the network.

7.3 Conclusions

The AB Tree model differs from previous models in that it adds a simple network structure to the two-clone AB models and antibody dynamics to B cell Cayley tree models. We have shown that the inclusion of antibody dynamics does not change the general conclusion of Weisbuch et al. (1990) that there can exist stable localized memory states in a Cayley tree immune network model.

Besides the immune, tolerant and extended localized steady-states, we have identified two other classes of localized system attractors: limit cycles and localized chaotic attractors. Global system attractors include virgin, percolation and chaotic attractors. Percolation attractors are stable steady-states where many, if not all, network levels are non-virgin. In the AB Tree model, percolation attractors coexist with localized memories in many parameter regimes.

The primary new variable introduced in the AB Tree model from the two-clone AB models is the network connectivity, or more precisely, $z$, the coordination number of the tree. As $z$ is increased, stable localized steady-states disappear, and only percolation and chaotic attractors remain (Fig. 3). This breakdown of localization is due to interactions with an increasing number of connected clones at higher levels in the tree. Chaotic attractors do not exist in the B cell Cayley tree model. In parameter regimes where the two-clone AB model shows limit cycle behavior, the AB Tree model exhibits chaotic behavior. But, in highly connected networks, limit cycle behavior reappears, along with an interesting new type of system attractor - a localized chaotic attractor.

In the dynamical simulations presented here, chaotic or oscillatory behavior usually percolates indefinitely through all levels. Information could not easily be stored in such attractors. However, based on the Lundkvist experiments we believe it likely that oscillatory or chaotic attractors exist in real immune networks (Section 7.2). The AB Cayley tree model leaves out important idioptypic interactions, such as internal images, and features such as gearing-up (Segel and Perelson, 1989) and separate spleen and blood compartments (Perelson and Weisbuch, 1992; De Boer
et al., 1993a,b). Whether including additional features in the model will serve to localize the dynamics in the network remains to be explored.

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FIGURE CAPTIONS

Figure 1. Topology of a homogeneous Cayley tree. Each node represents a clone – both the B cell population and its secreted antibody concentration. Each clone is connected to \( z \) adjacent clones. A Cayley tree with coordination number \( z = 1 \) is equivalent to a two-clone model. A Cayley tree with \( z = 2 \) corresponds to a linear chain with clone 1 as the root of the tree. With \( z \geq 3 \), a Cayley tree is a representation of a network without loops.

Figure 2. Dynamical response to a perturbation of a localized tolerance attractor at level 2. A perturbation of the localized steady-state at level 2 returns to its attractor. (a) B cells and (b) antibodies at levels 1 through 5 are shown. The connectivity parameter, \( z \), is set to 16, where a localized memory cannot exist. Other system parameters are set to their standard values: \( \theta_1 = 100, \theta_2 = 10^4, p = 1, s = 1, m = 1, d_B = 0.5, d_A = 0.05, d_C = 0.01 \). The initial conditions are \( b_1 = 5000, a_1 = 9000, b_2 = 17000, a_2 = 5000, b_3 = 631, a_3 = 3.19, b_4 = 3.16, a_4 = 2.1, b_5 = 2.09, a_5 = 0.605, b_6 - b_{10} = 2, a_6 - a_{10} = 0 \).

Figure 3. Bifurcation diagram with \( z \) as the bifurcation parameter. All other parameters are set to their standard values (see text). The vertical axis indicates the highest B cell population in the localized state (i.e. \( B_1 \) for the immune state; \( B_2 \) for the tolerant state). The localized steady-state remains stable for a wide range of values for \( z \). The lower branch is unstable. The localized state at level 2 exists for a slightly larger range of \( z \) than the localized state at level 1. Steady states also exist for larger values of \( z \), but they correspond to “extended localization” attractors or “percolation attractors”, where clones at many levels are sustained at high steady-state populations. (See Fig. 5)

Figure 4. Nondimensional level 3 field versus \( z \). The field experienced by level 3 clones, \( H_3 = A_2 + (z - 1)A_4 \), consists of two components. Steady state estimates in Section 3 were based on the assumption that \( A_2 \) dominates the field. As \( z \) is
increased, however, this assumption breaks down, and the localized immune state is lost.

Figure 5. Extended localized attractor in high $z$. Example of a system attractor past the limit point for a localized memory state ($z = 16$). Activation at many levels is referred to a “extended localized state” (Neumann and Weisbuch, 1992a). At $t = 0$ a system in a localized immune state for $z = 15$ has $z$ increased to 16. This localized state is slowly lost, and after a transient, an extended localized attractor is attained. When $z$ is increased further, this extended localization breaks down, and the system converges on a percolation attractor. The nondimensional concentrations of (a) B cells and (b) antibodies at levels 1 through 5 are shown. Other system parameters are set to their standard values: $\Theta_1 = 0.1$, $\Theta_2 = 10$, $\delta = 0.1$, $\sigma = 0.04$, $\rho = 2$, $\nu = 0.1$, $\mu = 20$, $\alpha = 1000$, and $\beta = 50$. The initial conditions are $B_1 = 418$, $A_1 = 9.773$, $B_2 = 26.8$, $A_2 = 0.0068$, $B_3 = 0.134$, $A_3 = 0.00396$, $B_4 = 0.112$, $A_4 = 0.0034$, $B_5 = 0.10$, $A_5 = 0.0031$, $B_6 = 0.089$, $A_6 = 0.0028$, $B_7 = 0.077$, $A_7 = 0.0025$, $B_8 = 0.062$, $A_8 = 0.0021$, $B_9 = 0.047$, $A_9 = 0.0013$, $B_{10} = 0.041$, $A_{10} = 0.00043$.

Figure 6. Bifurcation diagram of the localized immune state with $\delta$ as a variable. All other parameters are set to their standard values. The nondimensional $B_1$ population is plotted. As $\delta$ drops below 0.0136, a Hopf bifurcation occurs. The branch of the Hopf bifurcation consists of unstable limit cycles, while continuation of the primary branch leads to an unstable steady-state. Most attractors in this region appear to be chaotic.

Figure 7. Bifurcation diagram of the localized immune state with $\mu$ as a variable. The solid line indicates the nondimensional $B_1$ population in the localized, stable immune steady-state. Continuation through a Hopf bifurcation (at $\mu = 12.45$) leads to an unstable steady-state with 2 unstable complex eigenvalues. (The numbers in the figure legend indicate the number of eigenvalues with a positive real part on each branch). After the saddle-node bifurcation, an additional real positive eigenvalue appears, which gets larger for larger values of $\mu$. A second Hopf bifurcation occurs
at $\mu = 12.1$ as the complex eigenvalues re-cross the imaginary axis, but the single positive eigenvalue persists. Both branches born at the Hopf bifurcations define unstable limit cycles.

Figure 8. A two parameter $(\mu, \delta)$ continuation of the localized immune state. Assuming the standard parameter set for all other values, this diagram shows the combinations of $\mu$ and $\delta$ for which the localized memory state at level 1 exists as well as whether it is stable. Legend Key: SN = Saddle-node, HB-1,2 = Hopf bifurcation curves. The localized steady-state does not exist in the parameter regime below the saddle-node curve. The localized steady-state is stable only above the upper Hopf bifurcation curve (HB-1). This diagram qualitatively corresponds to Fig. 3 in Perelson and Weisbuch (1992).

Figure 9. Two parameter continuation $(z, \mu)$ of the localized immune state. All other parameters set to the standard values. Network connectivity, $z$, determines the existence of the localized steady-state; while the dynamical parameter, $\mu$, determines the stability. The steady-state is unstable below the upper Hopf bifurcation curve.

Figure 10. Time plots and phase plot projections of attractors as the localized steady-state becomes unstable. A 2-dimensional projection of a 10-dimensional state-space into the $a_1 - a_2$ plane is shown. Because this is a projection, trajectories may cross. Parameter values: (a, b) $d_C = 0.01$, (c, d) $d_C = 0.0067$, (e, f) $d_C = 0.0060$, and (g, h) $d_C = 0.0010$. Other parameters are set to their standard values. The initial conditions are $b_1 = 13900$, $a_1 = 9800$, $b_2 = 1300$, $a_2 = 10$, $b_3 = 3.4$, $a_3 = 3.2$, $b_4 = 2.4$, $a_4 = 1.7$, $b_5 = 2.07$, $a_5 = 0.58$, $b_6 - b_{10} = 2$, $a_6 - a_{10} = 0$. B cells and antibodies at levels 1 through 5 are denoted by the symbols asterisk, box, octagon, diamond and cross, respectively.

Figure 11. Dynamics of a chaotic attractor. The parameter $d_C$ is set past the Hopf bifurcation ($d_C = .005$), and hence in the chaotic regime. At time $t = 100$, the system is perturbed by a large ($10^5$) dose of $Ab_1$. (a) $z = 2$, (b) $z=33$. The same
sized injection has little effect on the more highly connected network. Other system parameters are set to their standard values: $\theta_1 = 100$, $\theta_2 = 10^4$, $p = 1$, $s = 1$, $m = 1$, $d_B = 0.5$, $d_A = 0.05$. The initial conditions are $b_1 = 13900$, $a_1 = 9800$, $b_2 = 1300$, $a_2 = 10$, $b_3 = 3.4$, $a_3 = 3.2$, $b_4 = 2.4$, $a_4 = 1.7$, $b_5 = 2.07$, $a_5 = 0.58$, $b_6 - b_{10} = 2$, $a_6 - a_{10} = 0$.

Figure 12. Phase and time plots of a localized limit cycle (a,b), a localized oscillatory transient (c,d), and a localized chaotic attractor (e,f). Attractors in a highly connected network ($z = 100$) with small bone marrow source term ($m = 2.5 \times 10^{-5}$) do not necessarily activate levels deeper in the network simply due to oscillatory behavior. All three trajectories shown orbit two unstable steady states. Initial conditions for limit cycle ($d_C = .00009$): $b_1 = 46.3$, $a_1 = 30.7$, $b_2 = .165$, $a_2 = 75.5$, $b_3 = .000785$, $a_3 = .00393$, $b_4 - b_{10} = 10^{-6}$, $a_4 - a_{10} = 0$. Initial conditions for localized transient ($d_C = .0025$) and localized chaos ($d_C = .005$): $b_1 = 7270$, $a_1 = 6970$, $b_2 = 126$, $a_2 = 2.04$, $b_3 - b_{10} = .00005$, $a_3 - a_{10} = 0$. Other system parameters: $\theta_1 = 100$, $\theta_2 = 10^4$, $p = 1$, $s = 1$, $d_B = 0.5$, $d_A = 0.05$.

Figure 13. Schematic diagram of some idiotypic interactions absent in a Cayley tree model. Internal images ($Ab_{2\beta}$) mimic the structure of the original antigenic epitope (Ag); therefore, they are topologically substitutable for antigen in a network model. $Ab_{2\alpha}$’s, which do not mimic antigenic structure, yet crossreact with more than one $Ab_1$ may serve as a model for network antigens.