Immune Network Theory

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INTRODUCTION

The theoretical development of idiotypic networks was initiated by Jerne (1974a). In a review, Jerne (1974b) attempted to put the network proposal into mathematical terms. Before describing Jerne’s and more modern efforts in detail it is worth remembering what Jerne said about this endeavor. “Although this task is a challenge to immunologists, I suspect that several would rather turn away from such ambitious and, for the present, unrealistic exercises in order to contemplate what they would call real experimental facts. To those I would reply that as long as the quantitation of the immune response remains elusive, immunology will remain a phenomenology, an ever accumulating catalogue of such phenomena as are at present out daily bread.”

Jerne constructed a differential equation to describe the dynamics of a set of identical lymphocytes. By identical Jerne meant cells that were indistinguishable with respect to their state of differentiation as well as to their receptors and to the antibody molecules they produce. To illustrate Jerne’s idea, call these identical lymphocytes, lymphocytes of type $i$, and let $L_i$ denote the number of lymphocytes of type $i$. Lymphocytes of type $i$ interact with lymphocytes of other types, e.g. lymphocytes of type $j$, and antibody of type $j$ via idiotopes and combining sites. The interactions can be either excitatory or inhibitory. The lymphocytes of type $j$ of course interact with other lymphocyte types and these with others and so on. Jerne suggested that the rate at which lymphocytes of a particular type increase or decrease in number is given by:

$$\frac{dL_i}{dt} = \alpha - \beta L_i + \sum_{j=1}^{m} \phi(E_j K_j t) - L_i \sum_{j=1}^{n} \psi(I_j K_j t).$$  (1)

In this equation, $\alpha$ is the rate at which lymphocytes enter set $i$ from other compartments in the immune system and $\beta$ is the rate (per lymphocyte) at which the lymphocytes die or leave the set. The functions $\phi$ and $\psi$ keep track of the excitatory and inhibitory signals. The first sum is over all excitatory signals
generated by idiotopes in the sets $E_i$ that are recognized with association constants
$K_j$ by the combining sites on lymphocytes of type $i$. The second sum is over the
inhibitory interactions generated by lymphocytes in sets $I_j$, whose combining sites
recognize idiotopes on cells in $L_i$. A further term would be needed to deal with
the effects of an external antigen. Recognizing that the number of elements in
the inhibitory and excitatory sets could change in time and that a differential
equation of this type would be needed for each element of the network, Jerne
concluded that there existed no satisfactory mathematical method of treating
network problems. In the subsequent 15 years methods have been developed that
allow us to treat networks of this level of complexity. In this paper I shall review
these new approaches and discuss some of the theoretical insights that result.

**COMPLETENESS OF THE REPERTOIRE**

Coutinho (1980) has postulated that the immune system in its ability to recognize
antigen is "complete" (also see Forni & Coutinho 1981). If the antibody repertoire
is complete then it follows that antibody molecules that have immunogenic
idiotopes will be recognized by other antibody molecules and an idio­
typic network
will be created (Jerne 1984). Attempting to prove that the repertoire is complete
is difficult. Perelson & Oster (1979) presented a simple theoretical argument
showing that a complete repertoire is attainable within the known parameters of
immune recognition. This argument, reproduced below, is based on the idea of
"shape space".

Binding between a receptor and a ligand or a paratope and an idio­
tope

generally involves short-range non-covalent interactions based on electro­
static charge, hydrogen binding, van der Waals interactions, etc. In order for the
molecules to approach each other over an appreciable portion of their surfaces,
there must be extensive regions of complementarity. In some cases, the com­
plementary regions may be planar, while in others they more closely resemble a
bump and a groove. Both shape and charge distributions, as well as the existence
in the appropriate complementary positions of chemical groups that can form
hydrogen bonds and interact in other ways are properties of antigens and anti­
obodies that are important in determining the interactions between these molecules.
We call this constellation of features the *generalized shape* of a molecule. Suppose
that one can adequately describe the generalized shape of an antibody combin­ing
site (paratope) by $N$ parameters: the length, width and height of any bump or
groove in the combining site, its charge, etc. The precise number of parameters
or their values is not important for the argument that follows, only that a finite
number of them is needed. Then a point in an $N$-dimensional space, "shape
space", specifies the generalized shape of a paratope with regard to its antigen
binding properties. If an animal has a repertoire of size $N_{Ab}$ then the shape space
for than animal would contain $N_{Ab}$ different points. One would expect these
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points to lie in some finite volume $V$ of the space since there is only a restricted range of widths, lengths, charges, etc. that an antibody combining site can assume (Fig. 1). For example, one would never find an antibody with a combining site dimension of one centimeter!

Antigenic determinants (epitopes or idiotopes) are also characterized by generalized shapes which should lie within $V$. For example, a combining site with a length of 2 nm cannot be expected to recognize a determinant 10 nm long. In order to estimate how well an animal with a repertoire of size $N_{Ab}$ can recognize molecular determinants, let us assume that a paratope and epitope fit together perfectly if they have the same shape, i.e. lie at the same point in $V$. (This is clearly a fiction because epitopes and paratopes must have complementary shapes. However, this is a useful mathematical fiction because it simplifies the argument and yields the same result as a more precise treatment which includes the notion of complementarity). If the paratope and epitope shapes are not quite complementary then the two molecules may still bind but with lower affinity. At some

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{Diagramatic representation of shape space. Within the space there is a volume $V$ in which paratope (●) and epitope (×) shapes are located. An antibody is assumed to recognize with affinity greater than or equal to $K$ all epitopes within a volume $V_{\alpha(K)}$ surrounding it.}
\end{figure}
low level of affinity, e.g. $10^4$ M$^{-1}$, we say the interaction is not specific and that the epitope and paratope are not complementary. To describe this we assume that each paratope specifically interacts with all epitopes that are within a small surrounding region in shape space, called a “recognition ball” (see Fig. 1). Let $V_{e(K)}$ (or for simplicity $V_e$) be the volume of a recognition ball when the threshold affinity is set at $K$. (If one wanted to be more precise one could assign an explicit affinity to each paratope-epitope pair depending upon their location in shape space. This approach will be taken with regard to more restricted models in subsequent sections). Because each antibody can recognize all epitopes within a recognition ball, a finite number of antibodies can recognize an infinite number of epitopes, i.e. one can put an infinite number of points into the volume $V_e$. If antibodies are multispecific then each paratope might be viewed as having multiple shapes, say corresponding to different pockets and grooves in the combining region. This case was analyzed by Perelson & Oster (1979) but will not be pursued here. Suffice it to say that with multispecific antibodies completeness of the repertoire is easier to attain than the analysis below shows.

To complete the argument, let us assume that antibodies are made with random shapes. Thus the $N_{ab}$ antibodies lie scattered at random in the shape space. If each antibody has roughly the same recognition volume $V_o$, then the total volume covered by all of the antibodies in the repertoire is $N_{ab}V_e$. If this volume is large compared with the total volume of shape space $V$, then one would expect that the various antibodies would have recognition regions that overlap and completely cover shape space. In fact, each epitope would on average be recognized by $N_{ab}V_e/V$ different antibodies, and the probability, $P$, that an epitope is not recognized by some antibody is (Perelson & Oster 1979)

$$P = e^{-N_{ab}V_e/V}.$$  

(2)

We can use Eq. (2) to quantify the completeness of the repertoire. Typically, of order 1 in 100,000 B cells responds to an epitope (cf. Klinman & Press 1975). We will use this value as an estimate of $p(K)$, the probability that an antibody recognizes a random antigenic determinant with an affinity above the threshold value $K$. To interpret $p(K)$ within the context of shape space theory notice that, if one randomly places an epitope in shape space, the probability that it lands in the volume $V_e$ surrounding any given antibody is $V_e/V$, the fraction of the shape space volume covered by a single antibody. (An easy way to see this is to consider throwing darts at the two-dimensional version of shape space depicted in Fig. 1. Assume that the darts are thrown at random and all hit the board. The probability that a dart will land in a recognition ball is then the area of the ball divided by the area of the dart board, $V$.) Thus, if the readout of immune recognition is B-cell stimulation

$$p(K) = V_e/V \approx 10^{-5}. \quad (3)$$
With this rough estimate, Eq. (2) predicts that animals with a repertoire of $10^5$ antibodies will only be marginal, i.e. $e^{-1}$ or 37% of epitopes will escape detection. However, if $N_{ab} = 5 \times 10^5$ then $P$ falls to $6.7 \times 10^{-3}$ and less than 1% of epitopes escape detection. If $N_{ab} = 10^6$ then $P = 4.5 \times 10^{-5}$ and essentially all epitopes will be recognized. Thus a repertoire of order $10^6$, composed of antibodies with random shapes, will be complete. This is interesting because the smallest known immune system, that of a young tadpole, is estimated to have $10^6$ lymphocytes and thus a repertoire of order $10^5$ to $10^6$ (Du Pasquier 1973, Du Pasquier & Haimovitch 1976). Smaller immune systems do not exist and the “back of the envelope” calculation given above suggests that this is the case because such immune systems would recognize antigen so infrequently that they would provide little, if any, protective advantage.

To summarize, we have argued that the repertoire will be complete if three hypotheses are satisfied: 1) Each antibody can recognize a set of related epitopes, each of which differs slightly in shape. The strength of binding may differ for different epitopes and is accounted for by differences in affinity. 2) The antibodies in the repertoire have shapes that are randomly distributed throughout shape space. 3) The repertoire size is of order $10^6$ or greater.

Less stringent forms of hypotheses 2) and 3) should also lead to complete repertoires. For example, antibodies need not be randomly distributed in shape space; some regions could have substantially higher density than others but empty regions larger than $V_e$ in volume need to be rare. Under such conditions a slightly larger repertoire might be needed. The distribution of antibodies in shape space is unknown. Antibody V-regions are not made at random but derive from recombination of germ-line V, J, and D gene segments, with added junctional and mutational diversity. Depending on gene usage one might expect regions of different density in shape space, and the existence of holes.

Completeness is not absolute. As our quantitative examples have shown there is a small probability that an epitope will not be recognized. However, when the completeness conditions are met, or even nearly met with some holes being present, the chances of antibodies recognizing idiotopes on other antibodies are so overwhelming that, as Jerne (1984) has said, “the idioptic network idea is unavoidable”.

Repertoire completeness only ensures that at least one antibody will recognize an idiotpe. Whether that recognition will lead to a successful regulatory interaction depends upon many other factors, such as concentrations and affinities of the interacting molecules. In the physical chemical theory of antigen-antibody reactions one typically finds that it is the product $KC$ of antibody affinity, $K$, and antigen concentration, $C$, that is important in determining the fraction of antibody combining sites bound by antigen at equilibrium. Thus at high concentrations low affinity interactions are significant, whereas at low concentrations only high affinity interactions are important. A repertoire which is
complete at one concentration level need not be complete at lower concentrations that require higher affinity interactions. For example, if one required an affinity level of $10^8 \text{ M}^{-1}$ for a response, then one might find only $10^{-8}$ or $10^{-7}$ of B cells responding. With $p(K) = V_{c(K)}/V = 10^{-7}$, repertoire sizes of order $10^8$ would be needed for completeness. Because of the interplay between affinity and concentration and the degree of interconnection in a network, dynamic models of the type proposed by Jerne in Eq. (1) become important. After discussing recent advances in modeling we shall return to the question of repertoire completeness and network connectivity.

ANTIBODY REPRESENTATIONS

One of the major stumbling blocks in formulating a mathematical model of an idiotypic network is determining which antibodies react with which other antibodies. In a system with a repertoire of say $10^7$ elements how can one ever determine all of the possible interactions? Three approaches have been taken. In the first, no attempt is made and one simply assumes some simple relationship among idiotypes and anti-idiotypes. For example, Hoffmann's plus-minus network theory (Hoffmann 1975, 1979, 1980, Gunther & Hoffmann 1982) only deals with two specificities, an antigen-specific population and its anti-idiotypic partner. Richter (1975, 1978) dealt with a linear idiotypic network (Fig. 2) in which antibodies and/or cells (a distinction between the two has generally not been made in models) at idiotypic level $i$ interacts with populations at levels $i-1$ and $i+1$, for $i=0,1,\ldots,l$, and antigen is considered level 0. Although $l$, the number of levels in the network, could be very high in simulation studies $l$ is generally chosen to be rather small, i.e. $l<10$. Hiernaux (1977) dealt with a small cyclic network (Fig. 2). By prescribing the topology of the network one has, in essence, determined that all the antibodies (cells) in the repertoire can be assigned to the few classes in the network diagram.

The second approach assumes that the network is so large and complex that it is impossible to determine the relationships between the elements and one simply assigns them at random (cf. De Boer 1988, Hoffmann 1982, Hoffmann et al. 1988, Parisi 1989). This approach begins to confront the complexity that inherently can be in a network.

The third approach, which is one that I have pursued, assumes that the interactions in a network are determined by the specific chemical interactions between the various cells and molecules in the immune system. The basis of these interactions is what we previously called generalized shape. Thus if one knew the shape of each molecule one could predict which molecules would react and the affinity of their interaction. Even though we do not know the actual shapes of molecules one can find simple mathematical representations of antibodies that allow us to compute the degree of complementarity between molecules and even
assgin an affinity to their interaction. Various rules will give slightly different results but this type of formulation makes it possible to begin asking detailed questions about the topology of idiotypic networks and how that topology might vary due to structural constraints among antibody V regions. The representation introduced by Farmer et al. (1986) assigns to each antibody two binary strings of length \( n \), one representing the paratope and the other an epitope or idiotope (see Fig. 3). An antigen containing a single epitope is represented by single binary string, whereas antigens with multiple epitopes are represented by multiple strings. With this representation shape space is a hypercube of dimension \( n \). If one chooses \( n = 32 \), then one can represent \( 2^{32} \approx 4 \times 10^9 \) different determinants in this shape space. Thus with a 32-bit computer, such as a VAX or SUN workstation, one can represent systems with diversity comparable to that expressed in the mammalian immune system. One can view the binary strings representing an antibody as being related to the string of nucleic acids or amino acids that code for the V region.

Complementarity can be defined by any of a number of rules. Fig. 4 illustrates...
the simplest rule: two determinants are complementary if some threshold number of bits in their binary string representations are complementary. The number of complementary bits can be used to assign an affinity to the interaction (Farmer et al. 1986). Although computing complementarity by comparing binary strings was chosen for convenience, there is evidence suggesting that in some cases complementarity at the level of DNA may imply complementary at the protein level. If a peptide is transcribed from one strand of a double stranded DNA molecule and a "complementary peptide" is synthesized by reading from the complementary DNA strand, then the peptide and complementary peptide may bind specifically and with high affinity (Bost et al. 1985a,b, Smith et al. 1987, Shai et al. 1987). Further, in the case of the hormone ACTH, antibodies against ACTH and antibodies against the complementary peptide seem to be an idiotypic-anti-idiotypic pair, leading to the speculation that idiotopes and anti-idiotopes

**Figure 3.** Antibody and its binary string representation.

**Figure 4.** Complementarity between paratopes and idiotopes can be assessed by aligning the paratope and idiotope strings and then summing the number of positions at which a 1 is matched by 0. Here 6 out of 8 bits of the paratope of $Ab_7$ are complementary to the idiotope on $Ab_4$. 
may represent complementary sequences in the hypervariable regions of such immunoglobulin pairs (Smith et al. 1987).

Other rules can also be used for determining complementarity. For example, since the strings represent molecules they need not be aligned when they interact. Thus the number of complementary bits can be summed or chosen to be the maximum over all possible alignments (cf. Farmer et al. 1986). Molecules generally do not interact over their entire length, but rather interactions tend to be localized. Thus one can use a complementarity rule in which the number of adjacent complementary bits is important (cf. Stadnyk 1987).

The bit string representation is very powerful. Paratopes and idiotopes need not be the same size nor do they have to be distinct. The paratope and idiotope can overlap or even be chosen to be identical as in the symmetric network theory of Hoffmann. Multiple idiotopes can also be represented and framework regions introduced.

An example of an idiotypic network generated from the bit string representation is shown in Fig. 5. To make the diagram easy to visualize only 10 antibodies are in the network. Here epitopes and paratopes have been chosen as random sequences of 8 bits. A line is drawn connecting two antibodies if their paratope and idiotope are complementary at six or more bits. The lines are oriented in the direction of paratope–idiotope recognition. Thus the paratope on antibody 6 recognizes the idiotope on antibody 7. The network does not resemble either the linear or cyclic network of Fig. 2; rather it represents a complex interrelationship between the antibodies in the network. To a certain extent the network resembles

![Diagram of an idiotypic network generated from the bit string representation.](image

*Figure 5.* An example of an idiotypic network generated using the complementary match rule of Fig. 4. Idiotopes and paratopes are each 8 bits long and have been chosen at random. A line has been drawn connecting $Ab_i$ to $Ab_j$ if the paratope on $Ab_i$ is complementary to 6 or more bits of the idiotope on $Ab_j$. Paratope-paratope matches can also be allowed but they are not shown here.
a map of the antibody interactions connecting the immune responses to the acetylcholine receptor and α-1,3-dextran mapped by Dwyer et al. (1986). The network diagram can be decomposed into levels so that it appears analogous to the classical linear picture with antigen being level 0, $Ab_1$ being the set of antibodies directed against the antigen, $Ab_2$ being the anti-idiotypic antibodies, etc. The $Ab_2$ population can be decomposed into anti-idiotypic antibodies whose paratopes recognize the idiotope of $Ab_1$ ($Ab_{2a}$), and internal image antibodies that have idiotopes which are recognized by the paratope of $Ab_1$ ($Ab_{2p}$) populations (Jerne et al. 1982). For example, if antibody 6 were an $Ab_1$, then antibodies 3, 4, and 9 would be anti-idiotypic, i.e. $Ab_{2a}$, and antibodies 2, 7, and 8 would be internal images, $Ab_{2p}$. Because our complementarity rule does not require all bits to be complementary, $Ab_{2p}$ antibodies need not be exact images. In this example, antibodies 2 and 7 are only complementary at 6 out of the 8 bits and hence would be poor internal images, whereas antibody 8 is complementary at 7 bit positions and hence would be a better internal image. Other possibilities also arise. The paratope of an antibody can recognize its own idiotope. Self-recognizing antibodies have been found by Kohler and called “autobodies” (Kang & Kohler 1986). In the figure, three antibodies are autobodies, a surprisingly large number. Antibodies, termed epibodies or $Ab_{2e}$, have been found (Bona et al. 1982) which are complementary to both idiotopes on $Ab_1$ and the antigen. In this example, if antigen is introduced the paratopes on antibodies 6, 7 and 9 recognize the antigen (not shown). However antibody 6 also recognizes the idiotope on antibody 7 and hence would be an epibody. The antibodies in the network have different connectivities. Antibody 6 interacts with six other antibodies, and antibody 4 interacts with five other antibodies and itself. These antibodies mimic the high connectivity self antibodies found by Holmberg et al. (1984) in newborn mice.

**PHASE TRANSITIONS IN IDIOTYPE NETWORKS**

Analyzing the topology of idiotypic networks in detail, I uncovered what appears to be a phase transition in the structure of the network (Perelson 1989). De Boer (1989) and De Boer & Hogeweg (1989c) have made similar findings. Consider a system containing $N_{Ab}$ antibodies and a single antigen. Let each paratope, idiotope, and epitope be exactly $n$ bits long. Use the simple complementarity rule in Fig. 4 in which paratope and idiotope or epitope are aligned and the number of complementary bits counted. The number of bits must be above a threshold, denoted $n_0$, for recognition. Starting with the antigen, determine all antibodies that have paratopes that are complementary to the antigen. These are labeled as being in level 1, i.e. belong to $Ab_1$. All antibodies that have paratopes that recognize idiotopes on antibodies in $Ab_1$ or which have idiotopes recognized by the paratopes of $Ab_1$ antibodies are placed in level 2, i.e. $Ab_2$, as long as they are not in $Ab_1$. We continue in this manner, assigning an antibody to level $i$ if it...
matches an antibody in level $i - 1$, and if it has not already been assigned to some previous level. This latter condition ensures that each antibody is assigned to a unique level. The network can then be represented as a tree with the antigen as its root.

Fig. 6 illustrates a network diagram drawn in this way. Notice all $N_{ab}$ antibodies in the system need not appear in the diagram. For example, if no antibody matches the antigen the diagram will contain only the antigen root. There is nothing special about the antigen, the diagram can “die out” at any level because of a lack of matches. Thus, beginning with any root all of the antibodies in the system need not be assigned to an idiotypic level, only those that are somehow are connected to the antigen appear. When different antigens are presented different subsets of the system may appear in such diagrams. Also, if a different set of $N_{ab}$ antibodies is constructed the diagram will most likely look different. For example, the number of levels need not be the same.

Both the probability of the tree lacking some of the antibodies in the system and the number of levels in the tree depend on the complementarity rule being used and the recognition threshold $n_0$. For example, consider a system with 100 antibodies each represented by a single string 32 bits long (i.e. $N_{ab} = 100$ and $n = 32$) and the complementarity rule of Fig. 4. If we choose $n_0 = 32$, so that all bits must match, then the tree will be trivial, almost assuredly containing only the antigen. The probability of a match is $1/2^{32} \approx 2^{-10}$ and hence the system would need to contain $5 \times 10^9$ antibodies in order to expect even a single match. On the other hand, if $n_0 = 10$, all antibodies will most likely match the antigen. Because

![Figure 6. A network of 10 antibodies drawn as a rooted tree.](image-url)
bits are chosen at random with 0 and 1 having equal probability, on average half of the bits will be complementary. Thus if \( n_\theta \leq n/2 \) we expect all molecules to match each other, and all of the \( N_{Ab} \) antibodies to be in level 1. This is not a very realistic case. At values of \( n_\theta > n/2 \) there should be some matching between network elements, but all elements will no longer match the antigen. Thus one would expect trees with increasing numbers of levels. As \( n_\theta \) approaches \( n \) matches become rare, and both the number of levels and the number of antibodies in the tree will decrease. As reasoned above, when \( n_\theta \) reaches \( n \) we expect no antibodies in the tree if \( N_{Ab} < 2^n \).

To summarize, if one varies \( n_\theta \) or, equivalently, the probability of an antibody recognizing an epitope or idiotope, one expects the graph of the maximum level reached in the tree versus \( n_\theta \) to approximate a smooth curve starting at one, rising, going through a maximum, and declining toward zero. Not surprising, this is precisely what we find via Monte Carlo simulations as we scan all possible values of \( n_\theta \). However, if one examines the curves that result for different values of \( N_{Ab} \) one finds a surprising feature: the graphs approach a curve with a singularity at a critical value of \( n_\theta \) as \( N_{Ab} \) becomes large. In Fig. 7 I illustrate this for systems of size 100, 300 and 500. The behavior shown in the figure is typical

![Figure 7](image_url)

*Figure 7. Phase transition in an idiotypic network. Shown are the results of 50 \( (N_{Ab} = 100) \) or 100 \( (N_{Ab} = 300, 500) \) Monte Carlo runs. In each run a network graph of the form shown in Fig. 5 was generated, and the maximum level reached recorded. The maximum level attained in all of the runs is plotted for systems with 100, 300, and 500 antibodies. The number of bits in each string, \( n = 20 \). In the graph for \( N_{Ab} = 500 \) a set of runs was done with \( n = 32 \) to mimic a connectance that could be attained with \( n_\theta = 16.5 \).*
for a system with a phase transition. There is a critical value of \( n_0 \), which I call \( n_c \), at which the number of levels in an idiotypic network rises very sharply. For the system with 500 antibodies a maximum of 29 layers are encountered at \( n_c \). For systems containing \( 10^7 \) antibody types, I imagine that at the critical point thousands of levels may be present. Outside the phase transition region the network may be minimal. Simulations with \( N_{Ab} = 10^7 \) are not feasible and thus it is important to understand how the phase-transition scales with system size.

A simple argument based on percolation theory (cf. Stauffer 1985) on a Bethe lattice can be used to explain the phase transition in idiotypic networks. A Bethe lattice is an infinite lattice in which each node is connected to at most \( z \) other nodes; \( z \) is called the coordination number of the lattice. The lattice can be drawn in levels (or generations) in the same manner as an idiotypic network (Fig. 8). Because the lattice is infinite some modification of the following argument will be needed to make it rigorous for a finite system but the general idea should remain valid. Let \( E(i) \) be the expected number of antibodies on the \( i \)th level, and let \( p \) be the probability that two antibodies are connected. Then, the expected number of antibodies on level \( i+1 \),

\[
E(i+1) = E(i) \times (z-1)p.
\]

If \((z-1)p > 1\) there is a positive probability that the lattice will grow to infinite size. When this occurs a disturbance created by an antigen at level 0 can affect an infinite number of antibodies.

![Figure 8. Percolation on a Bethe lattice with coordination number \( z \). Each antibody on the \( i \)th level is connected to 1 antibody on level \( i-1 \) and at most \( z-1 \) antibodies on level \( i+1 \). If each such connection occurs with probability \( p \), then the expected number of antibodies in level \( i+1 \) is equal to the number in level \( i \) times \((z-1)p\). If \((z-1)p > 1\) there is a positive probability that the lattice will grow to infinite size. When this occurs a disturbance created by an antigen at level 0 can affect an infinite number of antibodies.](image)
\(E(i+1) = p(z-1)E(i)\).

The factor \(z-1\) arises because each antibody on level \(i\), \(i \geq 1\), is connected to an antibody on level \(i-1\) and thus can be connected to at most \(z-1\) antibodies on level \(i+1\). Thus, on average, the total number of possible connections from level \(i\) to level \(i+1\) is \((z-1)E(i)\), and \(p\) is the fraction of these that are actually made. When

\[p > p_c = 1/(z-1),\]

\(E(i+1) > E(i)\), and the network will grow without bound as \(i\) increases. When \(p < p_c\), \(E(i+1) < E(i)\) and the graph will terminate after a finite number of levels. \(p_c\) is the threshold between these two qualitatively different behaviors and is called the critical percolation threshold. Precisely the same argument for a percolation threshold has been used to explain the formation of antibody-antigen precipitates and underlies the quantitative theory of the precipitin curve and the formation of microscopically visible cell surface receptor-ligand aggregates called “patches” (cf. Goldberg 1952, DeLisi 1974, DeLisi & Perelson 1976).

For idiotypic networks each antibody can, in principle, be connected to all others. Hence \(z = N_{Ab} - 1\) and

\[p_c \approx 1/N_{Ab}.\] (4)

Further, from the complementarity rule one can easily compute the probability that a paratope and idiotope are complementary. Because 0 and 1 are equally probable,

\[p = \sum_{i=n_0}^{n} \binom{n}{i} \left(\frac{1}{2}\right)^i \left(\frac{1}{2}\right)^{n-i} = 2^{-n} \sum_{i=n_0}^{n} \binom{n}{i}.\] (5)

Hence each value of \(n_0\) corresponds to a different value of \(p\). Using this correspondence one finds (Perelson 1989) \(n_c\), the critical value of \(n_0\) that corresponds to \(p = p_c\) to be approximately 15 for \(N_{Ab} = 100\), approximately 16 for \(N_{Ab} = 300\), and to be between 16 and 17 for \(N_{Ab} = 500\). Fig. 7 shows the validity of these three predictions.

The properties of the immune system on the two sides of the phase transition, and in the transition region, are summarized in Table 1. In the “pre-critical region”, where \(p < p_c\), i.e. \(n_0 > n_c\), the network is very sparse and composed of many unconnected components. Each antibody, on average, is connected to less than one antibody on the next level since \(p(z-1) < 1\). Including the connection to the previous level, each antibody is connected to less than two antibodies in the network. (De Boer (1989), discusses an alternative criterion for the phase transition derived from the theory of random graphs by Erdös and Rényi and based on the average connectance of each node). In the pe-critical region, no network \textit{per se} exists. Rather, there are many small, discrete, non-interacting...
subnetworks, or network “components”. Each antigen is connected to a small number of antibodies and these in turn are connected to rather few other antibodies. With one antigen one can not excite the entire network, only the component in which the antigen lies. In the “post-critical region” $p > p_c$, i.e. $n_\theta < n_c$, the network is highly connected. Although there still may be more than one non-interacting subnetwork, there is a non-zero probability that all antibodies are part of a single component. In general, the post-critical region is characterized by a single large component and many small ones. This is analogous to a large molecular network, i.e. a gel, being in equilibrium with many small molecular aggregates, i.e. a sol. As $p$ is increased or $n_\theta$ decreased the probability of a single global network increases. Concomitantly, the observed connectivity of the network increases. The number of antibodies at each level increases and in a finite system fewer and fewer levels are needed to account for all antibodies. Ultimately, when $p = 1$, all antibodies recognize the antigen and are on level 1.

Why is the existence of this phase-transition interesting? Among immunologists the relevance of idiotypic networks to the functioning of the immune system is controversial (cf. Cohn 1986). Langman & Cohn (1986) have argued that a complete idiotypic network is an absurd immune system. Some immunologists believe that idiotypic networks are an epiphenomenon and of no functional relevance, whereas others believe that idiotypic networks are the core of the immune system, accounting for much of the normal activity of the immune system in times of health and controlling the system in times of disease (cf. Coutinho et al. 1984). The phase-transition is a marker. On one side of it the network is so sparse that signals can not propagate through many idiotypic levels. Some idiotypic anti-idiotypic interactions will be present but the topology of the network will prevent a cascade of antibodies against antibodies from occurring. On the other side the network is highly connected and idiotypic interactions can lead to communication among all clones in the immune system. Signals have pathways by which they can propagate very deeply into the idiotypic network and network
interactions may dominate any response. Such systems will require control or else a small perturbation could trigger the entire immune system. Antibody affinities and concentrations become important in determining whether or not deep penetration of the network will in fact occur. Based on our knowledge of neural networks one can hypothesize that in the post-critical region the immune system will have the potential for very many different modes of activity, a richness that one might expect of a system that is to learn, have memory, and react in different ways to different antigens.

In order to assess the importance of this phase transition one must estimate parameters characterizing the immune system. From the percolation result, \( p_c \approx N_{\text{Ab}}^{-1} \), one sees that it is crucial to estimate \( N_{\text{Ab}} \), the number of different antibodies in the repertoire, and \( p \), the probability that two randomly chosen antibodies recognize each other with an affinity above that required to activate B cells. The size of the repertoire that is expressed in a given individual is not precisely known. A mouse contains approximately \( 10^8 \) small B lymphocytes. Average clone sizes are thought to be between 10 and 100 (Jerne 1984), and thus the expressed repertoire, i.e. the repertoire of immunoglobulins carried on the surfaces of B cells, would be between \( 10^6 \) and \( 10^7 \), values that agree with other estimates (Holmberg et al. 1986). Repertoires of \( 10^7 \) or larger are also quoted (cf. Klinman & Press, 1975, Sigal & Klinman 1978). Using these value for \( N_{\text{Ab}} \), \( p_c \leq 10^{-6} \). Since typical values for \( p \) are \( 10^{-5} \) it seems that, at the level of the expressed repertoire, not only is a phase transition possible but the immune system is in the post-critical regime, i.e. \( p > p_c \). In this regime the immune network is highly connected and deep penetration is possible.

If one considers the actual repertoire (Holmberg et al. 1986) represented by serum antibody, the situation changes. Not all B cells in the expressed repertoire are expected to be active. If 10% or fewer of B-cell clones are secreting antibody then \( N_{\text{Ab}} \) may be of order \( 10^5 \). If this is the case then \( p \) and \( p_c \) may be comparable and it is a delicate matter as to which side of the phase transition the immune system lies.

Topology is only one aspect of immune networks. It places bounds on what is possible. In the pre-critical region the network is very sparse and it is impossible for antigen or any internal perturbation of the network to spread throughout the immune system. In the post-critical region, the immune network is highly connected and it is possible for global excitation to occur. However, whether it does occur or not is now determined by the dynamical interactions between the elements of the immune system. In a dynamical model of idiotypic networks (Segel & Perelson 1988) described below, we have shown that the tuning of a single parameter can cause the behavior of the model to switch from network-like, in which many clones and their anti-idiotypic clones are excited, to a model in which only a single clone that recognizes antigen is excited. For random networks made of elements which can either be “on” or “off” conditions have
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been derived (cf. Weisbuch 1989) which ensure that the system will have rich
dynamical behaviors that remain localized in the network. In the real immune
system, T cells, antigen-presenting cells, various cytokines and growth factors
must play an important, if not crucial, role in regulating the activity of the
immune network. These controls seem to prevent global activation of the network,
still leaving the question of whether they allow substantial network activity.

SHAPE SPACE ANALYSIS OF IMMUNE NETWORKS

Large complex networks such as those generated by matching antibody bit strings
can only be studied by computer simulation. Farmer et al. (1986, 1987) and De
Boer and Hogeweg (cf. De Boer 1988, 1989; De Boer & Hogeweg 1989a,b,c,d)
have pioneered this approach. While insights can be gained by this approach,
one is uncertain if the dynamical equations being simulated are correct (cf.
Perelson 1988). Modeling the dynamics of the immune system mathematically
seems to be at the same stage as was modeling in neurophysiology before Hodgkin
and Huxley; there are many mathematical models but none clearly summarizes
a wide body of experimental findings. In fact, much of De Boer's work has been
aimed at pointing out that a variety of network models are unrealistic. A further
concern in all modeling, but especially when numerical solutions or computer
simulations are employed, is whether or not the parameter values chosen are
the most relevant ones. Dynamic behavior can change drastically with small
adjustments in parameter values (cf. Kevrekidis et al. 1988). Segel & Perelson
(1988, 1989a,b,c) have developed a class of simple models that captures the cross-
reactivity of immune networks and which are amenable to mathematical analysis.
With these models we have tried to emphasize certain principles of stability and
design of the immune system and we have begun to explore the ability of the
immune system to generate organized patterns of behavior.

The basis of this work is the creation of a one-dimensional shape space. We
describe the shape of a molecule by a single continuous variable \( x \) which, for
example, one can view as the height of a bump in the combining site. If \( x \) is
negative then it describes an indentation rather than a bump. Hence we assume
that molecules of shape \( x \) and \(-x\) are exactly complementary. Other molecules
\( y \), i.e. with shape \( y \), may also fit \( x \) but not as well as when \( y = -x \). To describe
this we assume the affinity of \( y \) with \( x \) is a gaussian centered at \( y = -x \).

Using this one-dimensional shape space we (Segel & Perelson 1988) formulated
a "toy model" embodying the dynamics of interactions in shape space. In this
model, the fundamental unknown function is \( b(x,t) \), which can be regarded for
definiteness as the number (or concentration) of lymphocytes with receptors of
shape \( x \) that constitute the immune system at time \( t \). If one were to plot \( b(x,t) \)
versus \( x \) at a fixed time, the graph would show the distribution of clones in shape
space. If the graph were a horizontal line, i.e. \( b(x,t) = \tilde{b} = \text{constant} \), then all clones
would be present at the same concentration. (Fig. 9). If some clones were present in high concentration then the distribution would have peaks (Fig. 9c). The distribution of clones should evolve in time. When antigen-expressing epitopes of shape \( x \) are present the system should respond with a high concentration of complementary clones with shape \(-x\). Memory in this system would correspond to the peak at \(-x\) remaining for long periods of time. Thus patterns in shape space should reflect both the internal activities of the immune system and its antigenic history. Consequently, an important feature of an immune system model is that it should be able to develop patterns in shape space.

The general problem of how biological systems develop pattern has been most intensively studied in developmental biology beginning with the pioneering work of Turing (1952). From the work of Gierer & Meinhardt (1972), Ermentrout et al. (1986), Ermentrout & Cowan (1979), Levin & Segel (1982) and others covering applications in fields as diverse as developmental biology, neurobiology and ecology, one finds that a general principle for the formation of pattern is the presence of influences which activate over short distances and which inhibit over long distances (cf. Meinhardt 1982, Oster 1988). This principle is sometimes called "short-range activation and long-range inhibition". To bring this principle to bear, Segel and I developed the following model:

The lymphocyte population is divided into two classes, stimulated and unstimulated. The structure of the model can be represented as

\[
\text{rate of population increase} = \text{influx from bone marrow} - \text{death of unstimulated cells} + \text{reproduction of stimulated cells.}
\]

\[
\begin{align*}
\text{(a)} & : t = 0 \\
\text{(b)} & : t = 100 \\
\text{(c)} & : t = 100
\end{align*}
\]

**Figure 9.** The distribution of clones in shape space. The dashed line indicates a uniform distribution in which each clone is present at the same population level. This is a potential steady state of the system, i.e. \( b(x,t) = b \). The stability of this uniform state can be examined by perturbing it (solid line). If the perturbed distribution (a) returns toward a uniform distribution (b) then the uniform distribution is said to be stable. In the case of instability, (a) evolves toward a less uniform distribution (c).
In mathematical form this equation becomes

$$\frac{\partial b}{\partial t} = m - db [1 - a] + r(B,b)a. \quad (6)$$

Here $m$ is the rate of supply of new cells from the bone marrow, $d$ is the death rate of unstimulated cells and $r(B,b)$ is the rate of growth of stimulated cells. This growth rate is assumed to depend upon the total number of lymphocytes in the system, $B$, as well as the size of the clone with receptors of shape $x$, i.e. $b(x)$. Perhaps the most important point in the formulation is that the fraction of cells of shape $x$ which are stimulated to grow, $a$, depends on both activating and suppressing signals. If shapes range between $L$ and $-L$, then the strength of the activation signal

$$A(b) = \frac{\text{fraction of } x\text{-cells' activating receptors}}{\text{bound when cell distribution in shape space is given by } b(y,t)} = \int_{-L}^{L} a(x,y)b(y,t)dy.$$ 

The function

$$a(x,y) = a_m(2\pi \sigma_a^2)^{-1/2} e^{-\frac{(x + y)^2}{2\sigma_a^2}}$$

which is a gaussian centered at $y = -x$ can be viewed as the association constant for $y$ binding to activating receptors on $x$ cells in the limit that only a small fraction of the receptors are bound. The constants $a_m$ and $\sigma_a$ represent the amplitude and the width of the gaussian.

The strength of suppressive signals, $S(b)$, is defined in a similar way using a gaussian kernel $s(x,y)$ of width $\sigma_s$ representing the affinity of "suppressive receptors". The fraction of cells activated, $a$, is then a function of $A$ and $S$ that increases (decreases) if more activator (suppressor) receptors are bound. For example,

$$a = \frac{A}{p + qS + A}$$

has these properties when $p$ and $q$ are chosen as positive constants. The principle of short-range activation and long-range inhibition is incorporated into the model by choosing the width of the activation gaussian greater than the width of the suppressive gaussian.

The suppressive receptors are not explicitly defined in the model. On B cells they may be Fc receptors (cf. Uher & Dickler 1986), receptors for interferon-$\gamma$ (cf. Reynolds et al. 1987), transforming growth factor-$\beta$ receptors (Kehrl et al. 1986a), or the immunoglobulin receptor itself, which when cross-linked can give a suppressive signal to B cells in some stages of development (cf. Teale & Klinman...

With this model we were able to show that patterns form if the short-range activation and long-range inhibition principle is followed (Segel & Perelson 1988, 1989a,b). However, unlike other systems in biology we were able to establish that patterns can also form if the inhibition is short-range and the activation is long-range (Segel & Perelson 1989c). Range in shape space is equivalent to specificity. Thus, short-range activation and long-range inhibition translates into specific activation and less specific inhibition. A signal which is non-specific has infinite range in shape space, i.e. it affects all cells. We have not been successful in generating a pattern with infinite range inhibition.

Specificity and range also correlate with the affinity threshold used to define a recognition ball in shape space. Thus in Fig. 1, as the affinity threshold is decreased the recognition ball will get larger and interactions can occur over a longer range. The pattern formation rules, short-range activation and long-range inhibition or vice versa, thus translates into having different affinity thresholds for activation and tolerance induction in B cells. This may relate to the difference in affinity thresholds for mature and immature B cells (Riley & Klinman 1986).

In addition to illustrating that patterns can be formed in shape space, one can learn several things from this highly simplified model. I shall discuss only one: the trade-off between good stability properties and good controllability properties. In designing a control system for an aircraft or an automobile one attempts to create a system that remains largely unaffected by small random disturbances, but one which can modify its course in response to a “purposeful” command. A system whose state more or less remains unaffected by small disturbances is called stable. If a system is too stable, it will be relatively insensitive to commands. Thus an airplane that remains virtually unbuffeted by even quite strong gusts of wind will also respond very sluggishly to a deflection of its rudder. Because of this, modern fighter planes are designed to be slightly unstable and computers constantly adjust their course.

The immune system is constrained by the same stability-controllability trade-off. Thus, as a general principle, we believe the immune system should be stable but not too stable. If this is the case, the immune system can remain insensitive to small random disturbances but yet be responsive to antigenic challenge. The concept of stability is further illustrated in Fig. 9.

Motivated by these considerations, we analyzed the stability of an immune system in a “virgin” state in which all clones have a population level determined by a balance between influx from the bone marrow and unperturbed death. The distribution in shape space was assumed to be uniform (Fig. 9a). The stability of other, non-uniform, distributions can also be analyzed, but this is more difficult mathematically. Because of the stability-controllability trade-off we suggested that the immune system has evolved so that its parameters are in the stable...
domain, but not too far from the borders of this domain. We then calculated 
relations between parameters (Segel & Perelson 1988) that corresponded to the 
boundary between stability and instability and showed that our model immune 
system was more responsive to antigenic challenge near this border than when 
far away from it. Further, we were able to show that the system had the capability 
of responding either as a network, with idiotypic and anti-idiotypic responses, or 
in a non-network manner with only the clones recognizing the antigen responding, 
the differences between these classes of responses having to do with the details 
of the clonal growth law $r(B,b)$. Even in network responses, we found that, 
because of subtle feedbacks in the system due to the range of the activating and 
suppressive interactions, clones which were neither complementary to the antigen 
or $Ab_1$ antibodies were excited. Thus the system spontaneously established back-
ground activity.

MEMORY IN A NETWORK ENVIRONMENT

Theorists have two views of memory. One view is dynamic in which clones are 
maintained at an elevated level due to stimulation via network interactions or 
retained antigen. In this view memory cells should be activated cells. The other, 
more classical, view is one in which memory is static and maintained by resting, 
long-lived memory cells. The views are not contradictory and memory may be 
carried by both static and dynamic means. Using the one-dimensional shape 
space model, Segel & Perelson (1989b) examined how long-lived memory cells 
would fare in a network environment. In this study memory cells were assumed 
to be identical to virgin cells except that they live longer, i.e. have a lower 
death rate $d$. The question asked was, in the absence of antigen would network 
interactions allow memory clones to be maintained at elevated levels or would 
the network try to self-regulate in such a way that memory clones would be 
reduced in population size so as to approach a common stable background level?

To study this question the parameters in the immune system model were set 
in a regime where a uniform distribution of clones in shape space would be stable. 
The death rate of one clone was then lowered in order to mimic its being a 
memory clone. From Eq. (6) it is easy to see that lowering the death rate of a 
clone increases its steady state population size. Segel & Perelson (1988) also 
showed that lowering the death rate tends to shift the parameters characterizing 
a clone toward a region of instability. They thus hypothesized that the memory 
clone might maintain an elevated population level by being an “unstable” island 
in a stable “sea”. Numerical solution of Eq. (6) showed that the memory clone 
persisted when its parameters were set in the unstable range, as was expected; but, 
surprisingly, the memory clone also persisted with its parameters set somewhat in 
the stable range. Further, the existence of the memory clone had an effect on the 
network and a set of clones centered around its anti-idiotypic partner had popula-
 tion levels that were elevated (depressed) compared with background when activation was shorter (longer) range than inhibition. This analysis does not argue for or against static or dynamic memory. It only shows that the classical notion of a memory cell is compatible with a simple network model of the immune system. It remains to be seen whether these conclusions remain valid with more realistic network models (c.f. Perelson 1988, Segel & Perelson 1989a).

NETWORK MODELS WITH BOTH CHEMICAL AND CELLULAR COMPONENTS

Idiotypic network models that have been formulated mathematically generally have not distinguished between cells and molecules; models by Hiernaux & Bona (1979), Varela et al. (1988) and De Boer & Hogeweg (1989c) being exceptions. Since idiotypic determinants are found on both cells and antibodies this was not considered an important issue for early models. This clearly needs to change and we need to come to grips with the different properties of antibodies, B cells and T cells. Idiotypic interactions can either stimulate or suppress. In the model of Jerne's given by Eq. (1) idiotypes were broken down into stimulatory and inhibitory subsets. Although both types of interactions may be necessary to control an idiotypic network they need not be built in to the properties of specific cell types. For example, it is well known that if cell triggering is assumed to be proportional to the fraction of cell surface receptors that are cross-linked, then little or no stimulation will occur in antigen excess (cf. Perelson & DeLisi 1980). Also various feedback signals that may be important in regulation can also be incorporated into idiotypic networks once chemistry is allowed. Here I would like to illustrate some of these points with what I consider to be one of the simplest idiotypic networks with chemistry. This model is derived from a one-dimensional shape space model that incorporates antibody–receptor binding but no cross-linking (Segel & Perelson 1989a). Possible inhibitory effects mediated by antibody-dependent cellular cytotoxicity or the binding of immunoglobulin complexes to Fc receptors are ignored here but can easily be included in later models.

Consider a system composed of two B cell populations, $B_1$ and $B_2$ (see Fig. 10). Let $B_1$ recognize antigen $G$ and assume that $B_2$ has receptors that are complementary to those on $B_1$. For example the receptors on $B_2$ may have an idiotope that is an internal image of the antigen. At a minimum, the following events seem important to model: Antigen binds to receptors on $B_1$, cross-links them and possibly leads to proliferation and the production of antibody, $A_1$. Antibody $A_1$ binds antigen and leads to its elimination. It also binds receptors on $B_2$, cross-links them and possibly leads to proliferation and the production of antibody $A_2$. Antibody $A_2$ can bind $A_1$ in solution to form immune complexes that are eliminated, or $A_2$ can bind receptors on $B_1$ and either stimulate or inhibit the cell depending on the level of cross-linking induced. Note that the formation
**Figure 10.** A simple idioptic network with chemistry. The network contains two populations of B cells, $B_1$ and $B_2$. The receptors on $B_1$ are complementary to the antigen $G$. The receptors on $B_2$ are complementary to those on $B_1$. When stimulated, via receptor cross-linking, $B_1$ and $B_2$ proliferate and secrete bivalent antibodies $A_1$ and $A_2$, which react in solution to form a complex $C$, or which bind to complementary cell surface immunoglobulin. Antibody $1$ bound to surface immunoglobulin by one Fab arm is called singly bound ($A_{1s}$), whereas it is called a cross-link ($X_1$) when bound by both Fab arms to two different cell surface immunoglobulin molecules.

of $A_1\sim A_2$ immune complexes eliminates $A_1$, the signal stimulating $B_2$. Thus the response of $B_2$ can turn off the signal that is stimulating it if immune complex formation dominates the chemistry or it can lead to the production of more $A_1$ and possibly greater stimulation through receptor cross-linking and stimulation of $B_1$. Predicting the outcome of such events is difficult and a mathematical model can help determine the various possibilities.

The basic chemical reactions underlying the model are the binding of $A_1$ to free receptor sites ($S_2$) on $B_2$:

$$A_1 + S_2 B_2 \stackrel{k^+}{\rightleftharpoons} A_{1s} B_2.$$  \hspace{1cm} (7a)

The concentration of free immunoglobulin receptor sites per $B_2$ cell is denoted $S_2$. Because the concentration of B cells can change in the model their concentration is indicated in the reaction. This reaction leads to the formation of an antibody-receptor complex in which $A_1$ is bound by one Fab. We call this species a singly bound antibody and denote its concentration per cell $A_{1s}$. A singly bound antibody still has one free Fab which can bind to another free receptor site ($S_2$) on $B_2$ to form a receptor cross-link ($X_1$) on the surface of $B_2$: 
As a similar set of reactions occurs between $A_2$ and receptors on $B_1$, i.e.

$$A_2 + S_1B_1 \xrightarrow{k_{+c}} A_{2c}B_1, \quad (7c)$$

$$A_{2c}B_1 + S_1B_1 \xrightarrow{k_{x+}} X_2B_1. \quad (7d)$$

In solution, the formation of antibody-antibody complexes ($C$) occurs:

$$A_1 + A_2 \xrightarrow{k_{x+}} C. \quad (7e)$$

For simplicity, consider $A_2$ to be the antigen which stimulates $B_1$. Also, assume that the rate constants $k_{x+}$ and $k_{x-}$ characterizing the reaction of $A_1$ with $S_2$ are the same as those characterizing the reaction of $A_2$ with $S_1$. A similar symmetry condition is applied to the cross-linking reactions (7b) and (7d).

The total number of immunoglobulin receptors per cell is assumed to be constant. In later models this restriction can be relaxed and receptor synthesis and internalization modeled. Since receptors are bivalent, the total number of receptor sites per cell $S_0$ obeys the following conservation law (Perelson & DeLisi 1980):

$$S_0 = S_i + A_{is} + 2X_i, \ i = 1, 2. \quad (8)$$

These chemical reactions can now be incorporated into a model for the growth and decay of the B-cell populations:

$$\frac{dB_1}{dt} = m + r(X_2, B_1, S_1)B_1 - \mu_b B_1, \quad (9a)$$

$$\frac{dB_2}{dt} = m + r(X_1, B_2, S_2)B_2 - \mu_b B_2, \quad (9b)$$

where $m$, is the rate of generation of new B cells in the bone marrow and $\mu_b$ is their specific death rate. The stimulation and subsequent growth of B cells is modeled by $r$, the specific growth rate function. I assume that $r$ depends on the degree of receptor cross-linking, $X$, the B-cell density, and the rate of antibody secretion $s$. Receptor cross-linking is included to model the degree of cell stimulation. If the B cells are growing in a lymphoid organ then space, nutrients and growth factors may limit the size of the clone. The density dependence models these effects. Lastly, as B cells differentiate into plasma cells their antibody secretion rate increases but their rate of growth slows or even stops. We model
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this by making the B-cell growth rate a decreasing function of the antibody secretion rate. A specific choice for \( r \) is:

\[
    r(X_2, B_1) = \left( \frac{r_0 X_2}{f X + X_2} \right) e^{-\lambda B_1} e^{-\eta},
\]

(10)

where \( R \) is the total number of immunoglobulin receptors on a B cell and \( f \) is a parameter controlling the fraction of receptors that need to be cross-linked to give a stimulatory signal. When \( X \) is equal to \( f X \) the term in parentheses is half the maximal growth rate \( r_0 \). The constant \( \lambda \) controls the density dependence so that growth slows only when \( \lambda B_1 \gg 1 \). Likewise, the constant \( \eta \) controls the decrease in growth with increases in the rate of antibody production \( s_i \).

The rate of antibody secretion \( s \) is assumed to be determined by the degree of B-cell activation. As a simple model I use the fraction of receptor sites cross-linked as an indicator of the state of stimulation. Thus for cell \( i \),

\[
    \frac{ds_i}{dt} = k_s q_i(X_i/S_0) - k_s s_i, s_i(0) = 0, i = 1,2.
\]

(11)

This equation has the property that the secretion rate starts at zero and ultimately reaches a steady value on a time scale determined by \( k_s \). The function \( q_i \) describes the dependence of the steady state secretion rate on the extent of receptor cross-linking. In the example given below (Fig. 11), \( q_i(X_i/S_0) = q X_i/S_0 \) was chosen for simplicity, where the constant \( q \) is the maximal antibody secretion rate. However, a function which rises monotonically and then saturates would also be a reasonable choice for \( q_i \). By using a differential equation to determine \( s \), we account for the delays involved in lymphocyte activation and the "gearing up" for large amounts of antibody secretion that occurs during B-cell differentiation into a plasma cell.

The concentration of antibody in solution is determined by a balance between secretion, degradation and binding to cell surface receptors and anti-idiotypic antibodies. Thus

\[
    \frac{dA_1}{dt} = s_1 B_1 - \mu A_1 - 2k_+ A_1 S_2 B_2 + k_- A_2 S_2 B_2 - 4k_+ A_1 A_2 - k_- C,
\]

(12a)

where \( \mu \) is the rate of antibody loss through catabolism. The factors 2 and 4 are statistical factors introduced because the rate constants are defined per site. An antibody in solution has two free sites and thus there are two ways in which it can combine with a free receptor site. Similarly, there are four ways in which a free site on \( A_1 \) can combine with a free site on \( A_2 \). The factor \( B_2 \) enters because \( S_2 \) and \( A_1 \) are concentrations of free and singly bound receptors per cell and antibody can bind receptors on any cell.
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The concentrations of singly bound antibody and cross-links change according to

\[
\frac{dA_{1s}}{dt} = 2k_+A_1S_2 - k_-A_{1s} - k_x + A_{1s}S_2 + 2k_x - X_1, \quad (12b)
\]

\[
\frac{dX_1}{dt} = k_x + A_{1s}S_2 - 2k_x - X_1. \quad (12c)
\]

The factor 2 multiplying \(k_x\) is also a statistical factor – either of the bound Fab arms of a cross-linked antibody can dissociate. Precisely the same equations hold for \(A_2, A_{2s}\) and \(X_2\) if the subscripts 1 and 2 are interchanged in Eqs. (12a)-(12c).

Lastly, the concentration of antibody complexes is governed by

\[
\frac{dC}{dt} = 4k_c + A_1A_2 - k_c - C - \mu_c C, \quad (13)
\]

where \(\mu_c\) is the rate of elimination of antibody complexes.

Introducing chemistry has clearly complicated matters. This “simple” system of an idiootype and its anti-idotype is described by a system of 11 ordinary differential equations for the variables: \(B_1, B_2, s_1, s_2, A_1, A_2, A_{1s}, A_{2s}, X_1, X_2,\) and \(C\). The conservation equations (8) can be used to eliminate two of the equations. Also, because the chemical reactions typically take place on a time scale of seconds to minutes, whereas cell growth and death and elimination of antibody and immune complexes typically occurs over a period of hours and days, one can further simplify the model by assuming the chemical reactions are at equilibrium on the time scale relevant to cellular changes. This can be done formally using the “method of multiple scales” (cf. Lin & Segel 1974) as shown in Segel & Perelson (1989a), and results in a mixed system of ordinary differential and nonlinear algebraic equations. This procedure is not the same as the quasi-steady-state assumption used in enzyme kinetics, and differential equations for the total amount of antibody and complex in the system remain.

Analyzing the dynamics of this system for different parameter values shows that the system can exhibit quite complex behavior: approach virgin or immune steady states, undergo sustained or damped oscillations, and exhibit aperiodic (i.e. chaotic) behavior. Figure 11a shows that under quite reasonable parameter choices the system can undergo sustained oscillations with the concentrations of idiotypic and anti-idiotypic antibodies fluctuating inversely with a period of approximately 80 days. These oscillations are reminiscent of those found by Rodkey & Adler (1983) in a year-long study of naturally induced auto-anti-idiotypic antibodies in the rabbit, in which one could also identify peaks separated by 80 d. The oscillations found by Rodkey & Adler were much more irregular than those in Fig. 11a. Choosing slightly different parameters gives rise to irregular
Figure 11. Dynamics of the two B-cell network. (a) The system oscillates with the \( A_1 \) and \( A_2 \) populations having an inverse relationship. The period is approximately 80 d. The parameters used in the numerical solution correspond to receptor affinities of \( 10^7 \) M\(^{-1} \). The antibody-antibody association constant \( k_{a+/a-} = 10^7 \) M\(^{-1} \). The number of receptors per cell, \( R = S_0/2 \), was taken as \( 10^5 \) or \( 1.67 \times 10^{-10} \) cm\(^{-2} \). The cross-linking equilibrium constant \( k_{c+/c-} = 10^{10} \), so that when multiplied by \( R \) it was of order one. The decay rates \( \mu_a = 0.3 \) d\(^{-1} \), \( \mu_x = 0.1 \) d\(^{-1} \), \( \mu_c = 2 \) d\(^{-1} \), correspond to 3 d B cell, 10 d antibody and 12 h complex lifetimes. An average of 5 d was chosen for "gearing up" to full antibody production, i.e. plasma cell formation. Thus, \( k_s = 0.2 \) d\(^{-1} \). The maximum antibody secretion rate \( q = 10^4 \) molecules per cell per second, or \( 1.44 \times 10^{-15} \) mol d\(^{-1} \). The maximal B cell growth rate \( r_b = 1.0 \) d\(^{-1} \), and \( f_c = 0.1 \) so that 10% of receptors need to be cross-linked for half-maximal stimulation. The parameters \( \lambda = 0 \) and \( \eta = 0.5 \). The unit of volume was chosen as 1 cm\(^3 \), and the cell influx rate \( m = 2.4 \times 10^4 \) cells d\(^{-1} \). The initial conditions were chosen such that \( B_1 \) and \( B_2 \) were in their virgin state, i.e. \( B_1 = B_2 = m/\mu_b \), \( A_1 = 0 \), and the "antigen" \( A_2 = 10^{-6} \) M. All other variables were initially zero. (b) Parameters same as (a) except the influx rate \( m = 2.4 \times 10^2 \).
system which is too stable will be sluggish and unresponsive to antigenic challenge; one which is unstable will be driven into immense activity by internal fluctuations. This led us to postulate that the immune system should be stable but not too stable.

In many biological contexts the development of pattern requires both activation and inhibition but on different spatial scales. Similar ideas can be applied to shape space. The principle of short-range activation and long-range inhibition translates into specific activation and less specific inhibition. Application of this principle in model immune systems can lead to the stable maintenance of non-uniform distributions of clones in shape space. Thus clones which are useful and recognize antigen or internal images of antigen can be maintained at high population levels whereas less useful clones can be maintained at lower population levels. Pattern in shape space is a minimal requirement for a model. Learning and memory correspond to the development and maintenance of particular patterns in shape space.

Representing antibodies by binary strings allows one to develop models in which the binary string acts as a tag for a specific molecule or clone. Thus models with huge numbers of cells and molecules can be developed and analyzed using computers. Using parallel computers or finite state models it should soon be feasible to study model immune systems with $10^5$ or more elements. Although idiotypic networks were the focus of this paper, these modeling strategies are general and apply equally well to non-idiotypic models.

Using bit string or geometric models of antibody combining sites, the affinity of interaction between any two molecules, and hence the connections in a model idiotypic network, can be determined. This approach leads to the prediction of a phase transition in the structure of idiotypic networks. On one side of the transition networks are small localized structures much as might be predicted by clonal selection and circuit ideas. On the other side of the transition profound idiotypic networks become possible, signals can percolate throughout the network, and antigen stimulation can affect large portions of the network. Whether signals actually have such profound effects or just stimulate local portions of the network depends crucially on antibody affinities and concentrations, molecules such as lymphokines which play roles in controlling the proliferation and differentiation of lymphocytes, and the dynamical laws governing the interactions among the cells and molecules of the immune system. These dynamical laws still need to be uncovered and provide a challenge to both experimentalists and theorists.

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