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MEMORY CAPACITY IN LARGE IDIOTYPIC NETWORKS

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Abstract

Many models of immune networks have been proposed since the original work of Jerne. Recently, a limited class of models (Weisbuch et al., 1990) has been shown to maintain immunological memory by idiotypic network interactions. We examine generalizations of these models when the networks are both large and highly connected to study their memory capacity, i.e., their ability to account for immunization to a large number of random antigens. We find that the introduction of continuous affinities destroys the memorization capability. However, if the models are reinterpreted so that the response of immunized clones is different from that of virgin clones, the memorization capacity can be improved.

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1. Immune Networks. The immune system is a complex interacting dynamical system with many facets. Its function, defense of the organism, is carried out in ways which vary from species to species and even within a given host because of its history. In spite of this complexity and variability, there are some principles behind the *function* which appear in all species. In particular, immune systems of vertebrates solve the self-non-self problem and the memorization problem. Briefly, for defense to occur, it is necessary to distinguish dangerous foreign bodies (antigens) from cells of the host. Furthermore, this defense is more effective if previously encountered antigens can be recognized, i.e., remembered: this is what we call memorization or immunization. One class of "theories" supposes that the various cells in the immune system interact and regulate each other in such a way that the two above problems are solved. These approaches have been called "network" theories because the interacting cells form a network (Atlan and Cohen, 1989; Bruni et al., 1979; Perelson, 1989b). They are to be contrasted with clonal selection theories (Burnet, 1959) where cell-cell interactions are not central to the defense mechanism, rather dynamics are antigen driven.

Network theories, originated by Jerne (1974), have seen a resurgence of interest (De Boer and Hogeweg, 1989a, 1989b; Perelson, 1989a; Weisbuch, 1990) in the last five years; our purpose here is to investigate the ability these new models to maintain immunization via idiotypic network interactions. One of the hopes of the network approach is that it can provide a dynamical memorization mechanism, i.e., memory without the use of long-lived "memory" cells; the memory is to be stored in the form of populations of cells which self-renew while neither increasing nor decreasing in size. Consider a clone (the family of cells which share the same antibody structure) Ab_1 responsible for immunization against an antigen Ag_1. After the antigen is eliminated, Ab_1 might be maintained in the body for a long time by a network generated "internal image" of the antigen, provided in the form of a complementary clone Ab_2. But then it is necessary to consider how this internal image Ab_2 is maintained. One might have to introduce an infinite sequence Ab_n, Ab_{n+1}, ..., or the process might bootstrap itself at some finite length. It was necessary to introduce quantitative models (Hoffmann, 1975; Richter, 1975) to see how this last possibility could occur. Depending on the model, the internal images are either due to collective effects (Parisi, 1990), or are due to a small number of clones which can coexist with the primary clone Ab_1 (Weisbuch, 1990; Weisbuch et al., 1990; Neumann, 1992). Although the model of Parisi is very elegant and provides a partial realisation of what Jerne was driving for, it has the inconvience of being very schematic and difficult to interpret biologically: the clones are either present or absent (no concentrations are considered), the dynamics occurs in discrete time steps like a cellular automaton, and the model uses negative affinities. The more recent models do not have these drawbacks, the clonal dynamics they incorporate is more realistic and easily interpretable. They have thus become regarded as "standard" minimal models, and provide a framework for numerous workers in the field. The question is whether these standard models can solve the self-non-self problem and memorization satisfactorily.

In what follows, we consider the memorization aspects of these standard models in order to determine whether immunization against many antigens is possible. We will define the memory capacity to be the typical maximum number of antigens the network can memorize. Generally,

it is difficult to calculate this memory capacity, both because the networks of interest are too large to be simulated, and because an analytical calculation is beyond hope, except in special cases. This explains why this question has not yet been addressed except when imposing the affinities to be 0 or 1 (Weisbuch, 1990; Weisbuch et al., 1990; Neumann, 1992; Weisbuch and Oprea, 1993). In what follows, we show that continuously variable affinities diminish the memory capacity of these models to the point of non-existence. However, the memory capacity of the models can be improved by a particular reinterpretation: if clones undergoing somatic mutations and affinity maturation (with T-cell help) see their field-response curve suitably modified, the memory capacity of the network is potentially large.

In section 2, we review the standard models, and discuss known results concerning immunization. Then in section 3, we introduce the notion of memory capacity and its relation to the number of fixed points in these networks. Section 4 gives the mathematical formulation of the problem and describes the approximations we use. Section 5, the heart of the paper, gives analytical and numerical results for the memory capacity in the standard models for a number of affinity matrix ensembles. Section 6 gives a qualitative discussion of dynamical aspects of memorization. Finally, section 7 summarizes our results and the light which they shed on the potential of these standard immune network models.

2. Clonal Dynamics and Idiotypic Interactions. The "standard" models deal either with B cells ("B models") (De Boer and Hogeweg, 1989a, 1989b; Weisbuch, 1990; Weisbuch et al., 1990; Weisbuch and Neumann, 1991; Neumann, 1992), or with B cells and free antibody concentrations ("AB models") (De Boer and Hogeweg, 1989b; Varela and Stewart, 1990; Stewart and Varela, 1990). The effects of T cells, MHC molecules, antigen-presenting cells or regulatory molecules such as cytokines are supposed to be absorbed into effective B cell dynamics. Thus in no way should the models be considered as microscopic; they are effective models which hopefully adequately describe the main features of the B cell dynamics. More recently, AB models have been proposed which include the effects of complexing of anti-bodies with antigen and their elimination, or which introduce delays before B cells become effectors (De Boer and Hogeweg, 1989b; De Boer and Perelson, 1991; De Boer et al., 1993a, 1993b; Segel and Perelson, 1991). It turns out that for the question of immunization, most of these models lead to the same fixed point equations and thus have the same memory capacity, so our results apply to them too. In this section, we briefly review the simplest of these models (the B models), and discuss known results.

The dynamics of real B cells is not well understood; nevertheless, it is clear that certain experimental conditions will activate B cells, leading to a cascade of events which culminates in the production of antibodies. The activation depends on the way the antigen is presented (in solution, on antigen presenting cells, etc...) and on the antigen concentration. It is widely believed that the signal which activates B cells is the cross-linking of membrane antibody receptors (Perelson and DeLisi, 1980). Cross-linking requires that the antigen be multi-valent, i.e., that the epitope (the part of the antigen which binds to the antibody) be present on the antigen multiple times, or that multiple copies of the antigen be presented by antigen-

presenting cells. (It is not surprizing then that IgM, the antibody molecule which is considered to be responsible for interactions in network models, has a high valency.) If an antigen is present only in very low concentration, there is little binding, little cross-linking, and thus no activation. Similarly, at very high concentrations, if the antigen is soluble, each membrane receptor will likely bind to a different antigen so that there will be no cross-linking either. Cross-linking and activation are expected to occur only in a window of concentration, leading to a bell-shaped dose response curve. This type of response curve for interactions between the B cells through their antibodies, called idiotypic interactions, is the starting point of network models. In order to incorporate monovalent antigens and their effects on B cells, it is necessary to have antigen-presenting cells. These cells are implicitly taken into account in the standard models, and common practice is to assume that the concentration of the antigen, be it mono or multi-valent, acts in a similar way to IgM concentration.

Rather than keep track of how many cells belong to a given clone (the set of cells giving rise to the same antibody molecule), the standard models use population dynamics where one considers instead clonal concentrations. The evolution equation for B_i, the concentration of clone i associated with antibody Ab_i, is taken to be:

$$\frac{dB_i(t)}{dt} = s_i(t) + (P(h_i(t)) - d)B_i(t). \tag{1}$$

$P(h)$ is the proliferation function or response curve describing cross-linking and thus activation. Often, it is taken to be a product of two threshold type functions (De Boer and Hogeweg, 1989a). The all or none activation of a cell is modeled in this population dynamics picture by a positive or negative growth rate of the clonal size so that $P(h)$ can be considered to be the *probability* of activation. $s_i(t)$ is a source term describing the fresh supply of B cells coming out of the bone-marrow. The precursers of B cells undergo DNA "surgery" in the bone marrow; at the end of this process, a given B cell and all of its descendants (neglecting somatic mutations) can produce only one antibody molecule type. The set of antibodies which can be produced in this way is called the *potential* or naive repertoire and is estimated to be about 100 times greater than the number of clones present in the system at any time (Freitas et al., 1986). For mice, the size N of the potential repertoire is expected to be greater than 10^9. $h_i(t)$ is defined as

$$h_i(t) = \sum_{j=1}^{N} J_{ij} B_j(t). \tag{2}$$

h_i is called the "field" felt by clone i, and J_{ij} is the affinity between the anti-bodies produced by clone i and clone j. In this minimal B model, the concentration of anti-bodies is taken to be proportional to the concentration of the corresponding cells themselves. This concludes the questions of idiotypic interactions, i.e., the interactions between the network of antibodies and B cells. If one introduces an antigen into the system, the field felt by clone i should be increased by $J_{iA}C_A$ where C_A is the concentration of the antigen introduced. Equation (1) defines the dynamics of the B cells within the standard models. In the "AB" models, for each index i,

a further equation is introduced for the corresponding (free) antibody concentration. In more complicated and realistic models (Segel and Perelson, 1991; De Boer et al., 1993a, 1993b), there is an additional equation for complex elimination or for gearing up. Weisbuch, De Boer, and Perelson (1990), hereafter referred to as WBP, showed that the minimal B model can maintain internal images, and thus gives rise to network memorization without the need for long lived "memory"cells: clonal populations are self-maintaining through their idiotypic interactions.

It is simplest to first describe network memorization at the two-clone level. Assuming that $s_i(t)$ is constant, it can be shown that the dynamics takes the system to a time independent solution of the dynamics (a fixed point). For small source terms, each clone will be either nearly absent ($B_i \sim s_i/d$), or be subject to a field $h \sim L$ or $h \sim H$, where these two values are given by the two solutions of $P(h) - d = 0$. (P being a bell shaped curve, there are two solutions as long as d is less than the maximum of P. This is necessarily the case biologically, otherwise one could never get clonal expansion.) This leads to a total of five fixed points if there is no self-affinity, only three of which are stable. If a clone concentration goes to zero in the absence of the source, it is said to be in a virgin state (V), and it is not activated. If a clone is subject to a field $h \sim L$, it is said to be in a vaccinated or immunized state (I). (Note that this state depends on the field, i.e., on the other clones, it is not a cellular property). To justify the nomenclature "immunized state", consider introducing an antigen complementary to the clone in question; the field seen by the cell will increase so that $L < h < H$, leading to proliferation of the clone. Finally, if a clone is subject to a field $h \sim H$, it is said to be in a tolerant state (T). Indeed, if an antigen complementary to the clone in question is introduced, its field will increase so that $H < h$, leading to suppression of the clone. Thus, this clone will not mount an immune response to complementary antigens, it is in a tolerant state. The stable fixed points for the two clone system correspond to (V, V), (I, T), and (T, I).

The three B cell states (V, I, and T) are not restricted to the two clone case, rather they occur in larger networks, and allow one to classify the fixed points of the dynamics. In the two clone case, the immunized clone is maintained in the network by an internal image of the antigen, in this case, a complementary clone. In the case of a general network, the immunized clone may be maintained by many complementary clones as in the Parisi model, or by just a few complementary clones as in the work of Weisbuch, De Boer, and Perelson (Weisbuch et al., 1990).

Implicit in all these models is an affinity matrix **J**. It is possible to measure affinities between particular antibodies (Vakil and Kearney, 1986), but in view of the number of potential antibodies even in a single individual, clearly the only attainable goal is to characterize **J** by its statistical properties. Thus for modeling purposes, one should consider expected or average (memorization) properties over an ensemble of affinity matrices. To be realistic, the J_{ij}'s should be continuously distributed, and the affinity matrix should have certain average connectivity properties. We will take a random or mean field limit where the J_{ij}'s are independent random variables. This amounts to modeling the immune system by clones which randomly sample a very large (shape) space. What is important is that this mean field choice allows analytic calculations and simpler numeric treatments (because of the symmetries). Another possible

limit is to consider highly structured affinity matrices. This was the choice of WBP which we now describe for completeness.

For the topology of their network, WBP use a Cayley tree. A Cayley tree is a tree graph (no loops) with constant degree, except for the nodes forming the leaves. The nodes of the graph label clones, i.e., i, and the affinity matrix for idiotypic interactions has entries of 1 for nearest neighbor nodes, 0 otherwise. This double constraint (only one non-zero value of J_{ij} and very low connectivity) enables the internal images of the two-clone case to be easily generalized to the network. For instance in the immunized state, (taking the limit $s \to 0$), the corresponding clone has a field of $h = L$, its nearest neighbors $h = H$ (tolerant state), and the next-nearest neighbors are in the virgin state. The Cayley tree network thus allows for localized fixed points of the dynamics in the form of clusters of clones which provide immunization against the antigen complementary to the immunized clone. Furthermore, these fixed points are attractors. (The stability of such fixed points may be modified when considering "AB" or more complicated models; the introduction of other dynamical variables or of delays in the proliferation of the B cells can stabilize or destabilize the motion (De Boer and Hogeweg, 1989b; De Boer et al., 1993a, 1993b)). It is possible to immunize against a large number of antigens as long as the clusters are non-overlapping: if p is the average degree of the Cayley tree, the network can memorize approximately $\sqrt{2N/p}$ antigens (Weisbuch and Oprea, 1993). This possibility depends on the low connectivity of the network and on the binary aspect of the affinity matrix. In reality, affinities take on a wide range of continuous values, and antibodies are multi-specific, that is they will bind to some extent to a large number of different antigens or epitopes. The question is then whether the standard models can give rise to immunization (memory) against a large number of epitopes when the connectivity and J_{ij} values are more realistic than those chosen by WBP. Our answer will be no, the main culprit being the continuous values of the affinities, and this is apparent at the level of the fixed points, there is no need to consider dynamical aspects.

3. Memory Capacity and Fixed Points. Whether or not the standard models lead to immunization against a large number of antigens depends on the ensemble of affinity matrices considered. It is a network question because a clone on its own in these models will collapse and disappear; one needs a collective effect to maintain internal images and memory. As mentioned above, the affinity matrix choice of WBP does lead to immunization against many antigens, but we want to consider more general (and potentially realistic) cases. In what follows, we assume as done in (Weisbuch et al., 1990) that each antigen is complementary to just one antibody (but see the two comments below). For immunization against a set of antigens, we require that the corresponding complementary clones be in the $h = L$ state. Other clones should be in the tolerant or virgin state because one doesn't want to develop immunizations against antigens never encountered. (Note however that the original Jerne picture of internal images of internal images and so on could lead to immunized clones which are not complementary to *external* antigens but rather to internal idiotypes.)

Some comments are in order.

(1) The one to one map from antigen to its complementary antibody is unrealistic: first, an antigen generally has several epitopes, and second, it is known that antibodies are multispecific, i.e., bind to a number of different epitopes. However, one might argue that during the immune response to the invading antigen, the somatic mutations and affinity maturations occuring after T-cell help may lead to a dramatic reduction of the multispecificity for one or a small number of clones which recognize a few of the antigen epitopes (Berek and Milstein, 1987). Thus one could have (after the infection and thus for the purposes of the memorization) just one or a few clones which interact strongly with the antigen. Then antibody interactions with foreign epitopes would be highly specific, while idiotypic interactions would remain multispecific. For simplicity of presentation, we keep the one to one (rather than one to few) map from antigen to antibody, but the generalization to the more realistic case simply decreases the memory capacity by the average number of epitopes recognized on an antigen.

(2) In the work of Weisbuch and Neumann (1991), memorization includes both immunization and tolerance, but we have chosen to consider only immunization. Tolerance in their model is possible because they assume each antigen is uniquely associated with one clone. We have just argued that this may be justifiable for immunization, but it is not possible to extend the argument for tolerance. Even assuming such a one to one map, tolerance in these types of models cannot be achieved unless there is an extremely low network connectivity (it is then enough to immunize against all clones which are reactive with the antigen).

We now come back to the question of immunological memory. Suppose it is necessary to be immunized against M antigens (or in the more realistic framework mentioned in the first comment, against M epitopes). We will require that the corresponding M complementary clones be in the immunized state ($h \sim L$). The question is then whether it is possible to recruit into the network other clones in the $h \sim H$ state so as to reach a (stable) fixed point of the dynamics. In the WBP model, it is sufficient to put the neighbors of these M clones in the $h = H$ state, and then find the corresponding clonal concentrations by solving a system of two equations, assuming that the immunized clones do not interfere with one-another. If one were allowed to choose these M immunized clones (rather than having them imposed upon us from the outside), the standard model with the network of WBP could be immunized against on the order of N/p epitopes, where N is the size of the network, and p is the connectivity of the Cayley tree. If, on the other hand, the antigens/epitopes against which one is to be immunized are given at random as is more or less the case in reality, that model can only be immunized against on the order of $\sqrt{2N/p}$ antigens (Weisbuch and Oprea, 1993). That is because as one tries to impose more clones to be in the immunized state, they interfere with previously immunized clones on the Cayley tree. We say that the memory capacity of the WBP idiotypic network is $M^* = \sqrt{2N/p}$. If one tries to memorize $M << M^*$ random epitopes, one is almost surely able to do so; if $M >> M^*$, one is almost surely unable to do so. Mathematically, the transition is smooth at finite N, but in our analysis and in Parisi's model, as N and $M \to \infty$, the transition is more and more abrupt so that one is sure to be able to memorize $(1-\epsilon)M^*$ and unable to memorize $(1+\epsilon)M^*$ epitopes in the large N limit for any fixed positive ϵ. Thus we define the memorization or immunization capacity of a general network by its transition

point M^*. A memory capacity on the order of N is very large, certainly adequate for biological purposes. (In the Parisi model, one has $M^* \approx N/3$.) A memory capacity proportional to $\sqrt{N}$ is possibly still acceptable, but it would be more satisfactory to have a larger capacity. As we will see in section 5, the standard models, with the standard interpretation, lead to $M^* \approx \ln N$ which is clearly too small for biological purposes.

We will calculate the memory capacity in the following manner. Assume one is given M random clones which are to be in the immunized state, and that one is to recruit further clones so that a fixed point is reached. We add $N' - M$ clones and put them into the $h = H$ state. If $M << M^*$, there almost certainly is a way to recruit $N' - M$ such clones such that the N' clones taken together form a realizable fixed point with all clonal concentrations positive. As M increases, there are fewer and fewer ways to do this recruitment, until when M becomes comparable to M^*, it is no longer possible to recruit clones and find a realizable fixed point. We will calculate the number of ways of recruiting clones to find a fixed point, as a function of M in the limit of small source terms. For small M, there will be an exponential (in N) number of ways to do the "completion", whereas for large M, the number of ways will decrease and approach zero. M^* is defined as that transition point where one goes from an exponentially large number to an exponentially small number of realizable completions. Naturally, an exponentially small number simply means that the *average* number of completions is small; this number should thus be interpreted as a probabilistic average in the ensemble of affinity matrices considered.

4. The equations for the fixed points. Despites their differences, the B and AB models, and most generalizations thereof, lead to the same fixed points equations, to a large extent because they use in the same way the activation function to describe the proliferation of B cells. (This is not so for the Parisi model, where activation is described with a threshold function, making the Parisi model identical to a spin glass or neural network model.) We are interested in the fixed points of the dynamics which can be interpreted in terms of immunization. Consider equation (1): $s_i(t)$ is a stochastic source term representing new cells coming from the bone marrow. For our modeling, clearly a fixed point is possible only if s_i is time independant. Thus we think of $s_i(t)$ as being some average value s_i plus fluctuations. If one has a stable fixed point for the above equations with the s_i constant, the fluctuations in time of the source terms should simply lead to fluctuations about the fixed point of interest. Thus, as a first approximation, we replace $s_i(t)$ by its average value s_i in the equations. With this replacement, the fixed points equations are obtained from equation (1) by setting the left hand side to zero:

$$B_i(d - P(h_i)) = s_i, \qquad 1 \leq i \leq N. \tag{3}$$

We shall deal with the limit where s_i is very small, $s_i \to 0$. Clearly the solutions of the fixed points equations as $s_i \to 0$ converge to the $s_i = 0$ solutions. This continuity and the fact that s_i is small experimentally (see discussion below) justifies our setting $s_i = 0$. In this limit, the solutions of equation (3) have a simple interpretation: at a fixed point of the dynamics, a given clone i is either absent, $B_i = 0$ (it is not recruited into the network), or it experiences a field

h_i that is such that $P(h_i) = d$, that is $h_i = L$ or $h_i = H$. Once given the fields $h_i = L$ or H for each clone i present in the system, one may solve the system of linear equations $\mathbf{J} \cdot \mathbf{B} = \mathbf{h}$ in the subspace spanned by the clones with $B_i > 0$. This gives the concentrations B_i for this particular fixed point. This is what we do in practice. For small (but non-zero) values of s_i the structure of the fixed points will be the same, namely each clone i may be in one of three possible states: 1) not recruited into the network, (virgin state; the clone is present at a very low concentration and a small modification of the field h_i has little effect on it); 2) it is recruited and a low activating field $h \sim L$ acts on it; 3) it is recruited and a high suppressive field $h \sim H$ acts on it. However, there is a difference between the fixed points for $s_i = 0$ and for s_i small: some of the solutions found for $s_i = 0$ will disappear when s_i is turned on because the field h_i may be such that the clone cannot stay in the virgin state. This difference is a question of meta-dynamics, and will be discussed in section 6. Overall, our limit $s_i = 0$ tends to over-estimate the number of fixed points, so that the memory capacities we will quote are in fact upper bounds.

Size of the source term. To see that the source term is experimentally small, it is important to realize that the label i corresponds to a unique antibody shape, not a collection of similar antibodies; s_i is then one over the characteristic time it takes for the precursor cells in the bone marrow to produce the rearrangement which will give the particular antibody Ab_i. It is estimated (Freitas et al., 1986) in mice that the potential repertoire is greater than 10^9. Furthermore, the bone marrow in mice produces about 2×10^7 new cells every day, so that it takes several months to produce by chance a cell of given antibody. (Note that it is possible that the bone marrow produces far fewer clones than it produces cells; it might then take up to a year to produce a particular antibody type.) Compare this length of time to the lifetime of typical B cells, 2 to 5 days. This shows that the rate of proliferation or suppression of B cells maintained in the network due to their mutual influence is much greater than the contribution from the source term. Thus in practice, s_i has a negligeable effect for the clones recruited into the network (i.e., which have $h \sim L$ or $h \sim H$). For the clones which are in the virgin state, the difference between $s_i \neq 0$ and $s_i = 0$ is in some sense dramatic, as the clones occur in small concentrations in the first case and not at all in the second. Nevertheless, the effect of $s_i \neq 0$ is negligeable for our purposes because the clonal concentrations tend to 0 with s_i. The fact that there are many of these virgin clones suggests that an important background field is produced by them. However, such a field, being due to many random clones, is nearly uniform (the same for all clones in the network). It is then easy to see that this background field can be absorbed into the definitions of L and H. Furthermore, biological constraints suggest that this contribution from the virgin clones is much smaller than L.

The mathematical problem. The method to obtain the $s = 0$ fixed points for a given network defined by an affinity matrix $\mathbf{J}$ is clear: one first chooses which clones $i_1, ..., i_{N'}$ in the system are to be recruited. Each recruited clone is assigned a field $h = H$ or L acting on it. Then one has to invert the system $\mathbf{J} \cdot \mathbf{B} = \mathbf{h}$ (where only the relevant lines and columns of $\mathbf{J}$ are retained), to obtain the concentrations $B_{i_1}, ..., B_{i_{N'}}$. Doing this for each possible choice of

the fields $h_{i_1}, ..., h_{i_{N'}}$ will provide us with $2^{N'}$ potential fixed points. There are thus at most 3^N fixed points for the whole system. But not all these fixed points have physical meaning. Indeed the matrix $\mathbf{J}^{-1}$ generally has some negative elements so there is no reason for the vector $\mathbf{B} = \mathbf{J}^{-1} \cdot \mathbf{h}$ to have all of its entries positive. We must retain only those solutions which have $B_i \geq 0$ for all i in order to keep the physical interpretation of the B_i's as concentrations. This will give us the real (realizable) fixed points. We are interested in the number of these fixed points. Clearly this number will depend on the affinity matrix $\mathbf{J}$ at hand, but since $\mathbf{J}$ is not known in practice, we consider statistical ensembles of affinity matrices. We are interested in average properties such as the mean number of fixed points for a network picked in the ensemble, and the corresponding memory capacity of the network. These properties depend on structural characteristics of the matrices of the ensemble, such as their mean connectivity, their continuous or discrete character, etc... For a general matrix $\mathbf{J}$ without any structure (the J_{ij}'s being independant identically distributed (i.i.d.) random variables), we will see that the number of positive solutions of the system $\mathbf{J} \cdot \mathbf{B} = \mathbf{h}$ is essentially on the order of one, rather than the maximum, $2^{N'}$. A parameter which has an important influence on the number of fixed points and thus on the memory capacity is the ratio L/H. This ratio characterizes the width of the activation window.

For the realizable solutions of the fixed points equations to be of biological interest, they must be attractors of the dynamics, so they must correspond to *stable* fixed points. The problem of studying the stability of a given fixed point is quite complicated since it supposes one is able to compute the eigenvalues of the linearized equations of motion. However this problem is very important if we want to interpret the memory capacity of the network in terms of the attractors of the dynamics according to which it evolves. The property of stability or non-stability will most likely vary between the B and AB models and generalizations thereof. It might be argued that the actual dynamics has been selected by evolution to give the greatest stability. This stability problem is beyond the scope of this article, but see section 6 for a qualitative discussion.

5. The memory capacity for some ensembles of J_{ij}. In this section we examine the problem of determining the number of fixed points and the memory capacity for several ensembles of affinity matrices $\mathbf{J}$. Some ensembles are only of academic interest, but they nevertheless provide insight into the mathematical problem considered. Most of the technical derivations are presented in the appendices.

5.1. The case $\mathbf{J}$ *diagonally dominant.* We first consider the unrealistic case where each clone i is given a large self-affinity J_{ii} and has little interaction with the other clones. If the matrix $\mathbf{J}$ is purely diagonal, the problem is trivial as the N clones evolve independantly from each other. For any choice of the fields $\mathbf{h}$, the vector $\mathbf{J}^{-1} \cdot \mathbf{h}$ has only positive entries, leading to the maximum possible number of fixed points. Clearly if we introduce small enough off diagonal elements J_{ij}, this positivity property will remain valid. More precisely, one has the following

sufficient condition: if all the off diagonal elements of $\mathbf{J}$ satisfy the bound

$$NJ_{ij} \;<\; f(L/H)\min_k(J_{kk}) \tag{4}$$

where $f(x) = (\sqrt{1+4x^2} - 1)/2x \sim x$ when $x \ll 1$, then for any choice of $\mathbf{h}$ with $h_i = H$ or L, the components of $\mathbf{J}^{-1}\cdot\mathbf{h}$ are all positive. This bound is obtained by writing the Neumann series for $\mathbf{J}^{-1}$ and bounding each term. This diagonally dominant ensemble corresponds to a "network" which has maximum memory capacity, $M^* = N$, as any of the clones can be set to the immunized state.

5.2. The case of a random matrix $\mathbf{J}$. We suppose here that the J_{ij}'s are given as i.i.d. continuous random variables, so that there is no particular structure underlying the network and all clones are statistically equivalent. This also means that we consider a highly connected network, where each clone experiences a collective influence from all the other clones in the system. The J_{ij}'s could be e.g. gaussian variables, but we expect the average properties not to depend on the detailed form of the J_{ij} distribution in the limit of large N, at least if the distribution at large affinities falls off sufficiently quickly. In the cases we will consider, the J_{ij}'s will be taken to be uniformily distributed in the interval $[0,1]$, but after rescaling, this is the same as any other interval $[0,x]$.

Since affinities are defined pair-wise, we should take the matrix $\mathbf{J}$ to be symmetric. However we consider the two cases, J_{ij} symmetric and J_{ij} non-symmetric. The non-symmetric case is unrealistic, but it is much simpler to analyze and it helps one understand the symmetric case. To find memory capacities in these networks, we calculate the probability that the fixed point with M given clones at $h = L$ and $N' - M$ given clones at $h = H$ have all clonal concentrations positive. Note that in a given ensemble this probability, $P(N', M, L/H)$, depends on N', M, and on the ratio L/H. Without loss of generality, we take the immunized clones to have index $i = 1, ..., M$ and the suppressed ones index $i = M+1, ..., N'$. We denote the set of concentrations B_i and the fields h_i acting on them by the column vectors $\mathbf{B}$ and $\mathbf{h}$. For each choice of the $N' - M$ clones, we seek the probability that the solution of the system $\mathbf{J}\cdot\mathbf{B} = \mathbf{h}$ has all of its entries positive. (It is understood that one is to truncate $\mathbf{J}$ to the space of recruited clones, $i = 1, ..., N'$.) The sum (over the choice of the $N' - M$ clones) of these probabilities gives the mean number of fixed points, denoted by $\mathcal{N}(N, M)$, containing the M immunized clones:

$$\mathcal{N}(N,M) = \sum_{N'=M}^{N} \binom{N-M}{N'-M} P(N', M, L/H). \tag{5}$$

Clearly, for M small, there are many ways to choose the $N' - M$ clones, so $\mathcal{N}(N, M)$ should be large. If M becomes very large, $\mathcal{N}(N, M)$ will decrease and tend towards 0. The transition point M^* is the memory capacity of the network.

5.2.1. The limit $L/H \to 0$. It is easy to see that as L/H decreases, it becomes more and more difficult to complete the network of M clones with $N' - M$ clones at $h = H$. Suppose

$M > 1$ and that we seek a fixed point with $N' - M$ recruited clones at $h = H$. We may write

$$\sum_{k=1}^{N'} J_{ik} B_k = L, \quad i = 1, ..., M \tag{6}$$

$$\sum_{k=1}^{N'} J_{jk} B_k = H, \quad j = M+1, ..., N'. \tag{7}$$

If the network were to behave as in the WBP case (and as is biologically plausible), the immunized clones should have much higher concentrations than the suppressed clones. Then for the first M fields to be anomalously low, it is enough for the upper left $M \times M$ submatrix of $\mathbf{J}$ to be anomalously low. This amounts to forcing the immunized clones to not interconnect. Then the probability for having a physical fixed point should be suppressed by $(L/H)^{M^2}$ as $L/H \to 0$ relative to the $L \approx H$ case. One expects this probability to be a monotonically increasing function of the parameter L/H which interpolates from zero for $L/H = 0$ to some N'-dependent value for $L/H = 1$. The end result would be a memory capacity proportional to $\sqrt{N}$, analogously to what happens in the WBP model. However the network with uniformily distributed J_{ij}'s does not behave as in the WBP case; one does not have a nice separation between immunized clones of large sizes and tolerant clones of small sizes. This makes it necessary to suppress the first M *lines* of $\mathbf{J}$, i.e., $M.N'$ rather than M^2 matrix elements (c.f. the last paragraph of section 5). The end result is a memory capacity which scales as $\ln(N)/\ln(H/L)$: clearly, this is too small to be biologically useful. unfortunately, the limit $L/H \to 0$ is in fact biologically relevant: the threshold values L and H which characterize the proliferation function P are experimentally such that $L \ll H$. Typical values are $L/H \sim 10^{-2}$ to 10^{-4} depending on the work; see Faro and Velasco (1993) for an overview.

In summary, in these standard models, the memory capacity is very suppressed compared to what it could be if L and H were comparable. However, in view of a possible extension of the model discussed in section 7, it is appropriate to understand the memory capacity when L and H are not very different. Analytically, we have been able to treat the general case, but we will first present the limit $L = H$ before dealing with L and H arbitrary.

5.2.2. The case J_{ij} non-symmetric. We suppose here that the J_{ij}'s are i.i.d. random variables uniformily distributed in $[0, 1]$ with J_{ij} and J_{ji} independent. This is an unphysical ensemble (note however that previous theoretical studies considered non-symmetric idiotypic interactions), but the results for symmetric and non-symmetric matrices are nearly identical. Essentially, the symmetry constraint $J_{ij} = J_{ji}$ seems to become unimportant in the large N limit.

The analysis can be done exactly if one takes the limit $L/H \to 1$, so that H and L are considered equal. The $2^{N'}$ systems of equations $\mathbf{J} \cdot \mathbf{B} = \mathbf{h}$ are now one and the same equation, namely $\mathbf{J} \cdot \mathbf{B} = \mathbf{1}$ up to a trivial scaling of the concentrations. $\mathbf{1}$ is the vector $(1, ..., 1)$. By a geometrical analysis which uses symmetry arguments, it is possible to show that the probability $P(N', M, 1)$ is equal to $1/2^{N'-1}$. Briefly, $\mathbf{J}$ is a random set of independent row vectors so that

the vector $\mathbf{J}^{-1} \cdot \mathbf{1}$ is equidistributed in each of the $2^{N'-1}$ sectors defined by the relative sign of the entries for each index. We refer to appendix A.1 for a proof.

We may now evaluate the memory capacity for this non-symmetric random network in the limit $L/H \to 1$. For this, we compute the average number of fixed points given that there are M specified clones and any number $N' - M$ clones to be added in order to obtain a physical fixed point. The mean number of fixed points containing the set of M clones is

$$\mathcal{N}(N, M) = \sum_{N'=M}^{N} \binom{N-M}{N'-M} 2^{-N'+1} = 2^{-M+1}(3/2)^{N-M}. \tag{8}$$

We then see that the memory capacity as defined in section 3 is $M^* = \lambda N$ with

$$\lambda = 1 - \frac{\ln 2}{\ln 3}. \tag{9}$$

5.2.3. The case J_{ij} symmetric. We consider here the more realistic case where the interactions between B cells are symmetrical. As before, the J_{ij}'s are taken as i.i.d. random variables uniformily distributed in $[0, 1]$, except that we now have $J_{ij} = J_{ji}$. Again we seek the mean number $\mathcal{N}$ of fixed points given a set of M immunized clones in the network. We first deal with the limit $L \to H$ because it is analytically simpler. Then we generalize the analysis to general values of L and H. Because the calculation involves many steps, we refer the reader to the appendices for most of the details.

There is no obvious way to generalize the geometrical analysis of appendix A.1, so we use a very different approach based on random matrix theory. The matrix $\mathbf{J}$ can be diagonalized in the subspace spanned by the recruited clones, and in the limit where N' is large, we may apply some known results (Metha, 1967) to obtain the properties of the eigenvalues and eigenvectors. From this, we obtain the probability distribution for the vector $\mathbf{B}$ solution of $\mathbf{J} \cdot \mathbf{B} = \mathbf{h}$, which allows us to estimate the number of fixed points. The calculation (c.f. appendix A.2) of the probability $P(N', M, L/H = 1)$ gives a value which decreases exponentially with N', $P(N', M, L/H = 1) \sim e^{-\beta N'}$, with $\beta \sim 0.68$ which within uncertainties (c.f. appendix A.2) is compatible with $\ln 2$, the value in the non-symmetric ensemble.

To obtain the memory capacity, we find the average number of fixed points including M given clones in the same way as for the non-symmetric case. One has

$$\mathcal{N}(N, M) = \sum_{N'=M}^{N} \binom{N-M}{N'-M} P(N', M, L/H = 1) \sim (1 + e^{-\beta})^{N-M} e^{-\beta M}. \tag{10}$$

It follows that the memory capacity in this limit $L \to H$ is given by $M^* = \lambda N$ where

$$\lambda = \frac{1}{1 + \beta/\ln(1 + e^{-\beta})}. \tag{11}$$

If $\beta = \ln 2$, we recover of course the memory capacity of the non-symmetric case.

Now we generalize the calculation to deal with the case L and H arbitrary. The calculation is a bit more complicated (c.f. appendix A.3); we find

$$P(N', M, L/H) \sim e^{-\beta f(r) N'} \tag{12}$$

where $r = M/N'$ and $f(r)$ is the expression given in equation (42) which in particular depends on L/H. The important point is that $f(r)$ has for $L \neq H$ a term proportional to N'. Thus $P(N', M, L/H)$ decays far more quickly to zero at large N' than in the case $L = H$. This decreases the memory capacity to insignificant levels: it crosses over from a linear behavior in N at $L = H$ to a logarithmic behavior $M^* \sim \ln N$ when L is not very close to H.

6. Stability of the fixed points. So far we have said nothing about the stability of the fixed points in the large random networks that have been considered. Suppose that a fixed point for such a network consists of N' recruited clones. Two conditions must be fullfilled for this fixed point to be stable:

1) The fixed point must be stable within the dynamics of the self-sustaining network formed by these N' recruited clones. Linearizing the dynamics about the given fixed point will provide an N' by N' matrix whose eigenvalues determine the stability of the fixed point. For large and random networks, we expect the probability for an eigenvalue to have a negative real part to be near one half. There is then naively an exponentially small probability in N' for the fixed point to be stable. To remedy this, the dynamics must be non-generic, for instance it might be nearly derived from a potential function (Varela and Stewart, 1990).

2) The fixed point must be stable with respect to meta-dynamics: that is, the fixed point must be stable against the introduction of fresh clones from the bone marrow. Thus, the introduction of the small source term of equation (1) for an unrecruited clone should not lead to growth of this clone. However, from a biological standpoint, we do not think it is necessary to take such a strict point of view. One can easily imagine that for purposes of maintaining immunization, one simply requires that clones which might be recruited into the network insert themselves without affecting the M preassigned immunized clones. This seems more realistic and is a less severe constraint.

If one nevertheless does take the strict point of view that the fixed point should be stable even within the meta-dynamics, each unrecruited clone i must experience either a low, unactivating field $h_i < L$, or a high, suppressive field $h_i > H$. Now if the affinities J_{ij} are i.i.d. random variables with a continuous distribution, the fields h_i for $i = 1, ..., N$ will form a statistical ensemble with a nearly continuous distribution. We then expect that to reach a stable fixed point, one will have to recruit clones until N' is a finite fraction of N, no matter how small the number of immunized clones, M, may be. Interestingly, it seems from the simulations of De Boer and Perelson (De Boer and Perelson, 1991) that their system dynamically creates such a state so that the $L < h < H$ region appears very rarely. Nevertheless, since it is rather undesirable to have such large values for N', it is probably best to argue that the models are no longer accurate in that regime, for instance because cells compete for limited resources.

In a more realistic matrix ensemble, the affinities are not taken at random, but reflect the continuity of stereochemical interactions, so that similar antibodies have similar fields. Then the following argument suggests that the fixed points will be always unstable to meta-dynamics. Consider two clones in the network, one with a low field and one with a high field. Imagine creating, via changes in the amino acid sequences, a path in antibody space starting at the first clone and arriving at the second. The associated field along this path will go from $h = L$ to $h = H$. All the clones in this path with $L < h < H$ are "forbidden"; then any fixed point will be unstable to meta-dynamics. There is however a way out of this difficulty: the intermediate clones need not be realizable by the germ line. Indeed, antibody sequences are obtained by recombining a limited number of gene sequences (neglecting somatic mutations). It seems likely to us that the potential repertoire of antibody sequences is sufficiently discrete for this source of meta-dynamical instability to be inapplicable.

Whatever the assumptions, it is clear that the number of fixed points for $s = 0$ is much greater than the corresponding number for s small. Thus the memory capacities previously calculated are actually upper bounds for the full problem including source terms.

7. Discussion. We have seen that memorization in the standard immune network models is satisfactory when L is very close to H: the memory capacity is then linear in N. Experimentally however, H and L differ by two to four orders of magnitude. We have also seen that when $L << H$, the standard models have a much smaller memory capacity, $M^* \sim \ln N$: memorization is for all practical purposes non-existent. The model of Weisbuch, De Boer, and Perelson escapes this bad behavior by having a memory capacity $M^* \sim \sqrt{N}$ which is independent of L/H. This is possible for two reasons. First, the connectivity of the network is so low that almost certainly two immunized clones will not influence one another as long as $M << \sqrt{N/p}$. It is thus much easier to have large immunized clonal populations without affecting the $h = L$ equations than in our $\mathbf{J}$ ensembles. Second, and perhaps most importantly, the affinities in the WBP model are 0 or 1. As a consequence of this, the field produced by one immunized clone is the same for *all* the clones connected to it, so that it is very easy to satisfy the $h = H$ equations with positive concentrations. This nice property dissapears when one introduces fluctuations in the affinity values: memorization in the WBP model is not structurally robust. To give a simple illustration of this, consider for instance a localized memory in the WBP model consisting of one immunized clone B_1 and its p ($p > 1$) nearest neighbors in the suppressed (tolerant) state. Now change the $J_{ij} = 1$ affinities by random infinitesimal amounts. If there is no source term ($s_i = 0$ for all i), at a fixed point, the suppressed clones B_i ($i \neq 1$) must have a field $h_i = H$; but since $h_i = J_{i1}B_1$, this is not possible unless all the J_{i1} are equal. Thus WBP fixed points are destroyed by infinitesimal perturbations: the limit $J_{ij} \to 1$ or 0 is singular. (To some extent, this is traceable to the non-invertibility of $\mathbf{J}$.) When there is a source term, a straightforward perturbative calculation shows that the relative change in the clonal concentrations of the fixed point is of order ϵ/s where ϵ is the relative size of the affinity fluctuations. Thus as s becomes small (which is the case biologically), the WBP fixed points become very sensitive to affinity fluctuations, so that for any reasonable estimates of s and of the intrinsic fluctuations of

affinities, the fixed points have some negative clonal sizes, and thus become unphysical. In sum, the WBP model does not satisfy the "Unpredictability Axiom" (De Boer and Hogeweg, 1989a). Note that this bad feature is apparent at the static level, i.e., the *fixed points* dissapear when the J_{ij}'s are continuous. It is thus not surprising that *dynamically* one finds damage spreading or percolation (De Boer and Hogeweg, 1989b; Neumann, 1992; Weisbuch and Neumann, 1991). In our opinion, this difficulty will always plague the standard models in their current formulation, making it difficult to solve the memorization problem satisfactorily.

We now point out that a small yet plausible modification of the standard models increases their memory capacity. During immunization, clones undergo somatic mutation, leading to higher antibody-antigen affinities by factors of 10^2 to 10^4 (Berek and Milstein, 1987). According to the theoretical models, the immunized clone should be able to respond to much lower concentrations of antigen than before immunization. The extent to which this is the case experimentally is not clear. One can easily imagine that during the somatic mutation process, a cell sees the number of its membrane antibodies or other molecular species change. Thus its activation function (proliferation and/or maturation functions) might be modified so that the threshold field for activation is shifted towards higher values. This would avoid an immune response to minute quantities of antigen, permitting recruitment of new clones during secondary and tertiary responses, as observed experimentally (Berek and Milstein, 1987). With this (slight) modification to the interpretation of the standard models, the limit $L \to H$ becomes more relevant. Indeed the field required by the immunized clones ($h = L$ in the standard models) could be increased by several orders of magnitude, until it became comparable to the high field required by the virgin clones. The model would then allow for memorization much more easily.

In closing, let us note that the standard models have had both successes (Weisbuch et al., 1990) and failures (De Boer and Hogeweg, 1989b; Neumann, 1992); we think it is worthwhile to continue their investigation. Our work has shown that these models encounter major difficulties for memorization from a purely static point of view, without consideration of dynamical issues which no doubt further diminish memory capacity. But we also saw that natural modifications of the models can change the picture significantly. In particular, it seems necessary to consider somatic mutations at least implicitly:

- to obtain a nearly one to one map between antigens (epitopes) and antibodies;
- to modify the threshold field of immunized clones.

We believe that the possibility that the proliferation function and the threshold field might depend on the history of the cell is appealing both biologically and theoretically, even outside of network models.

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APPENDICES.

A.1. The case J_{ij} non-symmetric, $L = H$. Suppose the affinity matrix elements J_{ij} are i.i.d. random variables, no symmetry condition being assumed. For specificity, we take J_{ij} uniformily distributed between 0 and 1, but the results hold for a general interval. We consider this ensemble because it leads to an exact solution (no approximations are necessary) when $L = H$.

As explained in section 5, to obtain the memory capacity, it is enough to determine the probability that the vector $\mathbf{J}^{-1} \cdot \mathbf{1}$ has all of its entries positive. We consider the problem from a geometrical point of view. In the above ensemble each matrix $\mathbf{J}$ can be considered to consist of N' independant row vectors $\mathbf{J}_1, .., \mathbf{J}_{N'}$, one for each line of $\mathbf{J}$. Each such vector $\mathbf{J}_i$ is uniformily distributed in the N'-dimensional cube $[0,1]^{N'}$ of N'-dimensional space. The vector $\mathbf{B} = \mathbf{J}^{-1} \cdot \mathbf{1}$ is the solution of the set of equations

$$\mathbf{J}_i \cdot \mathbf{B} = 1, \quad 1 \leq i \leq N' \tag{13}$$

where the dot represents matrix multiplication which here coincides with the standard scalar product. As a consequence of these equations, the vector $\mathbf{B}$ is perpendicular to the hyperplane which passes through the extremities of all the $\mathbf{J}_i$. In other words, defining $\boldsymbol{\ell}$ to be the line passing through the origin which is given by the equations $\mathbf{J}_1 \cdot \boldsymbol{\ell} = ... = \mathbf{J}_{N'} \cdot \boldsymbol{\ell}$, $\mathbf{B}$ is parallel to $\boldsymbol{\ell}$. So, if the vector $\mathbf{B}$ belongs to the positive sector $\{B_i \geq 0\}$ of N'-dimensional space, then the line $\boldsymbol{\ell}$ passes through this sector. Conversely, if the line $\boldsymbol{\ell}$ passes through the positive sector, it defines a vector $\mathbf{B}$ having all entries positive such that $\mathbf{J}_1 \cdot \mathbf{B} = ... = \mathbf{J}_{N'} \cdot \mathbf{B}$. Then by a rescaling one obtains a vector $\mathbf{B}$ of positive entries such that $\mathbf{J}_1 \cdot \mathbf{B} = ... = \mathbf{J}_{N'} \cdot \mathbf{B} = 1$.

Thus we seek the probability that the line $\boldsymbol{\ell}$ passes through the positive sector. It is easy to see that the condition $\mathbf{J}_1 \cdot \boldsymbol{\ell} = ... = \mathbf{J}_{N'} \cdot \boldsymbol{\ell}$ is unchanged if one adds the same constant to all the J_{ij}; thus we shift the J_{ij}'s by the vector $-\frac{1}{2}\mathbf{1}$ so that they are uniformily distributed in the cube $K = [-\frac{1}{2}, \frac{1}{2}]^{N'}$. By symmetry, the probability distribution of the $\mathbf{J}_{ij}$'s is clearly invariant by any orthogonal transformation which leaves the cube K invariant. It follows that for any sector (a sector being defined as the set of vectors $\mathbf{B}$ for which each entry has a specified sign), the probability that $\boldsymbol{\ell}$ passes through this sector is the same. There are in all $2^{N'}$ sectors which are mutually disjoint (up to some sets of measure 0), and a given line $\boldsymbol{\ell}$ passes through two opposite sectors, so the probability that the vector $\mathbf{J}^{-1} \cdot \mathbf{1}$ has all of its entries positive is

$$P_{\geq 0} = 2^{-N'+1}. \tag{14}$$

In fact, this result is valid for more general probability distributions. The only property used in our demonstration is the hyper-cubic symmetry of the $\boldsymbol{\ell}$ probability distribution. This follows directly from the fact that the probability distribution for the line vectors $\mathbf{J}_i$ has the same symmetry, once suitably translated. Clearly there is no need to suppose that the J_{ij}'s are uniformily distributed in a certain interval for this to be true. A sufficient condition is that the

probability distribution for the J_{ij}'s be symmetric with respect to its mean value. The most symmetrical example occurs when the J_{ij} are (i.i.d.) gaussian variables. Then the row vectors $\mathbf{J}_i$ are gaussian vector variables, and the line ℓ is uniformily distributed.

A.2. The case J_{ij} symmetric, $L = H$. Here we assume that the J_{ij} are independent random variables for $i \leq j$, all uniformily distributed in $[0, 1]$, but as in appendix A.1, our results extend to more general ensembles. The matrix $\mathbf{J}$ being symmetric, denote λ_i its eigenvalues, with the λ_i real and assumed given in increasing order. Let $|\Psi_i >$ be the orthonormal eigenvectors, $\mathbf{J}|\Psi_i >= \lambda_i|\Psi_i >$ for $i = 1, ..., N'$. We use Dirac's notation, so that $|\Psi >$ denotes a collumn vector, $< \Phi|$ a row vector, $< \Phi|\Psi >$ their scalar product, and $|\Psi >< \Phi|$ their outer (dyadic) product. Then we may write:

$$\mathbf{J} = \sum_{i=1}^{N'} \lambda_i |\Psi_i >< \Psi_i|, \tag{15}$$

and

$$\mathbf{J}^{-1} = \sum_{i=1}^{N'} \frac{|\Psi_i >< \Psi_i|}{\lambda_i}. \tag{16}$$

For a choice $\mathbf{h} = (h_1, ..., h_{N'})$ of the fields acting on the clones, the solution to the system $\mathbf{J} \cdot \mathbf{B} = \mathbf{h}$ is thus

$$\mathbf{B} = \sum_{i=1}^{N'} |\Psi_i >< \Psi_i|\mathbf{h} > /\lambda_i. \tag{17}$$

As for the non-symmetric case, we consider first the limit $L/H \to 1$ (the general case $L \neq H$ is given in appendix A.3). The problem is then to find the probability $P_{\geq 0}$ that the vector

$$\mathbf{B} = \sum_{i=1}^{N'} |\Psi_i >< \Psi_i|\mathbf{1} > /\lambda_i \tag{18}$$

has all its entries positive (with $|\mathbf{1} >= (1, ..., 1)$).

Let us begin with some properties of the eigenvalues and the eigenvectors of $\mathbf{J}$. First, since the J_{ij} are positive, the largest eigenvalue $\lambda_{N'}$ is positive and the corresponding eigenvector $|\Psi_{N'} >$ has all its components of the same sign, which we may take to be positive. Second, there is a variational principle for $\mathbf{J}$, so that

$$\lambda_{N'} = \max_{|\Psi>} \frac{< \Psi|\mathbf{J}|\Psi >}{< \Psi|\Psi >}. \tag{19}$$

If one writes $|\Psi_{N'} >= (\mathbf{1} + |\delta\Psi >)/\sqrt{N'}$, then a perturbative treatment of the equation $\mathbf{J}|\Psi_{N'} >= \lambda_{N'}|\Psi_{N'} >$ shows that the components of the vector $|\delta\Psi >$ are random variables with zero mean and standard deviation $O(1/\sqrt{N'})$. Thus as $N' \to \infty$, the vector $|\delta\Psi >$ represents a correction which goes to zero. Furthermore, one has

$$\lambda_{N'} = N'/2 + O(1). \tag{20}$$

Consider now the rest of the spectrum. For each eigenvector $|\Psi_i>$, $i \neq N'$, the orthogonality condition $<\Psi_{N'}|\Psi_i>= 0$ and the normalization $<\Psi_i|\Psi_i>= 1$ implies that the components of $|\Psi_i>$ are random variables with zero mean value and standard deviation $\sigma = 1/\sqrt{N'}$. (This can also be shown from random matrix theory. Note however that the eigenvectors are correlated because of the orthogonality conditions.) The components of the vector $\mathbf{J}|\Psi_i>$ can be considered as a sum of N' random variables; as N' becomes larger and larger, by the central limit theorem, these components become gaussian variables with mean value 0 and standard deviation of the order of 1. Then one sees from the equation $\mathbf{J}|\Psi_i>= \lambda_i|\Psi_i>$ that the eigenvalues λ_i ($i \neq N'$) are distributed in an interval centered at 0 and with a size $O(\sqrt{N'})$. In fact, it is known from random matrix theory that the eigenvalues of a random matrix have a probability distribution given Wigner's semi-circle law (Metha, 1967) and that two consecutive eigenvalues repell one-another. This property gives the spectrum what is called "rigidity". One may think of the spectrum as fluctuating around a mean position obtained by distributing the eigenvalues $\lambda_1, ..., \lambda_{N'-1}$ roughly equidistantly in an interval of size $\sqrt{N'}$ centered on 0. The distance between two successive eigenvalues fluctuates around a mean value $d_{N'}$ which scales thus as $1/\sqrt{N'}$.

In the expression for $\mathbf{B}$ in equation (17), let us replace the terms by their asymptotic values. For $i = N'$, we drop the $|\delta\Psi>$, and for the other terms, we project onto the hyperplane perpendicular to $(1, ..., 1)$. This gives the following approximation:

$$\mathbf{B} \approx |\mathbf{R}> /\sqrt{N'} + 2|\mathbf{1}> /N' \tag{21}$$

with $|\mathbf{R}>$ a random vector, the components of which are $O(1)$. The two terms on the right hand side are orthogonal, and a scaling analysis shows that the relative error introduced into either term by this approximation is $O(1/\sqrt{N'})$.

According to random matrix theory, the distribution of the matrix $\mathbf{J}$ truncated to the hyperplane $\sum_{i=1}^{N'} B_i = 0$ becomes in the limit $N' \to \infty$ the same as the Gaussian Orthogonal Ensemble (GOE) (Metha, 1967), so we deduce the probability law for the $|\Psi_i>$'s and the λ_i's in this limit: the distribution of the $|\Psi_i>$'s is invariant under any rotation which leaves the axis $(1, ..., 1)$ invariant. It follows that the vector $|\mathbf{R}>$ has a distribution which is invariant by any rotation in the hyperplane where it lives. Using the normalization of the $|\Psi_i>$'s, the squared norm of $|\mathbf{R}> /\sqrt{N'}$ is

$$\chi = \frac{<\mathbf{R}|\mathbf{R}>}{N'} \approx \sum_{i=1}^{N'-1} \frac{|<\Psi_i|\mathbf{1}>|^2}{\lambda_i^{\,2}} = \sum_{i=1}^{N'-1} \frac{|<\Psi_i|\delta\Psi>|^2}{\lambda_i^{\,2}}, \tag{22}$$

where the vector $|\delta\Psi>$ is as previously defined. Since the first term in the r.h.s. of (21) has a typical size $\sqrt{N'}$ times larger than the second term, we see that the vector $\mathbf{B}$ will almost always have negative components, unless the vector $|\mathbf{R}>$ has an exceptionnaly small size or unless it is oriented in a very special way (so that its negative components are all small), or more likely, a combination of these two posssibilities.

In order to estimate the probability $P_{\geq 0}$ that $\mathbf{J}^{-1} \cdot \mathbf{1}$ has all its entries positive, we will first obtain the probability distribution for the norm of the vector $|\mathbf{R}>$. Then we will determine

the "orientation factor", that is the probability that $\mathbf{B}$ has all its entries positive given that the vector $|\mathbf{R}>$ has a fixed norm but an arbitrary orientation. The scaling behaviour of $P_{\geq 0}$ as N' becomes large can then be obtained by using a saddle point expansion.

What is the probability distribution $P(\chi)$ of the squared norm $\chi =< \mathbf{R}|\mathbf{R} > /N'$? To make the calculation feasible, we make two approximations. First, we neglect the fluctuations of the eigenvalues λ_i, and work with a freezed version of the spectrum. We have set the positive and negative eigenvalues ($i \neq N'$) to be integer multiples of $C'/\sqrt{N'}$ where C' is a constant given by the Wigner semi-circle law (Metha, 1967) so as to obtain the correct eigenvalue density. The main source of error in this approximation comes from neglecting the fluctuations of the eigenvalue closest to zero. When this eigenvalue is very near zero, the norm of $|\mathbf{R}>$ becomes larger than expected. However, since we are interested in fluctuations which render the norm of $|\mathbf{R}>$ small, we are not too sensitive to this approximation. In our second approximation, we consider the random variables $< \Psi_i|\delta\Psi >$ in the limit $N' \to \infty$ as independant gaussian variables with zero mean and standard deviation proportional to $1/\sqrt{N'}$.

With these approximations, the problem is to find the probability distribution for the random variable

$$\chi = C \sum_{i=1}^{N'-1} \frac{{X_i}^2}{i^2} \qquad (N' \to \infty) \tag{23}$$

where the X_i's are independant gaussian variables with zero mean and unit standard deviation, and C is a constant in which numerical factors (C' and the standard deviation of the $< \Psi_i|\delta\Psi >$) have been absorbed. This constant merely induce a rescaling on the distribution $P(\chi)$, so for simplicity, we have omitted it in most of the presentation.

An integral representation for $P(\chi)$ may be obtained by Fourier transformation. The probability distribution for the n'th term, $u_n = {X_n}^2/n^2$, is easily seen to be

$$P_n(u_n)du_n = \frac{n}{\sqrt{2\pi}}\, \theta(u_n)\, \frac{du_n}{\sqrt{u_n}} \exp(-\frac{n^2 u_n}{2}) \tag{24}$$

$\theta(u_n)$ being the Heaviside threshold function. Defining the Fourier transform of a function $f(x)$ by the formula

$$\hat{f}(k) = \int_{-\infty}^{+\infty} e^{ikx} f(x)dx \tag{25}$$

one readily computes

$$\hat{P}_n(k) = \left(1 - \frac{2ik}{n^2}\right)^{-\frac{1}{2}}. \tag{26}$$

From standard properties of Fourier transformation one then finds the following expression for $P(\chi)$:

$$P(\chi) = \frac{1}{2\pi} \int_{-\infty}^{+\infty} dk e^{-ik\chi} \left(\prod_{n=1}^{\infty} \frac{1}{1 - \frac{2ik}{n^2}} \right)^{\frac{1}{2}} = \frac{1}{2\pi} \int_{-\infty}^{+\infty} dk e^{-ik\chi} \left(\frac{\sqrt{2ik}}{\sin \pi\sqrt{2ik}} \right)^{\frac{1}{2}}. \tag{27}$$

We are interested in the behaviour of $P(\chi)$ as $\chi \to 0$, so we use a saddle point expansion. The integrand in the previous expression is of the form $\exp f(k)$ with

$$f(k) = -ik\chi - \frac{1}{2}\sum_{n=1}^{\infty} \ln\left(1 - \frac{2ik}{n^2}\right) \tag{28}$$

By differentiating $f(k)$ one obtains the saddle point equation

$$\chi = \sum_{n=1}^{\infty} \frac{1}{n^2 + K} = -\frac{1}{2K} + \frac{\pi \coth \pi\sqrt{K}}{2\sqrt{K}}, \tag{29}$$

where we have set $k = iK/2$. We seek a solution K which is real and positive. It is not too difficult to see that for small enough χ such a solution K_c exists and that $K_c \to \infty$ as $\chi \to 0$. Keeping only the leading term of the last equation in this limit one obtains

$$K_c \sim \left(\frac{\pi}{2\chi}\right)^2. \tag{30}$$

The second derivative $f''(k_c)$ is easily obtained using the analytical expression for $f'(k)$. In the limit $\chi \to 0$, one has

$$f''(k_c) \sim -\frac{\pi}{2}\frac{1}{K_c^{\frac{3}{2}}} \sim -\left(\frac{2}{\pi}\right)^2 \chi^3. \tag{31}$$

The saddle point approximation then gives the following asymptotic behaviour for $P(\chi)$ as $\chi \to 0$:

$$P(\chi) \sim \frac{A}{\chi^2} e^{-\frac{\alpha}{\chi}}. \tag{32}$$

A and α are positive constants which depend on the value of the rescaling constant C of equation (23) which may be estimated numerically. We find $\alpha = \pi^2 C/8$.

We now consider the orientation factor, that is the probability that $\mathbf{B}$ has all its entries positive given that the vector $|\mathbf{R}>$ has a fixed norm but an arbitrary orientation. This factor is equal to $\Omega_{N'}(N'\chi/4)$, where $\Omega_{N'}(\rho^2)$ is the following conditional probability:

$$\Omega_{N'}(\rho^2) = \frac{\int d^{N'}x \delta(x^2 - \rho^2)\delta(<x|1>) \prod_{i=1}^{N'} \theta(x_i + 1/\sqrt{N'})}{\int d^{N'}x \delta(x^2 - \rho^2)\delta(<x|1>)}. \tag{33}$$

This is the portion of an $N' - 1$-dimensional sphere of given radius which lies in a concentric $N' - 1$-dimensional regular simplex of given size. We have written a computer program which computes this probability for any value of N'. We find that as $N' \to \infty$, the function $\Omega_{N'}(\rho^2)$ approaches a step function, $\Omega_{N'}(\rho^2) = 1$ for $\rho < \rho_c$ and $\Omega_{N'}(\rho^2) = 0$ for $\rho > \rho_c$, where ρ_c is a finite constant approximately equal to 0.5.

Given the probability distribution $P(\chi)$ and the orientation factor $\Omega_{N'}(\rho^2)$, we can now compute the large N' behaviour of the probability $P_{\geq 0}$ we were seeking:

$$P_{\geq 0} = \int_0^{\infty} d\chi P(\chi)\Omega_{N'}\left(\frac{N'\chi}{4}\right) \sim \int_0^{\frac{4\rho_c^2}{N'}} \frac{A}{\chi^2} e^{-\frac{\alpha}{\chi}} = A\int_{\frac{N'}{4\rho_c^2}}^{\infty} e^{-\alpha x} dx = \frac{A}{\alpha} e^{-\beta N'}, \tag{34}$$

with $\beta = \alpha/4\rho_c^2$. We thus find, as anounced, an exponential behavior for the probability $P_{\geq 0}$. We have verified this law by direct Monte Carlo simulation for small values of N', and we obtain $\beta = 0.68 \pm 0.015$. This is compatible with $\beta = \ln 2 \sim 0.693$ within statistical errors and possible systematic effects at small N. Furthermore, we have calculated numerically the value of C in equation (23) and this too leads to a value of β which is very close to $\ln 2$. There is thus good numerical evidence that the symmetric and non-symmetric ensembles give the same memory capacity at large N; unfortunately we have no good theoretical arguments which would validate this result.

A.3. The case J_{ij} symmetric, $H \neq L$. In this appendix, we study the same affinity matrix ensemble as in appendix A.2, but we no longer impose the simplifying condition $H/L = 1$. We shall see that when the quantity $H/L - 1$ is not very small (which is the case biologically), the memory capacity is drastically reduced from $O(N)$ to $O(\ln N)$. We use the same notations as before. Given a choice $\mathbf{h} = (h_1, ..., h_{N'})$ for the fields, the probability that the vector $\mathbf{B} = \mathbf{J}^{-1} \cdot \mathbf{h}$ has all its entries positive now depends on $\mathbf{h}$, but clearly only through the number M of low fields $h_i = L$ in $\mathbf{h}$. We may thus replace $\mathbf{h}$ by the vector $\mathbf{h}_M = (L, ..., L, H, ..., H)$ (where the M first entries are low fields) without loss of generality. Using the same notation as in section 5, we denote by $P(N', M, L/H)$ the probability that $\mathbf{B}$ has all its entries positive.

In the same spirit as in appendix A.2, we write the vector $\mathbf{B}_M = \mathbf{J}^{-1} \cdot \mathbf{h}_M$ in the form

$$\mathbf{B}_M = \sum_{i=1}^{N'} |\Psi_i >< \Psi_i|\mathbf{h}_M > /\lambda_i, \tag{35}$$

and we split the sum by replacing the last term by its projection onto the vector $(1, ..., 1)$ and the $N' - 1$ first terms by their projection onto the hyperplane orthogonal to $(1, ..., 1)$. This leads to an approximation for the vector $\mathbf{B}_M$ analogous to equation (21). The only difference lies in the respective sizes of the two terms thus obtained. These sizes are given by the scalar products $< \Psi_i|\mathbf{h}_M >$ which reduced to $< \Psi_i|1 >$ in the case $L/H = 1$. As before, we use the identity $\sqrt{N'}|\Psi_{N'} >= 1 + |\delta\Psi >$, where the "error" $|\delta\Psi >$ tends to zero as $1/\sqrt{N'}$. For $i = N'$ one has

$$< \Psi_{N'}|\mathbf{h}_M >= \frac{ML + (N' - M)H}{\sqrt{N'}} + O(1/\sqrt{N'}). \tag{36}$$

For $i \neq N'$ we write

$$< \Psi_i|\mathbf{h}_M >= L < \Psi_i|(1)_M > + H < \Psi_i|(1)^{N'-M} > \tag{37}$$

$$= -L < \Psi_i|(\delta\Psi)_M > - H < \Psi_i|(\delta\Psi)^{N'-M} > + \sqrt{N'}(L - H) < \Psi_i|(\Psi_{N'})_M >, \tag{38}$$

where the symbol $|(\Psi)_M >$ (respectively $|(\Psi)^{N'-M} >$) denotes the vector $|\Psi >$ truncated after the M'th entry (respectively before the $N' - M$'th entry). We have made use of the identity $< \Psi_i|(\Psi_{N'})_M >= - < \Psi_i|(\Psi_{N'})^{N'-M} >$.

Each of the three terms of equation (38) is a sum of nearly independent variables, so we treat them as gaussian variables as we did previously for the variables $< \Psi_i|\delta\Psi >$. Each term has a zero mean value. The standard deviations of the first and second term are respectively $L\sqrt{CM}/N'$ and $H\sqrt{C(N'-M)}/N'$ where C is a finite constant, equal to the squared norm of $|\delta\Psi >$. For the third term one must take care of the orthogonality condition $< \Psi_i|\Psi_{N'} >= 0$. It is not difficult to see that the consequence of such a correlation is that the standard deviation of the M'th partial sum $< \Psi_i|(\Psi_{N'})_M >$ is, as N' becomes large, of the form $\sqrt{r(1-r)}/\sqrt{N'}$ where $r = M/N'$. Thus the standard deviation of the third term is $(H-L)\sqrt{r(1-r)}$. Note that this is zero when $L = H$ which explains why that limit is simpler to analyze. We conclude that the $< \Psi_i|\mathbf{h}_M >$ are nearly gaussian variables with standard deviation $\sigma(M,N')/\sqrt{N'}$ where

$$\sigma^2(M,N') = C(L^2r + H^2(1-r)) + N'(H-L)^2r(1-r), \tag{39}$$

and the analog of equation (21) then reads

$$\mathbf{B}_M \approx \frac{\sigma(M,N')}{\sqrt{N'}}|\mathbf{R} > + \frac{2}{N'}(Lr + H(1-r))(1,...,1) \tag{40}$$

where the relative error is again $O(1/\sqrt{N'})$. In this equation, the random vector $|\mathbf{R} >$ is exactly the same as that of appendix A.2, possible numerical factors being absorbed in $\sigma(M,N')$. We are now faced with the same problem as before except that the relative size of the two terms in the equation is now greater by a factor $\sigma(M,N')/(Lr + H(1-r))$. One may thus directly write the large N' behaviour of the probability $P(N',M,L/H)$ as

$$P(N',M,L/H) \sim e^{-\beta f(r)N'} \tag{41}$$

where

$$f(r) = \frac{\sigma^2(M,N')}{(Lr + H(1-r))^2} = \frac{C(L^2r + H^2(1-r)) + N'(H-L)^2r(1-r)}{(Lr + H(1-r))^2}. \tag{42}$$

We see that when the ratio $r = M/N'$ is finite, the probability $P(N',M,L/H)$ has a behaviour of the form $\exp(-N'^2)$ rather than $\exp(-N')$ which was the $L/H = 1$ behavior.

To derive an estimate for the memory capacity M^* we use the following rough upper bound for $P(N',M,L/H)$:

$$P(N',M,L/H) \leq e^{-\beta\left(\frac{L}{H}\right)^2 N'} e^{-\beta(H-L)^2 \frac{r(1-r)}{H^2} N'^2} \leq e^{-\beta\left(\frac{L}{H}\right)^2 M} e^{-\beta(1-\frac{L}{H})^2 M(N'-M)}. \tag{43}$$

This gives the following majoration for the number of fixed points with M clones in the immunized state:

$$\mathcal{N}(M,N) = \sum_{N'=M}^{N} \binom{N-M}{N'-M} P(N',M,L/H) \leq \sum_{p=0}^{N-M} \binom{N-M}{p} e^{-\beta\left(\frac{L}{H}\right)^2 M} e^{-\beta(1-\frac{L}{H})^2 Mp} \tag{44}$$

$$= e^{-\beta\left(\frac{L}{H}\right)^2 M}(1 + e^{-\beta(1-\frac{L}{H})^2 M})^{N-M}. \tag{45}$$

One sees that $\mathcal{N}(M,N)$ will be a growing function of N as long as M satisfies

$$(N-M)e^{-\beta(1-\frac{L}{H})^2 M} > \beta(\frac{L}{H})^2 M. \tag{46}$$

This gives a memory capacity of the form

$$M^* \sim \frac{\ln N}{(1-\frac{L}{H})^2}. \tag{47}$$

Two comments are in order concerning the above derivation. The first concerns the approximation made by projecting each term of equation (35). In the limit $L/H = 1$, this is justified by the fact that the terms dropped are $O(1/\sqrt{N'})$ in relative size. This is not the case when $L \neq H$. A scaling analysis shows that the projection of the $N'-1$ first terms of equation (35) on the vector $(1,...,1)$ has a size comparable to that of the second term of equation (40). This modifies the factor before $(1,...,1)$ by adding to it a noisy component of comparable size and zero mean value. We did not take this into account for the presentation because it would have complicated unecessarily the formulae to obtain the same result.

The second remark concerns the dependence of the memory capacity M^* on the ratio L/H. Clearly the expression found for the probability $P(N',M,L/H)$ reduces to that of appendix A.2 in the limit $L/H \to 1$, which is to be expected. However in the limit $L/H \to 0$ we find an L/H-independent, positive value for $P(N',M,L/H)$, and a still growing memory capacity, although section 5 suggested that $P(N',M,L/H)$ must vanish as $(L/H)^{MN'}$ in this limit, which would make the corresponding memory capacity tend to 0 as $\ln(N)/\ln(H/L)$. (In fact the above analysis in terms of r gives a more symmetrical expression which is valid also when $N' = M$, suggesting that $P(N',M,L/H)$ must vanish as $(L/H)^{M(N'-M)}$.) It is not too difficult to see that the distribution that we postulated for the vector $|\mathbf{R}>$ in eq. (40) has drawbacks when L/H becomes too small. The term proportional to $(1,...,1)$ has a norm equal to $2(Lr+H(1-r))/\sqrt{N'}$. However, we know that in order for the equation $\mathbf{J}\cdot\mathbf{B}_M = \mathbf{h}$ to be fullfilled, the vector $\mathbf{B}_M$ cannot have a norm lower than H/N' (we assume that the vector $\mathbf{h}$ contains at least one high field). So the probability distribution of $\mathbf{B}_M$ falls down to zero in the region $||\mathbf{B}_M|| < H/N'$. One expects that this will have nearly no effect on the probability distribution of $|\mathbf{R}>$ as long as the relation $L/\sqrt{N'} \gg H/N'$ holds. We thus expect our analysis to be sensible as long as $H/L \ll \sqrt{N'}$.

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