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CAPACITY OF A MODEL IMMUNE NETWORK

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Abstract

The capacity of a model immune network in terms of the number of different antigens that can be vaccinated against without any memory lost is computed and tested by numerical simulations. We also investigate memory loss and failure to vaccinate due to overcrowding the network with too many antigens. The computations are done for two different strategies for proliferation, one implying all the antigen specific clones and the second one being more thrifty.

1. INTRODUCTION

The evaluation of the capacity of a neural net is a rather classical problem (Mezard et al (1988), Weisbuch (1990), Hertz et al (1990)), and the purpose of this paper is to compute the capacity of a model immune network in the same spirit. A neural net is able to retrieve memories of previously presented patterns, and the capacity problem relates to the maximum number of patterns that can be memorized without destruction of previously memorized patterns. A classical result about the standard Hopfield model is that its capacity scales as N, the number of automata, and equals 0.14 N, although its total number of attractors is exponential in N (Mezard et al (1988), Hertz et al (1990)). There are several models of Jerne idiotypic network models including those of Hoffmann (1979), Kaufman (1988), Varela et al (1988), De Boer and Hogeweg (1989), De Boer and Perelson (1991). Some efforts have recently concentrated on a discrete version of the network first presented by Weisbuch et al (1990) and further developed by Neumann and Weisbuch (1992a, 1992b). In this model, antigen presentation results in a local modification of the clone populations that form the attractors of the dynamics. In other words, the new attractor reached after antigen presentation only differs from the previous attractor in a localized patch of clones that are connected to the clones that recognize the antigen: typically these clones are the anti-idiotypic clones and maybe the anti-anti-idiotypic clones. The property of localized response ensures the independence
Fig. 1. Localized patches of clones perturbed by different antigenic presentations. Two vaccination and one tolerant attractors are represented. See figure 5 for more details.

of antigen memories: two unrelated antigens elicit uncorrelated responses. Memorization of one antigen, although perturbing the network in the vicinity of the clones specific for the antigen does not modify the populations responsible for the maintenance of the memory of other antigens - provided that the specific clones are far apart in the network (see Fig.1).

The network is then both sensitive to new antigens, and robust enough to maintain memories of previously presented antigens.

The independence property cannot be kept indefinitely when successive antigens are added to the network; since the network is finite in size, the local perturbations induced by the presented antigens have a finite probability of interaction which increases when new antigens are presented. Some scaling laws have already been obtained on immune network capacities, irrelevant of the actual topology of the network.

A lower limit for the total number of attractor in the network is:

$$3^N$$

where $N$ is the number of clones in the network and $p_s$ is the size of the patch perturbed by antigen presentation (Perelson and Weisbuch 1994). This exponential relation reminds the equivalent relation for neural nets or spin glasses (Mézard et al 1987).
But not all these attractors are of interest. The relevant question is rather the following: A living system must face frequent encounters with antigen during its life. Self antigens should elicit a tolerant response; dangerous external antigens should elicit vaccination. The nature of the localized response on each individual site of the network is then determined by the fact that the presented antigen should be tolerated or fought against. In this context, we can ask how many different antigens can be presented so that no overlap among different patches occurs? Weisbuch and Derrida, (Weisbuch 1990), obtained the following capacity for randomly presented antigens:

$$\sqrt{\frac{2N}{P}}$$

A generalized expression of this capacity is to be derived in this paper. On the other hand, it can be argued that the clones expressed by mammals have been optimized to the environment of the immune system, e.g., self molecules and frequently encountered parasites and pathogens, and thus can accommodate a larger number of antigens. If the system were optimized the capacity could follow a linear scaling law

$$\frac{N}{P}$$

which corresponds to close packing of patches. This optimization could have occurred during phylogenesis (e.g., the evolution of species) or it could have been carried during the epigenesis of the immune system (the build-up of the immune system during the animal lifetime).

The purpose of the present paper is to compute and check by numerical simulations the capacity of a shape space based model of the immune system.

We will first recall the basic definition of Weisbuch et al (1990) model and then define a random connection structure based on digits strings. This structure is proposed to capture the effects of shape based recognition and thymus clonal elimination. The local analysis of the results of individual antigen presentation will be based on computer simulations and simple mathematical calculations. The results are used to compute the capacity of the network taking into account those effects due to topological defects and those due to crowding because of previous antigenic presentations. The importance of different scenarios is then estimated, failure to remove the antigen or to vaccinate, and losses of memory of previous vaccinations. We will investigate the effects of two possible clonal response mechanisms: a simple mechanism such that all clones that recognize the antigen undergo proliferation and a thrifty mechanism where only one clone actually responds to the antigen.

Large scale computer simulations will be used to obtain statistics on network capacities and check our hypotheses on optimal networks.
2. LOCAL ANALYSIS

2.1. The mathematical model

The dynamical behavior of each element $i$ obeys a differential equation that describes the time evolution of the population $x_i$ of clone $i$

$$\frac{dx_i}{dt} = s + x_i(f(h_i) - d),$$

(1)

where $s$ is the source term corresponding to cells coming from the bone marrow, the function $f(h_i)$ defines the rate of proliferation, and $d$ specifies the rate of cell population decay. For each clone $i$ we consider the total amount of anti-idiotype stimulation as a linear combination $h_i$ of the populations of other interacting clones $j$. We call $h_i$ the field acting on clone $x_i$:

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

(2)

where $J_{ij}$ specifies the affinity between clones $x_i$ and $x_j$. The choice of the $J$ matrix defines the topology of the network (see section 2.3).

Fig. 2 displays the bell-shaped proliferation function $f(h)$ based upon two Michaelis-Menten saturation functions with the two thresholds $\theta_1$ and $\theta_2$ ($\theta_2 >> \theta_1$), and a maximum rate of proliferation, $p$:

$$f(h) = p \left( \frac{h}{\theta_1 + h} \right) \left( 1 - \frac{h}{\theta_2 + h} \right) = \frac{ph\theta_2}{(\theta_1 + h)(\theta_2 + h)}.$$ 

(3)

The proliferation function $f(h)$ has a stimulatory and a suppressive part with thresholds $\theta_1$ for activation and $\theta_2$ for suppression. Within the stimulatory part, $h < \sqrt{\theta_1\theta_2}$, $f'(h) > 0$, increasing the field increases proliferation; within the suppressive part, $h > \sqrt{\theta_1\theta_2}$, $f'(h) < 0$, increasing the field decreases proliferation. Similar dose response curves are found in receptor crosslinking (Perelson 1984).

2.2. The attractors of the Cayley tree

The immune network is defined by the affinities, $J_{ij}$. Unfortunately, our knowledge of the actual $J_{ij}$'s is very restricted. We will further use a connection structure where the $J_{ij}$ are 0 or 1 according to complementarity of cell receptors on a shape space. In order to simply define the vaccination and tolerance attractors, let us use for the moment the Cayley tree (see the diagrams on Fig. 5e and 5f), (Weisbuch et al. 1990),
Fig. 2. \( f(h) \), the log-bell shaped proliferation function of the field \( h \). \( L \) and \( H \) are resp. the activating and suppressive field values defined in the text.

which is the simplest connection structure that describes an infinite network. Consider a Cayley tree with \( k \) connections per site, and \( J_{ij} \)'s which can only be 0 (no connection) or 1 (maximum interaction when the connection exists). The root of the tree is selected by antigen presentation.

According to their distance to the root, the clones are numbered 1 (and called \( x_1 \) for the antigen specific clones), 2 (for the \( x_2 \) anti-idiotypic clones, specific for some \( x_1 \) ), 3 ,..., \( i \). The different fields \( h_1, h_2, h_3, \ldots, h_i \), experienced by clones 1, 2, 3, ..., \( i \) are given by:

\[
\begin{align*}
    h_1 &= kx_2 + A \\
    h_2 &= x_1 + (k - 1)x_3 \\
    h_3 &= x_2 + (k - 1)x_4 \\
    \ldots \ldots \ldots \\
    h_i &= x_{i-1} + (k - 1)x_{i+1}
\end{align*}
\]
Clone 1 experiences a field due to anti-idiotypic clones 2 plus the extra contribution of the antigen when it is present. A is antigen concentration expressed in units corresponding to a unit affinity for clone proliferation.

Let us start with the simplest configuration, corresponding to the hypothetical case where no antigen has yet been presented and all populations have the value \( s/d \). (A basic assumption of this model is that \( s/d \) is much smaller that the first proliferation threshold \( \theta_1 \), so that all proliferation functions are 0 in the virgin state). After presentation of the first antigen, memorization is obtained if some populations of the network reach a stable level higher than \( s/d \). To summarize more systematic studies, (Neumann and Weisbuch, 1992a,b), attractor configurations consist of shells of neighboring high (\( H \)) and intermediate (\( L \)) field nodes (\( H \) and \( L \) will be defined below). Upstream clones (i.e. with smallest \( i \)) experience intermediate fields (\( L \)) and have large populations sustained by the downstream (i.e with \( j = i + 1 \)) low populations which experience high suppressive fields (\( H \)). Important examples of these principles are given in the next paragraphs.

2.2.1. Vaccination.

Let us consider the case of antigen presentation to clone \( x_1 \) which results in excitation of clones \( x_2 \), while clones \( x_3 \) remain close to their virgin level (see Figs. 3 and 5.e).

In this case, one obtains low field \( L \) for \( x_1 \), and a large suppressive field \( H \) for \( x_2 \). The field equations allow one to compute the populations:

\[
\begin{align*}
  h_1 &= kx_2 = L \approx \frac{d\theta_1}{p - d} \\
  h_2 &= x_1 + (k - 1)\frac{s}{d} = H \approx \frac{(p - d)\theta_2}{d}.
\end{align*}
\]

\( H \) and \( L \) are the respectively the high field and low field intersections of the proliferation function \( f(h) \) with the decay term \( d \). In the approximation where \( \theta_1 \) is much smaller than \( \theta_2 \), \( H \) and \( L \) are computed by equating to 1 respectively the first or the second term in parentheses in equation (3). Of course, the solution remains localized only if the field \( h_3 \) on \( x_3 \) is much less than \( L \)

\[
h_3 = \frac{L}{k} + \frac{(k - 1)s}{d} < L,
\]

otherwise \( x_3 \) would also proliferate. The attractor does not remain localized if \( k \) is 1 (see further the case of singly connected clones in section 2.3.1). This attractor is interpreted as vaccination: when antigen is later presented, its elimination is much faster than in the virgin attractor since the relevant clone \( x_1 \) is present at a much higher population. To decide which attractor is reached when the antigen is presented, one needs to solve equations [4-7], to which a supplementary equation describing antigen dynamics is added:

\[
\frac{dA}{dt} = -KAx_1
\]
Fig. 3. Time plot of an antigen presentation resulting in a vaccination attractor. On the vertical axis are the clone populations on a logarithmic scale. Time in days is on the horizontal axis. In the vaccinated configuration the largest population is localized at the first level. $X_1$ is high ($H$) and sustained by an intermediate population ($L/m$) of $X_2$. The rest of the clones are virgin (V) (or almost virgin) after the system settles into this attractor. When antigen is presented again, it is eliminated faster than the first time. Simulation parameters were: $K = 10^{-6}$; $A_0 = 5000$; $d = 0.5$; $p = 1$; $m = 3$; $s = 1$; $\theta_1 = 2000$; $\theta_2 = 10^5$.

A vaccination attractor is usually reached for intermediate initial antigen concentrations, $A_0$, and intermediate values of the decay constant $K$.

2.2.2. Tolerance.

In general, which attractor is attained depends upon races for suppression among different clones. The tolerance attractor, for instance, is attained when $x_2$, the anti-idiotypic clone, reaches a field large enough to suppress $x_1$, the idiotypic clone, before $x_1$ reaches a field suppressive for $x_2$. Large initial antigen concentration, large connectivity $k$ and slow decay (small $K$) favor $x_2$ with respect to $x_1$ in this race and they drive the network to the tolerance attractor (see Fig. 5.f). A strong suppressive field acts on $x_1$ due to $x_2$'s. The $x_2$'s proliferate due to a low field provided by $x_3$'s, but $x_4$'s remain nearly virgin. This attractor is interpreted as tolerance since when antigen is
Fig. 4. Recognition by complementary digit strings. The two bits strings in the center of the figure, 1230 on top and 2103, are exactly complementary. 0230, 1130 and 1220 are approximate complementary of 2103, but 1231 is not.

later presented at level 1, clone $x_1$ is not able to expand and destroy the antigen since it is experiencing a suppressive field due to clone $x_2$.

2.3. The shape space and the related connection structure

Our numerical simulations were done for a partially random connection structure based on the following shape space.

We start from a regular shape space, based on n-digit strings, e.g. 4 digits varying from 0 to 3 (the base $b$ of the digit string is then 4). 2331, 3201, 0011... are possible examples of 4-digit strings representing shapes. Recognition occurs among complementary strings, when the sum of corresponding digits equals 3 (see Fig. 4).
For instance 1230 and 2103 are complementary. We shall also consider as partially complementary strings for which all digits except one are complementary, and the sum on the non-complementary digit is 2. 2103 is partially complementary to 0230 and 1130, but not to 1231. We exclude complementarity when the sum of 2 digits equal 4 because in a shape interpretation they would prevent the shapes to fit together, while a hole due to a sum of 2 would not as seen in Figure 4. One important consequence of this choice (exclusion of sum 4 errors) is the absence in the network of 4-loops. (In bit strings starting e.g. from a string 000000, one obtains two one error neighboring strings 011111 and 101111 which have as a common neighbor 110000 which closes the 4-loop; but this is so because sum 2 errors are accepted, which would correspond to sum 4 errors in our case). This is of importance since if 4-loops were present they would prevent localization of the immune response (Neumann and Weisbuch 1992b). In terms of topology and related immune response, for the 4-digit strings network the shortest possible loops are 6-loops. This shape space is intermediate between the bit string structures proposed by Farmer et al. (1986) and the low dimensional shape spaces of Segel and Perelson (1990). We consider it more consistent with the discrete genetics of the lymphocyte receptors, the 6 complementarity determining regions of immunoglobulins or the dozen or so amino acids contact with antigen during immune recognition (Gollub 1992).

Furthermore, randomness in the network structure is introduced to take into account clonal deletion of autoreactive T cells, but many other reasons contribute to it. The simplified differential model of the immune network that we are using does not describe the dynamics of T cells: it simply assumes that whenever T cells populations are present, they allow clonal expansion at a rate which is independent of the actual T cell population or activation state, but when T cells have been eliminated in the thymus, no clonal expansion of related B cells is possible. To take into account clonal elimination in the thymus, we eliminate a finite fraction of the clones from the shape space by a random sampling: the regular n-dimensional lattice corresponding to the complete n-digits strings set is then restricted to the remaining random set of those B cell clones able to proliferate. We will consider in the simulations elimination fractions varying from 0.4 to 0.8. A consequence of this randomness is that we loose the connectivity invariance that previously made us choose the Cayley tree architecture. Different clones might have different connectivities, and some careful analysis will be done in the next section (2.4) of the effect of local connectivity on the response to antigenic presentation.

We will further make a distinction between the results that are specifically related to the connection structure derived from the above digit string shape space, and results that apply to any random structure.

2.4. Topological failures

Two kind of mechanisms can prevent vaccination:
- mechanisms related to local topology, irrespective of the presence in the neighborhood of patches of perturbed populations. In these cases, even the first presented antigen would not achieve vaccination (even though the presentation parameters would be adequate to elicit an immune response if competent clones were available).

- mechanisms due to the presence in the neighborhood of patches of perturbed populations, e.g. vaccination is impossible when the competent clone is suppressed.

Of course when the antigen is recognized by several clones, the failure to develop an immune response might be due to a combination of mechanisms some clone being non-respondent because of topology, others because of suppression for instance.

As soon as a clone is connected to at least two neighbors vaccination can be achieved. But singly connected clones might pose problems. The following results, summarized in Figure 5, are obtained by simple simulations involving small set of clones using GRIND software (De Boer 1983) and simple field analysis.

- Isolated clones are not able to maintain any memory after elimination of the antigen. Their response is always a primary response (Fig 5.a).

Let us recall that isolated pairs of clones do maintain memory of antigen presentation resulting into vaccination or tolerance attractor according to the parameters of antigen presentation (Fig 5.b).

- In the case of a line of 3 clones, a quasi steady states is attained: clone \( x_3 \) is excited slightly above the threshold for growth \( f(h) \) is very slightly above \( d \) because of excitation by clone \( x_2 \) suppressed by clone \( x_1 \). The slow growth of \( x_3 \) is not sufficient to perturb the level reached by \( x_2 \) and vaccination persists for a period longer than the animal’s expected lifetime. This process takes 2 years to be achieved (Fig 5.c).

- In the case of a line of at least 4 clones, the existence of the fourth clone, excited by clone \( x_3 \) which is not suppressed by clone \( x_1 \) as is clone \( x_2 \), is enough to give a faster growth of clone \( x_3 \): a delocalized attractor is reached where vaccination is at level 3, clones \( x_2 \) and \( x_4 \) being suppressed and clone \( x_1 \) virgin (Fig 5.d). (a line does not have to be isolated: a single connected clone is connected to at least a 2 edges long stucture, the 3 clones of the structure having any connectivity larger or equal to 2, except for the last one which has a connectivity larger or equal to 1).

The above enumeration does not pretend to be exhaustive, but these are the only cases we were able to observe during the extensive numerical simulation done to obtain network statistics. We then conclude that other unobserved topological abnormalities are of very little statistical importance.
Fig. 5. Diagrams of attractors obtained for different local topologies. Ag indicate the clones specific for the presented antigen. Population levels are schematized by circles of different sizes and colors (O.S. means oversuppressed, V virgin, L suppressed and H high population).

a) An isolated clone can only be in a virgin attractor;
b) a pair of clones can be in a vaccination or a tolerance attractor;
c) a line of 3 clones evolves in several years to a metastable vaccination attractor;
d) when the antigen is presented to a single connected clone which starts at least one four clone pathway, the attractor is extended localized (no vaccination is achieved); the dotted lines represent possible connections to other clones;
e) and f), standard topology vaccination and tolerance attractors; the tolerance parameters the same as in figure 3 except that: $K = 10^{-7}$; $A_0 = 50000$. 

\[ 
\begin{align*}
\text{O.S.} & \quad \text{O.S.} \\
\text{V} & \quad \text{O.S.} \\
\text{L} & \quad \text{V} \\
\text{H} & \quad \text{L} \\
\end{align*}
\]
2.5. Computation of the probabilities of relevant topological features

In digit strings shape spaces, the boundary represents a finite fraction of the space. Since the connectivity at the boundary is different from that of the bulk, it is important to take it into account. The following sections might appear rather technical, and the uninterested reader might skip them. These sections are necessary to understand the numerical results that we obtained with networks made of a few hundred clones. But the influence of the topological defects decreases with the size of the network.

2.5.1. Fraction of end-points.

Apart from isolated clones, the main reason for topological failures are end-points of 4-lines which give rise to extended localization (Fig 5.d). The purpose of this paragraph is to evaluate the fraction of these end-points.

Let us call \( p \) the probability of occupation of a site of the lattice, and \( q = 1 - p \) the probability of emptiness of a site. Among occupied sites, isolated sites occur with a probability

\[
q^k,
\]

where \( k \) is the network connectivity. A given occupied node is an end-point with a probability

\[
p_2 = kpq^{k-1}.
\]

Failures to obtain vaccination on a competent clone is observed when this clone is an end-point of a line at least 4 nodes long. The probability \( p_3 \) that at least one 3-node line (or longer) starts from the neighbor clone is:

\[
p_3 = 1 - q_2^{k-1}
\]

where \( q_2 \) is the probability that one of the branches starting from the neighbor is not a line of at least 2 clones.

\[
q_2 = q + pq^{k-1}
\]

This last event occurs when the first node is empty \( (q) \) or if it is present, when none of the second is present \( (pq^{k-1}) \). \( P_{e4} \), the probability that a clone is the end-point of a line at least 4 nodes long is then:

\[
P_{e4} = kpq^{k-1}p_3.
\]

and a lower bound for the probability \( P \) of failure to vaccinate the first presented antigen is:

\[
P = (q + p(q^k + P_{e4}))^k
\]

In other word, vaccination fails if among the \( k \) \textit{a priori} competent clones none recognizes the antigen, or if all competent clones are either isolated or endpoint of a 4-line. The
expression is a lower bound because of the possible existence of scenario that we have not taken into account.

With the simulation parameters that we have chosen the first two events correspond to a failure to remove the antigen: in the first case the antigen keeps its initial concentration, in the second case its concentration is decreased below the excitation threshold of the competent clone and remains at this intermediate level. The probability of not removing the antigen $P_a$ is then simply:

$$P_a = (q + q^k)^k$$

2.5.2. The effective connectivity.

The following computation applies to the particular digit string shape space we are using. Because we are excluding partial complementarity when the sum of digits equal 4, strings that contain any number of 3’s have lesser than maximum connectivity. For instance string 3333 has only one neighbor (one exact and no approximate complementary shape) instead of 5 for string 2222. The average connectivity of the nodes is reduced below 5 because of these boundary effects in the shape space. It can easily be shown that the connectivity averaged on all the nodes for a network of $n$-strings of digits in base $b$ is given by

$$< k > = p \sum_{i=0}^{n} \frac{(i+1)(b-1)^i} {b^n} = p(1 + \frac{n}{b} - \frac{1}{b})$$

where $p$ is the probability of occupancy of a site and $i$ the number of digits less than $b-1$ in the string. Strings with a given $i$ are $(b-1)^i$ in number and their connectivity is $i+1$. The average connectivity is then reduced with respect to the connectivity of a node inside the lattice $k = p(n+1)$ by a quantity $\frac{p_n}{b}$. In other words, for a random sequence of $n$ sites, connectivity reduction occurs on each site with a probability $\frac{1}{b}$. When $n = b$, as in our simulations, the connectivity is simply $k = p \times n$. For the 100, 150 and 200 networks used in our simulations the effective connectivities are respectively 1.6, 2.4 and 3.2.

2.6. Failures due to crowding and the thrifty network

We will discuss here the effects of crowding the network with many antigenic presentations for two types of "strategies": simple nets respond with all their competent clones while thrifty nets use only one clone.

In a so called simple network, all the clones that recognize the antigen proliferate, and a large number of anti-idiotypic clones are suppressed. $p_s$ the number of suppressed
clones per presented antigen is:

\[ p_s = e k^2 \]

where \( e \) is the number of epitopes per antigen, each epitope being recognized by \( k \) clones, each suppressing \( k \) other clones. The patches are rather large and tend to overcrowd the network when their number increase, thus limiting the ability of the network to fight future antigenic challenges.

By responding to each antigen with only one competent idiotypic clone, a more *thrifty network* could preserve for future challenges some clones that are not indispensable to respond to the present antigenic challenge. Before discussing the biological validity of this assumption, let us evaluate how this thrifty use of idiotypic diversity increases the network capacity. Let us suppose that the size of the patch blocked by the vaccination against one antigen is \( p_s \) clones, and that because the antigen has \( e \) epitopes and the average connectivity corresponding to any n-string is \( k \), an average of \( c = ek \) idiotypic clones is able to recognize some epitope on the given antigen. In the thrifty strategy, a maximum of only one idotype proliferates. In the simple network all competent clones proliferate. The question is to evaluate for both strategies, the simple and the thrifty one, \( P_m \), the probability that after presenting \( m \) antigens to the network, none of them fails to evoke an immune response.

The mean field computation of thrifty network capacity is discussed here in some length because it applies to any type of network, including the simple network. Let us first compute the probability \( P_{i_{m+1}} \) that at least one competent clone is able to proliferate after \( m \) different antigens have been presented resulting in the creation of \( m \) non-overlapping patches of \( p_s \) clones each.

\[ P_{i_{m+1}} = 1 - \left( \frac{mp_s}{N} \right)^c \]

where the term in parentheses corresponds to the probability that one of the relevant clones is not able to proliferate; it is raised to the power \( c \) to express the probability that none of the \( c \) relevant clones respond. (For simple networks only one trial involving all the responsive clones is done and the exponent is 1). \( P_m \) is then computed by multiplying the \( P_{i_i} \) probabilities from 1 up to \( m - 1 \) antigens.

\[ P_m = \prod_{i=1}^{m-1} \left( 1 - \left( \frac{ip_s}{N} \right)^c \right) \]

Approximating the logarithm of the parenthesis by the second term,

\[ \log P_m = \sum_{i=1}^{m-1} \log \left( 1 - \left( \frac{ip_s}{N} \right)^c \right) \approx \sum_{i=1}^{m-1} -\left( \frac{ip_s}{N} \right)^c \]

and replacing the summation of the logarithms by an integration,

\[ P_m \approx \exp \left( -\frac{m^{c+1}p_s}{(c+1)(N)} \right) . \]
$P_m$ is close to 1 for a small number of presented antigens and decreases exponentially to 0 when $m$ is larger than a transition value corresponding to the argument of the exponential being 1. The transition for $m$ is given by:

$$m \approx (c + 1)^{\frac{1}{c+1}} \left( \frac{N}{p_s} \right)^{\frac{c+1}{c}}.$$

The transition width is equivalent, which implies a rather extended probability distribution.

The corresponding expression for simple networks without thrifty mechanisms is:

$$m \approx \sqrt{\frac{2N}{p_s}}.$$

The important result is that the scaling law relating capacity to the number of nodes varies between power one half for a network without any thrifty mechanism to a maximum power of one for a thrifty network with increasing connectivity. Since the maximum capacity of a network is proportional to the number of nodes, the thrifty strategy is thus extremely efficient. The number of nodes being of the order of $10^8$ or $10^{10}$, changing the scaling law from the square root to proportionality is then a tremendous gain.

The width of the probability distribution implies that some networks are better than other, and that there is still room for improvements. Evolution has still its part to play to select fitter nets.

3. Simulation results

3.1. Simulation methods

Dynamics of antigenic response were simulated by integrating simultaneously the population differential equations of networks of either 100, 150 or 200 clones. The connection structure was computed from a 4 digit shape space in base 4. A full network would then have 256 clones. We used the Livermore solver for ordinary differential equations, with automatic method switching for stiff and nonstiff problems (Hindmarsh 1983). The simulation parameters were the following: the maximum proliferation rate is $p = 1$, the decay rate $d = 0.5$, the two thresholds $\theta_1 = 2000$ and $\theta_2 = 10^5$ and the influx from the bone marrow $s = 1$. Rates are given in days$^{-1}$ and thresholds in cell populations. The antigen decay constant is $K = 10^{-6}$ day$^{-1}$ cell$^{-1}$. These parameter values are consistent with experimental data. The initial populations were all virgin.
and equal to $s/d = 2$. Antigens with the same digit strings as the clones and the same rules for recognition (exact or one error matching) by clones are randomly generated and presented to the network with an initial concentration $A_0$ of 5000.

After each antigen presentation, the network dynamics is simulated for 1500 days which ensures that attractors are actually reached, even for large transitions periods due to extended localization. The antigen is considered to be eliminated when its concentration is lower than 100. Clones with population larger than $10^4$ are considered as high level and those with population larger than $10^2$ as intermediate level. Vaccination is considered as achieved when at least one relevant clone is at high level. A new antigen is then presented to the network in its newly reached attractor. The averages were generally taken on 10 randomly generated sets of antigens applied to 10 randomly generated networks.

The thrifty mechanism is implemented by the following algorithm: the antigens have four independent epitopes which can be matched by relevant clones. Only one relevant clone is randomly selected among the set of relevant clones and the dynamics of the antigen removal and of the network is followed for 200 days to check whether the selected clone removes the antigen. If so, the final configuration of the network after 1500 days is used as the starting configuration for the next presentation. Otherwise, the same antigen is presented to another relevant clone starting from the previous attractor. The trial process is continued until antigen elimination or complete failure (in which case the attractor corresponding to the antigen previously eliminated is taken as the initial configuration for the next antigen). The averages were generally taken on 3 randomly generated sets of antigens applied to 10 randomly generated networks.

3.2. Antigen removal and vaccination

As can be seen in Figures 6 and 7 which summarize simulation results, the data are rather noisy, but they confirm the theoretical predictions. The high noise level observed on the direct failure probabilities, when a given number of antigens has been presented, reflects the randomness of the procedure. By measuring the integrated probabilities of failure on all previous antigen presentation, $P_a$ and $P$, we are averaging on the logarithm of the direct failure probabilities (see section 2.4) which explains the better quality of these plots.

Let us first consider the data concerning simple nets (Fig.6).

The probability of antigen removal or vaccination does not start from 1 at the first antigen presentation because of topological failures as explained in section (2.3). The theoretical predictions for the 100 clones nets are $P_a = 0.11$ and $P = .20$, the observations are $P_a = 0.21$ and $P = .34$. These figures are much smaller for 150 and 200 clones networks, which is indeed observed on the results, but the agreement with the theoretical predictions is poorer. The discrepancy is due to the fact that we used
Fig. 6. Performances of a 150 clones simple network. The shape space is made of digits strings of 4 sites with digits in base 4. Empty circles correspond to the probabilities of antigen removal after $m$ antigen presentations and empty squares to the probabilities of vaccination. The filled marks correspond to integrated probabilities up to $m$, e.g. the probability that all the $m$ antigens have been removed.

A connectivity of 5 in the theoretical evaluation of the topological probabilities; since most of the topological defects occur on the boundary of the shape space, this connectivity is only a loose approximation. Computing exact expressions for $P_a$ and $P$ is not worthwhile since these expressions would depend on which specific shape space we are considering and since biologically significant networks, much bigger, have presumably less topological defects. For our present purpose, the present level of approximation is sufficient.

For the simple nets the predicted probabilities should become $e^{-1}$ when $m$ the number of presented antigens is obtained from the theoretical expression from section
\[ m = \sqrt{\frac{2N}{k^2}} \]

since the number of epitopes were chosen to be one and \( k \) clones respond to the antigen, each of them being sustained by \( k \) anti-idiotypic clones (anti-idiotypic clones are never shared among common idiotypic clones since it would correspond to a forbidden 4-loop among the antigen, the idiotypic clones and the common anti-idiotypic clone). The use of the average connectivity make sense in this case since we are summing contributions of patches in different nodes of the network. For resp. 100, 150 and 200 clones networks the values of \( k \) are respectively 1.6, 2.4 and 3.2 and the theoretical predictions for \( m \) are then 8.8, 7.2 and 6.2. Crowding the network decreases more rapidly the performances of the more connected networks because the size of the patches increase as \( k^2 \). Comparison with the simulation results requires some interpretation. We must in fact evaluate the product of the probabilities of failures due to crowding while the primary data give the probabilities of failures due to crowding and topological defects. We can estimate the probability of topological failure by using the failure probability at first antigen presentation, and divide all observed probabilities by this quantity. The corrected simulation figures for \( m \) are then resp. 9, 8 and 7. In view of all the approximations that have been made, the agreement can be considered as satisfactory.

The equivalent computations for the thrifty network are made with \( c \), the number of available clones being \( 4 \times k \) (4 epitopes times \( k \) idiotypic clones). Since \( p_s \), the number of suppressed clones at each vaccination is simply the average connectivity \( k \), the ratio involved in the computation of \( P_m \)

\[
\frac{N}{p_s} = \frac{4^n}{n} = 64
\]

is constant for all 3 networks (100, 150 and 200 clones) used in the simulations. The theoretical prediction of \( m \) is 55 and the simulation results is 52 for the 200 clones networks. With respect to the simple nets, the increase in capacity is due to two independent reasons:

- The patch size of suppressed clones is reduced from \( k^2 \) to \( k \).

- The power law with respect to the number of patches, \( \frac{N}{p_s} \), is \( \frac{c}{c+1} = .93 \) for the 200 net instead of .5.

Figure 7 shows the results of the 150 clone network. The 20 first presented antigens are always removed for our 30 trials. Because of topological defects, initial vaccination probabilities are not 1. These probability eventually increase when the network fills up: the neighbors of singly connected clones reach high or intermediate populations, and the thrifty mechanism selects other clones to react with the antigen. The probability of antigen removal remains high when the network gets crowded: this is because some 30 percent of the clones already have high populations and are then able to react with the antigen. But the integrated probabilities over all previous events decline to 0 as predicted by theory (section 2.4).
Fig. 7. Performances of a 150 clones thrifty network. The shape space is made of digits strings of 4 sites with digits in base 4, but the antigen has four epitopes and a thrifty mechanism such that only one specific clone at a time proliferate against the presented antigen is used. Empty circles correspond to the probabilities of antigen removal after \( m \) antigen presentations and empty squares to the probabilities of vaccination. The filled marks correspond to integrated probabilities up to \( m \), e.g. the probability that all the \( m \) antigens have been removed.

3.3. Loss of vaccination

Crowding the network with antigen presentation results in failures in antigen removal and vaccination. The question also arises about loss of memory of previous antigenic presentation. If we refer to Hopfield model of neural nets, memories are pretty stable up to the capacity limit, but they completely collapse when one tries to teach a number of patterns over this limit (Mezard etal (1988), Weisbuch (1990), Hertz etal (1990)). Other neural nets models, like short term memory or palimpsests models, show graceful degradation: beyond the capacity limit, the most anciently learned patterns are
lost but memory of the most recently learned patterns persists (Nadal et al Weisbuch (1990)).

We then tried to answer the following question: What happens to previous vaccinations when a large number of antigens are added to the network? How frequently are memories lost? Are damages localized or does one observe catastrophic percolation of the damage?

At the local level, the events that can be observed are the following:

- When the antigen is presented to a high population clone, it is eliminated and the attractor remains unchanged.

- When the antigen is presented to an intermediate population (and thus) suppressed clone, it is not eliminated by that clone; whether elimination occurs because of another clone or not, the attractor remains unchanged.

-When, as shown on Figure 8a, the antigen is presented to a virgin clone (say #4) neighboring a suppressed clone (#3), which itself sustain a high population clone (#2), vaccination is usually achieved on the presented clone (#4), but the suppressed clone (#3) now experiences a field twice as big. It is then oversuppressed. If at least two or more clones remain to sustain vaccination on the previously vaccinated clone (#2), the previous vaccination remains, but each of the sustaining clones now has a larger population: it goes from $L/k$ to $L/(k - 1)$, where $k$ is the former number of sustaining clones. These oversuppression events can be checked by following the evolution after many antigen presentations of the ratio of suppressed clones to high level clones which reflects average $k$. For a 150 clones network this ratio varies from 2.6 - a little more than 2.4, the average connectivity - at the first antigen presentation, to 2.2 after 20 presentations.

If $k$ were 2, the remaining sustaining clone (#1) now has an excitatory population of $L$ which excites a neighboring clone (#0) (see figure); it (#1) then become oversuppressed and vaccination is lost on clone #2. This suppression of memory takes a long time, of the order of 4 years after the presentation of the second antigen, with our choice of parameters.

When have then checked the frequency of these events and also monitored their consequences to see whether any avalanche would result. In principle not all of them correspond to losses of vaccination, since extended localized attractors previously obtained by antigen presentation to end-points can also be destroyed by the described mechanism. But these last events are less frequent than losses of vaccination, since end-points are rare. The simulations were done with 100 and 200 simple nets, when the number of presented antigens were up to 10, i.e. eventually above the capacity limits. Losses of vaccination do occur. They typically involve one clone, as in Figure 8, more rarely 2 or 3, but never a finite fraction of the vaccinated clones, as in an avalanche process. The case where more than one clone is concerned probably imply 6-loops as
Fig. 8. Vaccination removal by successive antigen presentation.
a) Antigen is presented to a virgin clone (say #4) neighboring a suppressed clone (#3), which itself sustains a high population clone (#2), vaccination is achieved on the presented clone (#4), but the suppressed clone (#3) now experiences a field twice as big. It is then oversuppressed. The remaining sustaining clone (#1) now has an excitatory population of $L$ which excites a neighboring clone (#0), it then becomes oversuppressed and vaccination is lost on clone #1.
b) In the case of a six-loop, presentation of an antigen recognized by clone (#5) at distance 2 of the first responding clone (#1), results in the oversuppression of the intermediate clone, and the excitation of neighboring clones at level $\frac{L}{m-1}$.
Even when $m$ is as low as 3, the two clones field is enough to make clone (#3) proliferate, which results in the loss of vaccination at levels (#1) and (#5).

shown on Figure 8b. The frequency of all vaccination loss events goes up to 0.14 in the limit of capacity region for the-200 clones nets which are pretty crowded and connected. It always remain smaller for the 100 clones nets.
3.4. *Discussion of the results*

Large simulation times and data size prevented us from simulating larger nets, but anyhow the present agreement with theoretical predictions is sufficient to confirm the scaling laws on the variation of the integrated probabilities with the number of clones. Topological failures should be less important for networks of the size of real immune systems, from $10^8$ to $10^{10}$ clones, since the fraction of isolated clones and end-points decreases when connectivity $c$ and number of digits per site $b$ increase, which should further improve agreement with theoretical predictions.

Natural selection of networks with a connection structure adapted to self-antigens and most commonly encountered foreign antigens probably increases the capacity with respect with the random sets of antigens for which it has been evaluated here. A result such as $P = 10^{-2}$ at $m = 15$ for 200 clone simple networks implies that 1 percent of the networks are adapted to the sets of presented antigens. Some of these nets can possibly have been selected by natural evolution, then increasing the network capacity by a factor 2 (with respect to $m = 7$ giving a probability $P = e^{-1}$).

4. Biological interpretations

The large increase in the number of attractors due to a thrifty mechanism seems rather difficult to test experimentally. Indirect evidence is the fact the number of clones involved in a typical antigenic response is much smaller that the numbers that could be inferred from measuring the fractions of antibodies reacting against an antigen as tested by ELISA methods. A possible mechanism for thriftiness is the suppressive action of IgG binding to Fc receptors of lymphocytes (Nossal 1983, Gergely 1988). The induced decrease of proliferation favors the fast responding clones. If fast clones are not available, slower clones can respond. This is a possible explanation of public, commonly used by a large fraction of the population, and private idiotypes only used by certain individuals. The public idiotypes could be the faster clones commonly used, while private idiotypes might be used when the public idiotypes are not available, e.g., when they are suppressed by another clone involved in the response against another antigen.

Within the framework of this model, the main consequence of crowding the network is the possible lack of response against newly presented antigens, and possibly the use of private idiotypes when public idiotypes are not available.

When the network connectivity is large, as it is probably the case in the immune system, reducing the effective connectivity of a clone to one by presentation of antigens at distance 2, thus oversuppressing the sustaining anti-idiotypic clones, becomes a gradual process which finally ends in the suppression of a vaccination. It is then a possible mechanism for the loss of vaccination.
4.1. Peripheral tolerance

We have set aside the question of self antigens and tolerant attractors (see fig 5.f). Self antigens are presented early in life when the immune system is tuned up to evolve towards tolerant attractors when presented with antigens (Neumann and Weisbuch 1992a). The crowding of the network due to the presentation of $m_s$ self antigens results in the effective reduction of the number of available clones from $N$ to $N_{eff}$ where

$$N_{eff} = N - m_s k (k^2 + 1) \beta$$

The dependence in $k$ correspond to $k^2$ suppressed anti-anti-idiotypic clones plus the oversuppressed idiotypic clone for the $k$ clones responding to the antigen, and $\beta$, such that $0 < \beta < 1$, correspond to the fact that some suppressed clones belong to 6-loops starting from the antigen. In a first approximation, all the expressions previously computed for the network capacity remain valid when $N$ is replaced by $N_{eff}$. A secondary effect is the decrease in effective connectivity for those clones in the immediate neighborhood of the tolerant attractor. The effective connectivity is decrease by 1 or more seldom by 2 (in the case of six-loops made of the antigen, two idiotypic clones and two anti-idiotypic clones neighbors of the considered clone).

Gradual elimination of clones by oversuppression could also result in the loss of tolerance by the suppression of all the high population clones that oversuppress a self antigen-specific clone. This triggering of an auto-immune response by foreign antigens presentation is observed for a number of auto-immune diseases (see e.g. Cohen 1989). The mechanism discussed here is distinct from the idea of antigen mimicry often invoked, although some mimicry might exist among antigens which are recognized by clones at a distance 2 in the network. Finally, the model practically excludes the possibility of antigen induced catastrophic avalanches that would reshuffle the previous vaccination and tolerance attractors thus causing considerable damage to the immune system.

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