Dynamic stability in random and scale-free B-lymphocyte networks

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One of the most intriguing features of the immune system is regulation: a limited response when perturbed repeatedly. We propose a minimal network model for immune regulation in a lymphocyte network containing two types of elements: B lymphocytes and ligands that bind to their receptors. Effective interactions between B cells, mediated by other components of the immune system can be excitatory or inhibitory. In our model, B cell clones and ligand species are represented by nodes, and interactions by links. We expect that, as in many complex systems, the connectivity distribution is broad, motivating study of the model on a scale-free network; for comparison we study the same dynamics on a random graph. We characterize the dynamics of the model and its response to perturbations. Our model reproduces several key features of immune system dynamics: regulation (saturation of response), and more rapid response upon repeated perturbation with the same agents. Our results suggest that a scale-free network of interactions contributes to the regulation and dynamics of the immune system.

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I. INTRODUCTION

Lymphocyte-mediated immunity is a remarkable characteristic of jawed vertebrate organisms. Immunology has made spectacular advances in the last decades in terms of defining the genetic, molecular, and cellular components involved in these phenomena. In this work we propose a minimal model for immune regulation in a lymphocyte network.

Immunological activity is based on the activation of T and B lymphocytes generated by special ("combinatorial") somatic processes of gene rearrangement in which each lymphocyte acquires a unique membrane receptor. If activated, a lymphocyte may multiply and form cell clones with a variable number of cells; if it is not activated, it will likely die by apoptosis without ever dividing. Binding of the specific receptor (BCR or TCR) is important for cell activation and in determining whether or not the lymphocyte will survive and expand. B lymphocytes may further turn into plasma cells, which are short-lived cells that secrete soluble forms of the BCR to the extracellular space, where they are known as immunoglobulins (Ig).

Immunological memory, or the ability to generate secondary immune responses (more sensitive, intense, and prolonged) upon contact with previously encountered antigens, is believed to play an important role in anti-infectious immunity and to be the basis of the efficacy of some vaccines. T lymphocytes are involved in the generation of immunological memory. This memory, however, must be limited to avoid progressively higher responses upon repeated contacts with the same or similar antigens, as this would trigger damaging inflammatory reactions. Secondary responsiveness, therefore, must be submitted to some form of regulation, currently a subject of intensive investigation [1,2]. Regulation must also account for the absence (in normal organisms) of progressive immune responses to dietary proteins [3] and products of the autochthonous microbiota [4], which together represent by far the largest collection of foreign macromolecules to which the organism is daily exposed.

Above all, lymphocytes must be prevented from making progressive immune responses to the organism itself, including to other lymphocytes during their mutual interactions. Explanation of this kind of regulation, also known as natural tolerance, is a prime objective of any theory aiming to elucidate immunological activity [5]. Natural tolerance does not imply the absence of reactivity to body components, as demanded by initial versions of the clonal selection theory [6]. Self-reactivity, in the form of abundant autoantibody formation [7] and autoreactive T cells [8], is now accepted as part of healthy immunological physiology. (The transformation of these dynamically stable forms of autoreactivity into progressive, secondary immune responses characterizes a variety of autoimmune diseases [9,10]). These observations demonstrate the need to study the global dynamics of interactions within the immune system.

Diverse mechanisms mediate the interactions between B and T lymphocytes [11–13]. As a consequence of this multiplicity, distinct B cell clones may become functionally connected via a certain T cell population. Those mechanisms can generate effective interactions between B cell clones, allowing us to view the immune system as a highly connected network [14].

Given the motivation for studying immune regulation in a global context, we turn to the definition of an appropriate model. Several immune network models have been proposed [15–18]. These models describe clonal expansion and contraction in response to external stimuli and the inherent dynamics of the immune system. They assume a regular or

random network of interactions, in physical space [19,20] or in a space of molecular shapes [21,22].

Among the many network structures possible, three general classes, commonly known as regular, random, and scale-free networks, have attracted interest in modeling complex systems. By a regular network we mean a lattice structure with links between nearest neighbors, with each node (or site) having the same number of neighbors. A maximally random network (or Erdös-Renyi graph) is a collection of N nodes, with each of the $N(N-1)/2$ possible links present, independently with probability p. In this case the number of neighbors varies from site to site; the probability $p(k)$ for a node to have exactly k neighbors ("degree k") follows a Poisson distribution. (Structures that are random but preserve some degree of regularity are also possible, such as small-world networks). A scale-free network may be either random or regular; it is characterized by a degree distribution $p(k)$ that decays as a power law, so that there is no characteristic degree. Following the work of (Barabasi and co-workers [23,24]), it is now apparent that the connectivity structure of diverse types of natural and social systems are well represented by scale-free networks.

There is evidence that the network of interactions within the immune system is not maximally random. Early in ontogenesis, natural immunoglobulins spontaneously organize to form defined profiles of reactivity with complex mixtures of ligands (molecules that bind to specific B cell receptors), which from then on are robustly conserved despite continuous exposure to immunogenic materials. The form of these profiles is influenced by alleles of genes important in immunological activity [25]. The transfer of maternal IgG to the young also influences the pattern of immunological activity in specific ways [26]. These observations demonstrate highly organized immunological activity, influenced by specific genetic and molecular elements. The point is that, although the generation of lymphocyte receptors involves random shuffling of genetic material, the actual lymphocyte population of an organism is shaped by interactions with proteins, both intrinsic and foreign, so that the result is far from being a maximally random collection of receptors.

There are suggestions in the current immunology literature of structured networks. Given the evidence for a highly connected web of autoreactive components, coexisting with specific responses to foreign antigens, Varela and Coutinho [27] proposed a functional split of the immune system into central and peripheral parts, the connectivity of the former being much higher than that of the latter. Cohen [28] proposed a hierarchy of immune reactivity, in which certain T cell clones regulate the activity of various other clones. These proposals for structured immune interactions are better accommodated in a scale-free network than in a maximally random one, motivating our study of both architectures.

In our highly simplified model, each site in the network represents either a B cell clone or a species of ligand; in each realization, the network architecture is fixed. A variable defined at each site represents the clonal population or ligand concentration. The dynamics of the system involves steady generation and death of B cells and random input of ligands. A given ligand stimulates a certain set of B cell clones, and is in turn eliminated when these clones expand. There are also interactions, both excitatory and inhibitory, between specific pairs of B cell clones.

Starting with all population variables set to the same value, the system relaxes to a stationary state, with a broad distribution of population sizes, which is found to be stable to small perturbations. We study the response of the system, starting from the stationary state, to relatively large perturbations caused by a sudden increase in a small set of ligand populations. The perturbation represents a challenge to the immune system accompanying, for example, an infection or exposure to foreign proteins. The excess of ligands is eliminated by the system, which subsequently relaxes to a stationary state, generally different from that preceding the perturbation. The model exhibits regulation in the sense that the response to each perturbation is limited. Memory appears in the form of a sharpened response to repeated challenges with the same set of ligands.

The balance of this paper is structured as follows. In Sec. II we define the structure and dynamics of the model, Section III contains results obtained via numerical simulation. In Sec. IV we discuss, conclude, and suggest extensions of this work.

II. THE MODEL

Since immunological activity involves manifold, complex mechanisms, we must decide which part of the system we intend to model. B lymphocytes may bind substances directly to their membrane receptors (BCR) but, in general, they are not activated when this happens. By contrast, T lymphocytes are unable to bind isolated molecules to their receptors (TCR); the molecule (usually a protein) must first be captured and processed by accessory cells, and then presented to T lymphocytes along with certain accessory molecules [29–31]. Various types of cells may function as presenting cells for T lymphocytes; among them are the B lymphocytes themselves, a point of considerable importance in developing a network model.

We model the population dynamics of B cell clones, including a plausible set of effective interactions among such clones, mediated by T cells. Immune system components other than B cells are not, however, explicitly represented in our model. Each node of the network corresponds to a distinct B cell clone or to a species of ligand. The associated population sizes are denoted by the variables B_i (if site i represents a B cell clone) and L_i (if site i represents a ligand species). Interactions between pairs of B cell clones, and between B cells and ligands, correspond to links in the network. As discussed in the Introduction, a network model of effective interactions between B cell clones should feature a broad connectivity distribution. We therefore allow that certain clones interact with many others, while other clones interact with only a few. The broad distribution of connectivity is realized on a scale-free network; for comparison we study the same dynamics on an Erdös-Renyi network, in which the degree distribution $p(k)$ decays rapidly for large values of k.

Interactions between a pair of B cell clones may be either mutually excitatory or mutually inhibitory, leading to clonal expansion or contraction, respectively. The B cell-ligand in-

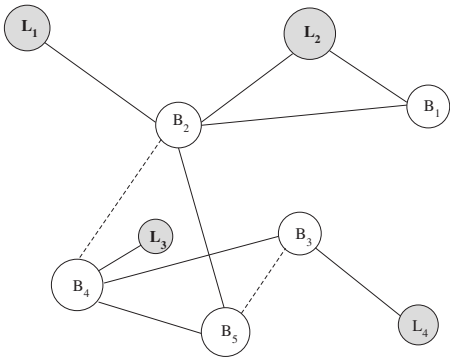

FIG. 1. Schematic representation of the components [lymphocytes (B) and ligands (L)] of our model and the interactions between them. Continuous lines represent excitatory interactions and dotted lines suppressive ones.

teraction is such that presence of the ligand stimulates expansion of the B cell population, while a B cell clone tends to reduce the quantity of the ligands that stimulate it. The rate of excitation of a clone is given a function $\alpha(\ln x)$, where α is Gaussian (see below) and x represents the sum of excitatory influences on the clone in question. (We believe direct interactions between different species of ligands to be unimportant in the present context; they are not considered in the model.) Figure 1 is a schematic representation of the model. Circles represent network sites: lymphocytes (B) and ligands (L). Continuous lines represent excitatory interactions and dotted lines suppressive ones.

The model evolves in discrete time; five kinds of events lead to changes in population.

(i) New B cells enter the system continuously, representing production in the bone marrow. Each clone receives a number β of new cells per unit time. The number of cells produced per unit time is fixed, independent of the population sizes $\{B_i\}$ and $\{L_i\}$. Ligands also enter the system at a fixed rate of β molecules per species and per unit time.

(ii) B cells continually leave the system due to cell death. Removal occurs at a fixed rate per cell, so that the number of cells removed per unit time from clone i is proportional to B_i. [Note that a B cell clone may disappear and subsequently reappear via mechanism (i).]

(iii) A B cell population grows due to interactions with ligands or other B cells. The contribution to the growth rate due to a neighboring ligand population (at site j, say) is given by the function $\alpha(L_j)$ (defined below), where L_j is the number of ligand molecules of type j. Similarly, for sites k bearing B cell clones having a stimulatory interaction with B cell clone i, the contribution to the growth rate of B_i is $\alpha(B_k)$.

(iv) B cells are eliminated by suppressive interactions with other B cell clones.

(v) Ligand populations are reduced due to the interaction with B cell clones.

The above dynamics is studied via numerical simulation. To generate an Erdös-Renyi random network of $m=N_L+N_B$ sites, we link each pair of sites with probability p, independently (we use $m=9000$ and $p=0.01$). To construct a SFN of m sites, we follow the Barabasi-Albert prescription [23,24]: $m_0=10$ connected sites are the initial seed of the network. Then a new site is added and connected to κ sites. (We use $\kappa=10$ in the studies reported here.) The probability of connecting the new site to a given site j is proportional to the number of sites already connected to site j. This process is repeated until a network of m sites has been grown. The network generated by this prescription shows a power-law degree distribution $P(k)\sim k^{-c}$ with $c=2.89(2)$. After constructing the network (either Erdös-Renyi or scale-free), N_L sites are selected to represent ligands (type-L sites) species and the remaining $N_B=m-N_L$ sites (type-B sites) represent B cell clones. Note that links between ligand sites, which constitute on average 25% of all links, are nonfunctional. After depleting these nonfunctional links, the degree distribution follows a power law with exponent=2.87(2), essentially the same as before pruning.

At each step in the evolution, the following sequence of events is realized:

(1) A site is chosen at random. The associated population increases by β, regardless of whether it represents an ligand type or a B cell clone.

(2) Another site i is chosen at random. If it is of type B, the corresponding population B_i reduced by λB_i. (Otherwise there is no change.)

(3) A pair of connected sites are chosen at random.

If both are of type L there is no change. In the case where one site is of type B (B_i, say) and the other of type L (species L_j, say), then B_i increases by the factor $1+\alpha(\rho_{L_j})$, where ρ_{L_j} is the number of ligands j per B_i cell. At the same time L_j decreases by $\gamma_L B_i$. If both are of type B and the interaction between them is excitatory, the population of each clone increases by the factor $1+\alpha(\rho_B)$, where ρ_B is the concentration of complementary B cell population. If both are of type B and the interaction between them is suppressive, the population of each clone decreases by the factor $1-\gamma_b B$.

If the result for a new population size, B_i or L_i, turns out to be negative, it is instead set to zero. The above events are repeated in sequence for a total of M steps. In the studies reported here on scale-free networks we use the values $\gamma_L=1/25$, $\gamma_b=1/50$, and $\lambda=1/100$; for Erdös-Renyi networks we use $\gamma_L=1/25$, $\gamma_b=1/10$, $\lambda=1/50$. The function mediating excitatory influences is $\alpha=0.3\exp\{-[\ln(x/1000)]^2/2\}$. This function reflects the fact that B cell activation is maximal for intermediate concentrations, and is small for both very low, and very high ligand concentrations [17].

III. SIMULATION RESULTS

Initially, all population variables are equal $A_i=B_i=1000$, $\forall i$. At short times the dynamics is dominated by the ligand-stimulated growth of certain B cell clones. B cell proliferation in turn causes a reduction in ligand concentration, leading to a decrease in the B cell population (due to the finite B cell lifetime), until a stationary state is established.

We adopted the following protocol to study regulation and memory in the model. Once a stationary state is attained, we perturb the system by increasing the population of a small number (ten) of randomly chosen ligand species. For each set of perturbed ligands, call the set of B cell clones directly linked to this set the "first-line clones." Following the per-

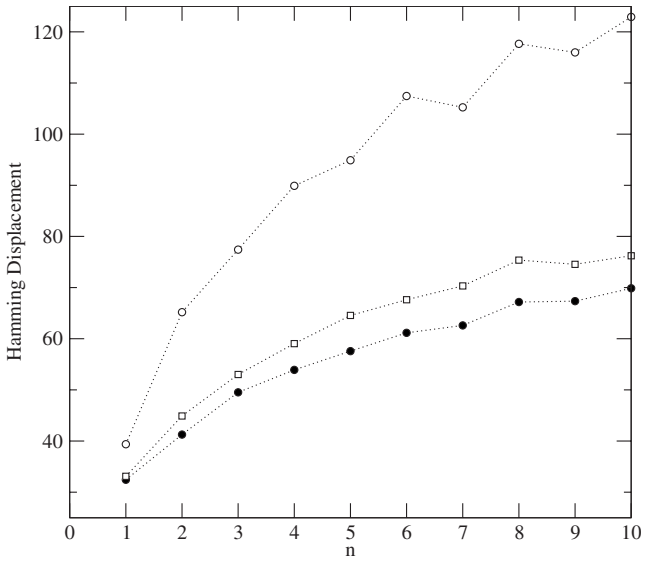

FIG. 2. Hamming distance per clone versus perturbation number n on the scale-free network, for the ten most connected clones (open circles), first-line clones (open squares), and averaged over all B cell clones (filled circles).

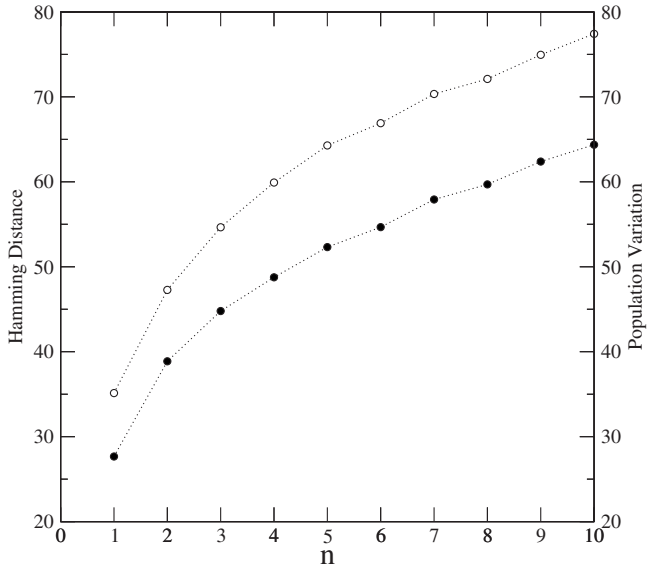

FIG. 3. Hamming distance (open circles) and population variation (filled circles) of first-line clones.

turbation, the first-line clone populations grow, so that the perturbation is suppressed, and the system relaxes to a stationary state. The perturbation/recovery protocol is repeated several times. We allow the system to reach a stationary state before perturbing it, always with the same set of ligands in a given study. (It is worth noting that, without suppressive interactions between B cell clones, the B cell population grows without limit following the perturbation, instead of reaching a steady state.) Following each perturbation we determine three quantities that characterize the response of the system: (i) the integrated excess mean B cell population I in the transient state; (ii) the time τ necessary for the mean ligand population decay to $1/5$ of its value at the moment of perturbation; (iii) and the average Hamming distance, defined here as $H=\frac{1}{N}\Sigma_i^N|B_i^{(n)}-B_i^{(0)}|$, where $B_i^{(n)}$ is the stationary average of B_i after n perturbations. ($B_i^{(0)}$ is the average prior to any perturbation.) In general, the Hamming distance is a measure of system response when perturbed. The Hamming distance averaged over first-line clones represents the immediate response to infection, while that averaged over the entire system reflects global reorganization. (Note that in the latter case, some clonal populations will actually be smaller after infection, but they make a positive contribution to H.) We interpret I as a measure of the overall immune response to the infection.

Figure 2 shows the Hamming distance per clone for three different sets of B cell clones, as a function of number of perturbation n, in the scale-free network. These results represent an average over 50 independent realizations. Open circles represent the Hamming distance of the ten most connected clones, the largest hubs of the network; open squares represent the Hamming distance of the first-line clones, and filled circles represent the Hamming distance averaged over all B cell clones. The Hamming distance saturates after about eight infections.

Figure 3 shows the Hamming distance (open circles) and the variation of first-line B cell population (filled circles). The latter is used in immunological experiments as a measure of specific immune response. In the case of first-line B clones, the Hamming distance and population follow the same trends, supporting our interpretation of Hamming distance as a measure of specific immune response, and its generalization to the other sets of B cells defined above.

Note that the Hamming distance averaged over the ten largest hubs is greater than that of the first-line clones or that averaged over all clones. This suggests that the perturbation initiated at the first-line clones propagates through the network until it is suppressed by the hubs. To test this hypothesis, we perform simulations (following the same procedure as described above), in which, once the system attains a stationary state following the first perturbation, we remove the 10 most connected sites from the network. (This procedure is used to test robustness of SFN against attacks and random failures [24,32–34].) The result (Fig. 4) is that the mean population of B clones grows by about 800%, showing that the hubs are responsible for regulation of the network.

Figure 5 shows the time τ needed to eliminate a perturbation as a function of the number of perturbations. Two different situations are studied. In the first (open circles), only the first hub (the most connected one) is a B cell clone, that is, the sites ranked 2–10 in order of connectivity all represent ligand populations. In the second case (filled circles) the ten most connected sites are B cell clones. After each infection the time necessary to eliminate the perturbation tends to be smaller, demonstrating memory. The enhanced rapidity of response is more marked when all ten of the most highly connected sites represent B cell clones, suggesting that memory is associated with regulation. Further evidence of memory is the systematic increase (Fig. 6) of immune response I (the area under the curve of the mean B cell population in the transient state) following each perturbation, followed by saturation, as observed experimentally [35].

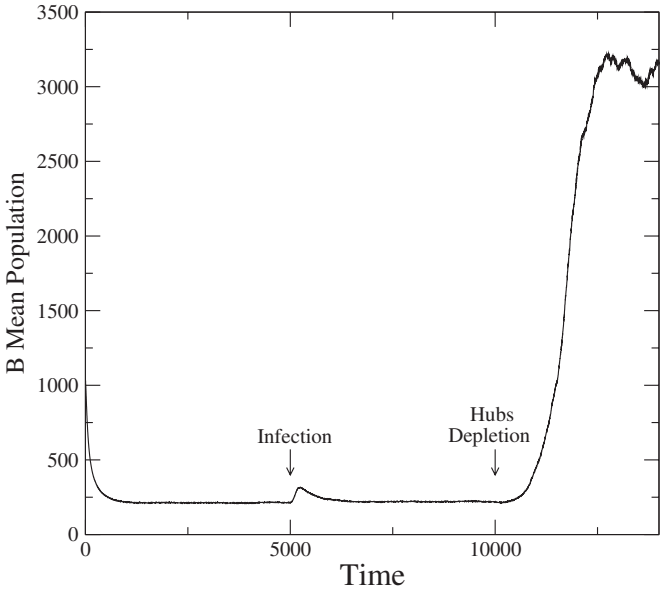

FIG. 4. Evolution of mean population of B clones. At $t=5000$ the system is perturbed and at $t=10\,000$ the ten most connected sites of network are deleted.

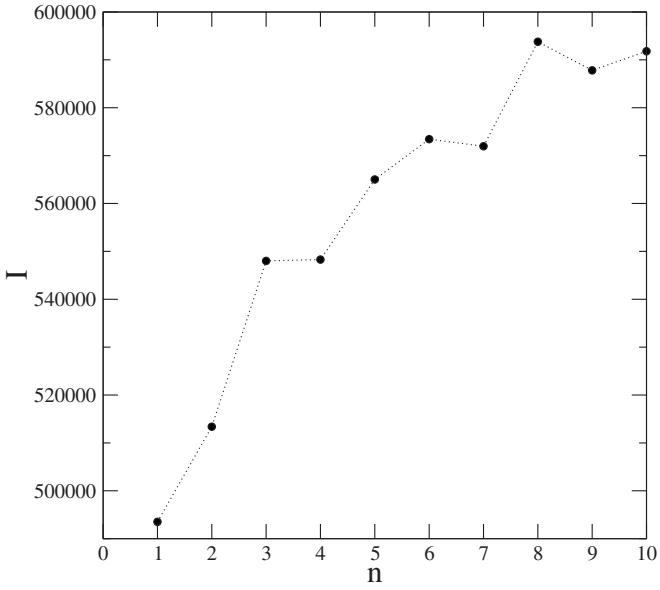

FIG. 6. Area I under the curve of the mean B cell population in the transient state as a function of number of perturbations, on a scale-free network.

We also performed simulations on Erdös-Renyi networks, following the same procedure as for the scale-free network. Figure 7 shows the Hamming distance per clone of three different sets of B cells clones, as a function of the number of perturbations. Open circles represent the Hamming distance of the ten most connected clones, open squares the Hamming distance of first-line clones and filled circles the Hamming distance averaged over all clones. The variation of Hamming distance in this case is about 7% while in the scale free network it is about 20%, showing that the response in the random network is weaker than in the scale-free network. The variation of τ as a function of the number of infections follows the same trends as observed in the scale-free network (see Fig. 8). The role of highly connected sites in the ER network is however different than in the scale-free case. The variation of Hamming distance of the ten most connected sites is *smaller* than that of the first-line clones. Moreover, depleting the ten most connected sites does not provoke the marked growth in B cell population observed in the scale-free network. These observations suggest that the sites with high connectivity are not essential to regulating the random

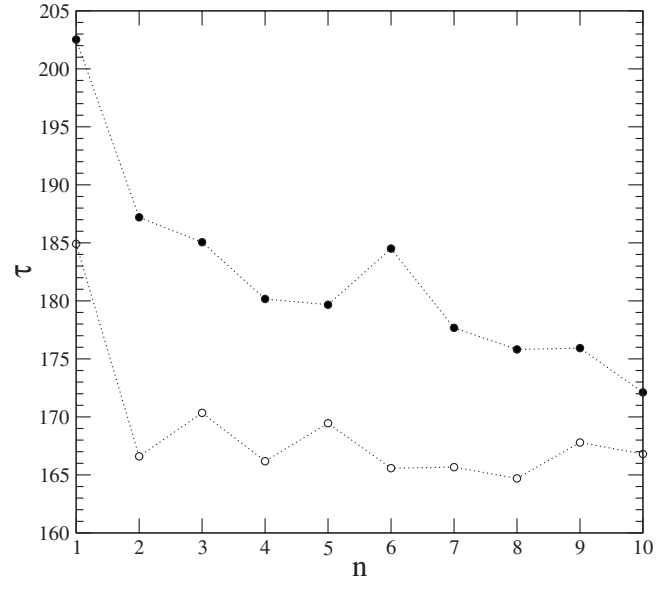

FIG. 5. Time τ needed to eliminate a perturbation as a function of the number of perturbations, on a scale-free network. We compare the case in which the ten most connected hubs represent B clones (open circles), with that in which only the most connected hub represents a B clone (filled circles).

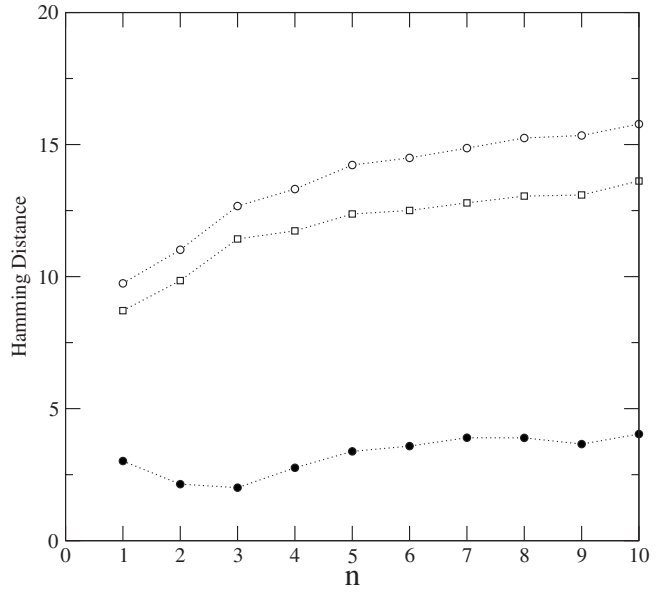

FIG. 7. Hamming distance per clone versus infection number n on the Erdös-Renyi network, for the ten most connected clones (open circles), first-line clones (open squares), and averaged over all B cell clones (filled circles).

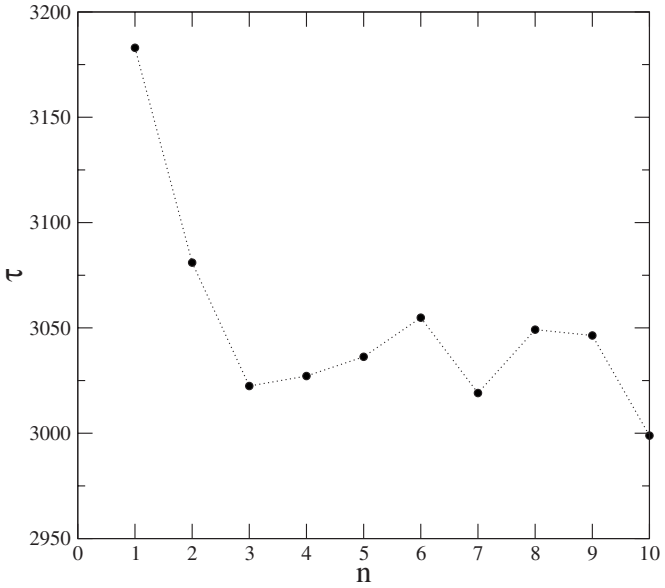

FIG. 8. Time τ needed to eliminate a perturbation as a function of the number of perturbations, on a random network.

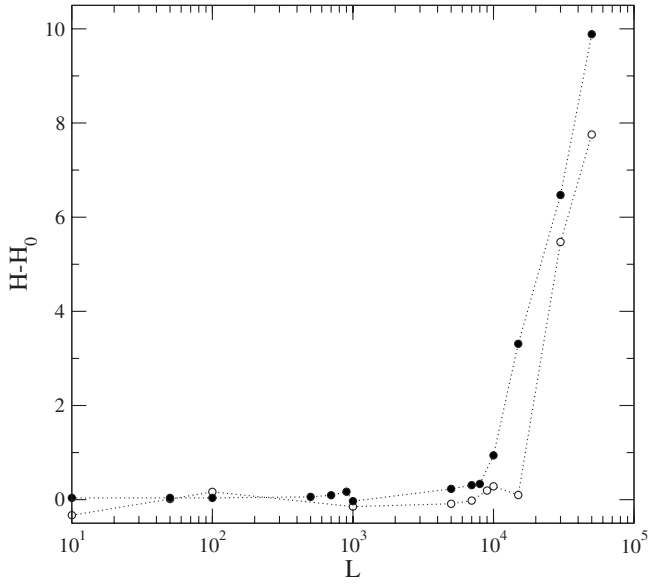

FIG. 9. Excess Hamming distance $H-H_0$ for two copies of the system, with and without perturbation function of L: for a scale free network (full circles), and for a random network (open circles).

network, as they are in regulating the scale-free network.

A series of studies were realized to probe the stability of the system. Once a stationary state is attained, we introduce a small perturbation and study the resulting variation in the mean Hamming distance of the B cell population. The perturbation is made by choosing randomly single ligand, not highly connected, among the 4500 in the network, and changing its population to a certain value L. Since ligands are suppressed by the system dynamics, they generally have very small populations in the stationary state, so that L is a measure of the perturbation. After a new stationary state has been reached, we calculate the mean Hamming distance H of B cell clones between this new state and that prior to the disturbance. Since the system is subject to a certain random drift over time, even in the absence of a perturbation, it is of interest to study $H-H_0$, where H_0 is the mean Hamming distance calculated for the same time interval but with no perturbation. Figure 9 shows $H-H_0$ as a function of L, for a scale-free network (full circles), and for a random network (open circles). Small perturbations produce no significant long-term change in configuration: the system remains in the same basin of attraction. For larger perturbations the system leaves the initial basin of attraction and visits many configurations until reaching a new basin of attraction. These results indicate that the system is locally stable.

The random and scale-free networks studied have the same number of nodes (N=9000) and the same mean number of connections (about 10 per node); the difference lies in how the nodes are connected. In the stability analysis we use the same set of parameters $(\lambda, \gamma_L, \gamma_b)$ so that we may compare directly the behavior of the two networks. Figure 9 shows that the Hamming distance grows more rapidly with L in the scale-free network than in the random one. The scale-free network presents a higher sensitivity to (large) perturbations, suggesting that the basins of attraction are more distant. In Fig. 10 we show the behavior of τ, the time necessary for the mean ligand population decay to 1/5 of its value at the moment of perturbation, as a function of L. In the scale free network (full circles) this time is smaller than in the random network (open circles). The greater change in B cell populations in the scale free network is accompanied by faster elimination of the disturbance.

IV. CONCLUSIONS

We introduce a network model for the population dynamics of B cell clones and associated ligands; both scale-free and random networks are investigated. Our simulations show

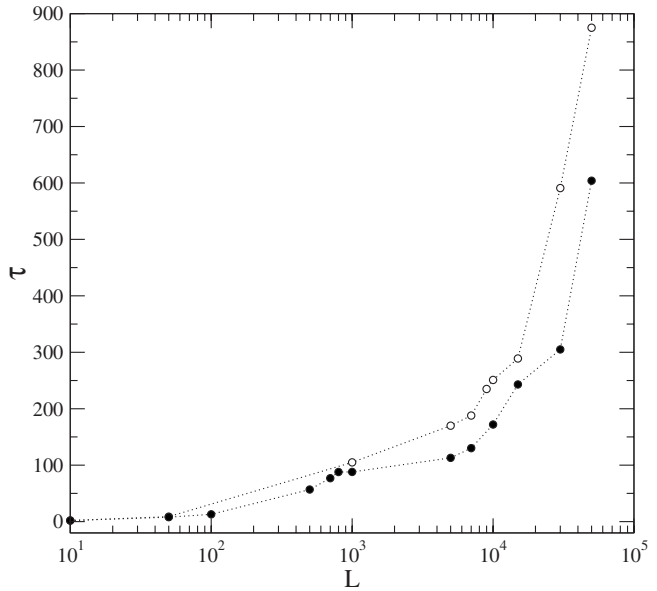

FIG. 10. Time τ needed to eliminate a perturbation as a function of the perturbation L: scale free network (full circles); random network (open circles).

that the model attains a stationary state following a certain initial transient. Once a stationary state is attained, we perturb the system by increasing the population of a small number of randomly chosen ligand species, and allow the system to relax to a stationary state. The latter may be different from that obtaining prior to the perturbation. The perturbation/relaxation protocol is repeated several times. The response to the perturbation is characterized by integrated excess B cell population in the transient state, the relaxation time of the ligand population, and the Hamming distance between the stationary B cell populations before and after the perturbation.

The Hamming distance saturates after several perturbations, which is reminiscent of the saturation of immune reactivity (e.g., specific antibody formation) observed experimentally under repeated administration of boosters. We find that in the scale-free network, the Hamming distance averaged over the ten largest hubs is greater than that of the first-line clones or that averaged over all clones. When the hubs are removed, we observe a much higher increase in the mean B cell population, showing that the hubs regulate the network by blocking the propagation of the disturbance.

In addition to the saturation of the response after several perturbations, our model exhibits another feature observed in immune systems. After each perturbation, there is a systematic increase in Hamming distance, and also a reduction in the time necessary to eliminate the perturbation, both characteristics of immunological memory. Two configurations were used to study this particular feature: in one, only the largest hub represents a B cell clone, while in the other the ten most connected sites all represent B cell clones. The return to the stationary state is faster in the second case, suggesting that memory is associated with regulation. Similar but less dramatic behavior is observed in a random network. Our results suggest that, in a random network, the sites with high connectivity are not essential to regulation, as they are in regulating the scale-free network. Our results also show that the system on the scale free network has a higher sensitivity to perturbations, and a faster response, than on the random network.

The model studied here resembles a spin glass in that the interactions between pairs of B cell clones are taken randomly as excitatory (i.e., ferromagnetic, $J>0$) and suppressive ($J<0$). Thus we may expect to observe many basins of attraction, just as the spin glass possesses many free energy minima. History dependence of the system configuration is another characteristic trait of spins glasses shared by the present model. It is therefore tempting to identify the persistent immunological profiles observed experimentally [36–38] with basins of attraction (stored patterns) of a spin-glass-like system [39]. Verification of this conjecture must await studies elucidating effective interactions between clones and global behavior of immune systems under perturbation.

In summary, our model of the B cell populations on a scale-free network reproduces several key features of the dynamics of the immune system: regulation, saturation of response, and more rapid response upon repeated perturbations with the same agents. This suggests that, as in other biological systems, a functional network of interactions characterized by a scale-free network may be responsible for the regulation and dynamics of the immune system. An alternative interpretation is that, if immune regulation is indeed structured as a scale-free network, this may confer the disadvantage of extreme sensitivity to the loss of hubs. As is known from studies of other scale-free networks, such systems are quite robust to random attack, but highly susceptible to attacks directed at the principal hubs.

ACKNOWLEDGMENTS

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[1] B. Stockinger, G. Kassiotis, and C. Bourgeois, Curr. Opin. Immunol. **16**, 775 (2004).
[2] S. Sakaguchi, Nat. Immun. **6**, 345 (2005).
[3] A. M. C. Faria and H. L. Weiner, Immunol. Rev. **206**, 232 (2005).
[4] R. Duchmann, E. Schmitt, P. Knolle, K. H. M. zumBuschenfelde, and M. Neurath, Eur. J. Immunol. **26**, 934 (1996).
[5] A. Coutinho, Int. J. Dev. Biol. **49**, 131 (2005).
[6] F. M. Burnet, *The Clonal Selection Theory of Acquired Immunity* (Cambridge University Press, Cambridge, 1959).
[7] A. Coutinho, M. D. Kazatchkine, and S. Avrameas, Curr. Opin. Immunol. **7**, 812 (1995).
[8] D. Stahl, S. Lacroix-Desmazes, L. Mouthon, S. V. Kaveri, and M. D. Kazatchkine, J. Immunol. Methods **240**, 1 (2000).
[9] D. J. Marks, N. A. Mitchison, A. W. Segal, and J. Sieper, Curr. Top. Microbiol. Immunol. **305**, 105 (2006).
[10] J. Sun, D. J. Earl, and M. W. Deem, Phys. Rev. Lett. **95**, 148104 (2005).
[11] Z. A. Nagy, P. V. Lehmann, F. Falcioni, S. Muller, and L. Adorini, Immunol. Today **10**, 132 (1989).
[12] J. Bayry, S. Lacroix-Desmazes, M. D. Kazatchkine, O. Hermine, D. F. Tough, and S. V. Kaveri, J. Immunol. **175**, 15 (2005).
[13] J. Bayry, S. Lacroix-Desmazes, V. Donkova-Petrini, C. Carbonneil, N. Misra, Y. Lepelletier, S. Delignat, S. Varambally, E. Oksenhendler, Y. Levy, M. Debre, M. D. Kazatchkine, O. Hermine, and S. V. Kaveri, Proc. Natl. Acad. Sci. U.S.A. **101**, 14210 (2004).
[14] N. M. Vaz and A. M. C. Faria, Cienc. Cult. **42**, 430 (1990).
[15] N. K. Jerne, Ann. Immunol. (Paris) **125C**, 373 (1974).
[16] N. M. Vaz and F. J. Varela, Med. Hypotheses **4**, 231 (1978).
[17] A. S. Perelson and G. Weisbuch, Rev. Mod. Phys. **69**, 1219 (1997).
[18] A. T. Bernardes and R. M. dos Santos, J. Theor. Biol. **186**, 173 (1997).
[19] F. J. Varela and J. Stewart, J. Theor. Biol. **144**, 93 (1990).
[20] J. Carneiro and J. Stewart, J. Theor. Biol. **169**, 391 (1994).
[21] A. S. Perelson and G. F. Oster, J. Theor. Biol. **81**, 645 (1979).

[22] J. Stewart and F. J. Varela, J. Theor. Biol. **153**, 477 (1991).
[23] A. L. Barabasi and R. Albert, Science **286**, 509 (1999).
[24] R. Albert, H. Jeong, and A. L. Barabasi, Nature (London) **406**, 378 (2000).
[25] R. Vasconcellos, A. Nobrega, M. Haury, A. C. Viale, and A. Coutinho, Eur. J. Immunol. **28**, 1104 (1998).
[26] H. Lemke, A. Coutinho, and H. Lange, Mod. Trends Immunol. **25**, 180 (2004).
[27] F. J. Varela and A. Coutinho, Immunol. Today **12**5, 159 (1991).
[28] I. R. Cohen, Immunol. Today **13**12, 490 (1992).
[29] R. H. Schwartz, in *Fundamental Immunology*, edited by W. E. Paul (New York, 1984) p. 379.
[30] P. J. Bjorkman, M. A. Saper, B. Samraoui, W. S. Bennett, J. L. Strominger, and D. C. Wiley, Nature (London) **329**, 512 (1987).
[31] S. Buus, A. Sette, and H. M. Grey, Science **235**, 1353 (1987).
[32] R. Cohen, K. Erez, D. ben-Avraham, and S. Havlin, Phys. Rev. Lett. **86**, 3682 (2001).
[33] R. Cohen, K. Erez, D. ben-Avraham, and S. Havlin, Phys. Rev. Lett. **85**, 4626 (2000).
[34] S. N. Dorogovtsev and J. F. F Mendes, Phys. Rev. Lett. **87**, 219801 (2001).
[35] B. A. Verdolin, S. M. Ficker, A. M. C. Faria, N. M. Vaz, and C. R. Carvalho, Braz. J. Med. Biol. Res. **34**, 211 (2001).
[36] L. Mouthon, A. Nobrega, N. Nicolas, S. V. Kaveri, C. Barreau, A. Coutinho, and M. D. Kazatchkine, Proc. Natl. Acad. Sci. U.S.A. **92**, 3839 (1995).
[37] L. Mouthon, M. Haury, S. LacroixDesmazes, C. Barreau, A. Coutinho, and M. D. Kazatchkine, J. Immunol. **154**, 5769 (1995).
[38] S. Lacroix-Desmazes, L. Mouthon, S. V. Kaveri, M. D. Kazatchkine, and M. E. Weksler, J. Clin. Immunol. **19**, 26 (1999).
[39] M. W. Deem and H. Y. Lee, Phys. Rev. Lett. **91**, 068101 (2003).