Physica A 389 (2010) 5903–5911

Contents lists available at ScienceDirect

Physica A

journal homepage: www.elsevier.com/locate/physa

Stochastic dynamics for idiotypic immune networks

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ARTICLE INFO

Article history:
Received 23 July 2010
Received in revised form 1 September 2010
Available online 16 September 2010

Keywords:
Random networks
Spin glasses
Theoretical immunology

ABSTRACT

In this work we introduce and analyze the stochastic dynamics obeyed by a model of an immune network recently introduced by the authors. We develop Fokker–Planck equations for the single lymphocyte behavior and coarse grained Langevin schemes for the averaged clone behavior. After showing agreement with real systems (as a short path Jerne cascade), we suggest, both with analytical and numerical arguments, explanations for the generation of (metastable) memory cells, improvement of the secondary response (both in the quality and quantity) and bell shaped modulation against infections as a natural behavior. The whole emerges from the model without being postulated a-priori as it often occurs in second generation immune networks: so the aim of the work is to present some out-of-equilibrium features of this model and to highlight mechanisms which can replace a-priori assumptions in view of further detailed analysis in theoretical systemic immunology.

1. Introduction

The purpose of the immune system is to detect and neutralize the molecules, or cells, dangerous to the body (antigens, which could be foreign invaders - e.g. viruses or bacteria - or deranged - e.g. cancerous - cells of the host), without damaging healthy cells [1]. In theoretical immunology there are two main strands to explain the functioning of the immune system that ultimately represent two approaches, *reductionist* and *systemic* for the modeling of nature in general [2]. In the former and most popular approach, lymphocytes basically operate independently or, better, the researcher focuses on the action of the single lymphocyte and on the details of its interactions (i.e. internal cascade signals, etc.) rather than on the global behavior of all the lymphocytes interacting with each other. In the second approach, the immune system is thought of as a whole and designed as a network of cells stimulated to proliferate by the affinity interactions of their exchanging antibodies (a functional idiotypic network [3]). Interestingly, the two approaches are not incompatible but complementary. While the former deals primarily with the response to a stimulus, the latter allows us to explain the ability to learn and memorize the immune system and the tolerance to low doses of antigen [4]. Indeed, reductionist and systemic viewpoints can be recovered as special cases (null and not-negligible connectivity respectively) of the general theory we are going to introduce.

The main constituents of an (adaptive) immune system are B-lymphocytes (B-cells), together with the T-lymphocytes, and free antibodies produced by B-cells. B-cells and T-cells have specific protein molecules on their surfaces, called receptors. The receptors of B-cells are antibodies (Immunoglobulin, Ig), which can recognize the antigen and allow the B-cells to connect to antigens in order to neutralize them. Finally, the purpose of killer T-cells is to attack and kill infected or deranged cells. The receptors of B- and T-cells have specific 3-dimensional structures, called "idiotypes". A family of B-cells generated by a proliferating B-cell is called a "clone"; a clone and the antibodies which it produces have the same idiotypes.

In a healthy human body at rest, it is estimated that the total number of "sentinel" clones generated from a single B-cell (the amount of identical lymphocytes) is about 10^2–10^4, the total number of clones amounts to some 10^{12}–10^{14} (such that

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doi:10.1016/j.physa.2010.09.004

diverse clones are around 10^8–10^{12}, and, remarkably, the amount of epitopes/idiotopes belonging to a given antibody are present in a smaller number, i.e. order of 10^2.

When antigens enter the body, those clones which recognize it will bind to it. Aided by helper T-cells, B-cells of an activated clone will proliferate, becoming antibody producing cells. The latter will secrete large numbers of free antibodies, which attach to an antigen, neutralize it, and trigger killer cells into action. The above is (a part of the) "clonal selection theory" and has been confirmed experimentally.

Still from an experimental approach, we briefly stress that the typical behavior of the immune response (which may vary in amplitude and length) is the so called "Bell-Shaped Response" [1]: namely, on a semi-logarithmic scale, the concentration c depends on time t, according to a Gaussian-like curve. During this response the development of memory cells appears: a fraction of cells which have undergone clonal expansion (memory cells) is kept active (even after a long time from the removal of the antigen) hence preserving information of previous infection; as a result, in a possible secondary re-infection, more intense and more specific antibody production will be achieved.

The amount of memory cells retained after an infection is not a constant and it is known to depend on the time of the infection and on the kind of the infection [1,4].

We notice that this approach, pioneered by Burnet [5], takes into account an enormous amount of different data, and absolutely does not rely on interactions among different lymphocytes, as it deals with the external antigen interaction with the immune system, where the network works at a completely hidden level.

The idea of an internal network appeared early in immunology [6], and its concretization happened when Jerne [7], in the 70's, suggested that each antibody must have several idiotopes which are detected by other antibodies. Via this mechanism, an effective network of interacting antibodies is formed, in which antibodies not only detect antigens, but also function as individual internal images of certain antigens and are themselves being detected and acted upon. These network interactions provide a "dynamical memory" of the immune system, by keeping the concentrations of antibodies (especially those representing encountered antigens) at appropriate levels. This can be understood as follows: At a given time a virus is introduced in the body and starts replication. At a high enough concentration, it is found by the proper B-lymphocyte counterpart: let us consider, for simplicity, a virus as a string of information (i.e. 1001001). The complementary B-cell producing the antibody Ig1, which can be thought of as the string 0110110 (the dichotomy of a binary alphabet in strings mirrors the one of the electromagnetic field governing chemical bonds) then will start a clonal expansion and will release high levels of Ig1. As a consequence, after a while, another B-cell will meet 0110110 and, as this string never (macroscopically) existed before, attacks it by releasing the complementary string 1001001, that, actually, is a "copy" (internal image) of the original virus but with no DNA or RNA charge inside. The interplay among these remembers the past infection.

2. Towards a unified description

The phenomena described so far can be regarded as the evidence of a collective behavior due to the mutual interaction among lymphocytes and immunoglobulins. This point of view has been developed by the authors in Ref. [8], where a unified model based on a statistical mechanics background and able to account for many well-known properties featured by the immune system was introduced. While the statics of the model has been investigated, here we want to focus on its dynamical features. Before doing so, we now briefly summarize the model.

We consider the most generic antibody as a chain made up of the possible expression of L idiotopes. The assumption that each antibody can be thought of as a string of the same length is based on two observations: the molecular weight for each Igs is very accurately close to $15 \cdot 10^4$ and each idiotope on average is as large as each other (see Ref. [9]). The elementary L idiotopes are,

$$\xi_1 = (1, 0, 0, \ldots, 0), \xi_2 = (0, 1, 0, \ldots, 0), \ldots, \xi_L = (0, 0, 0, \ldots, 1), \tag{1}$$

forming an orthogonal base in the L-dimensional space Υ of the antibodies in such a way that the generic ith antibody ξ^i can then be written as a linear combination of these eigenvectors $\{\xi^i\} = \lambda^i_1\xi_1, \lambda^i_2\xi_2, \ldots, \lambda^i_L\xi_L$, with $\lambda^i_\mu \in (0, 1)$ accounting for the expression (1) of a particular μth idiotope or its lacking (0).

In this way, as often done in modern modeling of antibody affinities [10,11], we relax the earlier simplifying assumption of "a perfect mirror of a mirror" for the interacting Ig simply assuming that the better the matches among idiotopes and the stronger the stimulus occurring between the respective clones via their immunoglobulins. Roughly speaking, recalling the previous example, both the strings (1001000), (1001001) are reactive with (0110110), but for the second the interaction is stronger as it matches all the entries. As a counterpart, the strings with several differences in idiotope/epitope linking (i.e. 0111110 in the same example) do not match and the corresponding lymphocytes are disconnected in the network they belong to (it is straightforward to understand that there are no links inside the lymphocytes of the same clone, namely they act paramagnetically among each other). The fact that the interaction of two Ig's is stronger when their relative strings are more complementary responds to the kind of interaction among their proteic structures: protein–protein interactions are dominated by weak, short-range non covalent forces which arise when the geometry of the two proteins are complementary, whatever structures are assumed.

Moreover, the system is made up of an ensemble of N different clones, each composed of M identical lymphocytes; a given lymphocyte is then described by the dichotomic variable $\sigma^\alpha_i = \pm 1$, with $\alpha = 1, \ldots, M$, and $i = 1, \ldots, N$, such that

the value -1 denotes a quiescent state (low level of antibodies secretion) while the value $+1$ a firing state (high level of antibodies secretion).

The ability of newborn lymphocytes to spontaneously secreting low dose of its antibody (corresponding to its genotype), even when not stimulated is fundamental in order to retain the network equilibrium (see e.g. [12]). We stress that within our approach the upper bound of the available firing lymphocytes is postulated, namely M is independent of time, so the exponential growth of a clone when expanding and firing after the exposition to the external antigen, is translated here in the growing response of a "clonal magnetization" m due to the external field, that is a situation with $\sigma = -1$ for almost all lymphocytes switches to a scenario with all $\sigma = +1$.

Now, to check immune responses we need to introduce the N order parameters m_i as local magnetizations, whose time dependence is given by

$$m_i(t) = \frac{1}{M}\sum_{\alpha=1}^{M}\sigma_i^{\alpha}(t). \tag{2}$$

From the magnetizations $m_i \in [-1, 1]$, which play the role of the principal order parameters, we can define the concentrations of the firing lymphocytes belonging to the ith family as

$$c_i(t) \equiv \exp\left[\tau\frac{(m_i(t)+1)}{2}\right], \quad \tau = \log M. \tag{3}$$

Note that the concentration is not normalized and ranges over several orders of magnitude, namely from $\mathcal{O}(10^0)$ when no firing lymphocyte is present, up to $\mathcal{O}(10^{12}) \sim M$ when the ith clone has saturated the number of possible firing lymphocytes. In general, the quiescence of a given clone is a collective state where $\sim 10^2/10^3$ clones are present; this can be understood, within a thermodynamical framework, relaxing the idea that the system works at "zero-temperature" (that is not really physical), in fact, a small amount of noise would change the quiescent concentration from strictly 1 to a slightly higher value.

We now introduce the Hamiltonian H which encodes the interactions among lymphocytes as well as the interactions among lymphocytes and the external antigens, providing a measure for the "energy" of the system. We first consider the interactions involving lymphocytes and antigens, the latter, acting as external input, are modeled as external fields. We start with the ideal case of perfect coupling among a given antigen and its lymphocyte counterpart: the antigen is described by the string $\bar{\xi}_i^{\mu} \equiv 1 - \xi_i^{\mu}$, $\mu = 1, \ldots L$, and the coupling with an arbitrary antibody k is h_k^i.

Following classical statistical mechanics [13,14], the interaction among the two can be described as

$$H_1(\text{Burnet}) = -c\sum_{k}^{N} h_k m_k, \tag{4}$$

where c represents the antigen concentration. Of course the generic external input $\tilde{h}$, stemming from the superposition of P arbitrary elementary stimuli, can be looked as the effect of a string $\tilde{\xi}$ which can be written in the idiotype basis such that $\tilde{\xi} = \sum_{i=1}^{P}\lambda_i\,\xi_i$, $\lambda_i = 0, 1$.

So far we introduced the one-body theory, whose "Hamiltonian" is encoded into the expression H_1. If we now take into account a "network" of clones we should include their two-bodies interaction term H_2, that is

$$H_2(\text{Jerne}) = -N^{-1}\sum_{i<j}^{N,N} J_{ij} m_i m_j. \tag{5}$$

As anticipated, the Hamiltonian is the average of the "energy" inside the system and thermodynamic prescription is that the system tries to minimize it. As a consequence, according to H_1, increasing the antigen concentration makes the antibody response grow such that if $c(t_2) > c(t_1)$, with $t_2 > t_1$, the same happens for each involved clone $m(t_2) > m(t_1)$ and viceversa. Moreover, according to H_2, two generic clones i and j in mutual interactions, assuming here $J_{ij} > 0$, tend to imitate one another, i.e. if i is quiescent, it tries to make j quiescent as well (suppression), while if the former is firing it tries to make even the latter fire (stimulation), and symmetrically j acts on i.

It is natural to assume J_{ij} as the affinity matrix: it encodes how the generic i and j elements are coupled together such that its high positive value stands for a high affinity among the two. The opposite being the zero value, accounting for the missing interaction.

If we consider the more general Hamiltonian

$$H = H_1(\text{Burnet}) + H_2(\text{Jerne}) = -c\sum_{k}^{N} h_k m_k - N^{-1}\sum_{i<j}^{N,N} J_{ij} m_i m_j, \tag{6}$$

we immediately see that in the case of $J_{ij} = 0$ for all i, j we recover the pure one-body description and the antigen-driven viewpoint alone. Different ratios among H_1 and H_2 will interpolate, time by time, among two limits for each clone.

We now briefly resume with how the interaction matrix J_{ij} is built up: Given two strings ξ_i and ξ_j, their μ-th entries are said to be complementary, iff $\xi_i^{\mu} \neq \xi_j^{\mu}$. As each entry μ of the i-th string (Ig) is extracted randomly according to the discrete

uniform distribution in such a way that $\xi_i^\mu = 1$ ($\xi_i^\mu = 0$) with probability 1/2, given a couple of clones, say i and j, therefore the number of complementary entries $c_{ij} \in [0, L]$ can be written as

$$c_{ij} = \sum_{\mu=1}^{L} [\xi_i^\mu (1 - \xi_j^\mu) + \xi_j^\mu (1 - \xi_i^\mu)]. \tag{7}$$

The affinity between two antibodies is expected to depend on how much complementary their structures are. In fact, the non-covalent forces acting among antibodies depend on the geometry, on the charge distribution and on hydrophilic–hydrophobic effects which give rise to an attractive (repulsive) interaction for any complementary (non-complementary) match. Consequently, we assume that each complementary/non-complementary entry yields an attractive/repulsive contribute. In general, attractive and repulsive contributes can have a different intensity and we quantify their ratio with a parameter $\alpha \in \mathbb{R}^+$. Hence, we introduce the functional $f_{\alpha,L} : \Upsilon \times \Upsilon \to \mathbb{R}$ as

$$f_{\alpha,L}(\xi_i, \xi_j) \equiv [\alpha c_{ij} - (L - c_{ij})], \tag{8}$$

which provides a simple measure of how "affine" ξ_i and ξ_j are. In principle, $f_{\alpha,L}(\xi_i, \xi_j)$ can range from $-L$ (when $\xi_i = \xi_j$) to αL (when all entries are complementary, i.e. $\xi_i = \bar{\xi}_j$). Now, when the repulsive contribute prevails, that is $f_{\alpha,L} < 0$, the two antibodies do not see each other and the coupling among the corresponding lymphocytes $J_{ij}(\alpha, L)$ is set equal to zero, conversely, we take $J_{ij}(\alpha, L) = \exp[f_{\alpha,L}(\xi_i, \xi_j)]/\langle \tilde{J} \rangle_{\alpha,L}$, being $\langle \tilde{J} \rangle_{\alpha,L}$ the proper normalizing factor so to keep the average coupling unitary.

Hence, nodes can interact pairwise according to a coupling $J_{ij}(\alpha, L)$, which is defined as:

$$J_{ij}(\alpha, L) \equiv \Theta(f_{\alpha,L}(\xi_i, \xi_j)) \frac{\exp[f_{\alpha,L}(\xi_i, \xi_j)]}{\langle \tilde{J} \rangle_{\alpha,L}}, \tag{9}$$

where $\Theta(x)$ is the Heaviside function returning 1 if $x > 0$, and 0 if $x \leq 0$; notice that the affinity matrix is symmetric, namely $J_{ij}(\alpha, L) = J_{ji}(\alpha, L)$. The coupling h_i^k between the antigen $\bar{\xi}_i$ and the antibody ξ_k is defined analogously.

We finally remark that the resulting Hamiltonian H describes a broken symmetry random-field random-bond Ising model [15,16]; also, the rule in (9) generated a well-defined topology for the idiotypic network which is shown to be approximable by an Erdös–Renyi graph [17,8] with averaged connectivity

$$\langle k \rangle = N e^{-\frac{L}{2}(\frac{\alpha-1}{\alpha+1})^2} / (\sqrt{2\pi L}).$$

3. Markov process for the lymphocytes

Once defined, the external field $\tilde{h}_i$ acting on the generic ith clone at time t, the state of the system at this time is given as the average of all its building lymphocytes, each of which is evolving time-step by time-step via a suitable dynamics. Following a standard statistical mechanics approach [18] the dynamics can be written as

$$\sigma_i^\alpha(t + 1) = sign\left(\tanh(\beta \varphi_i(t)) + \eta_i^\alpha(t)\right), \tag{10}$$

where $\varphi_i(t)$ is the overall stimulus felt by the i-th lymphocyte, namely (see Eq. (6))

$$\varphi_i(t) = N^{-1} \sum_j^N J_{ij} m_j(t) + \tilde{h}_i(t), \tag{11}$$

and the randomness is in the noise implemented via the random numbers η_i^α, uniformly drawn over the set $[-1, +1]$. The impact of this noise (temperature) on the state $\sigma_i^\alpha(t + 1)$ is tuned by β, such that for $\beta = \infty$ the process is completely deterministic while for $\beta = 0$ it is completely random.

In this framework the noise can be thought of as induced by several different agents such as the concentration of free radicals (which bind randomly, decreasing the strength of the interactions) or the concentration of fat molecules as cholesterol, which speeds down the drift velocity for the lymphocytes decreasing the effective connection strength among them: as a big difference with neural networks, whose graphs have neurons as nodes and synapses as static links, in immune networks the graph underlying the model is intrinsically dynamical, dependent on the blood flow instead of static neuronal tissues [19].

In the sequential dynamics, at each time step t a single lymphocyte l_t-randomly chosen among the $M \times N$- is updated, such that its evolution becomes

$$P[\sigma_{l_t}^\alpha(t + 1)] = \frac{1}{2}\left(1 + \sigma_{l_t}^\alpha(t + 1) \tanh(\beta \varphi_{l_t}(t))\right), \tag{12}$$

whose deterministic zero-noise limit (that switches the hyperbolic tangent into a sign function) is immediately recoverable by sending $\beta \to \infty$.

If we now look at the probability of the state $\sigma = (\sigma_1^1, \ldots, \sigma_N^1, \ldots, \sigma_1^M, \ldots, \sigma_N^M)$ at a given time $t + 1$, $P_{t+1}(\sigma)$, we get

$$P_{t+1}(\sigma) = \frac{1}{N}\frac{1}{M} \sum_{i,\alpha}^{N,M} \frac{1}{2}(1 + \sigma_i^\alpha \tanh(\beta \varphi_i(\sigma))) P_t(\sigma) + \frac{1}{N}\frac{1}{M} \sum_{i,\alpha}^{N,M} \frac{1}{2}(1 + \sigma_i^\alpha \tanh(\beta \varphi_i(F_i^\alpha \sigma))) P_t(F_i^\alpha \sigma), \tag{13}$$

where we introduced the $M \times N$ flip-operators F_i^α, $i \in (1, \dots, N)$, $\alpha \in (1, \dots, M)$, acting on a generic observable $\phi(\sigma)$, as

$$F_i^\alpha \Phi(\sigma_1^\alpha, \dots, +\sigma_i^\alpha, \dots, \sigma_N^\alpha, \sigma_1^\beta, \dots, \sigma_N^\beta, \dots, \sigma_1^M, \dots, \sigma_N^M) = \Phi(\sigma_1^\alpha, \dots, -\sigma_i^\alpha, \dots, \sigma_N^\alpha, \sigma_1^\beta, \dots, \sigma_N^\beta, \dots, \sigma_1^M, \dots, \sigma_N^M). \tag{14}$$

So we can write the evolution of the immune network as a Markov process

$$p_{t+1}(m) = \sum_{m'} W[m; m'] p_t(m'), \tag{15}$$

$$W[m; m'] = \delta_{m,m'} + \frac{1}{N}\frac{1}{M}\sum_{i=1}^{N}\sum_{\alpha=1}^{M}\left(w_i^\alpha(F_i^\alpha m)\delta_{m,Fm'} - w_i^\alpha(m)\delta_{m,m'}\right),$$

with the transition rates $w_i^\alpha(m) = \frac{1}{2}[1 - \sigma_i^\alpha \tanh(\beta\varphi_i)]$.

Furthermore as the affinity matrix is symmetric (cfr. Eq. (9)), detailed balance ensures that there exists a stationary solution [18] $P_\infty(m)$ such that (restricting $\tilde{h}_i(t) \to \tilde{h}_i \in \mathbb{R}\ \forall i \in (1, \dots, N)$)

$$W[m, m']P_\infty(m') = W[m', m]P_\infty(m),$$

which reads off as

$$P_\infty(\sigma; J, h) \propto \exp\left(\frac{\beta}{2N}\sum_{ij}^{N} J_{ij} m_i m_j - \beta c \sum_{i}^{N} \tilde{h}_i m_i\right) = \exp\left(-\beta H(\sigma; J)\right), \tag{16}$$

namely the Maxwell–Boltzmann distribution [20] for the Hamiltonian $H = H_1 + H_2$.

This allows an equilibrium statistical mechanics investigation as the free energy of the lymphocyte network can be written as

$$A_{N,M}(\beta, h) = -\frac{1}{\beta N}\mathbb{E}\log\sum_{\sigma} P_\infty(\sigma; J, h),$$

(where the operator $\mathbb{E}$ averages over the topology encoded in the affinity matrix) and by which we can argue, following [17], the critical noise β_c as $\langle k\rangle \tanh(\beta_c) = \langle J\rangle^{-1} = 1$. Hence, the system is able to reach a well defined equilibrium whose immunological properties (low dose tolerance, memory, self/non-self recognition, etc.) have been already investigated elsewhere [8].

It is important to stress that the concept of equilibrium here simply means equilibrium with respect to a particular choice of the quenched antibody network, ultimately encoded into the J_{ij}: there is furthermore a dynamic among hypersomatic mutations [21,22], the latter acting as a learning process [23] and not investigated here, that allows equilibration on larger time scales.

Finally, for this detailed balanced system, the sequential stochastic process (10) can be implemented on a machine via Glauber dynamics, with the following expression for the transition rate W_i

$$W_i(m) = \left(1 + \exp(\beta \Delta H(\sigma_i; J))\right)^{-1}, \tag{17}$$

where $\Delta H(\sigma_i; J) = H(F_i m; J) - H(m; J)$. We implemented this scheme in (part of) the simulations outlined for this work (in particular – for checking consistency with the next approach – in the hysteresis loops shown in Fig. 1).

4. Langevin dynamics for the clones

Computationally, dealing with $M \times N$ discrete variables is really expensive as far as both M, N already reaches $O(10^4)$ (which is however a poor immune network). Dealing with only N variables, even though continuously defined on $[-1, +1]$, is more appealing, such that in this section we coarse grain our interest moving from the single-lymphocyte, i.e. σ_i^α, dynamics to clonal dynamics, i.e. m_i, which we model trough Langevin equations [24].

We applied sinusoidal fields of the form $h(t, \omega) = h_0 \sin(\omega t)$, where h_0 takes into account the interaction trough the lymphocyte network J_{hi} and the antigen load c_h, ($h_0 = c_h J_{hi}$) such that its coupling with each clone depends on the complementary among their relative epitopal entries, while ω rules the timescale of the antigen. The equations of motion can be written as

$$\tau_1 \frac{\mathrm{d}m_1(t)}{\mathrm{d}t} = -m_1(t) + \tanh\left\{\beta\left[\sum_{j}^{N} J_{1j} m_j(t) + h(t, \omega)\right]\right\}, \tag{18}$$

$$\dots = \dots, \tag{19}$$

$$\tau_N \frac{\mathrm{d}m_N(t)}{\mathrm{d}t} = -m_N(t) + \tanh\left\{\beta\left[\sum_{j}^{N} J_{Nj} m_j(t) + h(t, \omega)\right]\right\}. \tag{20}$$

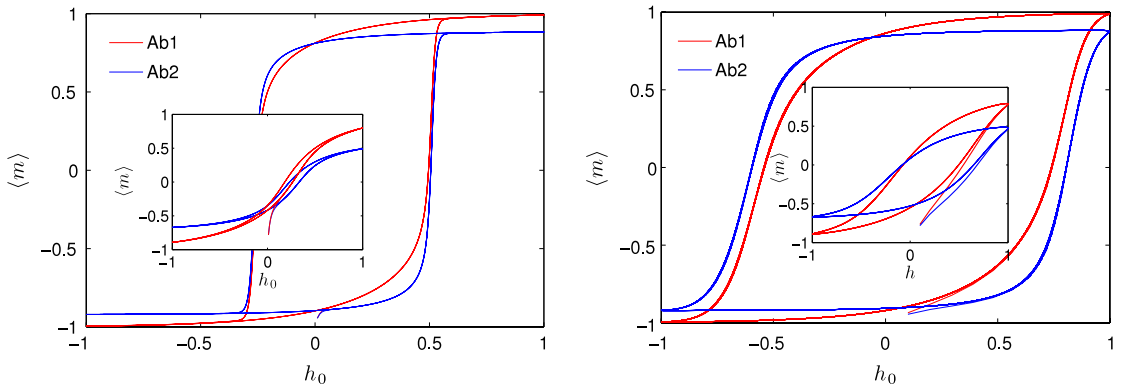

Fig. 1. Examples of hysteresis cycles in the immune system we simulate: They are obtained as fixed points of the Langevin dynamics introduced in Eqs. (18)–(20) for a system made up of $N = 5000$ clones. Ab1 (red curve) labels the first best matching antibody reacting to h_0, while Ab2 (blue curve) labels the second best matching antibody reacting to h_0. On the y-axis we show the concentration of firing lymphocytes and on the x-axis the amplitude of the external field. Two different frequencies are considered: $\omega = 0.1$ (left panel) and $\omega = 0.01$ (right panel). The importance of the level of noise is understandable by the inset, the main plots are obtained by setting $\beta_{\text{main}} = 15\beta_c$ while their inset shows the same simulation with $\beta_{\text{inset}} = 1.5\beta_c$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Note that each τ_i sets the timescale for the related clonal response: this can be recognized by analyzing the exponential behavior displayed when $J_{ij} = 0$ and noticing that an analogous exponential behavior is imposed by mitosis growth [25]. In what follows, as clonal expansion machinery is believed to be the same in the whole plethora of lymphocytes (and accounting for random differences as missed interactions with T helper, etc, into the level of noise β), we set its characteristic timescale $\tau_i = \tau$. Further, as the physical parameter is the ratio among the time scales τ and $2\pi\omega^{-1}$, we set $\tau = 1$ and start applying a field $h(t, \omega)$ to the immune system at rest, collecting the responding clones that we integrate via a step adaptive Runge–Kutta algorithm (with step increment set to 1.1): namely we consider an immune system made of by $N = 5000$ different clones (uniformly randomly generated), $L = 180$, $\alpha = 0.7$ and $\langle k \rangle \approx 45$; Results are shown in Fig. 1. We also checked over $\sim 10^2$ realization of the repertoire and, consequently, of the underlying network, that the results obtained are robust; qualitative robustness has also been checked within a close region in the parameter space (α, L), as well as over different magnitudes for the system size.

We want to show that our model (an ensemble of paramagnets ferromagnetically interacting) exhibits the phenomenon of "hysteresis" [26,27] and this may account for the generation of the memory cells, furthermore it can model naturally both the improvement of the quality of the antibody production in the second response and the time-dependence in the ratio of the obtained memory-cells. The hysteresis is a dynamical feature which essentially arises due to conflicting timescales interplaying. In ferromagnetic materials hysteresis is a well known phenomenon, both theoretically and experimentally: When an oscillating magnetic field is applied to a ferromagnet, the thermodynamic response of the system, namely its magnetization, will also oscillate and will lag behind the applied field due to the relaxational delay. Therefore, the two time-scales interplaying are given by the frequency of the external field ω and by the thermalization of the system itself. When relaxation is slower than field oscillations we have a delay in the dynamic response of the system which gives rise to a non-vanishing area of the magnetization-field loop; this phenomenon is called *dynamic hysteresis*.

As for the immune system, the two dynamical phenomena and related time-scales involved are the rise of the immune response (which may depend by the particular clone involved and its nearest neighbors) and the antigenic growth (which strongly depends by the given antigen, i.e. it can be intermittent due to lytic and latent cycles of several viruses [25]).

Since the two phenomena are interplaying, delays in the dynamic response gives rise to several interesting phenomena: when the infection ends and the concentration of the antigen vanishes, there can be non-zero -remanent- magnetization (lacking of the in-phase behavior appears), further, when the time period of antigenic oscillations becomes much less than the typical relaxation time of the clone, a dynamical phase transition toward a chronic response may appear [28] (see Fig. 3).

Ultimately this approach may bridge the Barkhausen effect [24] to the "Jerne avalanches" of antibody and anti-antibody [3], whose distribution and sizes are interesting information in theoretical immunology.

4.1. Improvement of secondary response

The introduction of a concentration c of a given antigen described by the external field h^i is able to increase the magnetizations (concentrations) of the nodes (lymphocytes) whose coupling is strong enough, provided that such a concentration is sufficiently high to break suppression exercised by their nearest neighbors. In general, if the concentration is large enough, several clones, different from the best matching (i), may prompt a response: some of them, say $j_1, \ldots, j_p$, (hereafter called spurious, in order to stress similarities with neural networks [23] and Ab2 in Fig. 2) respond because of a non-null coupling h^i_j, although $h^i_j < h^i_i$, others, say $j'_1, \ldots, j'_p$, (hereafter Jerne states for consistency, and AAb, AAAb in Fig. 2) respond because they display a strong interaction with the formers (large $J_{jj'}$) or with the specific Ig i itself (large $J_{ij'}$): so after

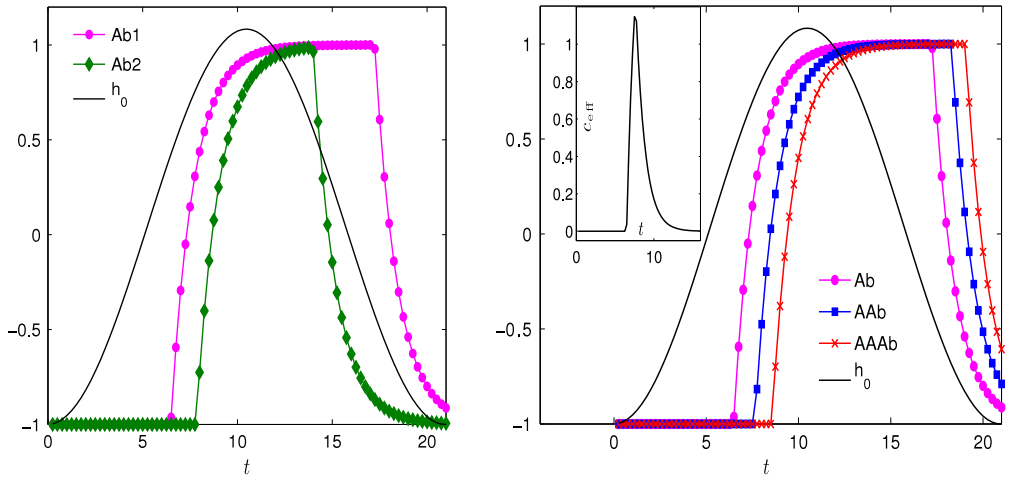

Fig. 2. Left: Hysteresis displayed by the stimulated best matching clone Ab1 and a spurious clone Ab2: At the end of the infection the relative difference, created by the stimulus, among the best antibody and its spurious state accounts for the improvement of the quality of further responses. Right: Example of the Jerne cascade (commonly seen in real systems [29]). At first, once the stimulus reached enough strength (implicitly accounting for the low-dose tolerance) the antibody responds (Ab); this is followed by the raise of the anti-antibody (AAb) and subsequently to the anti-anti-antibody (AAAb), in perfect agreement with the Jerne theory. The inset highlights the "efficacy concentration" of the lymphocytes, namely the difference among Ab and AAb.

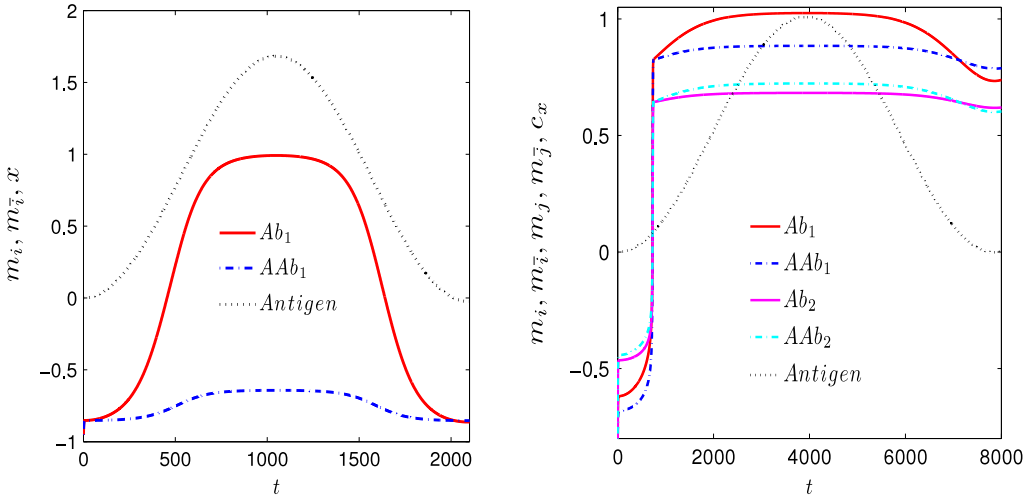

Fig. 3. Examples of the variability of the bell-shaped response. Ab1 and Ab2 label the first and second best matching antibody reacting with the antigen, respectively; AAb1 and AAb2 label the pertaining anti-antibodies. Left panel: a typical behavior, at $\omega = 1$; Right panel: a pathological example of a chronic response at $\omega = 0.1$: Remarkably, real immune systems are shown to display persistent excitations if the infections are prolonged for too long time (and are often called "post viral syndromes" [28]).

an antigen is introduced we have two kinds of response, the former against the antigen (Fig. 2 left panel), the latter against lymphocytes in expansion (Fig. 2 right panel). In this way, once the infection is over, the mutual interaction among all these agents is still at work determining memory effects.

The analysis we performed over different realizations of system $(\alpha, L, \langle k \rangle)$ highlighted that a given concentration of antigen (roughly order of 10^2 times the minimum dose, see [8]), the number of reactive spurious states is approximately twice the number of reactive Jerne states and, in general, Jerne states require a larger stimulus to react; this is due to the fact that the reaction is not directed, but rather mediated by the specific Ig i or by a spurious state j.

As it is immediate to check, there exist several of these spurious states undergoing clonal expansion. The numerical solution of Langevin equations for the whole system is (partially) shown in Fig. 2 left panel, which displays the typical behavior (at low value of noise) of the first two best-fitting clones (Ab1 and Ab2) elicited by an external antigen and, in Fig. 2 right panel the Jerne cascade is also well reproduced [7]: The improvement of both the quantity and the quality of the secondary response can be inferred from the pictures. At the first infection with the antigen h_1 both Ab1 and a spurious state Ab2 are elicited basically simultaneously. However, Ab1 experiences a higher field (because of the best matching with h_1) and the relevant AAb is also elicited. At the second infection of the same antigen the quiescent state of Ab1 and Ab2 are no longer the old ones as now different relative concentrations of the two clones are stored. In particular Ab1 shows higher

concentration than Ab2: Overall the immune response is stronger, due to both the remanent magnetization, and sharper, due to the mismatch among their relative concentrations after the infection.

As a consequence, if the stimulus is presented once again, the immune system is not simply translated from quiescence level of concentrations to remanent magnetization levels in a uniform way, but different values of the latter, among Ab1 and Ab2, account for an improved response even from the specificity viewpoint.

4.2. Bell shaped response

In this section we want to show that, within our model, the so called "bell-shaped response" [1] is recovered as the typical immune response and ultimately can be thought of as two hyperbolic tangents (standard response in statistical mechanics) merged at the higher value (see Fig. 3 left panel): the first one, increasing in amplitude, follows the antigenic spread, while the latter, decreasing in amplitude, follows the loss of the antigenic load after the antibodies' response reached a macroscopic value.

Before presenting our results it is worth taking a few lines to introduce more clearly our approach: usually when dealing with these dynamical features of the immune system, without passing trough the hyperbolic tangents (canonical responses of disordered mean field statistical mechanics) one has to work out dynamical systems for the evolution of the antigenic and antibody concentrations (which is indeed what is almost always done [30–33]). This accounts for $m(t)$ and $h(t)$, then one, carefully looking at the monotonic regions of the two behaviors, can parameterize and get $m(h)$. Within our approach we do not solve this kind of problem, instead we directly give an expression for the antigenic load and then we obtain $m(h)$ as a result. This techniques lacks an explicit time dependence (which can be odd), however it skips all the troubles about the details of the interactions which may strongly depend on the particular antigen [1], toward a description of "universal features" of the immune system.

We test immune responses with ideal mono-frequency viruses which are a clear simplification: however a more complex behavior can be obtained considering the antigen as a sum of several perturbing harmonics (i.e. Fourier analysis), which is allowed due to the linearity of the Hamiltonian H_1 with respect to the fields.

Typical (left panel) and atypical (right panel) results of responses found at different field frequency and magnitude are presented in Fig. 3.

5. Summary

In this paper we developed the stochastic dynamics of a lymphocyte model and showed its convergence to equilibrium; then we analyzed its out of equilibrium response directly applied in the framework of theoretical immunology so to coarse grain the description at the level of clones: This allowed to move on from Fokker–Planck structures to Langevin equations, and consequently highly decreasing the computation time for simulations. Our work is not meant as an exhaustive picture of the (adaptive response of the) immune system, but rather as a starting point in modeling its universal features by means of these techniques, once read in a proper disordered statistical mechanics framework.

In particular, we retrieved well known properties of the immune networks as Jerne cascades and multiple responses to stimuli. Furthermore, we have shown how our representation of the adaptive part of the immune system naturally and autonomously achieves/recovers the following properties:

- the genesis of memory cells can be played by the hysteresis in the network: these memories are not meant to be stable as in the neural counterpart but persistent on a timescale larger than that involved with the infection.
- the bell-shaped behavior of the immune system appears as the most common response of the system and not a postulate: in a nutshell it is the response of the system through an increasing (and then decreasing) hyperbolic tangent as in well known ferromagnets.
- the secondary response appears stronger and better than the first (depending on the strength of the antigenic concentration) because of the mismatch among the residual concentrations of the best fitting antibody and of the spurious states able to bind to the antigen after the primary infection. (This involves even the velocity of the antigenic growth – the frequency of the applied sinusoidal field – and its duration);
- increasing the noise, both the the quality and the quantity of the available retrievals decrease, which is intuitively in agreement with immunity pathologies;

All these different aspects of the immune system appear as features of a whole unified quantitative and very simple theory (whose statics already confirmed several other known features [8]) and the maturation and proliferation (ultimately the bell shaped) is no longer introduced as a postulate as in the second generation immune networks [34].

Among the several outlooks, surely a detailed Fourier analysis is to be achieved as the model is shown to display a very rich ensemble of timescales and aging is expected (in the sense of the violation of the fluctuation dissipation theorem).

We plan to report soon on several of the outlined directions of research.

Acknowledgement

The authors are grateful to Francesco Guerra, Raffaella Burioni, Pierluigi Contucci, Ton Coolen, Silvio Franz, Roberto Mulet and Giancarlo Ruocco for useful discussions.

This work is supported by the FIRB Project RBFR08EKEV.

AB acknowledges even the GNFM (Gruppo Nazionale per la Fisica Matematica) and INdAM (Istituto Nazionale d'Alta Matematica) for a travel grant.

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