Collective Dynamics in the Immune System Response

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(Received 5 June 1997)

It is suggested that the process by which the immune system learns how to recognize foreign invaders proceeds through a cascade of "metastable states" behaving like collective modes in a bit-matching space. [S0031-9007(97)04601-2]

PACS numbers: 87.22.–q

Recently, the simulation of the immune system (IS) has been drawing significant benefits from the resort to *cellular automata* (CA), namely, fully discrete dynamical systems evolving according to boolean rules [1,2]. CA appear particularly well suited to the simulation of biological systems mainly on account of their capability to naturally incorporate complex nonlinearities. In addition, owing to their space-time locality, they are almost ideal candidates for massively parallel processing. A prominent example of immunological CA is the Celada-Seiden model, which has been able to provide a number of fresh insights into the dynamics of the immune system response [3]. The Celada-Seiden automaton is characterized by a fairly high degree of sophistication which sets it apart from simple CA in the Ising class. The model includes the following entities: *antigens (Ag), B cells (lymphocyte B), plasma B cells, antigen processing cells (APC), T-helper cells (Th),* and *antibodies.* These entities move in a two-dimensional triangular lattice, and, once on the same site, they interact according to some rules.

For instance, each B cell is endowed with a receptor molecule, which controls the recognition of the invading antigens, and a MHC (major histocompatibility complex) molecule which mediates its subsequent interaction with Th cells. Upon recognition of a given antigen, the B cell incorporates it for internal chemical processing (endocytosis).

As a result of this internal processing, the B cell moves to a new internal state (B′) characterized by a different configuration of the MHC/Ag complex. The new B′ cell can now be recognized, via exposition of the MHC/Ag molecule, by the Th cells receptors. This cells-antigen complex, in turn, produces the signal (interleukin) triggering both B cell and Th cell reproduction via clonal division. The result is proliferation of clones of plasma B cells that finally secrete antibodies specifically prepared to attack the antigen (*humoral* response) and memory cells ready to counteract subsequent infections by the same antigen (memory of the IS).

In IMMSIM, the specific code implementing the Celada-Seiden automaton [4], both cell receptors and molecules are represented by bit strings of length l. Binding events are mediated by an *affinity potential* V which is a function of the Hamming distance of the two strings involved, namely, the number of matching bits (0's with 1's and vice versa).

For the present study, the affinity potential is chosen in the form of a truncated exponential: $V(m) = V_c \exp(\lambda \frac{m-m_c}{l-m_c})$ for $m_c \le m \le l$ and $V(m) = 0$ elsewhere. Here $\lambda = -\ln V_c$, V_c is equal to 0.05, m is the number of matching bits, and m_c is the "cutoff" match below which no recognition takes place. In addition, each cell is endowed with a set of internal degrees of freedom specifying its internal state (e.g., inert, stimulated, Ag processing, ...). Full details on the system specification are given in [4].

Based on a set of computer simulations, we have come up with the following picture of the immune system response. Antigens injected from time t_0 onwards start to interact with a random background of B cells, distributed along a Maxwellian

$$M_0(m, \mu_0, T_0) = (2\pi T_0)^{-1/2} \exp -(m - \mu_0)^2/2T_0$$

centered about $\mu_0 = l/2$ with variance $\sigma_0 = \sqrt{l}/2$. Here $T_0 = \sigma_0^2$ is the "temperature" measuring the scattering (uncertainty) around the mean value μ_0. Subsequently, after a given induction period, selective Ag interactions with B cells, lying in the tail of M_0 with matchings above m_c, trigger the growth of a new population of high-match B cells centered about a higher matching number $\mu_2 = m_c$. This growth proceeds via stimulation of B cells by Th cells and subsequent proliferation via clonal multiplication. This is the start-up of the learning process: B cells peaked about m_c trigger, in turn, the growth of

higher-match populations, in a sort of upward cascade in m space ending up with the highest available bit-match number $m = l$.

Such "bump-in-tail" distributions are often encountered in physics where they are usually associated with instabilities ensuing from their high energy/entropy content. In the immunological context, however, there is no thermodynamic principle forcing the release of the entropical excess associated with the bump in tail. On the contrary, the system dynamics is presumably geared towards a negative entropy production feeding the learning process that allows the IS to recognize foreign invaders. Hereafter, we are going to show that a quantitative measure of this learning process is provided by its *relative* entropy.

To be more specific, let us consider a dynamical process turning state 1 into state 2, characterized by distributions f^1 and f^2, respectively. The quantity G_{12} defined as

$$G_{12} = \sum_m f_m^2 \ln(f_m^2/f_m^1) \tag{1}$$

is the *relative* entropy or *Kullback information* of the process [5].

Owing to the inequality $\ln x \geq (1 - 1/x)$ (equal sign applying if $x = 1$), it is readily shown that G_{12} is positive definite and zero just in case the two distributions are exactly the same. According to [6], G_{12} represents the *information gain* encoding the extra knowledge associated with the availability of an additional distribution function. We observe that G_{12} may be related to a metric measuring the distance between distributions f^1 and f^2 in a suitable information space [7].

We shall consider the information gain associated with the transition from an initial state f^1 to a final state f^2, identified by their first three moments: $n_i = \sum_m f_m^i$, $n_i \mu_i = \sum_m m f_m^i$, and $n_i T_i = \sum_m f_m^i (m - \mu_i)^2$ (n_i is the number of individuals belonging to f^i, with $0 \leq n_i \leq 1$).

The total entropy of the "bound state" $(f^1 + f^2)$ is given by $H_{12} = H_1 + H_2 + H_X$, where $H_i \equiv \sum_m f_m^i \times \ln f_m^i$, $(i = 1, 2)$ are the entropies of the "pure" states f^i, and $H_X = \sum f_m^1 \ln(1 + f_m^2/f_m^1) + \sum f_m^2 \ln(1 + f_m^1/f_m^2)$ is the exchange entropy due to superposition of the two states.

Using Maxwellian states as interpolants, simple algebra on Eq. (1) yields

$$G_{12} = n_2 \ln \frac{n_2}{n_1} + \frac{n_2}{2} (\ln \theta_{12} + \theta_{12}^{-1} - 1 + \delta_{12}^2), \tag{2}$$

where $\theta_{12} = T_1/T_2$ and $\delta_{12} = (\mu_2 - \mu_1)/\sqrt{T_1}$.

Such a simple formula calls for a number of comments. The term $\ln \theta_{12} + \theta_{12}^{-1} - 1$ on the right-hand side (rhs) of Eq. (2) is the "thermal" component of the information gain, namely, the information gained through a differentiation of the two states via a temperature change (scale dilatation/contraction in m space). It is positive definite and vanishes only for $T_2 = T_1$.

The other term on the rhs of Eq. (2), δ_{12}^2, is the information gain associated with differentiation via shifts in m space and consequently it shows *explicitly* the desired dependence on the mean displacements we were looking for. It is also positive definite, regardless of the sign of the displacement δ_{12}, and symmetric under the exchange $1 \leftrightarrow 2$ so that it can serve as a metric distance between f^1 and f^2.

How do these notions map out onto the immune system response?

The information gain G_{12} alone cannot tell the whole story because its translational invariance does not allow us to distinguish between "smart" (high μ) and "dumb" states (low μ). Thus, this indicator has to be complemented with the sign of the mean matching separation δ_{12}. In other words, the sign of δ_{12} indicates whether the system has moved uphill (learning) or downhill (unlearning) along the learning landscape, the module of information gained/lost in such a process being given by G_{12}. Within this picture, G_{12} is naturally interpreted as the information cost associated with the process yielding a learning amount $|\delta_{12}|$. These considerations allow us to gain better insight into the actual results of the numerical simulations. The runs have been performed with the following parameters: $l = 12, m_c = 10$, grid size 16×15, $V_c = 0.05$, initial number of B, Th, and APC cells equal to 2000. The antigens are continuously injected at a rate of 300 units/step. All the input values are drawn from [3] which represents the basic reference with respect to the biological parameters of the model. The total number of antigens and B cells, as a function of time, is represented in Fig. 1. The B cells succeed to level off the Ag content after about 50 time steps. Since a single time step covers 1/10 of a typical B-cell lifetime, this corresponds to about two weeks in physical units. The dramatic drop of antigens after $t = 50$ is a clear clue that the IS has been capable of mounting a very effective response to the invading agents.

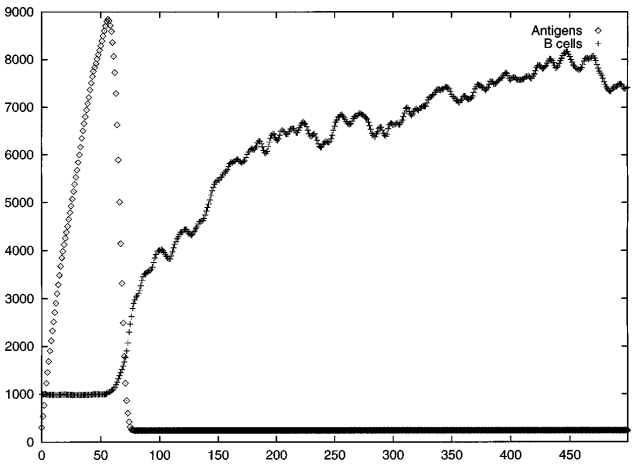

FIG. 1. The total number of Ag and B cells as a function of time.

More insight on the specific carriers of the IS response can be gained by inspecting the time evolution of the B-cell distribution function $f_m(t)$ reported in Fig. 2. Here f_m is the total number of B cells with matching number m versus the total number of B cells in the system.

At the beginning, only the initial Maxwellian corresponding to the mean bit matching number ($\mu = l/2 = 6$) develops. Subsequently, this Maxwellian sends individuals to a second mode, say M_{10}, corresponding to the lowest matching number ($\mu = m_c = 10$) recognizable by the system. The M_{10} mode behaves like an ordered (low temperature) metastable state, being fed by the tail of the M_6 and sending itself individuals to the upper-lying states. In a sense, it serves as an intermediate bridge to accomplish a *learning cascade process* taking $\mu = 6$ states into the final $\mu = 12$ (perfect learning) state.

Several aspects of such a process deserve particular attention like the dependency (if any) on the bit-string length and on the specific form of the affinity potential.

For longer strings ($l > 12$), we expect the number of learning stages to increase as $(l - m_c)$. Unfortunately, this hypothesis is hard to test because of the exponential complexity (2^{2l}) of the model. Any additional bit in the string requires a fourfold increase in computing time. To date we are not aware of any extensive simulation of the C-S model with l greater than 14. As a result, any quantitative assessment on the learning cascade must await further extensive numerical simulations. To make progress in this direction, we have recently developed [8] a parallel version of the code that will allow us to gather results up to l equal to 20.

As to the correlation of this process with the specific form of the potential, we observe that below the cutoff value m_c no mode may grow since the potential is strictly zero and cannot trigger any instability. Moreover, no strong dependence on the shape of the potential is expected, since the crucial feature is a nonvanishing potential capable of triggering the instability, rather than the shape of the potential itself. When this occurs, the initial value of the high-match ($m \geq m_c$) B cells should be barely forgotten regardless of the shape of the potential.

An interesting feature of the learning cascade is that it is realized via shifted bump-in-tail states, which stand out as "collective modes" of the immune system dynamics. This is to be contrasted to an alternative scenario whereby the initial Maxwellian would develop long (exponential or algebraic) tails rather than narrow bumps at high m.

It is worth pointing out an amazing analogy with the mechanism of "current drive" in fusion plasmas, namely, the dramatic rise of electric current triggered by injection of even minute amounts of radio-frequency power in a range of frequencies much higher than the mean electron speed ([9]).

Formally the analogy proceeds by identifying B cells with electrons interacting with antigens (photons) via the affinity potential $V(m)$ (electron-wave potential). Within this analogy, the mean bit-matching number μ can be seen as the electric current driven by the waves, perfectly in line with the interpretation of m as a fictitious "particle speed." In this context, it would be interesting to define a sort of learning efficiency as the analog of electric conductivity, namely, the ratio between the mean bit match μ and the strength of the affinity potential V_c.

In Fig. 3 we show the normalized mean match $\mu_n = \frac{\mu(t)-\mu(0)}{\mu(0)}$, $[\mu(0) = l/2]$, the entropy $H(t) = \sum_m f_m \ln f_m$, and the information gain $G(t)$.

The mean bit-match number is the most immediate indicator of whether or not the system is learning to withstand the antigens' attack.

As expected, after an induction time of about 50 time units, the mean bit match exhibits a sharp rise associated with the onset of the $\mu = 10$ mode. This is the time it takes the system to develop the catalytic growth of B cells lying in the tail ($m \geq m_c$) of the initial Maxwellian. It

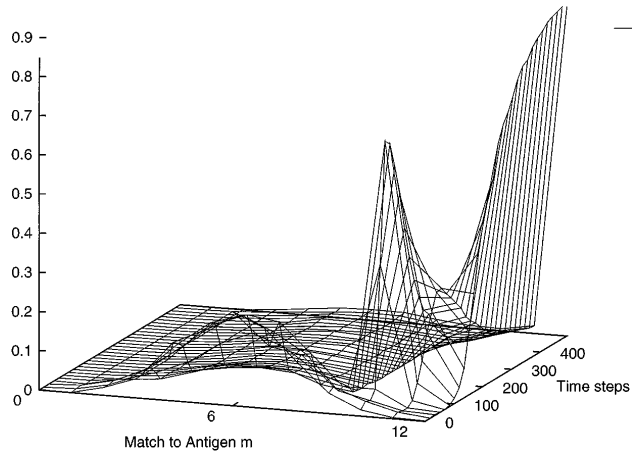

FIG. 2. The B-cells distribution $f(m,t)$ as a function of time.

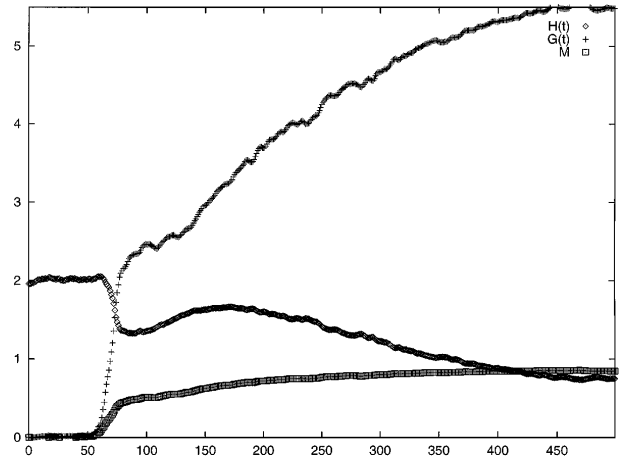

FIG. 3. Time evolution of the normalized mean match μ_n, standard entropy $H(t)$, and information gain $G(t)$.

is also the stage of substantial learning. The subsequent evolution shows a progressive improvement due to the disappearance of M_{10} in favor of the "smarter" M_{12} mode. Since the M_6 is continuously sustained from the exterior, it never dies out completely thereby preventing μ from achieving the top value $\mu = 12$ (perfect learning state).

After a stagnation period (up to $t \sim 50$), the entropy undergoes a sudden drop as a result of the IS primary response. Note, in fact, that the statistical dispersion of M_{10}, T_{10}, is significantly smaller than T_6. Subsequently, the simultaneous presence of competing modes causes a slight entropy increase, mainly contributed by the exchange entropy component. Finally, as the mode centered in $m = 12$ prevails, the entropy starts again to decrease monotonically. As a general remark, we observe that the entropy $H(t)$ does *not* behave like a proper H function, i.e., a monotonically decreasing/increasing function of time. Since our f_m is a standard probability density function (i.e., positive definite and normalized to one), our interpretation is that no standard H function can be associated to the C-S automaton dynamics.

Finally, we inspect the evolution of the information gain $G(t)$. As expected from previous analytical considerations, $G(t)$ proceeds much in sympathy with the mean match number $\mu(t)$. However, the sharp rise around $t = 50$ is significantly steeper, taking almost the connotations of a first order phase transition.

A semiquantitative assessment of the time evolution of $G(t)$ may be attempted on the assumption that the bump-in-tail modes behave like Maxwellian distributions. We want to stress that, due to the limited string length ($l = 12$) this is no more than a reasonable hypothesis. In other words, we have been able to test it just for the initial Maxwellian M_6. For higher-match modes longer strings are required. Nevertheless it is reasonable to state that the specific shape of these modes should not affect the qualitative features of the learning cascade.

By identifying state 1 with M_6 and state 2 with M_{10}, from Fig. 2 we infer $n_1 = 1$, $n_2 = 0.63$, $T_1 = 3$, $T_2 \sim 0.4$, $\delta_{12} = (10 - 6)/\sqrt{3}$. According to Eq. (2), this yields $G_{12} \sim 1.75$ in a satisfactory agreement with the data in Fig. 3. By modeling the subsequent evolution as a transition from M_{10} to M_{12}, we obtain $n_1 \sim 0.63$, $n_2 \sim 0.85/2$, $\theta_{12} \sim 1$, $\delta_{12}^2 \sim (12 - 10)^2/0.4 = 10$. Since M_{12} lies on the rightmost boundary of bit-matching space, we must account for finite-size effects. Some algebra yields $G_{fs} = G/2 + \frac{n_2}{2}\frac{T_2}{T_1}\delta_{12}/\sqrt{2\pi T_2}$, where the subscript fs stands for "finite size." The final result for the transition M_{10} to M_{12} is therefore $G \sim 2.8$, again in reasonable agreement with the results of the numerical simulation.

As a further observation, we note that, at variance with standard entropy, the information gain *does* behave like a proper $\mathcal{H}$ function; namely, it monotonically increases with time. This is conducive to the idea of a "maximum information-gain principle" [10] of the form $\frac{dG}{dt} \geq 0$ with the equality sign holding when the learning process is basically over. This is a direct consequence of G being a monotonic function of δ, which is quite reasonable in light of the interpretation of G as the information cost associated with the learning amount δ.

In turn, δ is a monotonic function of time because high-m bumps develop as a result of the depletion of lower-m "parents," hence after them. This is why the system dynamics exhibits a "built-in" time arrow.

The present study sets a pointer in the direction of kinetic theory (Boltzmann) as a valuable approach to the IS dynamics, possibly achieving an optimal compromise between CA microdynamics and macroscopic population dynamics.

Illuminating discussions with F. Celada and P. Seiden are kindly acknowledged.

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