On Immunological Memory as a Function of a Recursive Proliferation Process

Thomas Stibor
Fakultät für Informatik
Technische Universität München
Email: thomas.stibor@in.tum.de

Anastasio Salazar-Bañuelos
Hotchkiss Brain Institute
and
Department of Surgery, Division of Transplantation
University of Calgary, Canada
Email: salazara@ucalgary.ca

***Abstract*—We present a model that explains immunological memory as a consequence of the recursive proliferation of reactive and suppressive cells, where the relative proportion of these cells will set a probability for the emergence of a response (inflammation). We show that the underlying principle of the proposed model is a special case of Pólya's urn process. This insight reveals and explains the emergent functionality of the model. Additionally, experiments and simulations are performed to validate the obtained insight of the model.**

I. Introduction

The observation that the occurrence, intensity and quality of immune responses are influenced by previous events and responses is perceived as immunological memory, a property leading to the consideration of the "Immune System" as capable of cognition [1]. Although this ability to recall previous responses was known even before the concept of Immune System was coined [2], it is less clear how this memory is acquired, recalled or modified.

Classical explanations from Template Theory to Clonal Selection are based on pattern recognition, which classifies antigens as Self or Non-Self [3]. These explanations require the existence of a pattern keeper entity (memory cell), which determines the responses to a-priori classified Self or Non-Self antigens, and assumes that responses are antigen-driven. However, the existence of a memory cell as an entity that determines immune responses is problematic, and immunological memory continues to be one of the enigmas of current immunology [4]. Here, we propose that immune memory is not localized in a specific pattern-keeper entity, cell or molecule, but similar to the brain, it is a distributed memory, inherent in the structure of the system. This approach can be considered in line with the work initiated by Jerne [5], followed by Vaz and Varela [6], Coutinho [7], more recently by Carneiro [3] and León et al. [8], who understands the immune phenomenon at system level.

In this view, the quality, intensity and specificity of immune responses will depend on the way the system was generated, evolved, and modified. Any changes in this immunological memory will be a consequence a change in the structure of the system. As well, the discovery of the leading role of suppression in the determination of immune responses [9] and the concept of dominant tolerance as an explanation for the avoidance of autoimmunity [10] indicates that immune responses depend on the fine equilibrium between reactive and suppressive mechanisms; therefore any hypothesis of immunological memory must take this into account.

In this work we present a model that explains immunological memory as a consequence of the recursive proliferation of reactive and suppressive cells, where the relative proportion of these cells will set a probability for the emergence of a response (inflammation). The model proposes that immune memory is the result of the creation of an attractor, which determines the probability for a response. This probability can be small, making the response unlikely, or high, making the response almost certain, or anywhere in-between. For an external observer, the occurrence of inflammation is perceived to be a response to Non-Self and its absence is perceived to be a tolerance to Self, creating the illusion that the antigen determines the response. In contrast, we show that the attractor is the result of the proliferation of auto-reactive and suppressive clones in ontogeny, and the numerical relationship between auto-reactive and suppressor influences will produce the probability for the emergence of a response. This attractor will be maintained by virtue of large numbers of cells in a recursive proliferation process. Memory will be then a function of the attractor making the system respond within a probabilistic certainty, perceived as memory.

II. Recursive Proliferation Process

Denote $(-)$ a *suppressive* cell and $(+)$ an *auto-reactive* cell. At starting time $t = 0$ be given an initial collection $\mathcal{C}$ of $(-)$ and $(+)$ cells. At each time step $t = 1, 2, \ldots$, one cell is drawn randomly from $\mathcal{C}$ and is put back together with one additional cell of the same type into $\mathcal{C}$. That is, the probability to draw from $\mathcal{C}$ a $(-)$ cell is

$$p = \frac{\text{number of } (-) \text{ cells in } \mathcal{C}}{\text{number of cells in } \mathcal{C}}$$

and to draw a $(+)$ cell

$$1 - p = \frac{\text{number of } (+) \text{ cells in } \mathcal{C}}{\text{number of cells in } \mathcal{C}},$$

respectively (see Fig. 1). The collection $\mathcal{C}$ is dominated by suppressive cells if $p > 1/2$ and dominated by auto-reactive cells if $p < 1/2$, respectively. In Salazar-Bañuelos' immune

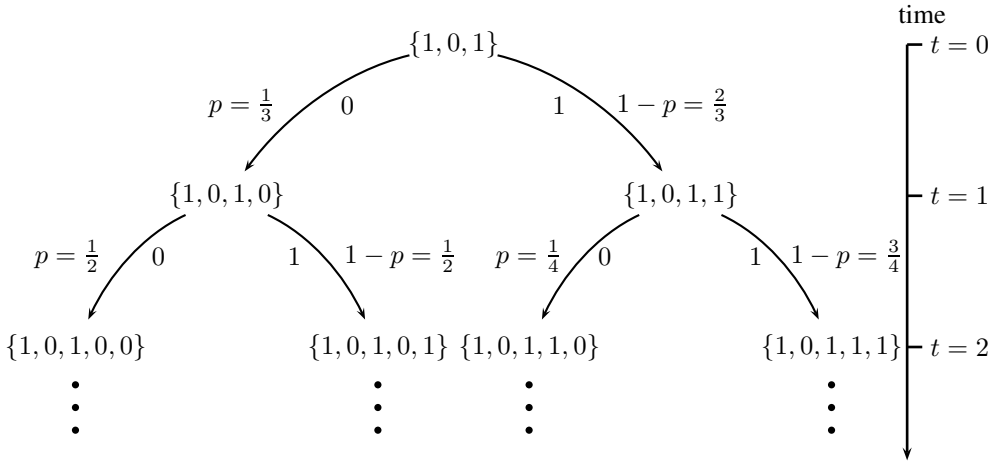


Figure 1. For the sake of clarity a $(-)$ cell is denoted as 0 and a $(+)$ cell as 1. In this example the initial collection $\mathcal{C}$ at time $t = 0$ consists of $\{1, 0, 1\}$, that is, one suppressive and two auto-reactive cells. The probability to add at time $t = 1$ a 0 to $\mathcal{C}$ is $1/3$ and to add a 1 is $2/3$. At time $t = 1$ the collection $\mathcal{C}$ can either consists of $\{1, 0, 1, 0\}$ or $\{1, 0, 1, 1\}$. The process is continued an infinite number of times.

model [11] this cell adding mechanism is called *recursive proliferation process* and is used as the underlying principle to model immune memory.

A closer investigation of this recursive proliferation process reveals, that this problem is a special case of Pólya's urn process [12], [13] which is defined as follows [14]:

> Given an urn which initially contains w white balls and b black balls. At each discrete time step (trial) we select a ball from the urn and then return the ball to the urn along with c new balls of the same color. This process is repeated indefinitely.

Set $c = 1$ and denote a $(-)$ cell as a white ball and a $(+)$ cell as a black ball, then the recursive proliferation process exactly matches with Pólya's urn process.

III. Properties of the Recursive Proliferation Process

Given an initial collection $\mathcal{C}$ of $(-)$ and $(+)$ cells, where w denote the number of $(-)$ cells in $\mathcal{C}$ and b the number of $(+)$ cells in $\mathcal{C}$. Let X_i be a random variable at time (trial) i with outcome 0 when a $(-)$ cell is selected from $\mathcal{C}$ and 1 when a $(+)$ cell is selected. Mathematically, this selection process is a sequence $\mathbf{X} = \{X_1, X_2, X_3, \ldots\}$ of binary random variables indexed by time. Let Y_n denotes the number of $(+)$ cells selected in the first n time steps, that is,

$$Y_n = \sum_{i=1}^{n} X_i, \tag{1}$$

then $\mathbf{Y} = \{Y_1, Y_2, Y_3, \ldots, \}$ is the partial sum process associated with $\mathbf{X}$. The proportion of $(+)$ cells in the collection $\mathcal{C}$ after n trials is

$$Z_n \quad = \quad \frac{b + cY_n}{b + w + c\,n}. \tag{2}$$

It is known [14] that when $c > 0$, Z_n converges with probability 1 to a random variable U that has the beta distribution with

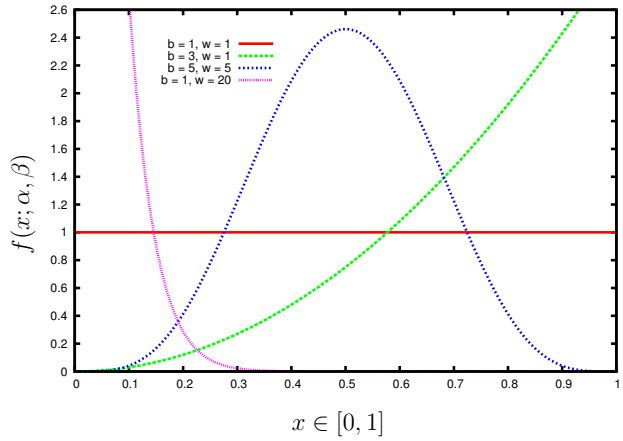


Figure 2. Probability density function of the beta distribution for different values of α and β, where $\alpha := b$ and $\beta := w$.

left parameter b/c and right parameter w/c. The probability density function of the beta distribution is

$$f(x; \alpha, \beta) = \frac{\Gamma(\alpha + \beta)}{\Gamma(\alpha)\Gamma(\beta)} x^{\alpha - 1}(1 - x)^{\beta - 1}, \tag{3}$$

where Γ is the gamma function (see Fig. 2). Suppose an initial collection $\mathcal{C}$ is given with one $(-)$ cell and one $(+)$ cell, then U is uniformly distributed (see Fig. 2). Hence, each proportion of $(-)$ and $(+)$ cells in $\mathcal{C}$ can occur with equal probability after some time steps. In point of fact, Eggenberger and Pólya [12] showed that in the limit the ratio of white balls to black balls could be any number between 0 and infinity. In other words, any feasible proportion of $(-)$ and $(+)$ cells in $\mathcal{C}$ can occur after a finite number of time steps. The interesting property of this stochastic process is however, that early events determine the ultimate outcome. This is also mentioned in [13]:

> "It is curious that the limiting properties of a Pólya-Eggenberger urn depend critically on the initial conditions."

The phenomenon can also be observed in the performed experiments provided in the following section.

IV. Experiments

As shown in Section III, any feasible proportion of $(-)$ cells and $(+)$ cells can be attained after an finite time steps. This is based on the fact that the random variable converges to a beta distribution, where the parameters of the distribution are determined by the number of $(-)$ and $(+)$ cells in the initial collection $\mathcal{C}$. This fact is demonstrated empirically in the following section.

A. Different Proportions of $(-)$ and $(+)$ Cells in the Initial Collection

In this experiment different proportions of $(-)$ and $(+)$ cells in the initial collection $\mathcal{C}$ are setup and the evolved proportions are plotted over time. For the sake of conformity, denote p the relative proportion of $(-)$ cells in $\mathcal{C}$ and $1-p$ the relative proportion of $(+)$ cells, respectively. One can observe that the experiments nicely match with the mathematical explanation provided in Section III. For an initial ratio of $1:1$ of suppressive and auto-reactive cells, the final relative proportion of those cells evolved overtime (that is the value of p) can result in any feasible ratio (see Fig. 3). In other words, the immune system can reach any state of the number of suppressive and auto-reactive cells. If the initial ratio is biased towards more suppressive or auto-reactive cells such as depicted in Figure 4, then still any final ratio can be evolved over time. However, the probability to evolve over time much more suppressive than auto-reactive cells is far higher. Observe that the probability density of the beta distribution for $w = 20$ and $b = 1$ that is 20 suppressive cells and 1 auto-reactive cell exponentially increases.

V. The Simulation

In this section the simulation presented in [11] is summarized. The core of this simulation is based on the recursive proliferation process, that is, Pólya's urn process. However, dynamical interactions of cells are also implemented for having a more realistic immune model.

A two-dimensional space is formed by discrete units representing cells in a tissue. The space is divided into a central restricted area, which simulates the central lymphatic organs (principally the bone marrow), and remaining space, which simulates peripheral non-lymphatic tissue. The cells (patches) produce, dissipate, and diffuse *chemicals*, which simulate the production of mediators or lymphokines by neighboring cells. Independent agents are created by simulating cells from the lymphatic system. These agents are divided into *stem cells* and *peripheral lymphocytes*, both of which are composed of two *sub-clones*: 1) an auto-reactive $(+)$ *sub-clone* that interacts with the *cells* by fractionally increasing the *chemicals* in the patch where the *cells* are located and 2) a suppressive $(-)$ *sub-clone* that decreases these *chemicals. Stem cells* are generated by recursion as previously described, starting from the creation of $(+)$ and $(-)$ *sub-clones* at a ratio of $3:1$, which favors the predominance of $(+)$ *sub-clones*. All *cells* and interactions are specific for one antigen, and all simulations take place from these initial conditions.

A. Clonal Expansion

This step simulates the origin of the lymphatic system from a few "mother cells" in early ontogeny, creating a colony of cells allocated to the central lymphatic system, mainly the *bone marrow*, from which all other lymphatic cells will be produced over the life of the individual. Because the recursive stochastic process that generates this colony forms both $(+)$ and $(-)$ *sub-clones*, the proportion of *sub-clones* will fluctuate with decreasing amplitude as the number of agents increases, reaching stability in direct proportion to the numbers of agents created. This colony does not migrate and does not interact with cells in the *peripheral system*, resembling the population of progenitor cells in the bone marrow. The functions described below can be simulated by the program.

B. Clonal Selection

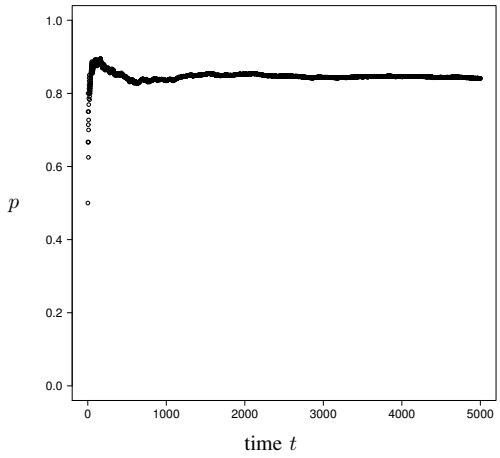
The initial condition was designed to favor a predominance of $(+)$ *sub-clones* over $(-)$ *sub-clones*, as seen when clonal selection does not take place. Clonal selection reverses this situation by eliminating a proportion of the $(+)$ *sub-clones* while clonal expansion is taking place, thus simulating the elimination of auto-reactive clones in the thymus [15].

C. Proliferation

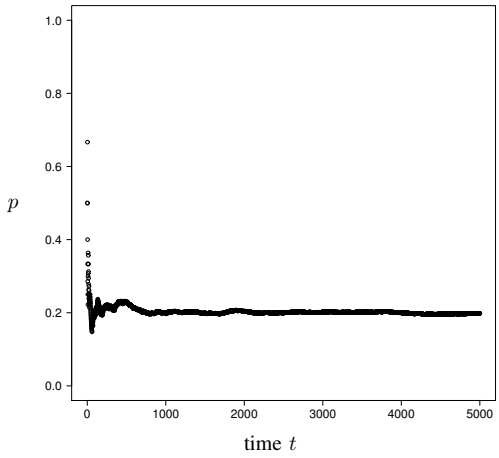
The *stem cells* in the *bone marrow* do not migrate to the periphery, but are the precursors of *peripheral lymphocytes*, which are identical to *stem cells* in all aspects except that they do migrate to the *periphery* and move randomly, interacting with the *cells* (patches) that they contact in their migration and decreasing or increasing the production of chemicals accordingly. The production of *peripheral lymphocytes* also is done by recursion; therefore the proportion of $(+)$ to $(-)$ *sub-clones* in the *peripheral lymphocytes* will mirror that proportion in the *stem cells*, only at higher numbers. The probability of discrepancy between the proportion of *sub-clones* in the *bone marrow* and the *periphery* will increase as the number of *stem cells* decreases.

D. Lymphatic-Ablation

This function eliminates all *peripheral lymphocytes*, leaving the *stem cell* colony intact in the *bone marrow*. This is used to illustrate that the system is robust, even for events affecting the entire *peripheral lymphocyte* population, since the recursive production of *peripheral lymphocytes* in the *bone marrow* will repopulate the *peripheral system*, maintaining *sub-clone* proportions similar to that of their progenitors. This highlights the fact that the system will be robust in direct proportion to the number of *stem cells* in the *bone marrow*.

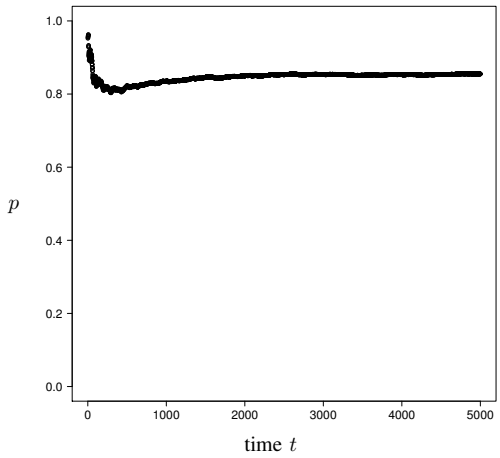


(a) Run 1 with initial collection $\mathcal{C} = \{(-), (+)\}$.

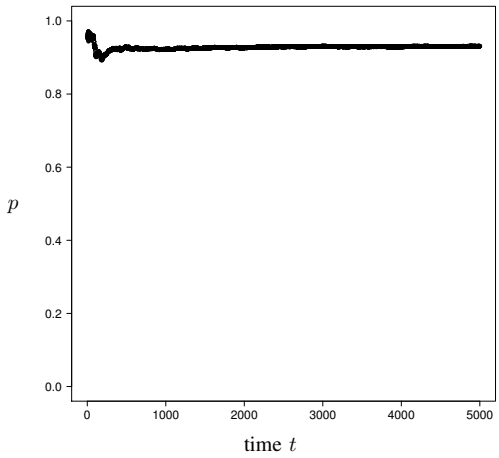


(b) Run 2 with initial collection $\mathcal{C} = \{(-), (+)\}$.

Figure 3. Initial collection consists of $\{(-), (+)\}$. After approximately 1000 time steps, the relative proportion of $(-)$ cells and $(+)$ cells convergences to some value p, where p denotes the relative proportion of $(-)$ cells in the collection. One can observe that the relative proportion of $(-)$ cells can vary between any value from $[0, 1]$. Additionally one can observe that early proportions (within the first 1000 time steps) of $(-)$ cells and $(+)$ determine the final value of p.



(a) Run 1 with initial collection $\mathcal{C} = \{20 \times (-), (+)\}$.



(b) Run 2 with initial collection $\mathcal{C} = \{20 \times (-), (+)\}$.

Figure 4. In this run the initial collection is skewed, that is, $\mathcal{C} = \{20 \times (-), (+)\}$. One can observe that the value of p prevalently converges to values in the interval $[0.8, 1]$. This is not a great surprise because the corresponding probability density of the beta distribution exponentially increases in that interval. Loosely speaking, the collection will be dominated on average by suppressive cells.

E. Danger

This function produces an instant increase in the *chemicals* released by the *cells* of an specific and defined area in the *periphery*. This simulates the effect of an acute injury that produces a focus of inflammation and shows how the system behaves according to the several situations that can take place.

F. Observations

We can observe the emergence of a phenomenon where critical local conditions reach a threshold. While the location and time for this phenomenon is undetermined, the probability for this to occur is directly influenced by the proportions between positive and negative factors, this proportion works as an attractor to the system.

G. Visualized Simulation Results

Figures 5 and 6 show the output of simulations[1] where the recursive proliferation of $(-)$ and $(+)$ cells follows the rule of Pólya's urn process and ends with either with a predominance of auto-reactive or suppressive cells.

Figure 5(a), shows the emergence of a self generating process once local critical conditions are reached. This process escalates with time (cf. Fig. 5(b)). By iterating the simulation, eliminating all cells and reconstituting them from the original population of clones, a similar result can be observed

[1]Written in NetLogo (`http://ccl.northwestern.edu/netlogo`).

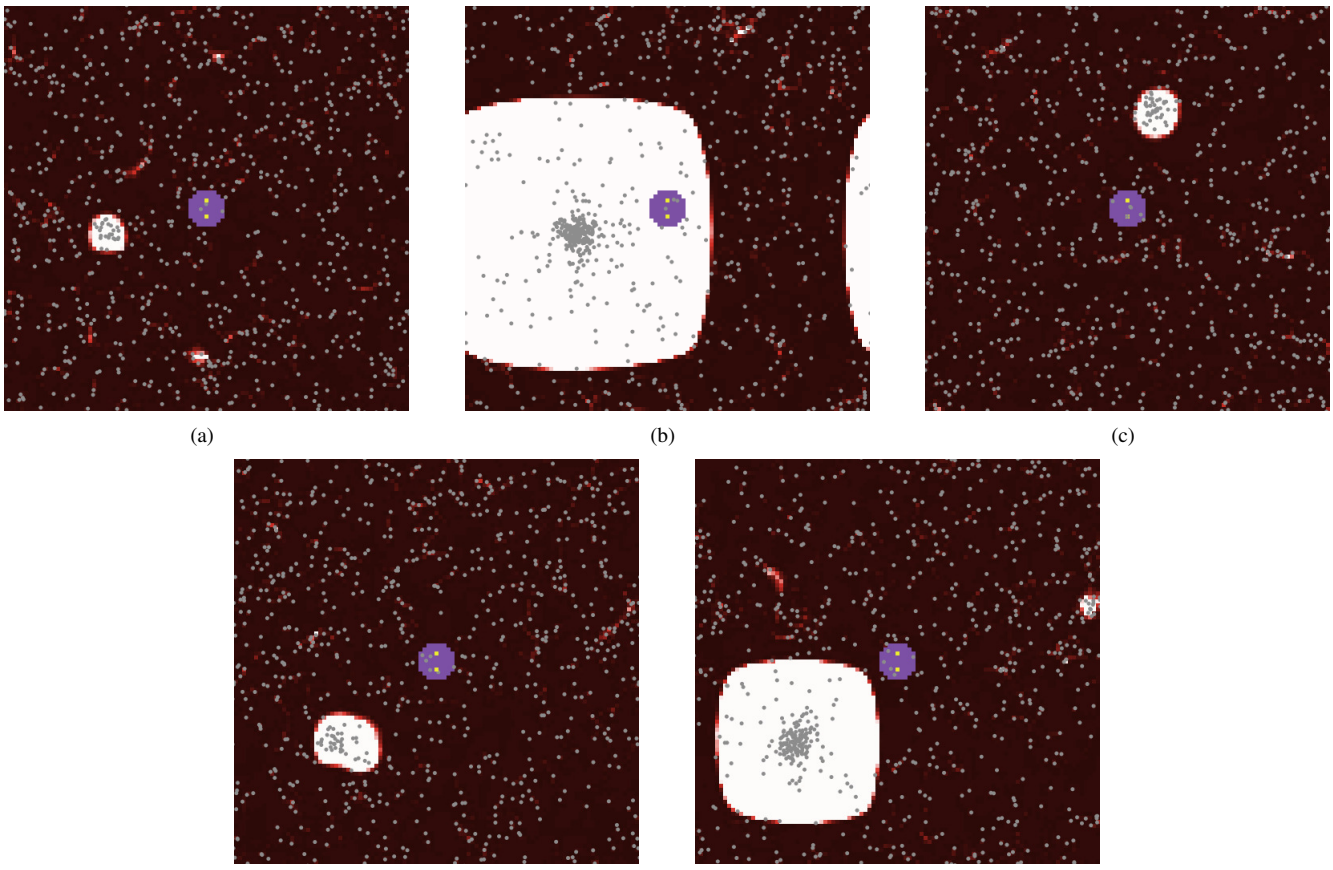


Figure 5. Output of a simulation where the recursive proliferation process ends in a predominance of auto-reactive cells.

(cf. Fig 5(c)). If an external factor produces critical local conditions as is seen here by increasing the mediator locally "Danger" (cf. Fig 5(d)) the increase in activity escalates indistinctly as when it emerges from cell activity (cf. Fig 5(e)).

Figure 6 shows the case when early in the recursive generation of clones, an elimination of positive clones takes place (Clonal Selection), ending in a slight predominance of negative or suppressive clones. In this case although local increase of activity can be observed all over the screen, this activity does not reach critical conditions (cf. Fig 6(a)), even after a period of time (cf. Fig 6(b)). The elimination of cells and their reconstitution based on the original clone selection, reproduce the same lack of emergence (cf. Fig 6(c)). If in this case we increase the mediator locally to reach critical levels "Danger" (cf. Fig 6(d)), then similar to the previous simulation, the increase in activity is down-regulated and prevented for escalation (cf. Fig 6(e)). This two examples indicates that the directions of the responses are kept within a certain level of predictability by the proportions produced by the recursive process, working as an attractor. the inclusion of Danger, highlights the fact that external factors other than cells can trigger a response, yet the result of this response will be a function of the attractor, and exemplified here by the two different outcomes in the evolution of identical Danger factors. The consistence of the response based in the attractor is what constitute the memory of the system, both by producing or preventing the spontaneous emergence of the phenomenon by cell activity, and by the escalation or control of external (Danger) factors.

VI. Discussion

The complexity of biological phenomena prevents their explanation by the reductionist approach. A problem with this approach is that it investigates components and interactions isolated from the totality of their environment, wherein everything is relevant to everything. Another problem is the impossibility of knowing the complete set of relevant factors with their specific weights and temporal status, making a complete logical-mathematical formalization of the phenomena at the cellular and molecular level practically impossible. Here, we have taken the approach of considering that to unveil the mechanisms behind a biological phenomenon, the phenomenon itself needs to be delimited. In other words, we should abandon attempts to find a mechanism capable of explaining how the Immune System (a concept) works, for the investigation of the mechanisms responsible for the phenomena itself as is our case here with immune memory, avoiding a self-referential and metaphorical concept, as is the case with the Immune System.

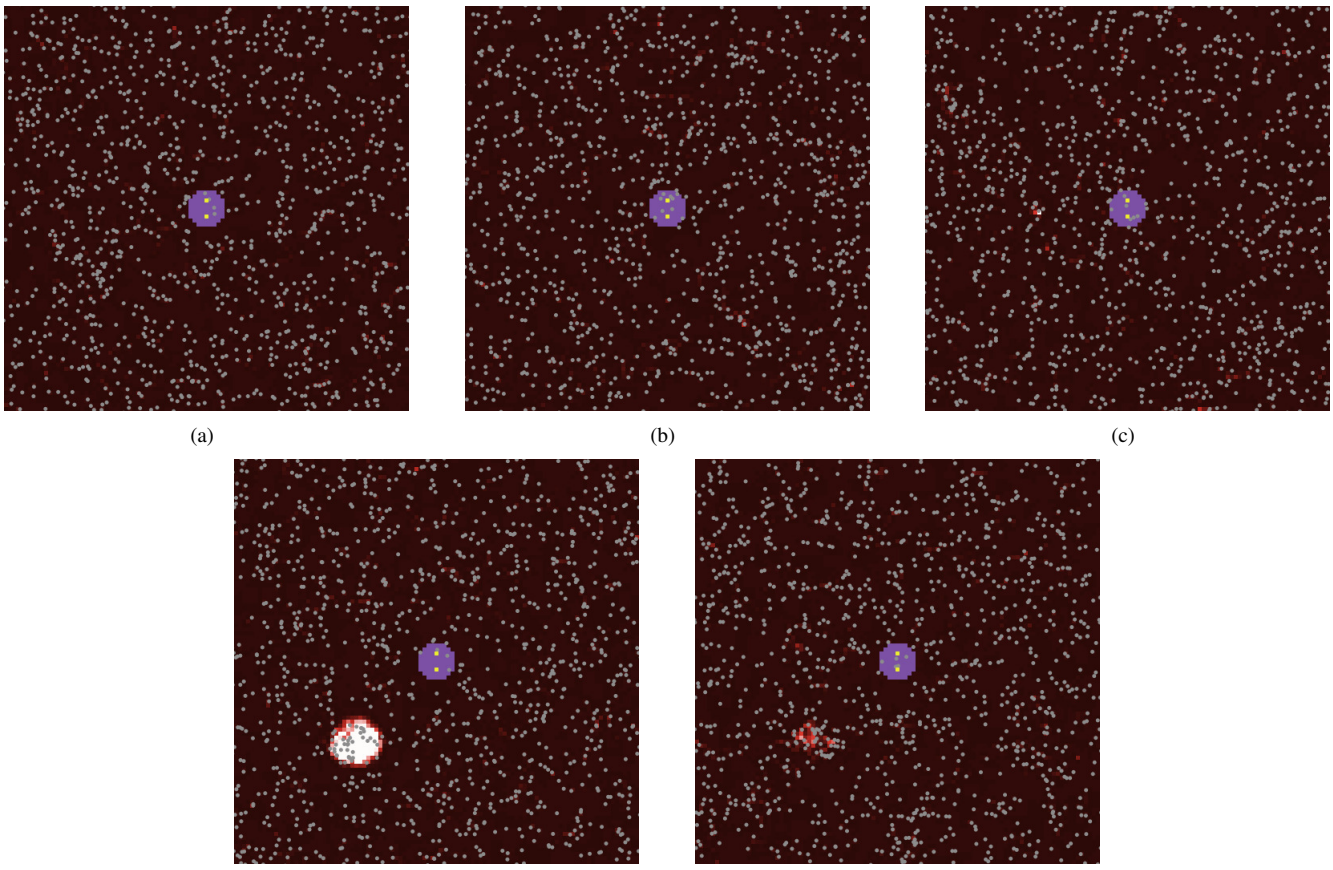


Figure 6. Output of a simulation where the recursive proliferation process ends in a predominance of suppressive cells.

Immune responses depend upon cellular and molecular interactions at the dynamic (microscopic) level of the system. However, these responses are not themselves cellular or molecular events, but rather they are new phenomena that emerge from these interactions in a holistic way, such as the well characterized phenomenon known as inflammation. In this view, immune memory is the result of the mechanisms that made previous events relevant for either the occurrence or prevention of inflammation as an emergent phenomenon.

The emergence of inflammation from the background microscopic level is the phenomenon itself. In this concept, the relevant factor for an immune response is that which triggers the emergence of the response (Butterfly Phenomena). Any factor can be a potential trigger, because at the microscopic level, everything is relevant to everything, whether it be a cell, molecule, or any other factor. In other words, any entity have the same ontologic value with respect to the emergence of the phenomena, even though the entities may have different ontologic values among themselves with respect to their individual interactions at the microscopic (dynamic) level. For the purpose of the emergence of a phenomenon, it follows that we can abstract the microscopic level into interactions that either increase $(+)$ or decrease $(-)$ the probability of the system for reaching the threshold for emergence of inflammation. In our example, the creation of the attractor by recursive proliferation processes is based on cellular clones as factors. However, it should be indicated that for the emergence of inflammation, such factors can include not only cells and molecules, but also any factor, including external ones. These factors become relevant if they overcome the attractor and trigger the emergence of inflammation. An example is the case of tissue injury (represented in this model as "Danger"), which does not constitute autoimmunity, but is the response to the local increase of pro-inflammatory factors that reach a threshold. Abstracting the microscopic level to positive or negative interactions for the emergence of the response has two implications. First, this abstraction permits the inclusion of all factors relevant for the emergence of inflammation, even those explicitly unknown to us, but whose precise description is irrelevant for the emergence of inflammation because they only have the possibilities of being pro-inflammatory, anti-inflammatory or neutral. Second, this abstraction permits the formalization for the generation of clones, which we have done here with the special case of Pólya's urn process.

Similar to any other emergent phenomenon from a complex, dynamical system, inflammation depends upon reaching local critical conditions, in this case, the equilibrium between pro-inflammatory and anti-inflammatory factors. Although such

equilibrium does not determine (in the sense of causality) the phenomenon, it does determine its probability, and this probability is kept relatively constant by virtue of the recursive stochastic process of cell proliferation reaching very large numbers, as shown here with the special case of Pólya's urn process. Whereas this equilibrium explains the consistency and predictability of the direction of future responses, such prediction is not deterministic as it is the case for antigen-driven responses in the classical explanation of immune memory, but rather is probabilistic. Because the probability has a small variation, it creates the impression of causality, interpreted as memory. In the mechanism here, immune memory is function of the attractor, and any change in this memory requires changing the attractor set point.

VII. Model Review

We consider that our model provides an insight to the fact that any immune responses occur on top of a system that has been previously created, evolved and changed as a consequence of a particular history. This system, which is primordially suppressive (dominant tolerance), provides the background and set point from which all immune responses occur, from physical trauma to autoimmunity. The probability for interactions to become relevant for the generation of inflammation is set by the systems previous condition. For instance, whether or not the presence of tissue specific antibodies (or any other factor associated with the development of autoimmunity) will lead to an autoimmune disease will depend upon whether their contribution can reach a threshold and overcome the attractor; however for exactly the same antibodies, the outcome can be different depending on the attractor set point. One attractor set point could produce a situation in which autoantibodies are relevant for the development of autoimmunity, whereas another set point could produce a situation in which they are irrelevant, as in a healthy carrier of autoantibodies. Our model does not ignore the importance of specific cellular or molecular interactions in the development of the immune response, but rather explains why these interactions become relevant for the emergence of inflammation.

One important aspect of the lymphatic system is its high turnover, with a constant production of lymphocytes and their elimination by several mechanisms including apoptosis. Although we did not include this in our simulations, the random elimination of agents will not substantially change the proportion of agents. In fact, after elimination of all peripheral lymphocytes in the function "lymphocyte ablation", the agents are regenerated by recursion from the clones in the bone marrow, thus explaining the robustness of the system. In contrast to the case with peripheral agents, we should consider that the resilience of the system, and in consequence its memory, is in direct relation with the number of clones in the bone marrow. As well, changes in the proportion of reactive and suppressor clones in the bone marrow can change immunological memory and increase or decrease the possibilities for inflammation to emerge. Therefore, we would expect that physical changes in the bone marrow would lead to changes in immunological memory. These changes in the dynamics of the system are interesting aspects of the model to explore further.

VIII. Summary

We explored and investigated Salazar-Bañuelos' immune model which suggests that immunological memory is a function of a recursive proliferation process. In this model the relative proportion of auto-reactive and suppressive cells will set the emergence of a reactive or suppressive immune response. We showed that the underlying principle of this model can be considered as a special case of Pólya's urn process. This crucial insight revealed and explained the emergent functionality of the model. It has not escaped our notice that the model consists of dynamical interactions of cells which were so far not considered in terms of the urn process. In future work these dynamical interactions have to be explored and linked to the principle of Pólya's urn process for obtaining a complete picture of this exciting model.

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