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In silico approach for viral mutations and sustainability of immunizations

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Abstract
In this paper we use virtual samples of individuals and a dynamical modeling proposed in a previous study to study the behavior of immune memory against antigenic mutation. Our results suggest that the sustainability of the immunizations is not a *stochastic* process, what contradicts the current opinion. We show that what may cause an apparent random behavior of the immune memory is the viral variability. This result can be important to investigate the durability of vaccines and immunizations.
Keywords: immune memory, computational immunology, viral mutation, stochasticity, vaccine, B cells.

I. Introduction

Immunoinformatics, also known as computational immunology is a new area of research that combines analytical tools and computational models that focus on the study of the immune system. In recent decades, models have been widely used to describe biological systems, mainly to investigate global behaviors generated by cooperative and collective behavior of the components of these systems. More recently, several models were developed to study the dynamics of immune responses, with the purpose of comparing the results obtained by simulations, with the experimental results, so the connection between the existing theories on the functioning of the system and the available results can be adequately established (Murugan & Dai, 2005; Castiglione & Piccoli, 2007; Davies & Flower, 2007; Sollner, 2006; Ribeiro et al., 2008). From an immunological point of view, these models contribute to a better understanding of cooperative phenomena, as well as they lead to better understanding of the dynamics of systems out of equilibrium. Mathematical formalization of the functioning of the immune system is essential to reproduce, with computer systems, some of its key biological characteristics and skills, such as the ability of pattern recognition, information processing, adaptation, learning, memory, self-organization and cognition.

Within this scenario, in 2001, Lagreca et al. proposed a model that uses techniques of multi-spin coding and iterative solution of equations of evolution (coupled maps), allowing the global processing of a system of higher dimensions. The authors showed that the model is capable of storing the information of foreign antigens to which the immune system has been previously exposed. However, the results obtained by these authors for the temporal evolution of clones, include only the B cells, not taking into account the antibodies population soluble in the blood. In 2006, one of the present authors has proposed (Castro, 2006) an extension of the Lagreca model, including the populations of antibodies. With this assumption, we considered not only the immunoglobulins attached to the surfaces of the B cells, but also the antibodies scattered in serum, that is, the temporal evolution of the populations of secreted antibodies is considered, to simulate the role in mediation of the global control of cell differentiation and of immunological memory (Lagreca et al., 2001; de Castro, 2005, 2006, 2007). In that work, our approach showed that the soluble antibodies alter the global properties of the network, diminishing the memory capacity of the system. According to our immuno-computational model, the absence or reduction of the production of antibodies favors the global maintenance of the immunizations. This result contrasts with the results obtained by Johansson & Lycke (2001), who stated that the antibodies do not affect the maintenance of immunological memory.

Without considering terms of antigen mutation, this same extension (de Castro, 2005, 2006, 2007) also led us to suggest a total randomicity for the memory lifetime, in order to maintain homeostasis of the system (Roitt et al., 1998; Abbas et al., 2000; Alberts et al., 2007; Tarlinton et al., 2008). This random behavior was also recently proposed by Tarlinton et al. (2008). In our earlier work (de Castro, 2005, 2006, 2007), the results indicate that, in order to keep the equilibrium of the immune system, some populations of memory B cells must vanish so that others are raised and this process seemed completely random. However, the results shown in this study suggest that the durability of immunological memory and the *raised-vanished* process is strongly dependent on the variability of viral populations.

The aim of this work is to show that the lifetimes of immune memory populations are not random, only the antigenic variability from which they depend upon is a random feature, resulting in an apparent randomicity to the lifespan of B memory cells.

II. Materials and methods

We have used a set of equations (coupled maps) that describe the main interactions in the immune system between entities that interact through key-lock match, i.e., that specifically recognize each other. This set of equations is solved iteratively, considering the viral mutations as initial conditions (de Castro, 2005, 2006, 2007).

In our approach, the molecular receptors of B cells are represented by bit-strings with diversity of 2^B, where B is the number of bits in the string (Perelson et al., 1996; Perelson & Weisbush, 1997). The individual components of the immune system represented in the model are the B cells, the antibodies and the antigens. The B cells (clones) are characterized by its surface receptor and modeled by a binary string. The epitopes – portions of an antigen that can be connected by the B cell receptor (BCR) – are also represented by bit-strings. The antibodies have receptors (paratopes) that are represented by the same bit-string that models the BCR of the B cell that produced them (Burnet, 1959; Jerne, 1974ab; Celada & Seiden, 1992; Seiden & Celada, 1992; Reth, 1995; Levy, 1996; Perelson et al., 1996; Playfair & Chain, 2005).

Each string shape is associated with an integer σ ($0 \leq \sigma \leq \mathrm{M} = 2^B - 1$) that represents each of the clones, antigens or antibodies. The complementary form of σ is obtained by $\bar{\sigma} = M - \sigma$, and the temporal evolution of the concentrations of different populations of cells, antigens and antibodies is obtained as a function of the integer variables σ and t, by direct iteration.

Using virtual samples – representing hypothetically 10 individuals (mammals) with the same initial conditions – we inoculated *in silico* each one of the 10 samples with different viral populations (110, 250 and 350) with fixed concentration, where the virus strains occur at intervals of 1000 time steps, that is, at each 1000 time steps a new viral population, different from the preceding one, is injected in the sample. When a new antigen is introduced *in maquina*, its connections with all other entities of the system are obtained by a random number generator (de Castro, 2005, 2006, 2007).

Changing the seed of the random number generator, the bits in the bit-strings are flipped and, taking into account that in our approach the bit-strings represent the antigenic variability, the bits changes represent, therefore, the corresponding viral mutations. Thus, in order to simulate the influence of viral mutation on the duration of immunological memory, the seed of the number generator is altered for each of the 10 samples. Figure 1 shows the design of the experiments.

III. Results and Discussion

To investigate the relationship between the viral variability and the memory time of the population of lymphocytes that recognized a certain species of virus, 10 virtual samples were used – representing 10 identical individuals what, in our approach, corresponds to keep the amount of interaction of the coupled maps with the same initial conditions in all samples. A lifetime equal to 110,000 time steps was chosen for the individuals.

To simulate the viral strains, at each 1,000 time steps, a new dose of virus was administered. Therefore, in this experiment were injected *in maquina* in the samples (individuals) 110 *distinct* viral populations and to represent the inoculation of *mutated* viral populations in each individual, the seed for the random number generator in the coupled maps was changed for each one of the 10 samples. It is important to clarify that in our approach, *distinct* viral populations are populations of different species and *mutated* viral populations are genetic variations of the same population.

Figure 1 shows more clearly the entities used to simulate the behavior of memory against the antigenic variability. In the scheme, for example, the virus identified by V1E 2 is a mutation of the virus V1E 1 (both belong to the same original population, who suffered mutation) and the virus V2E 1 is distinct of virus V1E 1 (belonging to viral populations of different species).

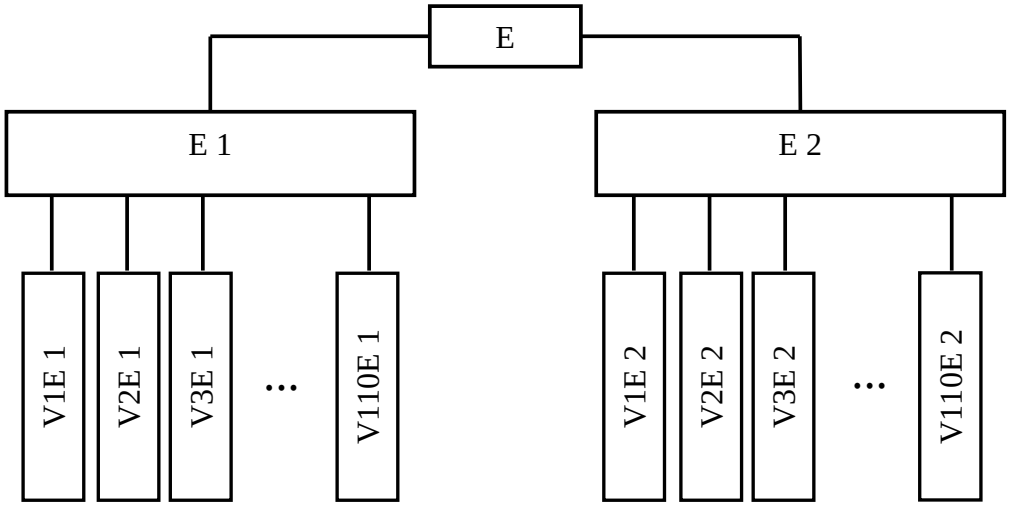

Figure 1. Design of inoculations of viral populations in the samples for the experiment E.

In Figure 2(a) - (j) it is possible to visualize separately the behavior of each one of the 10 samples, when we administer, in maquina, 110 injections (experiment E).

This results suggest that the sustainability of the immunization is dependent of the on viral variability and that the lifetimes of the memory populations are not completely random, but that the antigenic variability of which they depend on causes an apparent randomicity to the lifespan of memory lymphocytes.

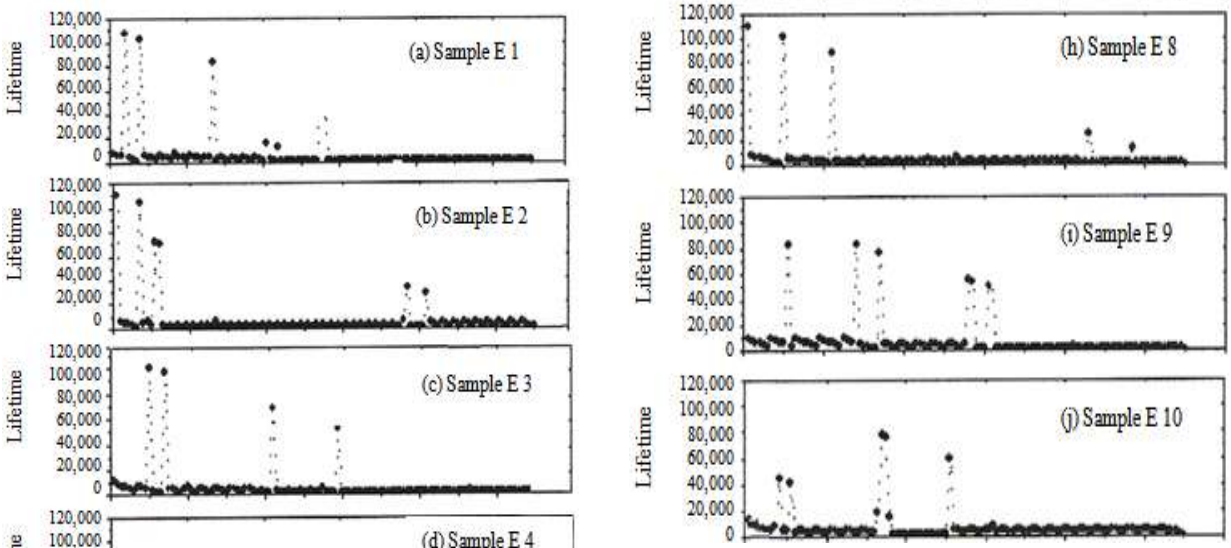

Figure 2. Lifetime of the clonal populations in each sample.

IV. Conclusions

In this article we present results that indicate that, besides the influence of populations of soluble antibodies, another factor that may be decisive for the durability of immunological memory is the antigenic mutation of the viral population, which brings on a reaction of the system.

We also show that the lifetimes of the memory clones are not random, but the antigenic variability from which they depend originates an apparent randomicity to the lifespan of the B memory cells. As a consequence, our results indicate that the maintenance of the immune memory and its relation with the mutating antigens can mistakely induce the wrong deduction of a stochasticity hypothesis for the sustainability of the immunizations.

Our results show that what presents a random aspect is the mutation of the viral species, resulting in an apparent unpredictable duration for the lifetime of the memory clones.

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