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Random behaviors in the process of immunological memory

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Abstract

We have used a system of coupled maps to study random variations in the immune memory process and the possible network immune memory that can remain for long time in the absence of antigenic stimulation through the idiotypic–anti-idiotypic interactions. Our approach describes the behavior of the immune network proposed by Jerne and considers that the cell–cell interactions routine results in maintenance of memory in a dynamic equilibrium. The critical values of the concentrations of antigens for the validity of the model and a phases diagram with three different phases are also obtained.

Keywords: Immune memory; Antibodies evolution; Memory-regenerating

1. Introduction

In the clonal selection theory proposed by Burnet [1–3], when a living body is exposed to an antigen (invader), some subpopulations of its bone marrow (B lymphocytes) respond through antibodies production. Each cell secretes only one kind of antibody, which is relatively specific for the antigen. By binding to these antibodies (receptors) and with a second signal, such as the T-helper cells [4–7], the antigen stimulates the proliferation of B-cells and antibodies secretion. While B-cells secrete antibodies, the T-cells play a central role in the regulation of the B-cells response and are fundamental in cell mediated immune responses. Lymphocytes, in addition of proliferating and differentiating into plasma cells, also differentiate into long-lived memory populations. Memory populations circulate through blood, lymph and tissues and, when exposed to a second antigenic stimulus differentiate into large lymphocytes capable of producing high affinity antibodies, pre-selected by the specific antigen.

Basically, there are two theories to explain the immune memory. The first considers that after the expansion of the B-cells, there occurs the formation of plasma cell and memory cells. The second hypothesis, due Jerne [8,9], considers that the immune system presents its memory and response capacity to the second invasion of

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antigens as an self-organization of the system. This allows the growth of cells populations that survive for a long time not a specific type cell that has a longer life than the other cells of the organism.

Different models based on clone dynamics have been proposed to describe cell proliferation and death, interaction between different cells, antibody secretion and interaction with antigens. The Celada–Seiden model [10–13], for example, is one of the most detailed lattice gas automata for the immune system response. Its complexity derives from the fact that in addition to the different cellular populations considered, also a molecular representation of the cell and molecular binding site is given in term of specific recognition between bit strings. The match between antigen and lymphocyte receptors is given considering the number of complementary bits in the bit-strings. For example, if the lymphocyte B is equipped with the binary string 00010101 ($l = 8$) and the antigen is represented by the string 11101010, then the probability to trigger a response is very high. In this model, the bit-string match is not required to be perfect, i.e., some mismatches are allowed like, for example, one bit from the eight bit string in the above mentioned example.

In this paper, we used an approach for immune system considering structural mechanisms of regulation that were not contemplated in the simplified model of bit-string proposed by Lagreca et al. [14]. In our approach, not only we treat the antibodies bound to the surface of the B-cells (surface receptors), but also the populations of soluble antibodies in the blood (antibodies secreted by mature B-cells), thus making the proposed model more similar to a real immune system.

In our model, we defined *clones* as an ensemble of B-cells, and the populations of antibodies are treated separately, to more appropriately study the evolution of the components of the immune system. Consequently, the results for the time evolution of the clones reported in [14] present only the time evolution of B-cells and not the evolution of the secreted antibodies populations. This is due to the fact that the set of coupled maps of their model considers only the antibodies bound to the surface of B-cells and not the dispersed antibodies in the serum. Moreover, the regulation of the immune response in the previous model is just done by apoptosis (programmed cell death) and by the Verhulst-like factor. It is not considered the fundamental role of the antibodies in the mediation of the global control of the differentiation of the B-cells. The Verhulst-like factor produces a local control of the populations of clones (B-cells) considering the several mechanisms of regulation. However, globally the immunological memory of the system [15] is strongly affected by the populations of soluble antibodies in the blood, what was contemplated in this work.

Our approach allows to model, in a more complete form the generation, maintenance and mechanisms of regulation of the immune memory through a network memory combining the characteristics of Burnet's clonal selection theory and Jerne's network hypothesis, considering the interaction idiotypic-anti-idiotypic proposed for Jerne. We also studied the behavior of the model for concentrations of antigens from 0.0001 to 1.5 and we obtained a diagram for three different phases of the immune system.

In the model presented here, we also considered a modified version of exact enumeration techniques, together with multispin coding [16–19] to allow the control of time evolution of populations over all high-dimensional shape space.

2. The computational model and biological entities

In the model discussed here, the B-cell molecular receptors (BCR) are represented by bit-strings with diversity of 2^B, where B is the number of bits in the strings. The entities present in the model are B-cells, antibodies and antigens. The B-cells are represented by clones, each clone being characterized by its surface receptor which is modeled by a binary string of B bits.

The epitopes portion of an antigen that can be bonded by the B-cell receptor (BCR) are also represented by bit-strings [20,21]. The antibodies have a receptor (paratope) that is represented by the same string as the BCR of the parent B-cell which produced them [4].

Each bit-string (shape) is associated to an integer σ ($0 \leqslant \sigma \leqslant M = 2^B - 1$), corresponding to each clone, antigen or antibody; the neighbors to a given σ are obtained by the Boolean function $\sigma_i = (2^i\ x$ or $\sigma)$. The complementary shape of σ is obtained as $\overline{\sigma_i} = M - \sigma$ and, through direct interaction, the time evolution of the concentrations of several populations are obtained as functions of integer variables σ and t.

The equations that describe the behavior of the populations of B-cell clones $y(\sigma,t)$ are iterates, for different parameters and initial conditions: