

A MULTI-AGENT SYSTEM TO SIMULATE AN APOPTOSIS MODEL OF B-CD5 CELLS

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ABSTRACT

Simulations of immune mechanisms become more and more numerous and accurate. The aim of such simulations is to reproduce in-machina, in-vitro and in-vivo experimentation. Then, it is possible to test the cell models and the consequences of their interactions. Thus, comparing the simulation results with the experimentation results experiences the validity of the model.

A distributed and cooperative system can advantageously be modeled by a multiagent system. Like this, the abstraction needed to model these phenomena is reduced. The immune system is included into highly cooperative and distributed systems. Moreover, it is quite easy to add or remove entities in the model and to improve their behaviors.

In this paper, we present a multiagent system that reproduces in-machina, a set of in-vitro experimentation on the apoptosis phenomena.

1. INTRODUCTION

The in-vitro experimentation, which have been made by the University Medical School of Brest, aim to bring up the B cell properties presenting the CD5 and CD72 surface molecules [JAM96]. The purpose is to find out the role of the CD5 receptor from which these B cells proliferate or, on the contrary, destroy themselves by apoptosis. These mechanisms are not well known and their dysfunction seems to be involved into the Chronic Lymphocytic Leukemia (CLL) [BOU80] [ROY80]. Therefore, we have used a simulation to test the hypothesis on the B-CD5 cell behaviors. Those hypotheses have been tested in-machina under different conditions and brought up their good validity when compared with the in-vitro experimentation.

We will start by a description of in-vitro experimentation made by the Academic Medical School of Brest. We will try to find out the concerned cells, their interactions and the experimentation modalities. Then, we will go on with the multiagent system allowing to model the experimentation. This system is based on an improved version of the model of [BAL97] [BAL98b] already used for different in-vitro simulations [BAL98a]. We focused on the internal biochemical reactions of the B cells according to their bound receptors. We will then work on the results that are made in-machina and compare them with the results that are obtained in-vitro. We will conclude with the limits of our multiagent system.

2. IN-VITRO EXPERIMENTATION DESCRIPTION

The CD5 molecule is expressed by all T cells but also a B cell subset. Resting B cells do not proliferate in response to CD5 ligation whereas cells preactivated with anti-IgM and IL-2 could do so. We specifically studied the effects of anti-CD5 and anti-IgM on apoptosis of CD5+B cells. Both ligation of CD5 or surface IgM (sIgM) resulted in apoptosis, as measured by several techniques. Apoptosis started earlier following ligation of CD5 than with sIgM, and both responses were time-dependent. CD5-induced apoptosis was independent of the epitope recognized or the way the antibody was presented to the B cells. CD5+B cells were more sensitive to apoptosis than CD5-B cells following anti-IgM treatment. Under the same conditions, engagement of CD5 or CD3 expressed by T cells failed to induce apoptosis. Our data indicate differences in the function of CD5 molecules on tonsillar B cells, compared with blood T cells and suggest that cross-linking the CD5-associated antigen receptor on B cell activates specific pathways responsible for apoptosis.

3. MULTIAGENT SYSTEM

In this section, we describe the basis mechanisms of the simulator.

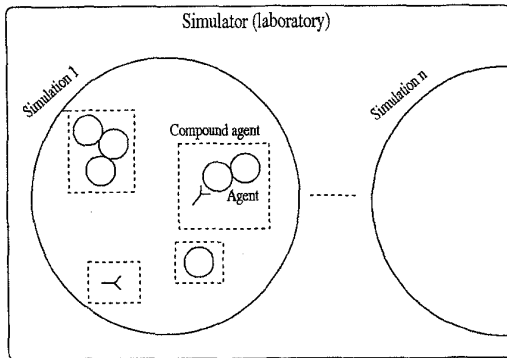


Figure 1. The simulator and its components.

The simulator is made up of agents grouped in compound agents. These agents evolve into a two-dimensional environment. A compound agent is made up of a set of agents. The agents have their own behaviors and receptors. A behavior is an algorithm which describes the way an agent reacts according to the environment stimuli and its internal state. The stimuli come from receptors and the internal state depends on the past of each agent. In practice, each compound agent lives one after another and makes the agents live (Figure 1). For an agent, to live means executing its behavior algorithm. Agents which belong to one compound agent are physically bound by their receptors. To sum up, we can say that a compound agent is considered as a single entity concerning its moves but is a mosaic of agents when talking about individual behaviors. The moves are calculated according to the influences between the receptors. During simulations, the compound agents merge at the time of creation of one or several binds or, on the contrary, divide when bind breaks occur (Figure 2).

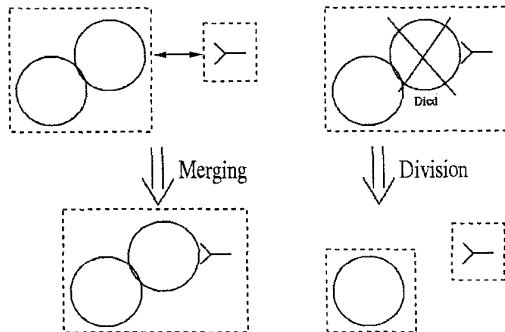


Figure 2. Merging and division of compound agents.

Now, we are going to describe the agents, what they represent and how they are modeled.

4. AGENT MODEL

An agent represents a cell or a molecule from the immune system. With regard to a cell, the agent is dotted with a group of receptors on its surface as well as an often complex internal behavior (Figure 3). In the case of the agent representing a molecule, it is dotted with a set of epitopes. Every agent is subject to the environmental rules. These rules only consist in subjecting the agents through their receptors to the influence of receptors of every other agent. This influence involves a moving of agents (relocation and rotation). The environment physical rules into which the agents evolve are explained in the following section. Moreover, according to the stimuli they received thanks to their receptors, the agents modify their behavior and internal state. For instance, the interleukine B cell receptors involve the division of this cell when bound to the interleukine agent's receptor.

Thus, the agents only communicate through their receptors. As previously seen, even if the agent can bound together, they keep their own behavioral independence. A complex made up of several agents is also an agent (compound agent) dotted with a center of gravity and a mass. This mass is the sum of masses of all its components. A compound agent is a single entity when talking about environment rules.

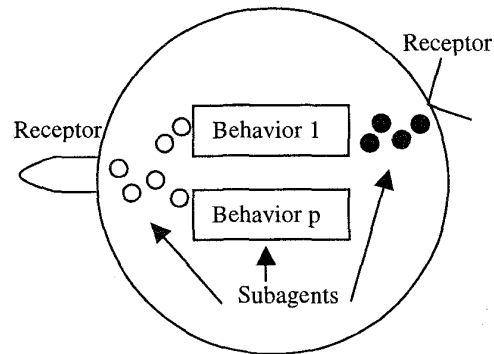


Figure 3. Agent description.

The binds are temporary. In fact, a break of bind may occur in three cases. Firstly, when one of the cells dies, the different bound receptors are free out and are able to bind again. The second case happens when the duration of the bind reaches a determined value. Lastly, in a case of molecule bound to a receptor, the agent internalizes the receptor and its molecule. The agent takes care of the internalization. Then, the internalized receptor and

molecule are both deleted. A new creation of one or several receptors may occur.

The agent is a multiagent too. It is compound with internal agents or subagents that represent the molecules into a cell. This approach reduces the abstraction needed to create a virtual cell and is easier to use than an algorithm for a non-developer person. The subagents have the same properties than a classical agent. They have behaviors, receptors, can merge and divide but they are not compound with sub-subagents. There are two types of subagents. The first consists of agents created by the receptors and the second corresponds to agents modeling and simulating behaviors (for instance apoptosis, necrosis, reproduction, or agent creation). These second agents can move but for the following simulations we have fixed them.

The interactions between agents are based on the receptor influences. These interactions are detailed in the following section.

5. INTERACTIONS

Interactions between agents are made by their receptors. Their affinity and distance into the environment determine the influence of a receptor on another one. An Euclidean distance or Hamming distances value the affinity between two receptors [STE94] [SMI97a] [SMI97b]. In these cases, a p dimensional vector represents the receptor. For example, the antigen presentation can use the Seiden and Celada mechanism [CEL92a] [CEL92b]. Each receptor on the agent's surface acts on the compound agent moving. Therefore, a resultant is calculated from all the influences of the agent's receptors belonging to the compound agent. The compound agent moves according to the resultant (Figure 4).

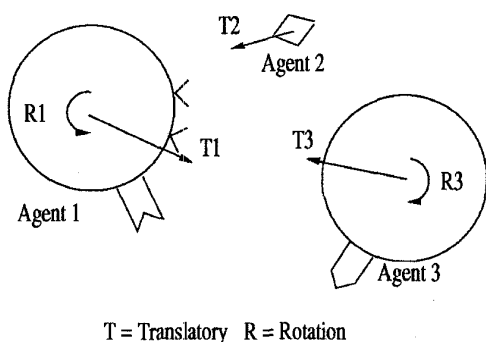


Figure 4. Interactions between agents.

As soon as the agents are described, it only remains to put them into their environment and to observe the result of both their behavior and interaction. The next section describes the B-CD5 agent.

6. B-CD5 AGENT MODEL

We only have to model the B-CD5 involved receptors and behaviors.

There are four types of receptors. The first is the B Cell Receptor (BCR) which activates the cell when bound. The second is the interleukine receptor (I₂) permitting the cellular division. The third and the fourth are supposed to be complementary and to keep on the activation or to increase the cell death speed (apoptosis).

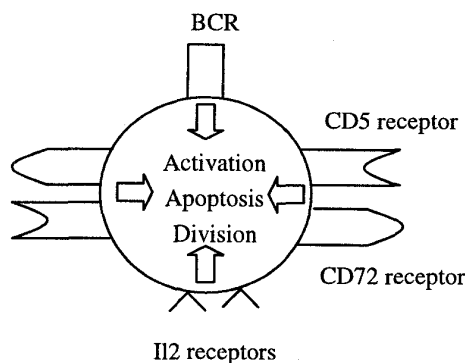


Figure 5. B-CD5 model.

To be activated, the BCR and the I₂ receptors must be bound.

When a receptor is bound, it creates internal agents (figure 5). These agents have three different aims. The first ones, generated by the BCR, CD5 and CD72 receptors increase the longevity of the cell if activated. If not, and this is the second type, the longevity is decreased. The third type is generated by the I₂ receptor and aims to produce the cellular division.

7. SIMULATIONS

These experimentation which are made in-vitro by the laboratory of immunology of Brest aim at the determination of the CD5 and CD72 receptors utility on B cells [JAM96].

The experimentation we present here consists in measuring the impact of the injection of an antibody directed against the B cell CD5 receptors. Thus, it is necessary to do two in-machina tests. In the first test, there is no anti-CD5 antibodies put into the virtual test tube. In the second test, they are placed when the number of B cell is at its maximum.

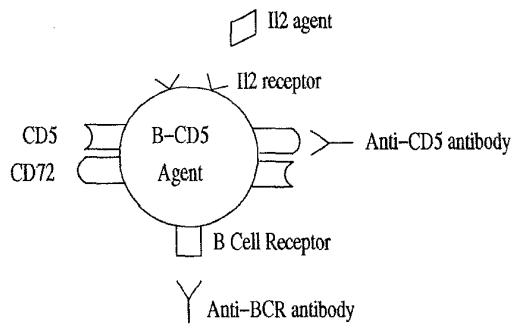


Figure 6. Agents implied in B-CD5 in-machina apoptosis experimentation.

In addition to the anti-CD5 antibody agents and the B cells, the simulation uses anti-BCR (B Cell Receptor) antibody agents which activate the B cells and interleukine 2 agents, which are the growth factors of the B cells (Figure 6).

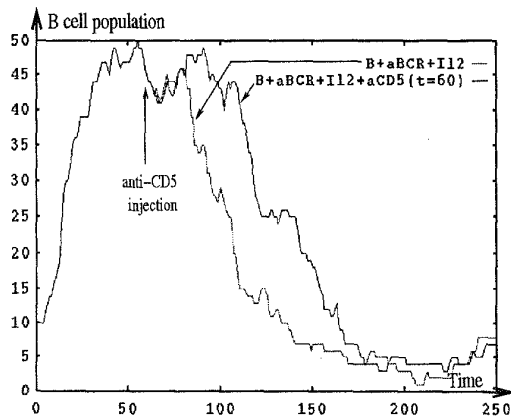


Figure 7. Evolution of the B-CD5 population.

As time goes by, the curve of B cell population is different if the anti-CD5 antibodies are put at the maximum of the proliferation ($t=60$) (Figure 7).

The assumption is that the anti-CD5 antibodies keep the B cells alive allowing them a latter apoptosis.

However, the simple action of the anti-CD5 antibody on a B cell does not explain the importance of the upholding of the population of B cells after the injection of anti-CD5 antibodies. Thanks to the simulation, we can say that at the maximum of the B cell population curve, the cells are agglutinated in complexes. Then, they strongly stimulate each other. The cells on the border of the complexes are the only one to be less stimulated. This means that they rapidly undergo the apoptosis. The dead cells do not stimulate the other cells any longer. Thus, a chain reaction follows which leads to a dramatic decrease of the number of living B cells. On the contrary, if some anti-CD5 antibodies are injected just before the drop of the curve, they

stimulate the cells on the border of the complexes. Therefore, this delays the chain reaction (Figure 8). Moreover, when the B cells are gathering together, all their CD5 receptors are not occupied (due to the geometrical constraints). The antibodies anti-CD5 are able to bind them. This increases the impact of the anti-CD5 on the B-CD5 activated.

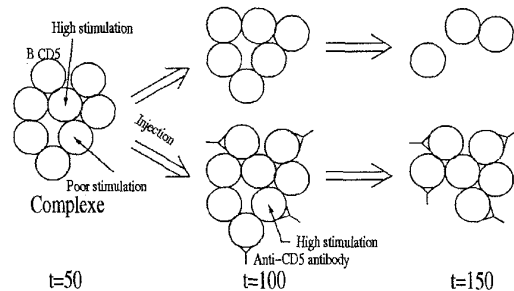


Figure 8. Anti-CD5 antibodies injection impact on B-CD5 cells.

These in-machina results have to be verified with a real experimentation. In fact, the simulation brings elements of reflection but today, it does not provide a ready-made solution. Moreover, the simulator has its own limits that we develop in the following section.

8. LIMITS OF OUR SIMULATOR

A living cell is very complex. Today, it is not possible to entirely model it. Numerous biochemical mechanisms occur inside a cell. The modeling of its interior has to be done by a virtual cell or agent programmer in order to build the internal mechanisms. As for the simulation the apoptosis of B-CD5 cells, the internal biochemical evolution is basically modeled. The purpose of the next step of the simulator development is to increase the number of agents composing a cell.

Furthermore, during a simulation, all the parameters are known. On the contrary, during an in-vitro and *a fortiori* in-vivo experimentation, hazardous phenomena can happen. This is the reason why simulations cannot replace in-vitro and in-vivo experimentation. However the knowledge of all the parameters of the simulation allows to verify whether the known mechanisms can explain the studied phenomena or not. It is the case in the simulation of immun complex formation as well as in the simulation of B-CD5 cell apoptosis. Finally, in-machina experimentation gives some indications and main directions without pretending to exactly reproduce the reality. This is one of the reasons why, our results are qualitative and not quantitative and they have to be taken cautiously. We must not forget that two different behaviors, two different mechanisms can have the same global result.

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