Immune System Simulation: Modeling the Mast Cell

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***Abstract*— Among the possibilities for simulating the immune system, the multiagent systems approach has proved to be attractive, since only the behavior of the types of agents is specified. The global behavior emerges from the interactions among agents. This feature is similar to the behavior of the immune system, consisting of large amounts of cell types that interact to maintain the body health. The simulation of the immune system requires modeling various types of cells and substances. This paper presents the modeling of a software agent that simulates the behavior of the mast cells. Some simulations were performed to validate the model.**

Keywords-mast cell; immune system simulation; in-silico models; multiagent systems

I. INTRODUCTION

Although much has been investigated about the immune system (IS), many interactions between cells and substances remain unknown [1]. One approach to try to circumvent this problem is to use computer models to simulate the IS biologic behavior, including the interaction between their cells and the diffusion of substances, in the hope of better understanding the IS principles [12]. This approach, known as *in-silico* research, can help researchers to understand the mechanisms of a complex system and to verify different hypotheses about its operation.

Simulating the immune system by multi-agent systems (MAS) approach has demonstrated to be very advantageous [4,7]. The MAS models can explore the emergence of complex functions on a macroscopic level from microscopic stochastic interactions. This feature is similar to the behavior of the immune system; consisting of large amount of cells of various types that interact restore the organism homeostasis.

Within this perspective, we are developing a simulator of the human immune system, based on the simulator initially developed by Folcik et al. [4]. In the current state of our simulator – named AutoSimune – it is already able to perform important simulations, especially in relation to viral infections and the events implicated in autoimmune conditions [7]. However, the evolution of the simulator requires the modeling of various types of cells and substances, in order to comprise all crucial activities involved in the IS, which can be subject of many investigations in the field. An important activity of the IS is related to inflammatory and allergic conditions. One of the cells that play a fundamental role in inflammatory and allergic processes is the mast cell, which is derived from mesenchymal cells and hosted in a variety of tissues. After some stimuli, they release preformed (heparin, histamine and other substances) and newly formed (prostaglandins, leukotrienes) mediators of inflammation, which induce cutaneous edema and some others biochemical and clinical manifestations of interest. These mediators assist in the recruitment of cells to respond to the infectious agent, but the excessive release of mediators may lead to serious complications in the host, due to anaphylactic reactions. Therefore, a suitable simulation model for studying the immune system reactions and the problems caused by autoimmunity must have an adequate representation of mast cell behavior.

This paper presents the modeling and implementation of a software agent that simulates the mast cell behavior. The agent was added to the system AutoSimune and some preliminary simulations were performed to validate the model. Simulation results showed that the mast agent general behavior simulates what is described in the literature. Some initial simulations were presented in [11]. Here are presented more simulations with a greater amount of agents.

II. THE MAST CELL

The mast cell precursors are formed in the bone marrow, released into the bloodstream and only differ on their arrival to the tissues [6]. Usually, mature mast cells are found near blood vessels, lymph vessels and nerves, occurring in large numbers in the nasal mucosa. The mast cell is characterized as a cell with a small globular nucleus that is often overshadowed by their cytoplasmic granules, which contain heparin, histamine, carboxipetidase, cathepsin G, chymase and tryptase [2].

Mast cells are the major cell types of the connective tissue responsible for prompt hypersensitivity which is mediated by antibodies - the IgE - specific to one particular antigen of the environment. It is noteworthy, according to Abbas et al. [2], the synthesis of IgE is dependent on the activation of T helper cells of the TH2 subset. It is likely that dendritic cells of the epithelium capture allergens, carry out the transportation of them to the lymph nodes, and present peptides to naive CD4 + T cells. B cells specific for certain allergens are then activated by TH2 cells and start producing antibodies of IgE type, which arrive through the circulation to tissues. Mast cells, since they contain Fc receptors, bind to these antibodies, which lead to sensitization of these cells, making them ready to respond to a subsequent encounter with the allergen. On this occasion, the sensitized mast cell,

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when contacting again with the same allergen, degranulates [6]. This action releases pharmacologically active mediators that cause harm to nearby tissues and intensify aspects of the immune response [6]. One of these mediators is histamine, which in this case can stimulate mucus production and increase tissue congestion, which may create a situation commonly known as “allergy”.

The role of this cell is well known in the type of immune response described above. However, mast cells seem to have an extreme importance in situations of ordinary inflammation. Indeed, as described by Kinet [5], there are experiments demonstrating that mast cells are able to orchestrate inflammation in various different situations. Hence, without the presence of this cell the inflammatory response to different diseases seems to be deeply affected. The same author explains the lack of recognition of the mast cells role in studies of inflammatory responses as follows [5]: *Maybe this absence of recognition is in part because of the well-publicized role of MCs in allergic diseases, which may have somewhat overshadowed their other potential roles in other contexts. Or, the omission may simply be because of the fact that inflammatory lesions do not contain MCs in great numbers when compared with, for example the numbers of lymphocytes and neutrophils in those lesions*.

Theoharides et al. explain that the mast cell has the ability to release different mediators depending on diverse stimuli, both endogenous and exogenous, and the most interesting in several situations is that degranulation is not necessarily observed: ... *mast cells appear to be activated through their Fc receptors by immunoglobulins other than IgE, as well as by anaphylatoxins, neuropeptides and cytokines to secrete mediators selectively without overt degranulation* [8].

III. Immune System Simulation through Multiagent Systems

The agent-based models have long been used to simulate, understand and predict emergent behaviors of complex systems [10], including the immune system [9]. Models of this nature use a bottom-up approach in their development where each agent represents an entity of the real system, and the agents may be heterogeneous, each with its own states and rules, having the ability to interact with other agents. For this reason, it is possible to test hypotheses about how cells interact and how some behavior emerges from such interactions. The model presented in this is an extension of the work of Folcik [4] that generated the simulator Basic Immune Simulator (BIS). An extension of BIS was necessary due to some of its limitations. BIS provides a monoclonal model, i.e., all T cells recognize all virus and each virus has only one antigen signature. In addition, a lymphocyte never makes a “mistake” such as attacking the body's own cell. In addition, BIS does not model mechanisms such as calculation of affinity, diversity generation, self-antigens, tolerance, among others, which are essential for simulations of phenomena related to autoimmunity and other diseases related to IS. Furthermore, BIS does not model antibodies as agents, preventing further attempt to define a specificity for them.

A. *Modeling of Time*

The passage of time is modeled using the concept of discrete time unit - called *tick* -provided by the framework. Each agent tells when to start to be called and the interval of each call. Ticks are the time intervals necessary for the transition from a state of the environment to the next. Therefore, all events scheduled to be executed must be completed before the next round occurs. Thus, during a tick, all agents scheduled for the given time will change their positions, release substance and analyze its neighborhood, based on information from the previous tick. Only when every agent has made its actions the tick ends and the information is updated.

B. *Modeling of Space*

The model includes five environments - or spaces - in which agents (or cells) are located. These spaces represent bone marrow, thymus, parenchyma, lymph and circulation, where three of these spaces are based on the spaces defined in BIS. The spaces are represented by a matrix of size m by n, called the framework grid. Each position in the grid has a coordinate (x, y) and can be occupied by one or more agents.

The possibility of a grid position being occupied by more than one agent is to simulate a 3D in which cells can pass over (and under) each other. Each agent, according to their rules, can move across the grid, at every tick, always to a position in its *Moore neighborhood* with radius equal to one. Agents can also obtain the list of agents that are close to him, in the same neighborhood. The exception, as described by Folcik [4], is when agents represent dendritic cells, which can get the list of agents around with a radius equal to two, to simulate the ability of these cells to scan its surroundings. Within the Bone Marrow space there are pre-immune B cells and dendritic cells. Dendritic cells present self-antigens to these cells in order to simulate the central tolerance of B cells.

The space that simulates the thymus contains pre-immune T cells and dendritic cells. In this case dendritic cells present self-antigens to T lymphocytes to simulate the mechanism of T cell central tolerance.

The parenchymal tissue space, which is based on zone 1 described by Folcik [4], holds parenchymal cells, dendritic cells and some pathogen, as appropriate. This is the space where immune reactions occur and, due to these reactions, this location will also receive cells such as macrophages, NK cell (natural killer), among others.

The lymph space - which is based on zone 2 of BIS - keeps the mature T and B lymphocytes, which are waiting for the arrival of some antigen-presenting cells to activate them. Finally, the circulation space houses various cells such as T lymphocytes migrating to the site of infection, granulocytes, among others, based also on BIS principles. This space will simulate the latency of the immune response due to the difficulty cells may have to arrive in the site of infection. Each space includes special agents”, termed portal agents [4], that are responsible for the transport of agents and chemical signals from one area to another.

C. *The granularity*

The model described in BIS used a level of granularity at which every cell of the body is represented by an agent. On

the other hand pathogens (viruses, in this case) and antibodies are modeled as substances. However, this level of granularity does not allow, for instance, to model pathogens with different specificities, or specific antibodies to a particular pathogen, among other limitations.

For this reason, the level of granularity chosen was the following: Everything that is included in the model, which is an antigen or contains an antigen is modeled as an agent. In other words, every component that can be recognized by PRR (pattern recognition receptors) is considered an agent.

D. The Specificity

The term specificity refers to the fact that adaptive immune responses are specific to the invading pathogen. Moreover, lymphocytes are specific for different antigens, i.e., these cells have specific receptors for different antigens. Thus, the model assumes that specificity refers to the fact that agents have a target pattern (a target antigen) that triggers their activation and guides their actions. At this point, we have a concept yet to be defined: Pattern. In the real world, pattern is a small molecular motif whose structure is defined, for instance, by amino acid sequences. In our model, we represent such patterns as arrays of binary symbols 0 and 1 (bit array).

E. Affinity

In immunology, the affinity is the force with which an antigen is recognized by a receptor. Likewise, in the model, the affinity is defined as the degree of similarity between the patterns provided by the antigen and its receptor: The higher the degree, the greater the affinity. Since the model uses a sequence of bits to represent molecular patterns, the affinity is calculated through the same method proposed by Floreano and Mattiussi [4], called the "*length of the longest common subsequence*". Given two patterns (bit streams) A and B, the method calculates the length of the longest contiguous subsequence of symbols that is contained in A and B simultaneously in the same order. The degree of similarity between two patterns is then defined as the length of the largest common subsequence both.

IV. MAST CELL MODEL

The agent that simulates the mast cell has been integrated and adapted to the simulator AutoSimune in order to emulate the behavior of the real cell and to allow the analysis of physiological and pathological conditions related to its action. When mast cell agents are in active state, they move randomly, searching for IgE antibodies. If certain concentration of bacterial enzyme is noticed, the mast cell agents release pro-inflammatory substances, generally defined as Mono-kine 1 (MK1) [5]. MK1 represents the set of proinflammatory substances present in innate immune responses, comprising: IL-12, IL-8, CCL3, CCL4, CCL5, CXCL9, CXCL10, and CXCL11.

If a mast cell agent interacts with an IgE antibody, the agent state changes to the sensitized state, which represents the mast cell - IgE binding through the IgE Fc receptor. In such a state the agent is still able to identify bacterial enzyme activity and release MK1, also moving randomly Still in the sensitized state, if an allergen binds to the IgE antibody, the mast cell degranulates. Once its lifetime is finished, it performs apoptosis.

V. RESULTS

For validating the mast cell agent, we introduced another agent in AutoSimune, representing an extracellular bacterial antigen able to: move, release an enzyme that degrades tissue cells, and reproduce. The purpose of this simulation is to check whether a circumstance of inflammation occurs for responding to the antigen, as described in the literature. Given the role of mast cells in this kind of situation, the immune reaction should not occur effectively in their absence or at least should happen more slowly.

In this study it was observed a more effective immune response to the antigen when the mast cells were present. When including these cells, there was some tissue damage, but the infection has been controlled and the bacterial agent was completely eliminated. On the other hand, in the absence of mast cells, the pathogen action was not controlled and serious tissue damage has occurred. Results are shown in Fig. 1 and Fig. 2.

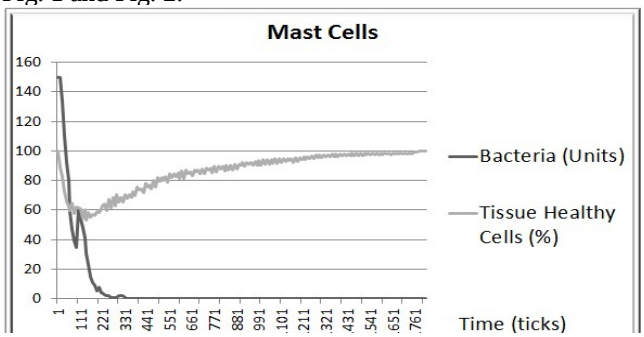

Figure 1. Effectiveness of the immune system to combat bacterial antigen in the presence of mast cells.

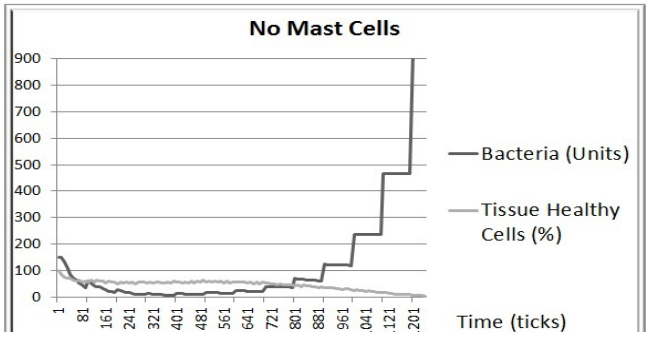

Figure 2. Combat against bacterial antigen without mast cells.

When fewer bacteria (80) were used its elimination in the absence of mast agent took more than twice as long as the case when these agents were present. Besides, we can notice that the control of antigen proliferation was ineffective. Results are shown in Fig. 3 and 4.

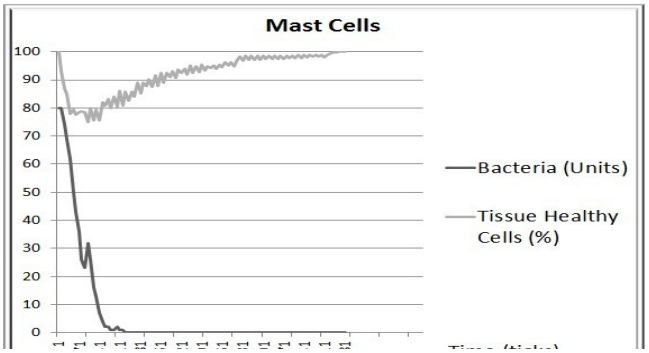

Figure 3. Effectiveness of the immune system to combat bacterial antigen in the presence of mast cells (smaller number of bacteria).

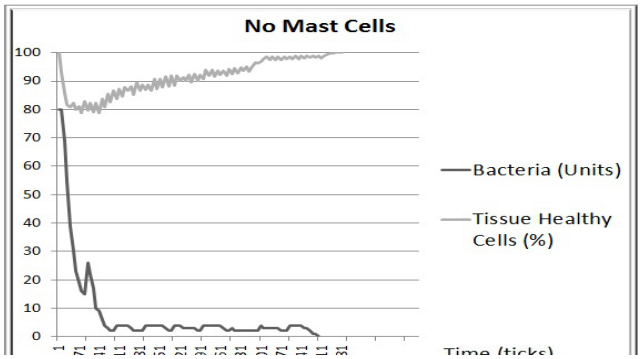

Figure 4. Smaller number of bacteria and no mast cells.

The model was also evaluated in relation to allergic reactions (Fig. 5).

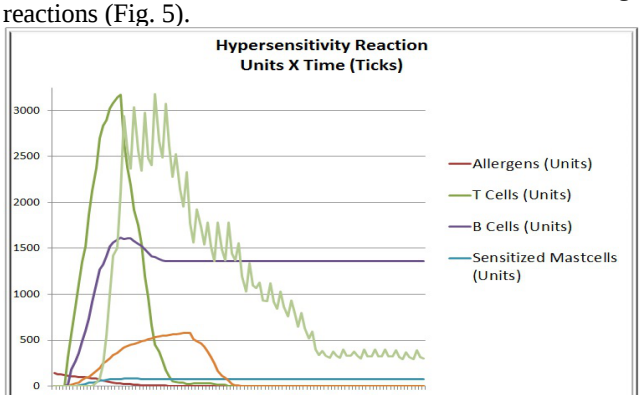

Figure 5. Allergic reactions

Agents were used to represent foreign allergens to the immune system that trigger hypersensitivity reactions, which are well known processes in the literature. It was observed mast cell degranulation with subsequent recruitment of inflammatory cells, elimination of pathogens, and small tissue damage.

VI. CONCLUSIONS

This paper presents the implementation of a software agent that simulates the behavior of mast cells, as reported in the literature. Despite the existence of research studies on multiagent systems applied to immune systems, the authors did not find any study that included the mast cell. In this work, we further extended our immune system simulator, termed AutoSimune, to include the definition of an agent to represent mast cells. Our simulator has a finer level of granularity and is capable to simulate specificity, affinity, and generation of diversity. The purpose of the incorporation of this agent is to increase the ability of the simulator, especially in its ability to emulate nosological entities associated with bacterial infections such as sepsis. The simulation results showed that the mast cell agent general behavior simulates what is described in the literature and that the mast cell has a fundamental role in the effectiveness of the immune response. Further simulations should be carried out widely to certify the adequacy of the model in various situations.

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