Situated Cellular Agents and Immune System Modelling

Stefania Bandini, Sara Manzoni, Giuseppe Vizzari
Dipartimento di Informatica, Sistemistica e Comunicazione
Università degli Studi di Milano–Bicocca
Via Bicocca degli Arcimboldi, 8, 20126 Milano, Italy
{bandini, manzoni, vizzari}@disco.unimib.it

***Abstract*— The Immune System (IS) constitutes the defence mechanism of higher level organisms to micro organismic threats: it is a real distributed system providing mechanisms of adaptation to unknown threats through the cooperation of heterogenous entities, and learning capabilities. This paper describes how the Situated Cellular Agents (SCA) model was applied to model the IS. After a brief description of the composing parts and internal mechanisms of the IS, the SCA model will be introduced and exploited to represent them[1].**

I. Introduction

The Immune System (IS) of vertebrates constitutes the defence mechanism of higher level organisms (fishes, reptiles, birds and mammals) to molecular and micro organismic invaders. It is made up of specific organs (e.g. thymus, spleen, lymph nodes) and of a very large number of cells ($10^{12} - 10^{13}$ in a man) of different kind that have or acquire distinct functions. The response of the IS to the introduction of a foreign substance (antigen) that might be harmful involves thus a collective and coordinated response of many autonomous entities.

Different models of the IS have been devised (mostly based on an analytical approach [11], and some others based on Cellular Automata (CA) [14]) for different purposes, from prediction of effects of experimental modifications on the IS, to educational programs [10]. To analyze and model the IS means to study natural means of detecting harmful intrusions and effectively respond to the threat. To study the IS represents thus a way to gain insight on possible methods to prevent and tackle threats to artificial systems, such as computer networks. In a scenario where computational devices and connectivity are spreading at an incredible speed, with a growing interest in mobile autonomous agents, security issues must be carefully considered and the biological metaphor could lead to novel and more effective security models (see, e.g., [6]). The latter is just one example of applications inspired by the IS, but even its adaptation and coordination mechanisms might be useful in other areas (e.g. autonomous aircraft control [8]). In fact the growing availability of inexpensive computational units, connected and distributed over a network that is more and more "un–wired" and being thus able to move, has highlighted the need of context–aware applications. The latter must thus be able to adapt to changes in the context of execution (both geographical and logical, with reference to user's profile, needs and tasks), and cooperate with remote entities to obtain information and, in general, to be able to carry out specific operations.

Most models for the IS follow an analytical approach: differential equations systems are set up to represent some part of the IS, then they are studied (generally using numerical integration). This approach, despite its popularity, has some limitations [7], but the main one, with reference to our approach, is the distance between immunologist language and the formal definition of a mathematical model of the IS.

Other approaches presented in the literature represent components and processes of interest of the IS and simulate its behaviour according to computational models. A relevant case, with reference to our approach, is the adoption of CA (see, e.g., [1][4]). In this case entities to be described are more than just variables or parameters in an equation: they can be related to data structures and even objects present in a particular body area (a cell in the CA) and interacting according to specific rules, defined by immunologists. In this approach there is a clearer correspondence between domain entities and model concepts, therefore it is easier for the immunologist to interact with it using her language, rather than the mathematical one. This change of approach even brings more insight on details of IS response process, allowing for instance to keep track of cell concentrations in specific areas (cells of the CA). The internal evolution of entities within a single cell of the CA is determined through a probabilistic mechanism that considers the possibility of every entity to interact with every other one present in the cell (i.e. the cell is a completely connected graph). A serious issue with this approach is that rules of interaction between cells and other IS entities must be defined as global. Therefore a computer system based on this kind of model has to know how to handle all possible interactions between different types of entities. This problem is particularly serious as research in the area of immunology is very active and the understanding of the mechanisms of the IS is still far from complete. A careful design, according to best–practices derived by research in the area of software engineering, can help facing technical aspects of this problem, but it probably does not make the system easier to understand. A further step in the direction of an increased accessibility for immunologists provides a direct corre-

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spondence between entities of the IS and autonomous entities of the computer system. The Multi Agent System (MAS) [5] approach is a well known computational model supporting simulation (see, e.g., [9]). The main goal of this paper is to show how it was applied in the modelling of the IS system through the adoption of Situated Cellular Agents [3]. The SCA model, a particular class of Multilayered Multi Agent Situated System (MMASS [2]), allows a more detailed representation of the interaction between entities, that are inherently space dependant more than just probabilistic. The graph structure representing the environment is more precise than the previously described CA approach because a node may contain at most a cell, that will be able to interact directly only with other adjacent cells, preserving detailed spatial relations between cells. Moreover the SCA model allows the representation of action–at–a–distance that will be exploited, for instance, to perform virus and antibody diffusion.

In the following Section some basic concepts related to the IS will be described, then some elements of the SCA model will be illustrated, in order to show how a multi agent approach can be suitably applied to simulate the IS. A through description of the IS, its components and its way of reacting in order to face infections is out of the scope of this paper; more details on the subject may be obtained from [13]. Nonetheless some kinds of mechanisms and interactions between the entities of the IS will be briefly illustrated, in order to show some examples of its internal modalities of collaboration, adaptation and learning. Conclusions and future developments will end the paper.

II. IS DESCRIPTION

The task of the IS of an individual is to detect the presence of antigens inside her body and react to eliminate the related threat. Examples of antigens are viruses, bacteria and parasites; their specific nature and characteristics are generally unknown to the IS, as well as the possible location where the infection will take place. Therefore it must be able to adapt to new threats, remember them in order to efficiently face following infections of the same kind, covering all the body. In order to carry out this task it is made up of static, located organs and mobile cells that exploit the cardio–vascular system and a dedicated network of channels called lymph system.

The main kinds of IS mobile entities are the following:

- *antibodies* are proteins able to bind to a specific antigen, neutralizing its possible harmful effects;
- *B lymphocytes*, also referred to as B cells, may bind to a specific antigen and are responsible for the production of antibodies related to it. They may also differentiate into memory cells, able to take part in future immune responses if the same antigen in encountered again;
- *T lymphocytes*, also referred to as T cells, can be divided into different categories according to their function: for instance *killers* are able to recognize cells infected by a specific antigen (i.e. containing it) and *helpers* enhance the production of antibodies, stimulating the proliferation of the related B cells;
- *antigen presenting cell* (APC), also called accessory cells, are a set of different kinds of cell (e.g. macrophages, dendritic cells) that are able to identify and process antigens in order to make them recognizable by T cells (e.g. a macrophage can phagocytize an antigen and present a part of it over its surface).

All these kinds of entities are able to circulate in blood, and the last three of them belong to the white blood cells category. Static parts of the IS have a role in the life–cycle of these cells: lymphocytes are generated in the bone marrow, and mature in the thymus. Both B and T cells take residence into lymph nodes, the spleen and other tissues where they can encounter antigens, proliferate and evolve (through mitosis), and mature into fully functional cells.

Leaving aside APCs, the entities described above are devoted to a specific antigen. This means that they are able to interact with a specific antigen, in a direct way (i.e. through the interaction of their membranes) or indirectly (e.g. through a direct interaction with an infected cell, or an APC that had ingested it). The fundamental element for all these interactions is the membrane of these entities: IS specific cells have a receptor (characteristic molecular configuration) repeated all over their surface. If it is chemically "compatible" with the surface of another entity they encounter they can bind with it. In order to be able to obtain B and T cells for a number of possible antigens, whose characteristics are unknown to the IS, a large number of B and T cells (10^{10} at least) with different receptors must be generated. Moreover, during the life of those cells, somatic mutations can bring the number of receptors up to the order of 10^{16}. In other words, the IS does not know what specific antigens will be encountered, but the "building blocks" of their membrane are known, so combining them in a sufficient number of variants will bring reasonable protection.

Figure 1 [2], shows two different kinds of response of the IS to defend the body from micro–invaders. The central column shows the evolution of a epithelial cell (EP) infected by a virus, denoted by a small circle. The latter enters the cell, proliferates inside it, and ultimately causes the burst of the cell, the release of more viruses and the cast of a damage signal. Another effect of the infection is that part of the virus is exposed over the membrane of the infected cell. There are thus two possible kinds of reaction to the infection, as the viruses to be neutralized may be found outside body's cells (e.g. freely wandering in the blood), or inside already infected cells. B cells specific for this antigen (i.e. with a receptor compatible to the virus membrane), are already able to capture and bind the free virus, but this is not enough to face the infection. Both kind of responses are triggered by an APC (denoted with A in Figure 1), that is activated by the damage signal and ingests a virus. Part of it is exposed in the membrane of the APC, and can be recognized by a helper T cell (T_{h2} in Figure) whose receptor is compatible with the virus membrane. These helpers can stimulate B cells to reproduce themselves, differentiating into B memory cells and plasma cells, which in turn will produce antibodies that are able to eliminate free viruses. This is generally called humoral reaction, and it is shown on the left side of Figure 1. The right side shows cellular reaction, the other kind of response to an in-

[2]This Figure was taken from R. Puzone, B. Kohler, P.Seiden, F. Celada, IMMSIM, a flexible model for in machina experiments on immune system responses, *Future Generation Computer Systems*, Vol. 18, No. 7, pp. 961–972, Elsevier, 2002.

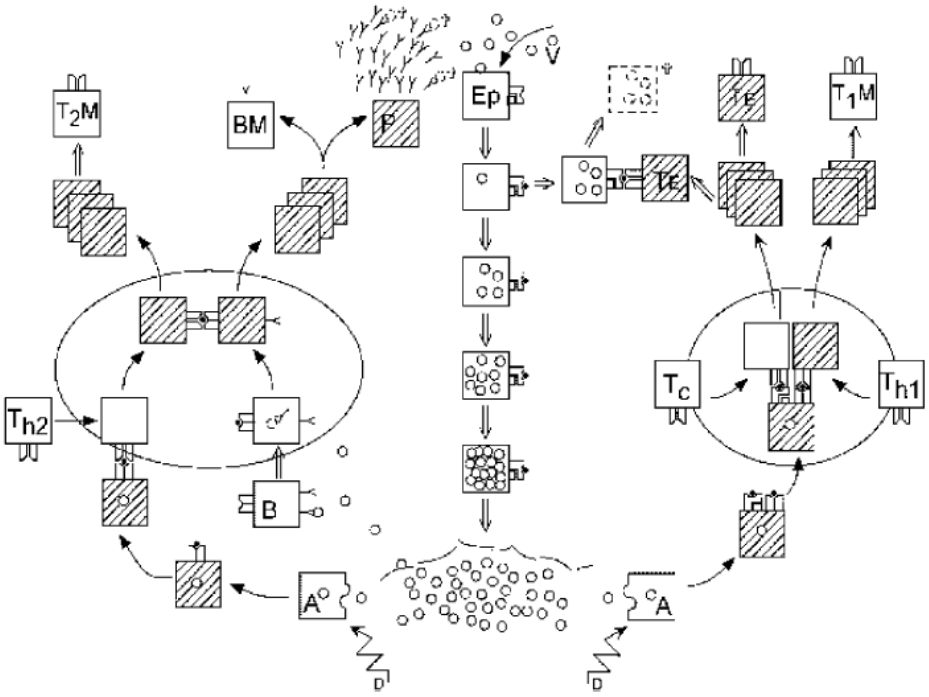

Fig. 1. Scheme of IS humoral and cellular response to a viral infection.

fection whose task is to eliminate infected cells. The APC cell exposing the ingested virus can activate other helpers that will in turn activate killer T cells (denoted by T_c in Figure). The latter will proliferate and bind to infected cells, eliminating the related threat.

III. SCA MODEL

A system of Situated Cellular Agents can be denoted by:

$$< Space, F, A >$$

where A is a finite set of agents, F is a finite set of fields, and *Space* is a single layered environment where agents are situated, act autonomously and interact by means of reaction or through the propagation of fields.

The possibility to define different agent types introduces heterogeneity, in other words the chance to define different abilities and perceptive capabilities. Defining T the set of types, it is appropriate to partition the set of agents in disjoint subsets corresponding to different types. The set of agents can thus be defined as

$$A = \bigcup_{\tau \in T} A_\tau$$

where $A_{\tau_i} \cap A_{\tau_j} = \emptyset$ for $i \neq j$. An agent type τ is defined by

$$< \Sigma_\tau, Perception_\tau, Action_\tau >$$

where:

- Σ_τ defines the set of states that agents of type τ can assume;
- $Perception_\tau : \Sigma_\tau \rightarrow [\mathbb{N} \times W_{f_1}] \ldots [\mathbb{N} \times W_{f_{|F|}}]$ is a function associating to each agent state the vector of pairs

$$\Big(c_\tau^1(s), t_\tau^1(s)\Big), \Big(c_\tau^2(s), t_\tau^2(s)\Big), \ldots, \Big(c_\tau^{|F|}(s), t_\tau^{|F|}(s)\Big)$$

  where for each i ($i = 1 \ldots |F|$), $c_\tau^i(s)$ and $t_\tau^i(s)$ express respectively a receptiveness coefficient to be applied to the field value f_i and the agent sensibility threshold to f_i in the given agent state s. In this way, agents situated at the same distance from the agent that emits a field can have different field perceptive capabilities of it.
- $Actions_\tau$ denotes the set of actions that agents of type τ can perform, and will be described in Section III-C.

A. Space

The *Space* consists of a set P of sites arranged in a network (i.e. an undirected graph of sites). Each *site* $p \in P$ can contain at most one agent and is defined by $< a_p, F_p, P_p >$ where $a_p \in A \cup \{\perp\}$ is the agent situated in p ($a_p = \perp$ when no agent is situated in p, in other words p is empty); $F_p \subseteq F$ is the set of fields active in p ($F_p = \emptyset$ when no field is active in p); and $P_p \subset P$ is the set of sites adjacent to p.

B. Fields

A field $f_\tau \in F$ that can be emitted by agents of type τ is denoted by

$$< W_\tau, Diffusion_\tau, Compare_\tau, Compose_\tau >$$

where:

- $W_\tau = S \times \mathbb{N}$, where $S \subseteq \Sigma_\tau$, denotes the set of values that the field can assume; given $w_\tau \in W_\tau$, $w_\tau =< s_\tau, i_\tau >$,

where $s \in S$ represents information brought by the field and $i_\tau \in \mathbb{N}$ represents its intensity.

- $Diffusion_\tau : P \times W_\tau \times P \rightarrow (W_\tau)^+$ is the diffusion function of the field computing the value of a field on a given site taking into account in which site and with which value it has been emitted. Since the structure of a $Space$ is generally not regular and paths of different length can connect each pair of sites, $Diffusion_\tau$ returns a number of values depending on the number of paths connecting the source site with each other site. Hence, each site can receive different values of the same field along different paths.
- $Compare_\tau : W_\tau \times W_\tau \rightarrow \{True, False\}$ is the function that compares field values. For instance, in order to verify whether an agent can perceive a field value.
- $Compose_\tau : (W_\tau)^+ \rightarrow W_\tau$ expresses how field values have to be combined (for instance, in order to obtain the unique value of the field at a site).

C. Situated Cellular Agents

An agent $a \in A$ is thus defined by $< s, p, \tau >$, where: $s \in \Sigma_\tau$ denotes the *agent state* and can assume one of the values specified by its type; $p \in P$ is the site of the *Space* where the agent is situated; τ is the *agent type*.

The behavior of Situated Cellular Agents is influenced by agents situated on adjacent positions and, according to their type and state agents are able to synchronously change their states. Synchronous interaction (i.e. reaction) is a two–steps process. Reaction among a set of agents takes place through the execution of a protocol introduced in order to synchronize the set of autonomous agents. When an agent wants to react with the set of its adjacent agents since their types satisfy some required condition, it starts an *agreement* process whose output is the subset of its adjacent agents that have agreed to react. An agent agreement occurs when the agent is not involved in other actions or reactions and when its state is such that this specific reaction could take place. The agreement process is followed by the synchronous reaction of the set of agents that have agreed to it. Reaction of an agent a situated in site $p \in P$ can be specified as:

$action : reaction(s, a_{p_1}, a_{p_2}, \ldots, a_{p_n}, s')$
$condit : state(s), position(p), agreed(a_{p_1}, a_{p_2}, \ldots, a_{p_n})$
$effect : state(s')$

where $state(s)$ and $agreed(a_{p_1}, a_{p_2}, \ldots, a_{p_n})$ are verified when the state of agent a is s and agents situated in sites $\{p_1, p_2, \ldots, p_n\} \subseteq P_p$ have previously agreed to undertake a synchronous reaction. The effect of a reaction is the synchronous change in state of the involved agents; in particular, agent a changes its state into s'.

Other possible actions are related to the asynchronous interaction model, related to field emission and to the perception–deliberation–action mechanism. Agent emission can be define as follows:

$action : emit(s, f, p)$
$condit : state(s), position(p)$
$effect : added(f, p)$

where $state(s)$ and $position(p)$ are verified when the agent state is s and int position is p. The effect of the emit action is a change in the active fields related to sites involved in the diffusion, according to $Diffusion_f$.

The effect of an agent perception of a certain field f_i can be defined as

$action : trigger(s, f_i, s')$
$condit : state(s), position(p), perceive(f_i)$
$effect : state(s')$

where $perceive(f_i)$ is verified when $f_i \in F_p$ and $Compare_\tau(c^i_\tau \cdot i_{f_i}, t^i_\tau) = true$ (in other words, field intensity modulated by an receptiveness coefficient exceeds the sensitivity threshold for that field). The effect of the trigger action is a change in agent's state according to the third parameter. The last possible action for an agent causes a change in its position and can be specified as follows:

$action : transport(p, f_i, q)$
$condit : position(p), empty(q), near(p, q), perceive(f_i)$
$effect : position(q), empty(p)$

where $empty(q)$ and $near(p, q)$ are verified when $q \in P_p$ and $q =< \perp, F_q, P_q >$ (q is adjacent to p and it does not contain agents). The effect of a transport action is thus to change the position of the related agent.

IV. IS MODELLING

The IS is a natural system providing inherent adaptation, coordination and learning mechanisms. The fundamental IS elements to obtain adaptivity are membrane and receptors: there is no prior knowledge on possible threats, and it must base its working on really basic elements (i.e. electromagnetic forces between molecular structures), the "building blocks" of the possible interactions. Coordination mechanisms are based on the specialization of certain cells, that will become able to interact and activate their specific working when activated by the direct interaction with other entities with compatible membrane (e.g. B cells and compatible viruses, T killers and cells infected by compatible antigens). The learning mechanism provides the production of specific memory cells, that spread over the environment in order to be able to newly activate a previously performed reaction. An important aspect is that this memory is not centralized but distributed, incrementing robustness of the system, as the death of a few memory cells (that is physiologic) doesn't hinder its ability to recognize a known virus. Moreover this feature enables a local and faster reaction to infections as the related signals must not reach a specific organ, travelling through the cardiovascular or lymph system, in order to activate the IS response.

A complete specification of this extremely complex system with concepts described in the SCA model cannot be given in this paper for space reasons, but some examples of how mechanisms described above can be formalized will be reported in the following.

Entities described in Section II can be divided in cells and other substances like viruses and antibodies. Basically the latter can be treated as signals, moving through the space (e.g. a

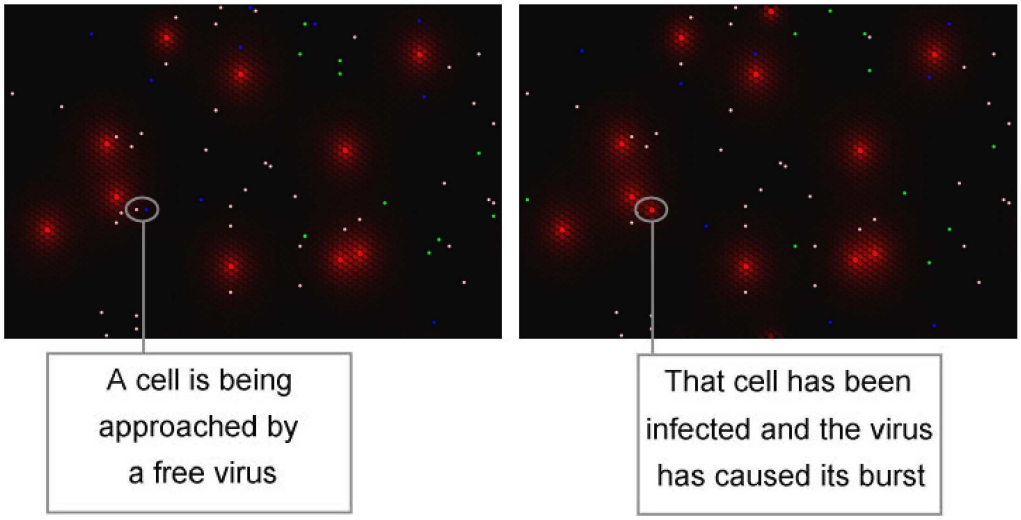

Fig. 2. Two screenshots taken from the prototype of the Multi Agent IS simulation system. In the first one, there is a free virus in lower–left quadrant. It will infect a close cell whose burst is shown in the second screenshot.

lymph node) until they interfere (i.e. a specific antibody neutralizes a free virus) or are are perceived by another entity (i.e. a virus penetrates a cell, or is ingested by it). Interference between these entities can easily be viewed in terms of specific kind of field composition, in which two signals with certain values neutralize themselves. These considerations led to model these non–cell entities as fields. More precisely a field *humor* could be defined as follows:

$$F_h = < W_h, Diffusion_h, Compare_h, Compose_h >$$

with $W_h = \{virus, antibody\} \times \mathbb{N}$.
Given a humor $w_k \in W_h$ we have that $w_k = < ht_k, m_k >$, where the first element indicates the kind of humor and the second is the specification of the membrane related to the entity. The composition of humors is only defined for compatible entities (i.e. incompatible ones simply ignore each other), and more precisely, given $w_1, w_2 \in W_h$

$$Compose_h(w_1, w_2) = \perp \ \ if \ \ ht_{w_1} \neq ht_{w_2} \wedge m_{w_1} = m_{w_2}$$

.

In this case the $Compare_h$ function is defined as a type compatibility test, assuming value $true$ only when humor types of the compared fields are the same.

While humors are represented as fields, cells are modelled as agents. This decision is based on the fact that cells have a state, a behaviour that is much more complex than that of a humor (e.g. may require cooperation with other cells), and thus require concepts related to SCA agents. To model a generic cell agent its related type must be defined:

$$Gen = < \Sigma_{Gen}, Perception_{Gen}, Action_{Gen} >$$

where $\Sigma_{Gen} = \mathbb{N} \times \mathbb{N} \times W_h \times \{dead, alive\}$. The state s_{Gen} of agent $a_{gen} \in A_{Gen}$ is thus defined as $< cl, ll, m, v >$ where the first element represent the current virus load, the second is the lethal load, the third represents possibly infecting virus, with the related membrane, and the last is an indication of the cell vitality. To include a humor definition will be useful when the specification of a generic cell will be modified to define other specific entities. For instance plasma cells are able to generate antibodies, whose specification will be part of their state.

The perception function is simply defined as the mechanism of infection, the penetration of a virus inside the cell that triggers its reproduction inside it until the current viral load reaches the lethal level, when the cell will die and diffuse all the viruses it contains. The perception function can thus be defined as $Perception_{Gen} = (1, < virus, k >) \ \forall \ s_{Gen} \in \Sigma_{Gen}$. A stochastic element could possibly be introduced in order to introduce a form of non–determinism.

The specification of $Action_{Gen}$ must reflect what was said above with reference to cell's behaviour, but when infected the cell must also be able to react with specific T cells whose receptor is compatible with the infecting virus. This interaction can only take place between adjacent generic and killer T cells that agreed to react.

$Action_{Gen}$ can thus be defined as follows:

- $action : trigger(s_{Gen}, f, s'_{Gen})$
  $condit : f =< virus, k >, s_{Gen} =< cl, ll, v, alive >,$
  $cl < ll - 1, position(p)$
  $effect : s'_{Gen} =< cl + 1, ll, f, alive >, F_p = F_p - \{f\}$

- $action : trigger(s_{Gen}, f, s'_{Gen})$
  $condit : f =< virus, k >, s_{Gen} =< cl, ll, v, alive >,$
  $cl \geq ll - 1, position(p)$
  $effect : s'_{Gen} =< cl + 1, ll, f, dead >, F_p = F_p - \{f\}$

- $action : emit(s_{Gen}, f, p)$
  $condit : s_{Gen} =< cl, ll, f, dead >, f =< virus, k >,$
  $cl > 0, position(p)$
  $effect : s_{Gen} =< cl - 1, ll, f, dead >, added(f, p)$

- $action : react(s_{Gen}, a_{TK_k}, s'_{Gen})$
  $condit : s_{Gen} =< cl, ll, f, alive >, f =< virus, k >$

$$effect : s'_{Gen} =< 0, ll, f, dead >$$

This is clearly a loose specification of humors and generic cells, as their mobility means were not indicated. The latter, and the definition a field diffusion function as well, should be designed with reference to the specific environment in which the entities are situated. If it is a blood vessel, the effect of pressure should be suitably modelled, for instance through the definition of another field influencing humor diffusion and cells mobility.

A prototype for a multi–agent system based on this specification was designed and developed using Repast [12], a Java based software framework supporting the development and execution of agent based simulations.

The membrane and receptors, previously simply defined as natural numbers, must be represented as limited data types. For this prototype we chose to adopt an 8–bit representation for receptors and membranes. Compared to the number of possible different receptors present in a fully developed and functional IS this may seem small, nonetheless this value is typically used by other CA–based simulators.

A subset of cell interactions that characterizes the IS was implemented, and the number of active entities that can be simulated is quite small compared to CA based systems, therefore the prototype should be considered as a demonstrator of the potential of this approach, especially in the educational area. One of the currently implemented interactions is cell infection performed by free viruses, cell burst and damage casting. Moreover specific APC cells (macrophages), wandering throughout the environment trying to phagocytize free viruses were also implemented. In the left part of Figure 2 a free virus is about to approach a cell and infect it, while in the right part it has penetrated, proliferated and caused the cell burst. This causes the casting of a damage signal, diffusing from the burst site.

V. Conclusions and future developments

IS internal mechanisms are naturally distributed, providing adaptation to unknown threats, cooperation among its composing parts, learning capabilities obtained through a decentralized memory approach. The adaptation is based on the usage of real basic elements of interaction between entities as "building blocks" for possible countermeasures to infections. Once a response was undertaken suitable memory cells are generated, in order to be able to recall it and carry it out quickly when newly necessary. Reaction is based on the cooperation of specialized entities, with precise tasks and roles in the IS working.

In this paper a Multi Agent approach to IS simulation through the adoption of the SCA model was presented. A brief description of IS composing parts and internal mechanisms was given, and the application of concepts define in the SCA model to represent them was illustrated. This work is a result of a project done in collaboration with immunologists whose goal is the development of models and instruments for immunology, and the identification of biological models and mechanisms that can be exploited in computer science. A prototype based on the SCA model for IS simulation was developed and will be evaluated by immunologists in order to define future developments and applications.

The design of robust and secure distributed systems may draw inspiration from many biological mechanisms and metaphors, but this kind of operation should be carried out with caution. In fact a partial transport of concepts and mechanisms from an area to another one could bring disappointing results.

For instance, the IS has an intrinsic adaptation mechanism, that is built on extremely basic elements, with no assumption on possible threats. To assure security in an artificial system, like a computer network, one can exploit previous experience and knowledge on previous attacks, but new ones might use basic interaction mechanisms (i.e. the synthetic counterparts of cellular membranes) in a novel way. Defining precisely this basic level of interaction is not an easy task, as different technologies, protocols and parts of operating systems are involved, and should be considered in their context. The granularity level in monitoring and control of various operation defines the possibility to perform an effective adaptation, but even the overhead related to the various checks.

Another important feature of the IS is its distributedness: no assumption can be made on the location where the next intrusion might happen, so the monitoring must involve all the system. The extreme diffusion of personal and portable computational devices, that are more and more connected to corporate networks despite their mobility and position, makes extremely hard to define clear boundaries and interfaces. To have just a few nodes able to detect and face an intrusion will probably become an ineffective policy.

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