USING MULTI-AGENT SYSTEMS TO STUDY PARACRINIENNE CELLS INTERACTION

Lynda Dib
University Badji Mokhtar, Computer Science Department, BP12 Annaba, Algeria

Keywords: Multi-agent model, System of multi-agent simulation, Agent interaction, Paracrinien communication.

Abstract: This paper presents our multi-agent framework for modelling and predicting the emergent behaviour resulting from the presence of distinct environmental conditions that lead to bad interaction of cells in their tissue. As the cellular interaction is an important behaviour permitting the survive of cells in their tissue, the objective of *our simulator* is to be a virtual world of cellular biology while *analyzing and simulating the control mechanisms during the paracrinien communication between cells* in order to help its specialists to better understand, to good interpret and to warn changes of cell states according to its actual internal state and to the state of its environment.

1 INTRODUCTION

Biological, especially the study of the human body is a complex field. In biological phenomena numerous parameters intervene but their exact influence is often difficult to determine. If it is easy to find a mathematical model describing the evolution of an illness for example, but it is difficult in contrast to model and to understand what happens at the cell level.

The modelling of the biological and medical systems by the multi-agent approach is in its early stages (Giuliano, Denzinger, Merelli, Miles, Tianfield, &Unland, 2005). Several recent works are interested in the modelling of cellular behaviour, for example, the modelling of intracellular signals (Boss, Jonker, & Treur, 2005). Other works are interested on the intercellular modelling, for example, the multi-agent simulation of cellular migration (Dib, Guessoum, Bonnet, & Laskri, 2005) (Dib, Guessoum, Laskri, Fartas, & Guettar, 2006) (Dib, Guessoum, & Laskri, 2006). The multi-agent system models the neurons functioning (Colloc, 2005), and the control mechanisms modelization, for the formation of granulomes during the tuberculosis infection (Segovia-Juarez, Ganguli, & Kirshner, 2004). Using multi-agent systems to study cells interaction (Dib, &Guessoum, 2007) (Dib, 2008). Our system falls into in this category. The aim of our work is about offering to biologists the possibility to model and to simulate the complex systems containing cells, molecules and their interactions in their environment. Agent paradigm provides a very good solution to model and simulate cells and their interactions, especially the paracrinien communication.

Paracrinien signaling, acting on cells immediately adjacent to the sending cell (to a proximity <1mm), is a complex phenomenon. Paracrinien signals (mediators) are chemical substances with local diffusion, in an extracellular middle (Berridge, 1985). They are recognized by every cell using the membrane’s receptors (Smith, Hill, Lekowitz, Handler, & White, 1983).

That the cell is considered as a structural and functional unit of the organization cannot live in isolation, so it is necessary that there is a highly developed communication network between it (Masliah, & Housset, 2008). The big vital functions (such as the breathing, digestion, movements, etc) are not possible because **cells communicate between each other** in a harmonious way. Every cell receives and sends signals permanently toward the neighbouring cells (Berridge, 1985) (Smith, 1997). These multiple signals are messages that cells interpret. In response to the whole received message, the cell chooses an action: to divide, to specialize or to die (Chauffert, 2004).

This article presents our system simulating the paracrinien communication. It is organized as follows: In the second section, we describe the proposed model for the simulator realization. The third section will be devoted to the simulation and

Dib L. (2009).
USING MULTI-AGENT SYSTEMS TO STUDY PARACRINIENNE CELLS INTERACTION .
In *Proceedings of the International Conference on Biomedical Electronics and Devices*, pages 276-280
DOI: 10.5220/0001555702760280

the results obtained by the system. The conclusion is made in section fourth.

2 MULTI-AGENT MODEL

Our system is composed of three categories of agents: Cells, Molecules and Mediators. We also distinguish a set of objects: the environment, the receptors and the extracellular matrix.

2.1 The Agents

2.1.1 The Cells

The AgentCell is principally defined by a set of characteristics represented by the following parameters:

– *CE*: Cellular Energy,
– *NR:* Number of Receptors bounded to the cell,
– *LinkR*: state of the liaison between the cellular membrane plasmic and the Receptors. This last, takes the value 1 if the receptors are attached to the AgentCell membrane plasmic, the value 0 if this junctions is not established,
– *NRBM:* Number of Receptors Bounded to the Mediators,
– *NFR:* Number of Free Receptors,
– *NAR:* Number of Active Receptors,
– *NNAR:* Number of No Active Receptors,
– *StatC:* internal Stat of AgentCell,
– *VN:* Vector of AgentCell Neighbouring,
– *VR:* Vector of Receptors belonging to the AgentCell.

In a paracrinien interaction the communicating AgentCell realizes the following actions:

– definition of the achieved goal (secretion or reception of a paracrinien signals) according to the internal state of the signalling AgentCell and to the environmental information;
– sending (secretion) of the mediator by the signalling AgentCell;
– activation of the target AgentCell's receptor;
– reception of the mediator by the target AgentCell;
– interpretation of the mediator (signal captured by the target AgentCell's receptor);
– response appropriate to the received mediator.

From the biological real characteristics of the communicating cell the automaton concerning its behaviour is realized (Figure 1).

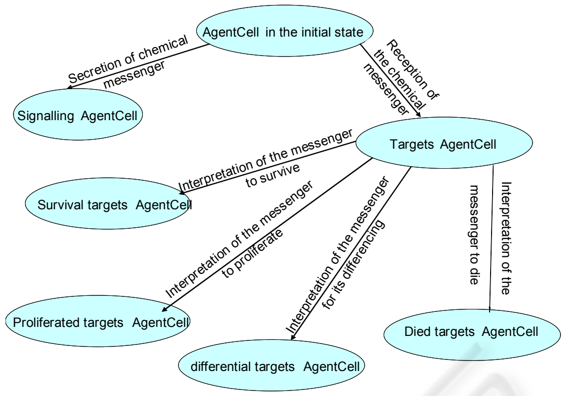


Figure 1: Behaviour Automaton of a communicate cell.

2.1.2 The Molecules

The cells consist of a molecule assembly. All the activities of the cell, including the different cellular structure formations, depend on the interaction of a particular group of molecules. We distinguish three important groups: water, the inorganic ions and the organic molecules.

The AgentMol is principally defined by a set of characteristics represented by the following parameters:

– *numMol*: number of the Molecule,
– *RC*: Rate of Concentration of the actual quantity of molecules in the environment. The *RC* may be increased '*RCA*' or decreased '*RCD*'.
– '*LimitMin', 'LimitMax'*, express a minimal and maximal limit of resource or molecule concentration, in the environment, that will not be clear.

2.1.3 The Chemicals Mediators (CM)

A Chemical Mediator (CM) is a molecule that can be attached to a cellular receptor. In our system a CM is generated from a molecule.

An AgentCM has the same characteristics as an AgentMol. It is described in our model by a set of characteristics represented by the following parameters:

– *State:* describes the current state of the AgentCM,
– *LCMR:* Link between Chemical Mediator and Receptor. This parameter takes the value 1 when the link between AgentCM and receptor is established and 0 in the contrary case,
– *CMInterpreted*: this parameter takes the value 1 when the AgentCM is interpreted by the target AgentCell and 0 in the contrary case,
– *CMA*: CM Active or no.

Also, an AgentCM possesses certain behaviour during the communication between two AgentCells. At every behaviour the AgentCM passes from its current state to another that can be the inactivate state, the destroyed or the captured state.

From the biological real characteristics of the chemical molecule (mediator) the automaton concerning its behaviour is realized (Figure 2).

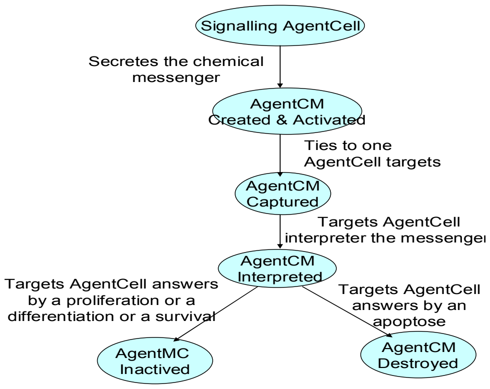


Figure 2: Behaviour Automaton of a communicate mediator.

2.1.4 The Objects

In addition to these agents, we find other very important entities in the simulated system: the environment and the receptors.

– The environment is represented by a particular class 'Environment', and evolves dynamically to every change of the cellular and the mediator state. It contains a cell population, represented by a vector '*Vcell*', a population of molecules and resources for the cellular survival (sugar, k+...) represented by another vector '*Vmol*',

– The receptors are protein molecules situated on the membrane or in the cell. The receptor is principally defined by a set of characteristics represented by the following parameters:

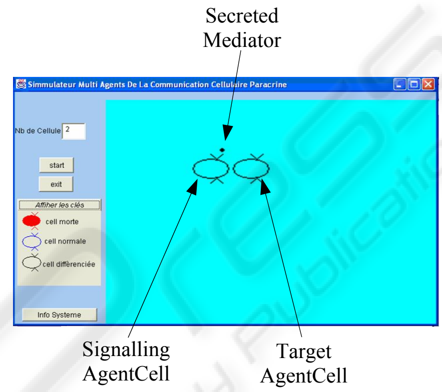
  - *TR*: Type of Receptor,
  - *SR*: Stat of Receptor. This parameter takes the value 1 where the junction between CM and receptor is established and the value 0 in the contrary case,
  - *RA*: Receptors are activated or not. This parameter takes the value 1 where the Receptor is activated, the value 0 in the contrary case.

3 SIMULATION

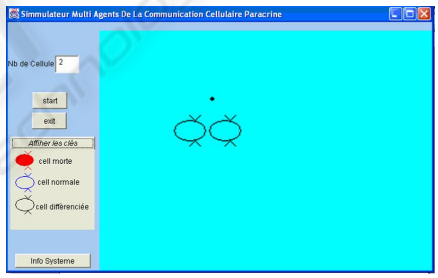
Our model has been implemented in the DIMA environment (Development and Implementation of Multi-Agent system) (Guessoum, Meurisse, & Briot, 2002). DIMA groups classes that can be re-used and/or adapted to easily construct agents.

The simulator, witch is the scheduler can be activated, suspended, resumed or stopped.

In our multi-agent simulator the paracrinienne communication is realized by an interaction between the AgentCells and an interaction between the AgentCell and AgentMC.



a)- Send of the mediator at the ınstant t0.



b)- Send of the mediator at the instant t1.

Figure 3: Simulation of the communication.

After a time T, the communicating AgentCell executes the following signalling stages:

– If the AgentCell is in the sending state (it is a signalling AgentCell), so it secretes (activates) a messenger in the extracellular environment. This messenger is an AgentCM sent from the signalling AgentCell to its nearer AgentCell, (Figure 3 (a&b)).

– To identify the neighbour AgentCell that has the smallest distance, target AgentCell, we applied the equation used in (Dib, 2008).

– Once the target AgentCell and AgentCM are identified the communication, the attraction between specific receptors of targets AgentCell and AgentCM, will be achieved as follows:

  - the AgentCM looks for identifying a specific receptor to this mediator in its membrane. In an affirmative case, it sends an attraction signal to the AgentCM but in the contrary case it ignores it.

- When the research is positive, the AgentCM-Receptor link will be established, and the AgentCM passes from its active state to the captured state (Figure 4). In the contrary case the AgentCM will seek among other AgentCell's neighbors the opportunity to communicate. If no neighbor has a specific receptor permitting the establishing of the AgentCM-Receptor link so this AgentCM will be ignored by any neighbor and it will passes from its current status (active) to the new one "destroyed".

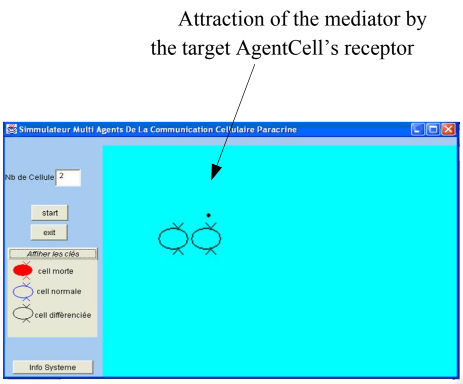


Figure 4: Simulation of the attraction of the chemical mediator by the target cell.

- Once the attraction between target AgentCell and AgentCM is realized then the target AgentCell responds to this action by treating the received signal and generating an appropriate response;
- Once the cellular response is generated so the target AgentCell passes to a new state corresponding to the produced response (Figure 5);
- The AgentCell finish the communication by the inactivation of the AgentCM (mediator). This

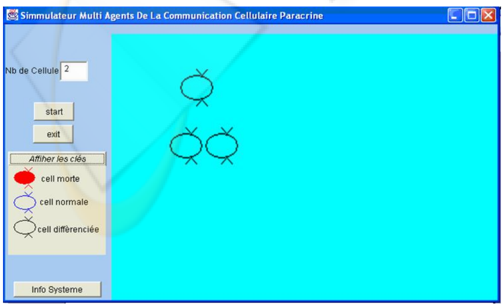


Figure 5: Simulation of the communication: Target AgentCell responses to this message by a proliferation and the system generate a daughter AgentCell.

stage must be fast to permit other mediators to express themselves. An AgentCell can react simultaneously to origin signals. The evolution of the simulation is illustrated by the following figures.

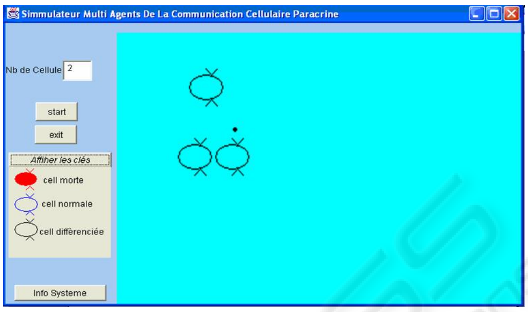


Figure 6: Simulation of a new communication: Send of the mediator.

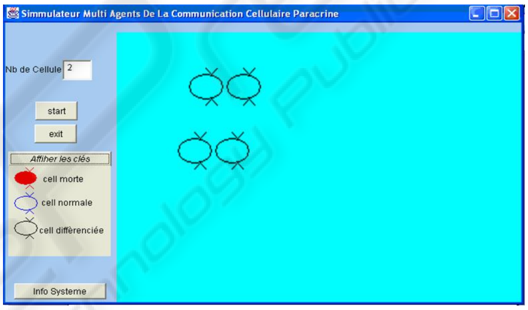


Figure 7: Simulation of a new communication: Target AgentCell responses to this message by a proliferation and the system generate a daughter AgentCell.

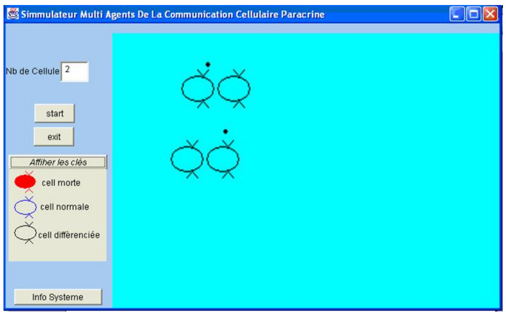


Figure 8: Simulation of communication between two pairs of AgentCell.

Cellular Answer Generated by the Signalling AgentCell. The link of the AgentCM to the target AgentCell's receptor provokes an appropriate cellular response that can be the cellular survival, the cellular proliferation, the cellular differentiation or the cellular death (Figure 9).

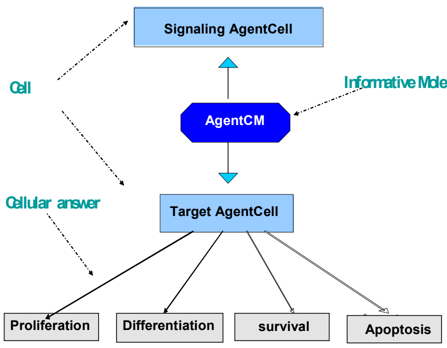


Figure 9: Interaction paracrinien: communication between two AgentCells and target AgentCell's response after its interaction with the AgentCM

In our framework, this response, which is the result of the interaction between two different types of agent (AgentCell and AgentCM), moves the AgentCell and the AgentCM from their current state to another state appropriate for the generated response.

4 CONCLUSIONS

In this article, we presented our system that we have realized under the multi-agent platform DIMA. It allows to model and to simulate the biological cellular environment specifically the cellular interaction process via chemical mediators (paracrinien communication). This modelling is achieved through interactions between the different agents of the system.

The simulation achieved by our system reflects the reality of the biologic nature. The objective of our system *is* to be a virtual world of this cellular biology helping its specialists to better understand, to good to interpret and warn changes of cell states according to its actual internal state and to the state of its environment.

In this system, the cells (AgentCell) communicate with each other to live, to control their growth as well as for regulating their functions. The cell is either normal (in an initial state), or signalling cell (secrets mediator) and whether a target cell (receipts mediator and generates an appropriate response). At the same time, the chemical mediator (AgentCM) is either active (identified and attracted by the target AgentCell's receptor) and whether an ignored mediator (not identified by the target AgentCell).

From our simulator, all these biologic phenomenons are studied and simulated as well as the evolution of a cellular population in the time is calculated and is presented to the user by a sequence of animated images.

REFERENCES

Dib, L. (2008). Multi-agent systems simulating the physiological role of plasmic membrane. *Elsevier Journal "CBM: Computers in Biology and Medicine"*. Volume 38, Issue 6, 676-683.

Dib, L., & Guessoum, Z. (2007): Using Multi-agent Systems to Study Cells Interaction. *SWIN:The Systemics and Informatics World Network. ITSSA Journal "International Transactions on Systems Science and Applications"*. Vol 3, Num 3, 269–278.

Dib, L., Guessoum, Z., Laskri, M.T., Fartas, H., & Guettar, M. (2006). Système multi-agent simulant l'endocytose et l'exocytose. *Troisième International Workshop AMINA: Applications Médicales de l'Informatique Nouvelles Approches.* Faculté de Médecine de Monastir Tunisie, Déc.

Dib, L., Guessoum, Z., Bonnet, N., & Laskri, M.T. (2005). Multi-agent system simulating tumoral cells migration. *Published in "LNCS", AI'05: Advances in Artificial Intelligence.* (pp. 624 – 632). Australia.

Dib, L., Guessoum, Z. (2006). CellMigration system. *Published by "IOS Press book": "Advances in Intelligent IT: Active Media Technology. Fourth IEEE International Conference on Active Multi-media AML'06.* (pp. 400 – 403).

Boss, T., Jonker, C-M., & Treur, J. (2005). Modeling the dynamics of intracellular processes as an organization of multiple agents. *In MAS- BIOMED 05 First Intrnational Workshop on Multi-agent systems for Medicine, Computational Biology and Bioinformatics*. (pp. 107-121).

Colloc. J. (2005). Un Système multi-agent neuronale : vers des systèmes d'information Epigénétiques. *SIM'*05. 5(4).

Giuliano, A., Denzinger, J., Merelli, A., Miles, E., Tianfield, S., & Unland, H. (2005). *MAS- BIOMED 05 First International Workshop on Multi-agent systems for Medicine, Computational biology and bioinformatics*; Ultrecht, Hollande 2005

Guessoum, Z., Meurisse, T., & Briot, J. P. (2002). Modular construction of agents and adaptive multi-agent systems in DIMA. *TSI, thematic number: Environment of development of multi-agent systems.*

Chauffert, B. (2004). Cours sur la biologie cellulaire PCEM 1-PC K,

Masliah, J., & Housset, C. (2008). PCEM2- Biochemistry - cellular Biology. Cellular communication and physiopathology: example of the tumorigeness

Berridge, M. (1985). The molecular basis of communication within the cell. 253(4):142-150,.

Smith, A. D. (1997). *Oxford Dictionary of Biochemistry and Molecular Biology.* Oxford University Press,.

Smith, E. L., Hill, R. L., Lekowitz, I. R. J., Handler, P., & White, A. (1983). Principles of Biochemistry: Mammalian Biochemistry, 6th ed. McGraw-Hill. Chapters 11 through 20 describe in detail the Biochemistry of the endocrine systems.