Multi-agent systems simulating the physiological role of plasmic membrane

Lynda Dib*

Department of Computer Science, University of Badji Mokhtar, bp 12, Annaba, Algeria

Received 22 May 2007; accepted 17 March 2008

Abstract

This paper presents our multi-agent framework for modelling and simulating the physiological role of plasmic membrane specially the ‘endocytosis by receptors’ and the ‘exocytosis’ mechanisms.

As the dysfunction of a plasmic membrane may cause several illnesses (the family hypercholesterolemia, the dilation and the permeability of blood vessel, the allergic reactions as the asthma, rums of hays, hives, etc.), the objective of our multi-agent framework is to be a virtual world of cellular and molecular biology while simulating the physiological role of plasmic membrane in order to help its specialists to better understand, to good interpret and to warn changes of cell interaction and cell adaptation with its environment via its plasmic membrane.

The architecture of our multi-agent framework is composed of a set of reactive agents. These agents use an ontology (named OntoCell) to communicate and to represent their knowledge. OntoCell describes the knowledge of cellular biology.

Our framework is implemented with a multi-agent platform (named DIMA).

Keywords: Multi-agent system; Simulation; Plasmic membrane; Interaction through the membrane; Endocytosis by receptors; Exocytosis

1. Introduction

The biology, specially the study of the human body is a very complex field. In biologic 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, it is difficult in contrast to model and to understand what happens at the cell level.

Several models have been proposed for the study of the cellular behavior such as the cellular automaton [1], the agent based models [2–5], the mathematical model [6]. These solutions required a deep knowledge of the studied phenomenon. In our approach, we propose a multi-agent model of cellular modelization.

The modeling of the biologic and medical systems by the multi-agent approach is in the beginning [7]. Several recent works are interested on the modeling of the cellular behavior. We can mention, as example, the modeling of intracellular signals [8]. Other works are interested on the intercellular modeling. For example, the multi-agent simulation of the cellular migration is permitting to apprehend the migratory capacity of normal or tumoral cells [9,10]. The multi-agent system modeling the neurons is functioning [11], the control mechanisms modelization, for the formation of granulomes during the tuberculosis infection [12]. Using multi-agent systems to study cells interaction [13]. Our system integrates in this category. It focuses on the modeling and the simulation of the physiological role of the plasmic membrane.

The cells import and export substances by diffusion or by some transports systems located in the plasmic membrane. The transmembranous cannot vehicle macromolecules, so the cell uses the vesicle way. The transport vesicle possesses at its surface two categories of proteins. One is capable of distinguishing the molecules transported by the vesicle and the other for the recognition of the target organite.

In this last transport mechanism, when the cell switches the substances toward its cytoplasm, it achieves an ‘endocytosis’ and when it transports them toward its extracellular environment; it achieves an ‘exocytosis’. This paper proposes a multi-agent model to simulate the dynamics role of plasmic membrane, in describing endocytosis and exocytosis mechanisms.
In the endocytosis, we distinguish three forms that differ by vesicles’ sizes and the specificity for the transported molecules, the endocytosis by receptors, the pinocytosis and the phagocytes. The endocytosis by receptors is known for the cholesterol internalization as Low Density Lipoproteins ‘LDL’. The familial hypercholesterolemia is the hereditary illnesses due to various mutations categories affecting LDL receptors. The endocytosis and the exocytosis are the fundamental processes of cellular life consisting in the internalization of portions of plasmic membrane and membranous proteins towards intra- and extra-cellular compartments.

The aim of our work is about offering to biologists the possibility to model and to simulate the complex role of plasmic membrane. Agent paradigm provides a very good solution to model and simulate cells and their interactions. The Architecture of our multi-agent framework is composed of a set of reactive agents. These agents use an ontology (named OntoCell [14]) to communicate and to represent their knowledge. OntoCell is a cellular ontology that we constructed in order to describe the knowledge of cellular biology. Hence, OntoCell represents the concepts of cellular bases, their components, their behaviours and their interactions [14].

This article presents our system simulating the physiological role of plasmic membrane specially the ‘endocytosis by receptors’ and the ‘exocytosis’ mechanisms. It is organized as follows: In the first section, we present the physiological role of plasmic membrane in the biology domain (the ‘endocytosis by receptors’ and the ‘exocytosis’ mechanisms in their nature). In the second section, we describe the multi-agent model. In the third section, we present and analyse the experimental results.

2. Physiological role of plasmic membrane in biology

Membranes surround cells and organites. They assure multiple functions as separation, molecular exchange between compartments, recognition of biologic or other cells. The membrane, which is a fluid structure, can distort itself in order to achieve its physiological working that summarizes by its power to swallow or to expel some voluminous substances.

The physiological role of plasmic membrane especially the ‘endocytosis by receptors’ and the ‘exocytosis’ mechanisms is the molecular exchange mechanisms.

The exocytosis is the transport of molecules toward the outside of the cell via the secretion vesicles. These vesicles fuse with plasmic membrane and free their content (Fig. 1).

The endocytosis is the absorption of macromolecules, particular substances and even other cells, in some specialized cases. The material to ingest is progressively included in a small portion of plasmic membrane that invaginate at first, then detaches by pinching to form an intracellular vesicle containing the substance or the ingested particle (Fig. 2).

3. Multi-agent model

Multi-agent systems offer a very powerful tool for studying the physiological role of plasmic membrane.

We thus propose to represent the cells and the molecules by autonomous and active entities (agents). Our multi-agent system is therefore composed by four categories of agents, defined by a cell population, a molecule population and a Macro and Micro molecule population, which act and interact in their environment [15,16]. In this model, a cell is represented by an agent ‘AgentCell’, a molecule is represented by an agent ‘AgentMol’, a macromolecule is represented by an agent ‘AgentMacroMol’ and a micro molecule is represented by an agent ‘AgentMicroMol’. We also distinguish a set of objects: the environment, the vesicle, the receptors, the ligand and the extracellular matrix.

3.1. Agent model

Agents representing cells, have only a partial vision of the universe in which they evolve. Each agent perceives its environment. According to the environmental information, its internal state and its behavior it takes one or several decisions. Every decision modifies its internal state, its behavior or its morphology. The agent communicates only with a reduced number of
other agents. In our system, four agents have been identified for the modelization of the physiological role of plasmic membrane. They will be described in follows.

### 3.1.1. Cell model

The AgentCell is principally defined by a set of characteristics represented by the following parameters: IS: Initial Size in the normal case, VS: Variable Size in the growth case, CE: Cellular Energy, RN: Number of Receptors bounded to the cell, LinkC: state of the Cell Link with other AgentCell neighboring. This last, takes the value 1 if the AgentCell establishes junctions with its neighbors, the value 0 if junctions with its neighbors are not established. NB: Number of Vesicles formed by the cell, LinkB: state of the link between the plasmic cellular membrane and the one of the vesicle. This last one takes the value 1 if the AgentCell establishes a junction between its membrane and the one of the vesicle, the value 0 if the vesicle is not attached to the cell.

An AgentCell possesses a position ‘pos’, in the studied window, which is generated randomly by the system, an orientation in its environment and one or several simple or complex behaviors. The AgentCell, observes and interacts with the others and tries to adapt; all changes in the environment as a function of its internal and external context of its current state and, this, in the aim to grow, to survive and to collaborate with all other agents for the realization of a common task [9,10]. The AgentCell realizes the following actions:

1. tests the rate concentration of molecules in the environment;
2. decides which method of regulation will execute according to the rate concentration identified in the environment (the mechanism of regulation can be by ‘endocytosis’ if the rate concentration increased or by ‘exocytosis’ in the contrary case);
3. attraction of molecules by the receptor of AgentCell;
4. forms a vesicle containing the receptor and the molecule;
5. transports this molecule toward its inside or its outside according to the chosen method of regulation;
6. controls the rate concentration of the substance in the environment.

### 3.1.2. Molecule model

The cells are constituted of a molecule assembly. All the activities of the cell including the different cellular structure formation 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 ‘RC’ or decreased ‘RCD’, ‘LimitMin’, ‘LimitMax’, express a minimal, maximal limit of resource or molecule concentration, in the environment that will not be clear. An AgentMol possesses a position ‘pos’, in the window of study, which is generated randomly by the system, and is represented by a small red circle (molecule consumed or expelled by the AgentCell) or orange circle (existing molecule in the environment at the initial state).

### 3.1.3. Macromolecule model

Macromolecule is a large molecule from which smaller useful molecules can be extracted. This particle is represented by an agent ‘AgentMacroMol’ which is modelled by an AgentMol specialized in cell-environment interaction and adaptation.

### 3.1.4. Micromolecule model

Micro molecule is a small molecule that can be absorbed and used by a cell or organism. This particle is represented by an agent ‘AgentMicroMol’ which is modelled by an AgentMol specialized in cell-environment interaction and adaptation.

### 3.2. Object model

In addition to these agents, we find other very important entities in the simulated system: the environment, the vesicle, the receptors, the ligand and the extracellular matrix. These different objects are the components of the biologic ontology that we constructed ‘OntoCell’ [14–17].

1. The environment is represented by a particular class ‘Environment’, evolves dynamically to every change of cellular 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’.
2. The vesicle (a circle of protein) formed by the cell is of two types: the first vesicles are composed of the clathrine protein and the second of the adaptathin protein.
3. The receptors are protean molecules situated on the membrane or in the cell and act at the level of the cellular core, capable to receipt endogen molecules (produced by the organism) or specific medicines.
4. The ligand, which is a molecule, is capable to attach to a cellular receptor.
5. The extracellular matrix includes a basal membrane that serves as a support of the polarized cells and the interstitial tissue. It forms a frontier with the conjunctive tissue and plays a primordial role in the cellular migration being the first rampart against tumoral invasion. It is represented, in the window of study, by a straight and thick black line.

### 4. Simulation

The agents of our framework are reactive and communicate by message passing. They are programmed with the development and implementation of multi-agent (DIMA) system [18] environment. DIMA provides a set of classes that can be reused and/or adapted to construct easily agents. For our system, we have used an ATN-based framework (augmented transition network). The ATN is an automaton that represents the agent behaviour.
4.1. Simulation of the environment in the initial state

The simulator, which is the scheduler, can be activated, suspended, resumed or stopped. The following sections describe some examples of simulations that we have realized with our framework.

4.1. Simulation of the environment in the initial state

A plasmic membrane limits every cell (Fig. 3). This last has for role the contact of the cell with outside achieving the transfers of substances, energy and information.

In a healthy environment a cell population, a molecule population and a macro- and micromolecule population are in a normal functioning (Fig. 4).

The aim of the simulation achieved by our system is to reflect the reality of the biologic nature. So, in our simulator initially, a set of identical cells are created forming thus a healthy tissue. Each AgentCell is activated, in a normal state, has a position in the window of study and interacts with its neighbouring AgentCells or adapts to all changes in its environment. After, a set of molecules, macromolecules and micromolecules are also created and active and at the end, a healthy environment (population of healthy AgentCell) in “normal” working is generated (see Fig. 5).

And so, the healthy environment is created and all agents (AgentCell, AgentMol, AgentMacroMol, AgentMicroMol) are active and in their initial state.

The graphical coherence of the environment in our framework requires that the elements in this environment ‘AgentCell and AgentMol’ obey the three following constraints:

The cells should not overflow the imposed borders by the environment. Therefore, they should be created inside. To satisfy this constraint we applied the following equation:

\[ (X_{\text{Center}}^1 + R^2 < X_{\text{EnvironMax}}^3 \text{ && } X_{\text{Center}} - R = 0) \quad (1) \]

\[ (Y_{\text{Center}}^4 + R < Y_{\text{EnvironMax}}^5 \text{ && } Y_{\text{Center}} - R = 0) \quad (2) \]

Neither cells nor molecules should be in intersection. To satisfy this constraint we applied the following equation:

\[ \text{Distance between the two centers} < 2 \times R \quad (3) \]

The molecules should not be represented inside the cells. To satisfy this constraint we applied the following equation:

\[ X_{\text{CenterM}}^6 + R^2 < X_{\text{Center}}^i + R \text{ && } X_{\text{CenterM}}^M - R < X_{\text{Center}}^i - R \quad (4) \]

\[ Y_{\text{CenterM}}^6 + R^2 < Y_{\text{Center}}^i + R \text{ && } Y_{\text{CenterM}}^M - R < Y_{\text{Center}}^i - R \quad (5) \]

4.2. Simulation of endocytosis by receptors

Endocytosis is the process of macromolecules penetration in a cell by fixing on the external surface of plasmic membrane (their fixing on the specific surface receptors) and formation of membrane vesicles.

In our framework and after a time \( T \), the AgentCells verify the rate of resource concentration in the environment. If this rate is increased, AgentCells adjust it by realizing endocytosis by receptors (decreased regulation process).

This process is illustrated by Fig. 6, describing the behavior of the cell in the biologic reality and by Fig. 7 describing the behavior of the AgentCell in our framework.

The simulator initially identifies the cells having the least energies, by calculating the \( \text{minEC} \), which is the minimal cellular energy, and the nearer molecules, and by calculating the \( \text{minD} \) which is the minimal distance between a cell, and all the nearer molecules. To calculate these distances we apply the following equations:

\[ D^9[j] = \text{Math.Sqrt}((X_{\text{Center}}^{10}[i]-X_{\text{CenterM}}^{11}[j])^2 + (Y_{\text{Center}}^{12}[i]-Y_{\text{CenterM}}^{13}[j])^2)) \quad (6) \]
Once a cell and molecules are identified, the attraction of these molecules to the specific receptors of the AgentCell will be achieved. These last, forms vesicles of transport containing receptors and molecules, consumes these vesicles then separates molecules from receptors. This vesicle of transport will be divided into two parts, one carrying the molecule and the other carrying the receptor. Finally, the recycling of the receptor (return to the initial place on the plasmic membrane of the AgentCell) will be achieved (Fig. 8).

4.3. Simulation of exocytosis

Exocytosis is the process of exit that allows the cell to expel big molecules to the extra-cellular environment.

In our framework and after a time $T$, the AgentCells verify the rate of resource concentration in the environment. If this rate is decreased, cells adjust it by realizing exocytosis (Augmented Regulation process).

This process is illustrated by Fig. 9 describing the behavior of the cell in the biologic reality and by Fig. 10 describing the behavior of the AgentCell in our framework.

The simulator achieves exocytosis by identifying cells having higher energy while calculating the maxEC, which is the maximal cellular energy, as well as the localization of the free space, in the environment, where the injected molecules will be placed.

The concerned AgentCell forms a secretion vesicle (that contains the molecule to throw out) below the plasmic membrane, establishes a junction between its membrane and the one of secreted vesicle, and finally the exocytosis ends by incorporating the vesicle membrane inside the plasmic membrane of the AgentCell (Fig. 11).
Fig. 7. AgentCell behavior in the endocytosis by receptors.

Fig. 8. Simulation of the endocytosis by receptors.

Fig. 9. Cell behavior in the exocytosis.
5. Conclusion

In this article, we presented our system that we have realized under the multi-agent platform DIMA. Our system permits modeling and simulating the interaction and adaptation of the cellular process with all changes achieved in its environment. To live, the cell (AgentCell) feeds from resources (sugar, oxygen …) from its environment. These resources can be modified by the contribution of products, by blood or by the different consultations done by the AgentCell.

The simulation achieved by our system reflects the reality of the biologic nature, diffusion of substances toward the inside or the outside of the AgentCell. Thus, in our system, the AgentCell communicates and adapts himself with all changes appearing in its environment by regulating the concentration rate relative to the substances around the AgentCell membrane.

The objective of our framework is to be a virtual world of this cellular biology helping its specialists to better understand, to good interpret and to warn changes of cell states according to its actual intern state and to the state of its environment. Our system uses the strength of ontologies for a collective understanding of messages exchanged between agents. These ontologies permit to capture the semantics of the biologic domain.

During the transport vesicle possesses (the molecular exchange) especially the ‘endocytosis by receptors’ and the ‘exocytosis’ mechanisms cells are brought to modify their shape, their polarity, and their cohesion. The whole of these modifications conduct cells to interact with their neighbouring cells or adapt to all changes in their environment via their plasmic membrane.

From this system, physiological role of plasmic membrane is 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.

Conflict of interest statement

None declared.
References


Dr Lynda Dib received her Bachelor’s degree in computer science from the University of Annaba in 1994. Her engineering thesis is entitled ‘Realization of a generator of Graphic interface to model thesaurus based on Petri nets’. In 1997 she received her Master’s degree in computer science from the University of Annaba. Her Master thesis is entitled ‘IGMA: development of a multi-agents generic interface’. In 2006 she received her PhD degree in computer science (Bioinformatics) from the University of Annaba. Her PhD thesis is entitled ‘Analyze, by computer modeling and video microscopy, of the dynamic behavior of individual cells and cellular populations, in cancerous pathology’. Her interested activities of research include Bioinformatics, Ontology, Knowledge representation, Petri network, and Human–Machine Interface.