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**An Agent-Based Approach for Building
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Engineering for Complex and Adaptative
Multi-Agent Systems**

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An Agent-Based Approach for Building Biological Systems: Improving the Software Engineering for Complex and Adaptative Multi-Agent Systems

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Abstract. Biological systems are typically open, distributed and complex systems, comprised of multiple interacting autonomic elements that exhibit emergent behavior. Design and development of such systems is a non-trivial task that by definition requires specific software engineering approaches, including the use of specialized modeling techniques. Multi-agent systems are a relatively new way to address complex systems. Usually the idea is that the agents used are rather simple, and the complexity and adaptability of such a system are modeled by the interaction between these agents. This paper starts situating the reader in the biological systems context. Then it describes how multi-agent systems can fulfill their needs of modeling and simulating. To exemplify, we briefly describe five applications with different targets and approaches in this area. Finally, we present the research challenges for developing software engineering of multi-agent systems capable of implementing the behavior of complex and adaptative systems such as a biological system or any other with those characteristics.

Keywords: Multi-Agent Systems; Open Systems; Complex Systems, Biological Systems, Software Engineering for Multi-Agent Systems.

Resumo. Sistemas biológicos são sistemas abertos, distribuídos, e complexos compostos de múltiplos elementos autônomicos interagindo entre si, e exibem comportamento emergente. O projeto e desenvolvimento destes sistemas é uma tarefa não-trivial que, por definição, requer abordagens de engenharia de software específicas, incluindo técnicas de modelagem específicas. Sistemas multiagentes são uma forma relativamente nova de representar sistemas complexos. A idéia é que os agentes representam uma forma simples de representar as entidades, e a complexidade e capacidade de adaptação de tais sistemas podem ser modelados através das interações entre estes agentes. Este artigo começa situando o leitor que não é da área de medicina no contexto de sistemas biológicos e então descreve como sistemas multiagentes podem complementar suas necessidades de modelagem e simulação. Para exemplificar, descrevemos sucintamente cinco aplicações com diferentes metas e abordagens nesta área. E, por fim, apresentamos os desafios de pesquisa no desenvolvimento de uma engenharia de software para sistemas multiagentes capazes de implementar o comportamento de sistemas complexos e adaptativos tais como um sistema biológico ou qualquer outro que compartilhe as mesmas características.

Palavras-chave: Sistemas Multiagentes, Sistemas Abertos, Sistemas Complexos, Sistemas Biológicos, Engenharia de Software de Sistemas Multiagentes.

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1 Introduction

Much effort has been expended on the development of an appropriate software engineering approach for multi-agent systems in the last years [1][2]. Several methodologies, frameworks, platforms and techniques have been developed and proposed seeking to support software engineers in multi-agent system development: from coordination of multi-agent systems [3] to several strategies of negotiation between agents [4][5], for instance.

The systems, which exhibit some characteristics as autonomy, pro-activity, interactivity and adaptative, might be modeled and developed as multi-agent systems. For instance, not only are biological systems an excellent applicability of multi-agent systems concepts; they also can inspire new models for self-adaptation, self-protection, self-healing, heterogeneity, self-organization, cooperation and coordination mechanisms.

Other modeling and simulation of biological systems have been proposed through the ordinary differential equations (e.g., [6][7]) or cellular automata (e.g., [8][9][10]). However, differential equations are quite distant from the language of physics. And considering computational models based on cellular automata, it would be necessary to know how to handle all possible interactions, which in most situations it is not possible because emergent behavior appears over time from the interactions.

Furthermore, from the biological modeling point of view, the agent approach is more biologically plausible since it does not rely on obtaining information about the overall system state; rather, its behavior is based solely on its internal state, its perception of the local environment state and the actual physical state of the local environment. Biological plausibility at this abstract modeling level is important to attract biologists to use and work with models and simulations in general [11]. Hence, agent technology can be exploited to develop a suitable conceptual framework for simulation in order to analyze system behavior and eventually to infer new components and functions. In addition to the expected contribution of agents in computational biology as a technological framework, since biological systems should be modeled as complex adaptive systems, we see another challenge to deal with, i.e., the possibility of designing incredibly complex systems through models suitable for representing and analyzing biological systems from different viewpoints: static-structural, dynamic and functional.

Moreover, the ability to predict system behavior with a model helps evaluate model completeness as well as to improve our understanding of the mechanisms of biological processes.

With regard to a multi-agent system point of view, it is our belief that modeling the behavior of biological systems as a multi-agent system is the most appropriate way of understanding the process of some self-* concepts, such as self-organization, self-protection, self-healing and self-optimization. It contributes to the development of novel techniques using the software engineering approach for multi-agent systems.

Outline

This paper is organized as follows: Section 2 starts situating the reader in the biological systems context. Section 3 presents not-agent-based related works. Section 4 describes

the characteristics of multi-agent systems that can fulfill their needs of modeling and simulation. Section 5 briefly describes five applications in this area in order to illustrate the multi-agent system approach applicability. Section 6 presents the research challenges for developing software engineering of multi-agent systems capable of implementing the behavior of complex and adaptative systems, such as a biological system or any other with those characteristics. And finally, Section 7 concludes the paper and presents the future works.

2 Characteristics of Biological Systems

Biology is the study of complex adaptative reproducing systems. Systems biology is the quantitative study of biological systems, aided (or hindered) by technological advances that permit computational analysis of observations [12].

A biological system, understood as a computational system, represents computational units that might be interpreted, on different levels of abstraction, as proteins, cells, tissues, organs, etc.) running in parallel (following well-defined patterns of behavior determined by the potential bio-chemical reactions in which they might be involved) and organized in hierarchies of subsystems an organism can be described as a system of organs, then each organ as a system of tissues and further the tissues as systems of cells, etc.). They interact, collaborate, communicate and interrupt each other. Underlying this paradigm is the assumption that each part of such a system (each subsystem) has its own identity, which persists through time [13].

By abstracting biological systems on the level of their behavior, we obtain behavioral models that share many characteristics with computational systems. Thus we have concurrency, event-driven and cause-effect behaviors and branching-time dependence, all in the context of distributed control [13].

Biological systems are complex [14], consisting of a set of components interacting with each other and with an external (dynamic) environment. By its definition (of complex systems), biological systems have the following characteristics:

- Relationships are **non-linear**: a small perturbation may cause a large effect, a proportional effect, or even no effect at all;
- Relationships contain **feedback loops**: the effects of an element's behavior are fed back in such a way that the element itself is altered;
- They are **open systems**: matter or energy can flow into and/or out of the system;
- They have a **memory**: they are dynamical systems that change over time, and prior states may have an influence on present states;
- They may be **nested**: the components of a complex system may themselves be complex systems, e.g., an organ is made up of cells which are complex systems. Many biological systems are described hierarchically as components of subsystems.
- They may produce **emergent phenomena**: emergence [15][16][17][18][19][20][21][22][23] can be seen as an evolving process that leads to the creation of novel coherent structures, patterns of behavior, and properties at the macro level that dynamically arise from the interactions between the parts at the micro level. The functioning of the system can only be understood

by looking at each of the parts in the context of the system as a whole, however, not by simply taking the system apart and looking at the parts. Emergence can neither be controlled nor predicted nor managed. There are simply no levers that can be pulled in order to produce a particular kind of emergent result.

- They are **self-organizing** systems: dynamical and adaptive systems functioning without external direction, control, manipulation, interference, pressures or involvement [16][24]. It constantly adapts its spatial, temporal and/or functional structure by organizing its components in a more suitable way in order to improve its behavior, performance and/or accuracy. While such a system may get input from outside the system this input should not comprise control instructions [25].

Self-organization and emergence have some similarities and some differences. They are both self-sustained systems that are not directly controllable or manipulable in any way from the outside. They both evolve over time; however, only self-organizing systems need to exhibit a goal-directed development. Emergent systems consist of a larger number of low-level (micro-) entities, which collaborate in order to exhibit a higher level (macro-) behavior. The unavailability of one or more of those lower level entities does not abrogate the functioning of the system (graceful degradation) while this may be the case in self-organizing systems.

There are also other characteristics that should be pointed out. For instance, consider the Immune System (IS). The IS of vertebrates constitutes the defense mechanism of higher level organisms to molecular and micro organismic invaders. It is made up of specific organs and of a very large number of different kinds of cells that have or acquire distinct functions. The response of the IS to the introduction of a foreign substance (antigen) that might be harmful thus involves a collective and coordinated response of many autonomous entities. And the IS provides inherent mechanisms as:

- **Learning:** they must be able to newly activate a previously performed reaction. For instance, this feature enables a local and faster reaction to infections as the related signals must not reach a specific organ, traveling through the cardiovascular or lymph system, in order to activate the IS response. There is no prior knowledge on possible threats, and the IS must base its working on really basic elements.
- **Coordination:** the coordination mechanisms are based on the specialization of certain cells, which will become able to interact and activate their specific working when activated by the direct interaction with other entities with compatible membrane.
- **Self-protection:** it is the mechanism that contains the learning mechanism. Once the organism has been attacked, the IS must be able to self-protect it from other attacks of the same type through the creation of antibodies, which neutralize possible harmful effects;
- **Self-healing:** again, through the creation of antibodies.
- **Adaptative:** there is no prior knowledge about possible threats.

3 Not-Agent-Based Related Works

This section presents the four main not-agent-based works for modeling and simulating biological systems in order to subsequently offer an overview about the benefits of

the multi-agent systems approach for this propose. They are: mathematical modeling, Monte Carlo methods and simulation, cellular automata, and Petri net tools.

Basically, the different types of model (that might be combined) are [12]:

- Deterministic models, which are based on differential equations (ordinary or partial).
- Stochastic models, which are based on Monte Carlo methods or statistical distributions.
- Discrete event (in time), e.g., cellular automata.
- Continuous event (in time), e.g., rate equations, which will not be further described in this paper.

Considering the deterministic or stochastic models, large-scale linear systems can be modeled deterministically, while often a stochastic model is more appropriate with nonlinearity. And considering discrete time, it is favored when variables only change when specific events occur. For its part, continuous time is favored when variables are in constant flux.

3.1.1 Mathematical modeling: Differential equations

The most widespread formalism is differential equations (ordinary and partial), which describe the rate of production of a system component as a function of concentrations of other system components.

It is possible to describe the evolution of the system with differential equations (e.g., [7]). For instance, a reaction network of interacting macromolecules can be described mathematically by a set of nonlinear ordinary differential equations that track the effects of these simultaneously occurring reactions. By applying a set of rules, it is possible to express an arbitrarily complex reaction network as a set of differential equations.

For instance, the differential equations approach is useful for hypothesis testing. If the mathematical consequences of the mechanism do not agree with the observations, it is necessary to search for the problems in the hypothesis. If the consequences agree with the observations, then it is possible to have some confidence in the mechanism.

3.1.2 Monte Carlo Methods and Simulation

Monte Carlo simulation is a method for iteratively evaluating a deterministic model using sets of random numbers as inputs. This method is often used when the model is complex, nonlinear, or involves more than just a couple uncertain parameters.

The goal of the Monte Carlo method is to determine how random variation, lack of knowledge or error affect the sensitivity, performance or reliability of the system being modeled [26].

Several works have been proposed for the biological systems modeling and simulation through Monte Carlo Methods (for instance, [27][28][29][30]).

3.1.3 Cellular Automata

Several biological systems have been modeled and simulated through cellular automata [31] (e.g., [32][33]). A cellular automaton is a discrete model that consists of an infinite, regular grid of cells, each in one of a finite number of states. The grid can be in

any finite number of dimensions. Time is also discrete, and the state of a cell at time t is a function of the states of a finite number of cells (called its neighborhood) at time $t-1$. These neighbors are a selection of cells relative to the specified cell, and do not change. Every cell has the same rule for updating, based on the values in this neighborhood. Each time the rules are applied to the whole grid a new generation is created.

Cellular automata were studied in the early 1950s as a possible model for biological systems. Stephen Wolfram [31] points out that even the most complex equations fail to accurately model biological systems, but the simplest cellular automata can produce results straight out of nature. Moreover, these models take advantage of the extreme simplification of the physical system and of the efficient computer implementation of models compared with differential equation models.

3.1.4 Petri Net Tools for modeling and simulating biological systems

In contrast to the classical mathematical descriptions mainly based on ordinary differential equations, the specification of complex systems is based on behavioral modeling. And Petri Net tools can be used with this purpose.

The most basic Petri Net [34][35] is a directed, bipartite graph in which nodes are either places or transitions, where places represent Boolean conditions and transitions represent activities. Tokens in places represent local (atomic) states signifying that the condition associated with that place holds.

The placement of tokens in the net, called marking, defines the Petri Net's global state. A Petri Net can be "executed" or simulated by moving tokens according to a firing rule; when all the places with arcs leading to a transition have a token, the transition is enabled and may fire by removing a token from each input place and adding a token to each output place. The results of the simulation can be visualized as graphs or analyzed quantitatively or qualitatively.

The work proposed in [36] surveyed Petri Net formalisms and tools. They were compared based on their mathematical capabilities as well as by their appropriateness to represent typical biological processes. They measured the ability of these tools to model specific features of biological systems and answered a set of previously defined biological questions.

4 Multi-Agent Systems for Medicine and Computational Biology

In order to apply multi-agent systems for medicine and computational biology, or more specifically, for modeling and simulating biological systems, it is necessary to understand how the characteristics of multi-agent systems contribute to the field.

It is also important to understand how the multi-agent systems fulfill the open problems of modeling and simulating biological systems and what are the advantages of such application compared to the existent ones described in the previous section.

4.1 Adequacy of Multi-Agent Systems for Modeling and Simulating Biological Systems

An agent is an interactive computer system that is situated in some environment and that is capable of autonomous action in this environment in order to meet its design

objectives [37]. And multi-agent systems are a sets of agents interacting in a given dynamic environment.

We identified the characteristics that make multi-agent systems an appropriate tool to tackle biological systems modeling and simulation problems through the following claims:

- Agents are **autonomous** entities: an agent is capable of acting without direct external intervention;
- Agents are **interactive** entities: an agent communicates with the environment and other agents;
- Agents are **pro-active** entities: an agent is goal-oriented, i.e., it does not simply react to the environment;
- Agents and multi-agents systems have the capacity for **adaptation**: an agent is capable of responding to other agents and/or its environment to some degree, and a multi-agent system might adapt itself to a specific state through the learning processes;
- Agents can have the capability of **learning**: an agent is able to modify its behavior based on its experience;
- Agents can be **rational**: an agent is able to choose an action based on internal goals;
- Agents can be **mobile**: an agent is able to transport itself from one environment to another.
- Multi-agent systems can handle the complexity of solutions through **decomposition, modeling** and **organizing** the interrelationships between components [2].
- Multi-agent systems provide abstractions that allow decomposing a biological system to a set of agents;
- Multi-agent systems provide **flexibility** for modeling more sophisticated, globally emergent behavior;
- Multi-agent systems by their nature are powerful tools for modeling **complex systems** [2]. Modeling complex systems implies a deep understanding of the system both in terms of its structure and its behavior and multi-agent systems allows this specification.
- Software agents embody **distribution** and **heterogeneity** and, thus, they are indicated as the new abstraction for the engineering of complex distributed systems;
- Multi-agent systems are capable of being **open systems**: agents may enter and leave the environment at their will, and the systems have no single point of control.
- Multi-agent systems are capable of being **self-organized**: agents could be organized in a structure that might evolve to a different structure according to the agents' behavior, performance, and others.
- Multi-agent systems can produce the **emergent behavior**: the global effect resulting from the interaction of the individuals is often unpredictable and non-deterministic.
- Finally, the **locality** is an intrinsic feature of an agent: the agents' decisions are taken considering only the local environment and not the global average.

All of these characteristics make the multi-agent system a suitable paradigm for modeling and simulating biological systems, considering the nature of the systems presented in Section 2.

4.2 Advantages of Multi-Agent Systems compared to Not-Agent-Based Related Works

None of the mathematical models used for describing biological systems allow expression of partial information about a system, i.e. to formally describe open systems. Moreover, depending on the system's complexity, there would be an explosion of differential equations; for example, to model it with more than 50 equations to model a subsystem. Another drawback is the absence of an abstraction for the models. Physicians must deeply understand mathematical methods in order to model the system, while multi-agent systems can provide the right level of abstraction for that.

Compared to the Monte Carlo methods, multi-agent systems are not just probabilistic dependent. More than reproducing the emergent behavior, they can provide advanced mechanisms existent in biological systems, such as learning and adaptation that, as far as we know, are not possible to implement through Monte Carlo simulation. Those mechanisms not only make the model more complete but also allow the optimization of self-organization, for instance.

Considering the cellular automata approach, the multi-agent system approach for modeling and simulating biological systems might be more suitable since it provides an easier way of represent the interactions between entities through the agents' interactions. Moreover, the software engineering for multi-agent systems can provide powerful techniques, methods and tools for the engineering of modeling and simulation of biological systems. For instance, self-organization of biological systems could be modeled through the self-organization modeling techniques existing in agent-oriented methodologies that accomplish this purpose.

Addressing the Petri Nets approach for modeling biological systems, they are not suitable for studying systems exhibiting continuous dynamic behavior that: (1) cannot be described by a set of discrete states, (2) cannot be broken down to atomic processes, or (3) are dependent on spatial properties. Examples include fluid dynamics and protein folding. And multi-agent systems could address all of these different kinds of behaviors.

The MAS model is a powerful tool used to described local behavior and leaves the system free to simulate all events just by interactions between agents. However, the goal here is not to prove that multi-agent systems simulation is better or not than the not-agent-based related work cited. They are all powerful ways of modeling and simulating biological systems and have been proven to work. Instead, it is important to understand how multi-agent systems complement these approaches in nature and behavior.

5 Exemplar Applications of Multi-Agent Systems for Modeling and Simulating Biological Systems

In order to give an overview of modeling and simulation of biological systems using multi-agent systems, we are going to present five different approaches that are exemplar applications with this proposal.

5.1 Immune System Modeling with Situated Cellular Agents

This work proposes an agent-based immune system modeling in order to discover novel and more effective security models, e.g., for mobile agents. The idea is that the IS (Immune System), which constitutes the human defense mechanism of higher level organisms against micro organism threats, has several characteristics in common with the multi-agent systems; for instance, it is a distributed and adaptative system, based on cooperation of entities to achieve its goals; it is composed by heterogeneous autonomous entities; and it presents some learning mechanism in order to develop and evolve its self-protection mechanism when an attack occurs. Basically the authors analyzed and modeled the IS as a way of studying natural means of detecting harmful intrusions and effectively respond to the threat. Thus, to study the IS represents a way to gain insight into possible methods to prevent and tackle threats to artificial systems.

They built a model based on Situated Cellular Agents (SCA) model [39]. The SCA model is a particular class of Multilayered Multi Agent Situated System (MMASS [38]) that allows the representation of the interaction between space dependant entities. They built the model in a way that the elements and mechanism of the IS can be represented as the interaction between entities. It is comprised of the following mobile entities: antibodies, B lymphocytes, T lymphocytes, and antigen. And the other IS entities: blood, lymph nodes, tissues, and membranes. The agents implement the cells' characteristics and behaviors.

They developed a prototype using Repast (Recursive Porous Agent Simulation Toolkit) [40][41], which supports many languages: Repast J for Java, Repast.Net for .Net, and Repast Py for Python. Repast has been used for other simulation related works in the following projects: e.g., Patterns in Multi-scale Tumor Growth [42][43], Agent cell [44], Business strategy [45], etc.

The main contributions are the intrinsic adaptation mechanism developed because it is not possible to predict the threats to the system, and the distributed-ness developed because no assumption on the location where the next intrusion might happen can be made.

5.2 Modeling molecular self-organization

This work [46] proposes to model and simulate molecular self-organization through self-organization models of multi-agent systems. The authors state a problem of optimal aggregation in the process of molecular self-assembly and, given N molecules, the goal is to achieve the optimal aggregation, i.e., the lowest-energy organized structure that they can form. With this case study it would be possible to achieve an insight into a definition of the common patterns that make possible the emergence of order from apparently disordered systems.

In the proposed solution, the primitive molecule is a group of four cells. Both molecule and aggregation of molecules are agents or composed agents that can be split. The cell interactions are nearest-neighbor only and based on repulsion/attraction. The possible shapes for the molecules are: two cells are neutral, one is positive, and one is negative; or all four are neutral.

The solution is based on three steps:

- i. It is started with a computational scheme that resembles the Metropolis MC simulation;

- ii. The Rules are introduced in order to avoid the limitations of the Metropolis algorithm
- iii. The formation of low-energy ordered structures is speeded up

In the proposed algorithm, the agent might move to a new position (stochastically), might merge with another agent (deterministically), or split into two different agents, based on learning/adaptation mechanism. The agents learn the best arrangement by comparing the energy made by several molecules with the energy of the most stable agents of equal or smaller size. Whenever an energetically good solution is found, all of the agents share this information and modify their actions

The splitting is done to keep the agent as the most stable unit of its size or smaller in the simulation, and is an intelligent action because it exploits the experience gained globally.

The results were the most impressive thing deriving from this work. Figure 1 shows the comparison between Monte Carlo simulation and multi-agent systems simulation. In the graph that shows the energy spent (fig. 1.a), the blue curve (lower) represents the agent-based simulation, and the red curve (upper) represents the Metropolis, which is a Monte Carlo simulation method. Note that the former spent much less energy than the latter. Figure 1.b illustrates the intermediate process of the assembly and Figure 1.c illustrates the final aggregation.

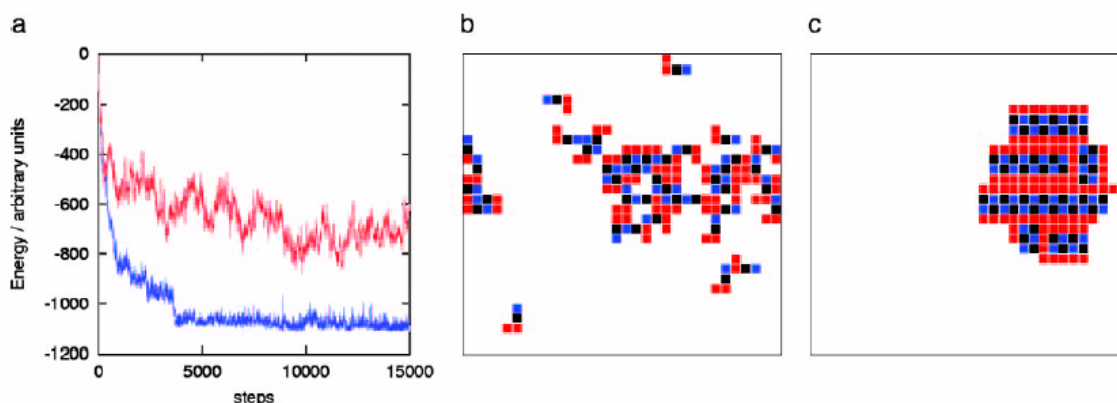


Figure 1 - Simulation Results [46]

5.3 Simulation of mitochondrial metabolism

The mitochondrial metabolism is another suitable application for simulations based on multi-agent systems. The modeling of metabolic pathways, which describes chains of enzymatic reactions, is useful to understand living systems.

This work [47] proposes a solution for the metabolism pathways modeling with a multi-agent system in the context of the mitochondrial metabolism. The multi-agent system developed uses a 3D continuous space where the agents are situated. As mentioned before, Situated Agents use space as a modality of their interactions. The distances between agents are used to describe neighboring rules.

One entity is a simple molecule and each reaction is described by interactions between entities. In the model (see fig. 2), each entity is represented by a reactive agent which is situated in a 3D space. Each agent (molecule) is reduced to its gravity center and its interacting points [47]. Thus molecules can be seen as communities of linked

agents. An interacting point is a portion of molecule that could be affected by external forces. Furthermore, forces and torques are applied at the molecule's center of gravity.

B

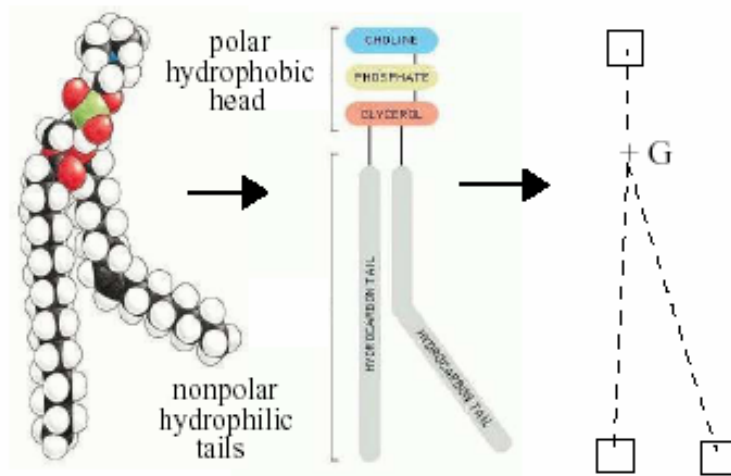


Figure 2 - Application to a phospholipids [47]

The model is capable of modeling and simulating internal dynamics, e.g., respiratory chain reactions since interacting points could induce forces with intensity depending on the distance between agents, and the forces applied by neighboring molecules induce torques.

5.4 Modeling the Dynamics of Intracellular Processes as Organization of Multiple Agents

This work [53] proposes the modeling of the dynamics of complex biological processes as an organization of multiple agents. This modeling perspective helps in the identification of the organizational structure occurring in complex decentralized processes and handles complexity of the analysis of the dynamics by structuring these dynamics according to an organizational structure.

More specifically, they group dynamic properties at different levels of aggregation in the organizational structure, and relate to each other according to the organizational structure. The authors illustrated the applicability of this organizational modeling approach through a case study which is the organization of intracellular processes.

The solution proposed is based on two previous works: Agent-Group-Role (AGR) [54], and Temporal Trace Language (TTL) [55]. They combine both strategies in order to model and simulate the intracellular processes.

An AGR organizational structure for an overall process or organization is a specification based on a definition of groups, roles and their relationships. They created an AGR-model of *E.coli*'s organizational structure. Then they extended the AGR organization modeling approach with the dynamic modeling language: TTL.

The TTL is used to model and analyze the internal and external dynamics of agents and of MASs. It allows the specification of dynamic properties and offers possibilities to specify and execute simulation models.

Basically, the proposed solution combines the modeling and specification of dynamic properties in the three aggregations levels: at the (highest) aggregation level of

the organization as a whole, at the aggregation level of a group within the organization, and at the (lowest) aggregation level of a role within a group.

Furthermore, they identified that certain logical inter-level relationships can be identified between properties at the different levels. And, they show that if the inter-level relationships between the dynamic properties are known, they can be used for diagnosis. For instance, a software environment can automatically check whether such properties hold for a given (empirical or simulated) trace over time for the dynamics of an organization.

They also created a software environment to enable the simulation of executable organization models specified at a high conceptual level. And the input of this simulation environment is a set of dynamic properties.

Briefly, the analysis method for the dynamics from an organization modeling perspective can be defined as follow:

- Specify state properties and dynamic properties of the overall process
- Identify the agents and their roles within the overall process
- Specify state properties and dynamic properties for the behavior of these roles
- Identify groups of roles
- Specify dynamic properties for groups
- Specify dynamic inter-group role interaction and transfer properties
- Identify inter-level relations between dynamic properties at different levels of aggregation: relating role, group and organization dynamics
- Specify executable dynamic properties
- Simulate dynamics based on executable dynamic properties
- Check given traces of dynamics against dynamic properties

5.5 Modeling and Simulation of Stem Cells Systems

The reconstituting potential of tissue stem cells makes them target cells in different types of clinical settings, particularly with respect to the emerging field of regenerative medicine. In order to use the full functional potential of stem cells, it is necessary to achieve a comprehensive insight into general regulatory principles of cellular differentiation and lineage specification. Only on the basis of such a comprehensive understanding will it be possible to quantitatively describe and predict cellular differentiation and, therefore, to control regenerative processes *in vitro* and/or *in vivo*, e.g. by the targeted (re-)programming of cells.

Much work has been done in building agent-based simulations of stem cells [48][49][50][51][52]. For instance, stem cells are a prime example of a self-organizing system where individual agents react to their local physical, chemical and biological environment.

In order to support the claim that the agent approach is more suitable than other modeling approaches, existing approaches have been taken and recast in the agent-based modeling and simulation framework, which has demonstrated a number of clear advantages of the agent approach over existing approaches [26].

To date the authors have produced formal and mutually consistent specifications of many of the key predictive models of stem cell behavior within their agent framework. They have also produced simulations and visualizations of these models. They argue that visualization of stem cell simulations may hold the key for the integration of new models of stem cell organization into the wet lab culture. Wet labs are laboratories where chemicals, drugs or other materials or biological matter are tested and analyzed requiring water, direct ventilation and specialized piped utilities

In the [49] approach, each stem cell which is represented by a cell of the cellular automata approach is implemented as an agent in the agent-based model. They modeled and simulated the stem cells in a dynamic environment with the capabilities of division and determined (stem cells which have reached their cycle phase and which are surrounded by stem cells become determined).

They run several simulations comparing the CA model and the agent-based model and they discussed that the agent-based simulation gives a more biologically plausible handle on how things might be working at the micro-environment level.

6 Research and Development Challenges in Software Engineering for Multi-Agent Systems to Model and Simulate Complex Systems

The main purposes of Agent-Oriented Software Engineering are to create methodologies and tools that enable inexpensive development and maintenance of agent-based software. The software should be flexible, easy-to-use, scalable and of high quality. Agent-oriented software engineering research proposes a variety of new metaphors, formal modeling approaches, development methodologies and modeling techniques, specifically suited to the agent-oriented paradigm. Nevertheless, the research is still in its early stages and several challenges need to be faced before agent-oriented software engineering can deliver its promises.

The multi-agent organization modeling techniques for analysis and simulation allow the management of the inherent complexity of the dynamics of multiple processes within a society by choosing the right level of abstraction. Despite the appealing nature of multi-agent systems, there is still a lot of work to be done before these kinds of systems are widely accepted and become a practically usable paradigm for the development of complex software systems.

Considering biological systems, depending on the complexity of the biological properties we want to model, we can go as deep as necessary with representing the biological entities involved. More complex models provide more accurate information. Still, as the costs of simulation grows with the complexity of the model, we have to find the right level of abstraction that gives, with acceptable costs, the information we are looking for. Observe that in biology, as in all the empirical sciences, we cannot hope to reach the level of having complete information concerning a biological phenomenon. Thus, no matter how complex is the model we choose, properties requiring a bigger complexity always exist [13].

The specification model, e.g. agent-oriented, can help by identifying the system structure, critical component roles and responsibilities, functions and interactions (which are generally poorly identified). Of course, to create models we need languages and suitable notations.

Furthermore, proving properties in biological models can mean verifying properties related to the system/process behavior (e.g. safety properties; liveness properties; simulations of system dynamics; checking for causal relationships...). Any property can be formally proved by using well known methods such as equivalence checking, model checking, simulation and model synthesis.

Given those claims, we briefly highlight the research areas and the improvements in software engineering for multi-agent systems to model and simulate complex systems, particularly biological systems:

- Design Methods for agent systems: design patterns and components.
- Organizational structuring and design for agent systems
- Practical coordination and cooperation frameworks for agent systems
- Agent architectures
- Agent notations and development methodologies
- Agent representation formalisms
- Dependable agent systems
- Experiments and case studies
- Methodologies for agent-oriented analysis and design
- Model driven development for agent systems
- Ontology and multi-agent systems
- Software development environments
- Verification and validation techniques
- Scalability in simulation
- Truly open and fully-scalable agent systems
- Agents learning techniques (agents learn appropriate protocols and behavior upon entry into system)
- Develop reasoning capabilities for agents in open environments
- Develop agents' ability to adapt to changes in environment
- Run-time reconfiguration and re-design
- Domain-specific models of reasoning
- Education and training (of physicians).
- Undertake research on methods for ensuring security and verifiability of agents.

7 Conclusion and Future Works

We believe that biological systems, which are complex systems, can be modeled and simulated as multi-agent systems and that the agent paradigm is well-fitted for the right abstraction levels.

We depicted the main biological systems characteristics and we showed how the multi-agent systems contribute to their modeling, development and simulation. Furthermore, we briefly highlighted the main not-agent based related works that address

the problem of modeling and simulating biological systems. Thus, we discovered how the multi-agent systems could solve the current open problems left by those works.

In order to illustrate more specifically how these issues would be addressed by the multi-agent systems, we briefly described five application examples with this proposal.

Finally, we cited the main research and development challenges for the software engineering of multi-agent systems that would be improved with the modeling and development of biological systems through the simulation.

For future work, we are going to study agent-based simulation tools and methodologies for using them. Moreover, we are going to select some biological systems to implement on them. As a second step, we will propose a methodology (extended from one that already exists or not) for the modeling of the biological agent-based systems, and we will develop both the environment for modeling the biological system as well as the middleware for its development. This includes the use of design patterns and components inside the middleware that would be reused in other types of complex systems.

Based on the experiments and on the iterative development of the methodology and middleware, we will reuse and develop (as necessary) new methods of learning, adaptation, and self-organization mechanisms necessary for the simulation of the biological agent-based system, which could be reused in other complex systems. Other possible future work is the development of formal methods for proving biological properties.

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