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A multiagent and multimodel approach for the experimentation on biological complex systems.

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ABSTRACT

The advent of the computer and of computer science, and in particular virtual reality, offers new experiment possibilities with numerical simulations and introduces a new type of investigation for the complex systems study : the in virtuo experiment. This work lies on the framework of object oriented-modeling and multiagent systems. The aim is to combine the systemic paradigm and the virtual reality. We propose a generic model for systems biology based on reification of the interactions, on a concept of organisation and on a multimodeling approach. By "reification" we understand that interactions are taken as autonomous agents. An application to a disease study : the allergic urticaria.

1. INTRODUCTION

Within the framework of the study and the comprehension of complex systems, the **experimentation** has been proven to be the best tool for investigation of the living, from both historical and empirical standpoints.

In vivo*:** In the disciplinary field of study of the living systems, in other words in biology, the experimentation on the real system is called ***in vivo experimentation. These *in vivo* experiments may, in some cases, raise technical or ethical problems. Then, the biologist must find alternative methods to circumvent the given constraints.

In vitro*:** A model is an artificial representation of the phenomenon or of the object of the study. The alternative method consists in testing this representation's behavior under the effect of actions that can be carried out on the model. This is the case of the ***in vitro experimentation where a sample or a physical model built by analogy with the real system, is experimented.

In silico*:** Unfortunately, the observation of a real sytem, of a sample or of a physical model, can sometimes interfere with the studied phenomenon. Moreover, even with *in vitro* experimentation, the technological means are often too limited to permit the detailed observation of the phenomenon. In that case, we use a theory that allows the possibility of the building of predictive numerical models starting from concrete data. It is then possible to simulate these numerical models thanks to the use of a computer in order to obtain ***in silico computations. In general, the *in silico* tools [16] use methods of mathematical resolution based on the ordinary [12] or partial [15] differential equations, or on stochastic tools[11]. In other words, the biologist builds a mathematical model that he implements using a computer. *In silico* computations provide results that are checked against measurements on the real system. The concordance of the results allows the validation of the predictive model. If it is invalidated, the model designer can modify the model and simulate it again. Moreover, there are tools for the mathematical model analysis such as the bifurcation's analysis or as the parameters' estimation, both providing the means to deduce models' properties. Finally, there are the formal methods coming from the process algebra such as κ calculus or π calculus[4]. These methods open the prospect of pointing out models' properties of the studied complex systems. The *in silico* computations has been providing an alternative method to the *in vivo* and *in vitro* experimentations for several years.

Object-oriented approach: Members of systems biology community have been recently working on object-oriented approaches[14]. It began with statecharts representation of biological systems [9] and was followed by agent-based simulation[6]. These method provides modeling modularity, flexibility and reusabililty. Our work can be located within the framework of this object oriented method to model the biological complex systems, putting emphasis on the multimodeling. We want however to improve the method by making it compatible with the definition of virtual reality and the systemic paradigm.

The rest of the paper is structured as follows : the first part introduce the *in virtuo* experimentation. Section 2 presents our systemic paradigm based modeling method, describing *Organisation*, *Interaction* and *Con-*

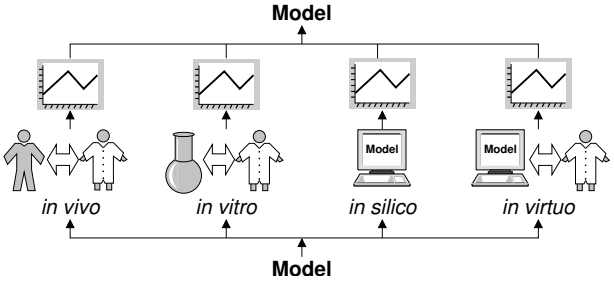

Figure 1: The diagram represents the various means of experimentation. from the left to the right : traditional *in vivo* and *in vitro* experimentations, computations *in silico* and finally the experimentation *in virtuo*. In the four cases, experiments are carried out accordingly to the model. The results obtained give space for the evolution of the theoritecal model.

stituent. Section 3 shows how the generic model is specialised to integrate each different biological models. Section 4 presents aour application.

2. *IN VIRTUO* EXPERIMENTATION

The advent of the computer and computer science, and in particular virtual reality, now offers new experiment possibilities with numerical simulations and introduces a new type of investigation : the ***in virtuo*** experiment.
Initiated in 1997, the "in virtuo" project of the European Center for Virtual Reality (CERV), carried out in collaboration with medical institutions, proposes to apply *in virtuo* experimentation to biology (see figure 1). We develop a workbench for numerical simulations using multiagents approach, in order to develop a true laboratory for experimentation *in virtuo* in biology.
The *in virtuo* approach takes place within the intersection between biology and virtual reality(VR). We take as basis the definition of the VR given by the french community[5]. We focus on the principle the autonomy of the numerical models and also of the entities that populate the virtual worlds[17].
The virtual world is the model of the living system that we want to experiment. It is currently our main goal to build and to make this world virtually alive, and this is the first step towards *in virtuo* experimentation. The study of the user interface and the real-time simulation are relegated to the background.

3. M.A.S. FOR COMPLEX SYSTEMS

Autonomy principle is a major principle of the multiagent systems (MAS). Moreover, among the agents ancestors, we find the cellular automata which have been used for complex systems study during the 40's, so that MAS provides a good candidate to study complex systems. Works on self-organisation of social insects[2] are an example of this type of recourse to the agents. In addition to the autonomy principle, notions of robustness, emergence, self-organisation and adaptibility underlie the MAS.
In this study, an agent can be considered as an engine that is continuously following a three stroke cycle of perception, decision and action, and as belonging to the reactive agents family.
In this section, we describe the multi-modeled method built on systemic paradigm and with MAS. We emphasise on the notions of interaction, constituent and organisation.

From autonomy to multimodeling: If we define the models that populate our virtual universe with the principle of autonomy, we can easily make them coexist. Their autonomy allows them to adapt themselves independently, and to interact with the environment or with another entity too. Thus, we talk about multi-model universe. The models can have very different natures, as developed in this article.
Usually, the modeling of the biological mechanisms differs according to the standpoints we take. The multimodeling approach allows the construction of coexisting different viewpoints that describe the living. It is then possible to construct models with different modeling levels and granularity (from molecule to cell, and then to organ) or with different modeling natures (chemical, geometrical, mechanical, etc. ..). It is why numerical multi-modeled, multi-scaled and multi-skilled models can be considered in order to combine the respective points of view of biochemists, doctors, cellular or molecular biologists. We claim VR and MAS are the tools of predilection for an interdisciplinary study.

Interaction reification: The 20th century has experienced an important change of method : the emergence of the systemic paradigm complemented the reductionist and analytical paradigms. The appeal to the systemic approach leads us to focus on the interactions rather than on components themselves. The idea to directly model the interactions by associating to each of them an autonomous agent derives from this considerations. We therefore had to modify the usual MAS modeling, and consequently the way of modeling a complex system too. We talk about "interactions reification".
As a consequence, to each interaction will correspond a process. To schedule these processes, we have chosen asynchronism because the complex systems are often composed of circular, unstable or oscillating mechanisms which result from the asynchronism of interactions. In order not to introduce any bias in the simulation of the systems, we use a random scheduling of the agents. In that way, we counter the prevailing of an interaction on another, in the case of competition between two of them. We made the choice of considering exclusively chaotic

asynchronous iterations to schedule the agents and, consequently, to schedule the interactions too.
The concept of *Interaction* agent being defined, the organisation concept needs now to be exposed.

Organisation: The organisation is a central concept in systemic. An organisation is a layout of relations between constituents that form a new unity. It defines a structural and a functional aspect of a system.
We need now to consider the organisation as being an object containing constituents and interactions (figure 3) from a computing standpoint. Moreover, a composition relation between the organisations can exist when a system is made of sub-systems. This is the hierarchical level organisation. For example, a transduction pathway is part of a system cell, which is itself a part of the system organ, which is itself part of the human system, the organism, etc... In this example, we use a composing procedure, but it is also possible to use a decomposing process: decomposition of transduction pathway into chemical chains, chemical chains into molecules, molecules into atoms, etc... The problem is that the decomposition cannot be infinite.
To simplify the modeling and to obtain an end to the decomposition process, a sub-system can be taken as a simple constituent if it has no autonomous action on its environment, and if it is purely reactive. In that case, the management of the interactions between the new constituent and its environment can be delegated to its root organisation. The influence of the sub-system is modeled by upper level interactions.
When a sub-system is operationally closed [18], it can be considered as being autonomous. Its response to a stimulus will depend on its internal states. It is therefore not possible to delegate the management of its interactions on the environment to a superior organisation. From the root organisation standpoint, the sub-system can be considered as being the same as an interaction between its inputs and outputs.It is then possible to model it with an autonomous agent. We now have to apply this generic framework of modeling to our domain of interest : biology.

4. MULTI-MODEL FOR THE BIOLOGY

In this section we present the different models implemented with this generic method.

Chemical modeling: In order to adequately model biological systems, we have to model the chemical reactions which are the basic elements of the chemical networks. A molecule cannot be individually modeled to represent systems containing billions of molecules. To overcome this problem, we appeal to the notion of molecular concentrations, and we apply the principle of interactions reification. For every reaction between molecular types, we create a *Reaction* agent that accomplishes the following three strokes engine :

1. Reading of the concentrations of the chemical species involved in the reaction
2. Calculation of the reaction speed and integration on the time step using a classical method (e.g. Runge-Kutta)
3. Concentrations update according to the amount of transformed species.

Reaction agents accomplish three steps one after the other, in a n-long cycle, n being the number of agents. The order of interventions randomly changes from one cycle to the other. This method allows the modeling and the simulation of the kinetic of enzymatic reactions (thanks to the Henri-Michaelis-Menten equations), of dimerisation, of oxydo-reduction, of ligand-receptor associations... The approach has already been applied to works on coagulation [10]. The mathematical proof of the convergence of this method has been recently established[1]. The convergence has an order of 2, whatever the classical method chosen in step 2 of the engine.
Finally, in order to describe chemical networks, we define an organisation *Reactor* that contains the constituent *Species* and the relations between these constituents : the *Reaction* agents.
We now have to model the molecular species diffusion in space. This is an essential mechanism of the chemical messages transmission. The adopted solution to translate the diffusion phenomenon and to add a spatial dimension to the chemical reactions models consists in the partitioning of space. Each piece of space becomes a *Compartment* organisation and contains a *Reactor* sub-organisation. *Diffusion* agents are transportation relations between these organisations. *Diffusion* agent are close to the *Reaction* agents in their way of proceeding. They use the laws of Ficks and represent the diffusion trough a 2D surface. Finally, the diffusion through a membrane and the method of the *Reaction* agents give us access to the describing of the chemical model of a cell.

Modeling of the cell: The *Compartment* organisation contains at least one *Reactor* sub-organisation representing the chemical environment in the tissue. It can also contain some more complex sub-organisations : cells.
These cells can be modeled in different ways (figure 2), thanks to our multi-model approach. From a biochemist standpoint, a cell can be defined as an organisation composed of sub-organisations (i.e. chemical reactors), of

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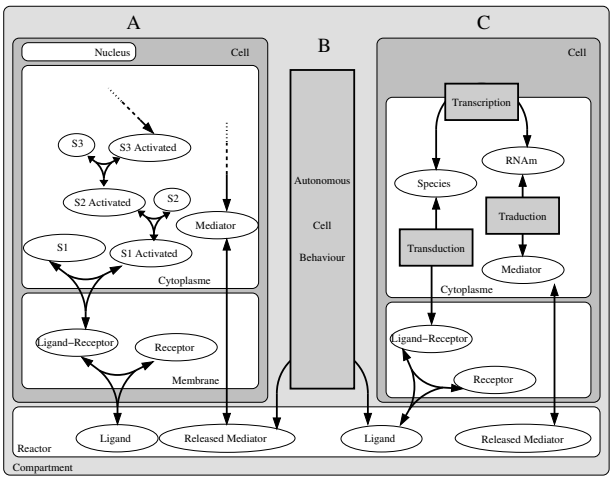

Figure 2: The three means of cell's modeling. On the left, chemical and transport interactions constitute a predictive model. On the middle, cell is taken as an autonomous agent. On the right, the hybrid method using autonomous "black box" interactions allows the modelig of the cell.

constituents (i.e. the molecular species), and of interactions (i.e the *Reaction* and *Diffusion* agents)[13].

The cell is an autonomous system. When the cell's behavior, which needs to be modeled, is simple enough, the cell can be modeled by an autonomous agent. Consequently, the sub-organisation modeling the cell can be replaced by an autonomous agent producing the same behaviour. From the root organisation viewpoint, this system is equivalent to an interaction between species which are normally in relation to the cell.

Finally, it is possible to replace an autonomous subsystem in the cell with agents to create a hybrid model containing predictive parts (reactors and *Reaction/Diffusion* agents) and other parts that are either predictive or explicative, which fill in the "holes" of the chemical model. The behaviour of these sub-systems can be produced by any artificial intelligence tool (neuronal networks, cognitive Maps, states machines..).

The hybrid solution it the most often used. The chains of chemical reactions defining the behavior of a cell cannot be completly described.

This section only defines a cell's chemical's modeling method. It seems desirable to give the cells spatial dimensions. Giving the cell a shape would allow the cell to move in space and eventually to interact with other cells.

Collision managment: In order to give the cell a shape, a *Shape3d* constituent has been added to the *Cell* organisation. This constituent is defined with a position, a mass, a 3D shape, a color... Giving spatial dimensions to the simulation raises a major problem well known in the VR domain : the problem of collisions. We have solved this problem while still remaining within the described multi-model reasoning. When two *Shape3D* constituents

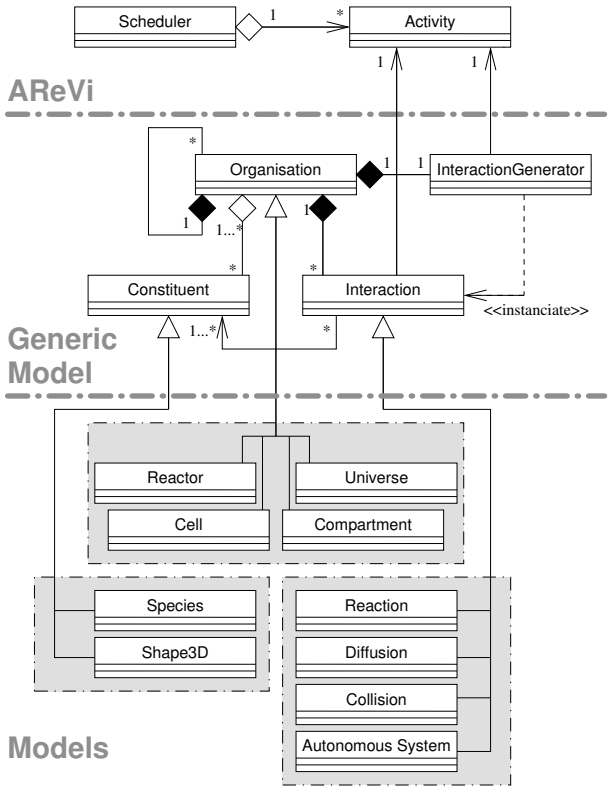

Figure 3: This classes diagram shows the integration of the described models which inherits from the generic model.

are in collision, a *Collision* agent simulates the interaction between the two shapes, by applying a given pressure on them. The *Compartment* organisation which contains the cells creates a *Collision* agent when two shapes are at a certain distance from one another. Next, the *Collision* agent has an autonomous life : it destroys itself when the two components are too far away from each other. To create collisions, the *Compartment* organisation has a collisions detection unit. This unit verifies whether relations between the constituents of the organisation or of the sub-organisations should emerge or not. Consequently, the management of the collisions is partitioned within each compartment.Thus, the simulation's complexity remains in O(n).

Integration in AReVi: All the modelings mentionned here were integrated into the same software architecture.

Programs were developed thanks to the AReVi [7] library. AReVi is an autonomous entities simulation library, as well as a 3D rendering library. The UML diagram of the figure 3 shows this architecture. The application includes three levels:

At the top level, the AReVi library instanciates a scheduler. This scheduler randomly initiates activities (chaotic asynchronous iterations). An activity is the active part of an agent. Then, the generic model defines generic

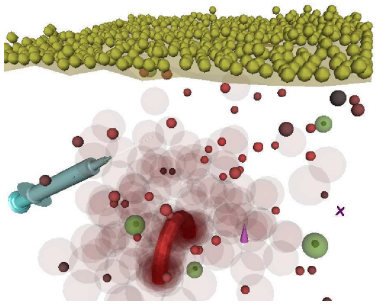

Figure 4: *In virtuo* experimentation allows to observe oedema formation following the injection of allergen in the skin. The sreenshot shows the plasma flows in the tissue.

objects : interaction, component and organisation. Last, the different models inherit from the generic model. The *Shape3D* and the *Species* inherit from the class *Component*. The chemical *Reaction*s, the *Diffusion* reactions, the *Collision*s and the simplifications of autonomous systems inherit from *Interaction*. The chemical *Reactors*, the *Compartments*, the *Cell*s and the *Universe* inherit from *Organisation*.
This is the generic model that allows all these models to cohabitate and to interact in the same virtual universe.

5. APPLICATION TO THE URTICARIA

We already have implemented this multimodeling method in the context of a complex disease study : the allergic urticaria. We have modeled a 600μm cube of skin.In this model, sub-models were included: cell's models (mast cells, macrophages, keratinocytes), a macroscopic model of the capillary vessels, a membrane's model (a basal membrane separating the epidermis of the dermis). These entities are located in a partitioned environment that allows the molecular species' diffusion. The cell's models have been implemented using *Reaction* agents between the cells' receptors and the diffusing molecules. The simulation led to the observation of the effects produced by allergen on the tissue (histamin liberation, capillary vasodilatation, oedema formation: figure 4).
In the current state, we can now affirm that two important thing have been shown. The first one is the validity of the generic model on an application example. The other one is the basis for the establishment of a biological model improving disease comprehension. We wish to show the retroaction and the amplification function of the nervous fibers in the pathology. This type of model renders possible the testing of *a priori* influences of a drug on the system [1].
The real-time interaction between the user and the application is a basic property of the virtual reality according to the technical Fuchs' definition[5]: *Virtual reality techniques are based on* ***real-time interaction*** *with a* ***virtual world****, by the use of a* ***Behavioral interface***[2] *allowing the pseudo natural* ***immersion*** *of the user in this environment.* Wishing to remain within the VR domain, user interfaces were implemented so that the user could have an interaction at any time during the simulation's course :

- A viewer which is provided by AReVi, enabled the observation of and the moving through the model and to interact with the constituents *Shape3D*.
- A virtual syringe allowed the injection of any quantity of molecules anywhere in the model.
- An inspector plots on a graph the species quantities we want to observe in a given place of the model.

Consequently, in order to study and to understand the urticaria, the researcher can experiment the principle of the disease by virtually injecting in the skin a certain amount of allergen which diffuses and activates the urticaria mechanism.

6. CONCLUSION

We can now affirm that we have developed major improvements in the design of a virtual laboratory for experimentation in biology, in the context of *in virtuo* the experimentation. We are able to provide a generic modeling method for the multimodeling approach which is the heart of this virtual laboratory. We deliberately put a stress on the interaction's reification, for it is intrinsically related to the systemic paradigm. Once again, by "reification" we understand that interactions are taken as autonomous agents. This was achieved in works concerned with the modeling of social organisation [3]. The model here exposed differs from these works, for interactions are taken as the "only" active objects in the simulation. We introduce this vision into the systems biology field, using multiagent systems according to both the concept of organisation and the chaotic asynchronous iterations.
This model will naturally have to evolve as regards to the operational aspect of the organisation's model. A mechanism for the emergence of new relations between the constituents of the organisations has to be defined. This could plausibly be achieved by generalising the method used for the collisions detection. The collisions detectors could be taken as elements filling in a more general task, becoming detector/generator of relations. when the generic model will be stable, it will be possible to look for a solution to distribute the simulation. The possible distribution of computation could lead to both simulation and experimentation on broader models.

2 Interface exploiting a human "natural" behavior and not implying any important or complex apprenticeship period before being usable.

As to the biological aspect, we keep working on the development of the urticaria model which needs to be completed in order to give significant results. We work on the addition of a nervous fiber model to observe its influence on the allergic reaction. The objective is to test hypothesis concerning the mechanisms of amplification, retroaction, and inhibition... which all are characteristic mechanisms of complex systems. We currently plan to test the effect of drugs such as anti-histaminics which reduce the allergic response. In addition to that, we study the possibility of interfacing our application with a norm such as SBML [8]. SBML allows the simplification of the model definition and provides the possibility to exchange data with the systems biology community.

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