The Virtual Reality applied to the biology understanding: the in virtuo experimentation

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The virtual reality applied to the biology understanding: the *In Virtuo* experimentation.

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Abstract: The advent of the computer and 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 multi-agent systems. We propose a generic model for systems biology based on reification of the interactions, on a concept of organization and on a multi-model approach. By ``reification" we understand that interactions are considered as autonomous agents. The aim has been to combine the systemic paradigm and the virtual reality to provide an application able to collect, simulate, experiment and understand the knowledge owned by different biologists working around an interdisciplinary subject. In that case, we have been focused on the urticaria disease understanding.

The method permits to integrate different natures of model. We have modeled biochemical reactions, molecular diffusion, cell organisations and mechanical interactions. It also permits to embed different expert system modeling methods like fuzzy cognitive maps.

Keywords: multi-agent system, systems biology, *in virtuo*, interaction reification, virtual reality

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Introduction

The models of systems we study become more and more complex. The diversity of organizations, of structures and of interactions is responsible for this complexity. These organizations can be structured in different levels that are initially kown. The human using his free will, plays a determinating role in this structuration. Structuration can also emerge during the evolution thanks to the various interactions between the components. These interactions can have different natures. They can work with different spatial and temporal scales. There is no theory able to formalize this complexity and no formal proof method like to those we have with the highly formalized models. Being deprived of formal proof, we have to experiment the systems during their progress. Thus, experimental *a posteriori* validations are provided. The conceptual, methodological and experimental framework provided by the Virtual Reality (VR) fits the modeling and the study of complex systems. The aim of CERV[1] is to use VR to study complex systems.

Within the framework of study and understanding of biological complex systems, the experimentation has been proven to be the best tool for investigation of the living, from both historical and empirical standpoints. Here, we present a new biological experimentation method based on Virtual Reality : the *in virtuo* experimentation.

The rest of the paper is structured as follows : the first part introduces the virtual reality and the multi-model construction aim. Section 2 defines the *in silico* and the *in virtuo* experimentations. Section 3 presents our systemic paradigm based modeling method, describing *organization*, *Interaction* and *Constituent*. Section 4 shows how the generic model is specialised to integrate each different biological models. We finally present the application to the study of a complex disease: the allergic urticaria.

1 Virtual Reality for experimentation on complex systems

The *in virtuo* approach takes place within the intersection between biology and virtual reality (VR). Biology being defined as the study of the living complex systems, the VR ougth to be briefly defined.

1.1 Definitions for virtual reality

Defining a scientific domain is not an easy thing to do. It is even more difficult when this domain is in constant development. Therefore any definition of VR is naturally subject to criticism. We expose here the definitions which have structured our work. The first one, a functional and theoretical definition given by Fuchs(1) :

*Virtual reality allows the user to extract himself from the physical reality, in order to experience a virtual change in **time**, **place**, and/or type of **interaction** : interaction with an environment simulating reality or interacting with an imaginary or symbolic world.*

A technical definition can complete the previous one :

*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.*

The virtual world is the model of the living system 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 experiment is possible only if the user can interact with the virtual model. This interaction is possible by recoursing to interfaces. VR interfaces have already been studied in the context of expert system an VR (Savage-Carmona, 1998). In this work, their deepened study is premature and is relegated to the background. But we must keep in mind to remain within the VR field, and therefore within the *in virtuo* experimentation field. Likewise, real-time[3] must not be forgotten in the simulation.

These two definitions define the domain in a broad manner. Nevertheless, we will complete them in order to situate our work more precisely within the VR field.

1.2 Autonomy in the virtual universes

To these classical definitions, we must add the notion of autonomy that presents itself to us by essence, by necessity, by ignorance and by conviction, to construct our virtual worlds (2) :

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1 European Center for Virtual Reality

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

3 By real-time, we mean that we master the instructions' execution time. For example, during an experiment, ten seconds of the real time (the one of our watch) may correspond to one virtual second (the one of the potential world).

- By essence, because we try to model systems which are made up of entities like cells. Those are autopoietic systems and are, by definition, autonomous systems (3).
- By necessity, for the entities that constitute the universe can adapt their behavior, during execution, to the modifications of the conditions of the limits (due to unpredictable interactions, disruptions or modifications of the environment) .
- By ignorance, because the inexistence of models for the global system behavior leads to autonomise the model of the components. In other words, we would study emerging behaviors.
- By conviction, by accepting the distribution of the control of the evolution of the virtual universes between, on the one hand, the users, and, on the other hand, the numerical models that populate these universes.

Thus, we decide to take as a principle the autonomy of the numerical models and also of the entities that populate the virtual worlds. These considerations apply to the study of the biological complex systems.

1.3 From autonomy to multi-model universe

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 standpoint we take. The multi-model 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.

Therefore, given the definition of the VR we gave, it seems that VR is the tool of predilection for an interdisciplinary study. Now, we will apply the VR concept to the traditional bioinformatics systems.

2 From *in silico* to *in virtuo*

2.1 Traditional *in silico* methods for the Biology

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.

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.

Unfortunately, the observation of a real system, 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 (4) use methods of mathematical resolution based on the ordinary (5) or partial (6) differential equations, or on stochastic tools(7). 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, π calculus(8) or the brane calculus(9). 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. But we can criticize those for making the user passive during the calculation. These tools only provide the ability to observe the model but not really to experiment it.

2.2 Virtual lab for the *in virtuo* experimentation

(Fu & Bradford, 95) have presented an hybrid modeling scheme showing the need to integrate different models in one application. Members of systems biology community have been recently working on object-oriented approaches(10). It began with statecharts representation of biological systems (11) and was followed by agent-based simulation(12). Multi-agent systems avantages in dynimical environments, have been presented in (Pendharkar, 99). A recent article presented a blackboard architecture for the modeling(13) of intra and extra cellular processes. This method provides modeling modularity, flexibility and reusabililty. Our work can be located within the framework of this agent-based method to model the biological complex systems, putting emphasis on the multi-model. We want however to improve the method by making it compatible with the definition of virtual reality and the systemic paradigm.

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 multi-agent approach, in order to develop a true laboratory for *in virtuo* experimentation in biology. The *in virtuo* experimentation is more than the simple observation of the numerical models processing on a computer. The user can test the reactivity and the adaptibility of the model in progress. Thus, he can take the most of behavioral properties of the numerical models that populate the virtual universes. We need now to define how our multi-modeled universes and our autonomous entities work.

3 Modeling the living complex system

Autonomy principle is a major principle of the multi-agent 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 provide a good candidate to study complex systems. Works on self-organization of social insects(14) are an example of this type of recourse to the agents. In addition to the autonomy principle, notions of robustness, emergence, self-organization and adaptibility underlie the MAS.

In this section, we describe the multi-modeled method built on systemic paradigm and with MAS. We emphasize on the notions of interaction, constituent and organization.

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.

3.1 Interaction reification

The 20th century has experienced an important change of method : the emergence of the systemic paradigm complemented the reductionist and analytical paradigms. Speaking in a sketchy manner, we could say that reductionism is interested in the description of the studied system components, while the systemic paradigm leads us to focus on the relations between these components.

Interaction is the basic concept of this last paradigm. Usually, when the MAS are used for the study of complex systems, relations between the components are modeled by message mailings, components being modeled by agents.

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 these considerations. We therefore had to modify the usual MAS modeling (figure 2), and consequently the way of modeling a complex system too. We talk about "interactions reification".

As a consequence, to each interaction a process corresponds. Processes of that kind will not allow a simultaneous execution, since it is a microprocessor that executes the computer program. This implies that we have to choose between synchronism and asynchronism scheduling. This choice will affect the state of the virtual world which is experienced by the agents during a cycle. A cycle is the time step corresponding to one, and only one activation of each agent.

- In the case of synchronism, during a cycle, each agent perceives the environment at the state of the start point of the cycle. The environment modification induced by the agents' actions are effective at the end of the cycle. In that case we consider each action are performed at the same time.
- When asynchronism scheduling is considered, we made the hypothesis that events occur at different time. Each agent modify the environment when activated. The next activated agent will perceive this modification during the cycle.

Synchronism is the characteristic of the differential calculations and, more broadly, of the analytical methods. Since we wish to take distance from classical reductionist analytical methods, we have chosen asynchronism to schedule the agents. In addition to that, the complex systems are often composed of circular, unstable or oscillating mechanisms which result from the asynchronism of interactions.

Futhermore, in biological systems, some interactions compete themselves for the same structural constituent. Then, if synchronism was chosen, there would be no way to assure the conservation of the amount of a constituent. For example, we can imagin two transport interactions that have to carry the same constituent to another place. If they see the state of the world at the startpoint of the cycle, the both will transport the constituent. At the end of the cycle, the constituent will be duplicated.

Finally, in order to not 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 a relation 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 organization concept needs now to be exposed.

3.2 Organization

The organization is a central concept in systemic. This notion has already been used in MAS design(Gruer, 02). An organization 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 organization as being an object containing constituents and interactions (figure 3) from a computing standpoint. Moreover, a composition relation between the organizations can exist when a system is made of sub-systems. This is the hierarchical level organization. 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.

3.2.1 Organization/Constituent :

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 organization. The influence of the sub-system is modeled by upper level interactions.

3.2.2 Organization/Interaction :

When a sub-system is operationally closed (3), 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 organization. From the root organization standpoint, the sub-system can be considered as being the same as an interaction between its inputs and outputs (see figure 4). It is then possible to model it with an autonomous agent.

Thus, we have two ways of stopping this “infinite” regress in the decomposition process by looking at a “leaf” organization as a constituent or as an interaction. We now have to apply this generic framework of modeling to our domain of interest : biology.

4 Model integration for biology

In this section we present the different models implemented with this generic method. As in physics where relaxation and transport phenomena are considered, we have two interaction’s types. First, we expose the time dependent interactions: the chemical reactions. And then, we present a sample of time and space dependent interaction type: the diffusion. We will discuss on the microscopic and mesoscopic chemical reactions modeling. We expose how those interactions are associated to build a cell model, how collision are managed. Finally, we present the integration of these models.

4.1 Time dependent interactions: The chemical reactions

In order to adequately model biological systems, we have to model the chemical reactions which are the basic elements of the chemical networks. These networks are the main way of communication and of regulation of the living organisms. In most chemical messengers communication cases, huge quantities of molecules are involved. 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 (15). The mathematical proof of the convergence of this method has been recently established[4] . The convergence has an order of 2, whatever the classical method chosen in step 2 of the engine.

The figure 5 show an example of test results obtained by simulationg a classic model of the Map Kinase transduction pathway(16). Each reaction have been modeled by an *Reaction* agent The action step of an enzymatic reaction apply the law :

$$V = (Vmax * [P]) / (Km + [S\})$$

V is the reaction speed, *Vmax* is the max speed, [*S*] the substrate concentration, [*P*] the product and *Km* is the Michaelis-Menten constant. Naturally, this interaction-based method is slower than the traditionnal ODE solver tools. The use of this method is justified by the context of the multi-modeling. Contrary to the classical chemical calculation methods, the *Reaction* agents method permits to add, to modify or to destroy any reaction during the simulation. The simulation can adapt itself to any unexpected perturbation or modification.

Finally, in order to describe chemical networks, we define an organization *Reactor* that contains the constituent *Species* and the relations between these constituents : the *Reaction* agents. This organization does not contain any space dimension, since the species concentrations are supposed to be homogenous in the chemical reactor. As a consequence, *Reaction* agents only represent time-dependent relations.

We now have to model the molecular species diffusion in space. This is an essential mechanism of the chemical messages transmission.

4.2 Diffusion reactions

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* organization and contains a *Reactor* sub-organization. *Diffusion* agents are transportation relations between these organizations (figure 6). *Diffusion* agent are close to the *Reaction* agents in their way of proceeding. They use the laws of Ficks and represent the diffusion through a 2D surface. This method allows the modeling of the transportation of molecules through a cell membrane. The three times engine of the agent will be as follow:

1. Reading of the concentrations of the chemical species in two adjacent compartment.
2. Calculation of the diffusion speed and integration on the time step.
3. Concentrations update according to the amount of transported species.

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.

4.3 Microscopic molecule simulation

There, the chemical reactions have been described at a macroscopic level. But in the case of intracellular biochemical reactions, the number of involved molecules is not enough. Then, the deterministic methods cannot be used(17). By using the method we present, it is possible to model the chemical phenomenon at a mesoscopic and microscopic level. We are working at the introduction of the Gillespie algorithm (18) in our model. The *Reaction* and *Diffusion* agents will have to adapt themselves and to choose between a differential method or between the Gillespie algorithm. This to perform the interactions in and between the chemical reactors.

4.4 Cell models

The *Compartment* organization contains at least one *Reactor* sub-organization representing the chemical environment in the tissue. It can also contain some more complex sub-organizations : cells.

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[4] P. Redou, S. Kerdélo, J. Tisseau, manuscript in preparation

These cells can be modeled in different ways (figure 7), thanks to our multi-model approach. From a biochemist standpoint, a cell can be defined as an organization composed of sub-organizations (*i.e.* chemical reactors), of constituents (*i.e.* the molecular species), and of interactions (*i.e* the *Reaction* and *Diffusion* agents)(19).

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-organization modeling the cell can be replaced by an autonomous agent producing the same behaviour. From the root organization viewpoint, this system is equivalent to an interaction between species which are normally in relation to the cell (see 3.2.2).

Finally, it is possible to replace an autonomous sub-system in the cell by agents to create an 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 behavior of these sub-systems can be produced by any artificial intelligence tool (neuronal networks, cognitive Maps, states machines,...). The fuzzy cognitive maps have already been apply to *in virtuo* modeling (Querrec, 05)

The hybrid solution is 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.

4.5 Collision managment

In order to give the cell a shape, a *Shape3d* constituent has been added to the *Cell* organization. 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 are in collision, a *Collision* agent simulates the interaction between the two shapes, by applying a given pressure on them. The *Compartment* organization which contains the cells creates a *Collision* agent when two shapes are at a certain distance from another one. 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* organization has a collisions detection unit. This unit verifies whether relations between the constituents of the organization or of the sub-organizations should emerge or not. Consequently, the management of the collisions is partitioned within each compartment (figure 8). The number of compartments is chosen proportionnal to *n*, the number of simulated entities (*i.e.* when the simulation size grows, the number of compartments increases). Thus, on average, the number of entities in a compartment is constant and the simulation's complexity remains[5] in $O(n)$.

4.6 Integration of the whole

All the models mentionned here were integrated into the same software architecture. Programs were developed thanks to the AReVi (20) library. AReVi is an autonomous entities simulation library, as well as a 3D rendering library. It is a C++ written library. The UML diagram of the figure 9 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.
- The generic model defines generic objects : interaction, component and organization.
- 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 (3.2.2) inherit from *Interaction*. The chemical *Reactors*, the *Compartments*, the *Cell*s and the *Universe* inherit from *organization*.

This is the generic model that allows all these models to cohabitate and to interact in the same virtual universe.

5 Application

We already have implemented this multi-model method in the context of a complex disease study : the allergic urticaria. We have modeled a 600µm cube of skin (figure 10). In this model, sub-models were included : cell's models (mast cells, macrophages, keratinocytes), a macroscopic model of the capillary

[5] The complexity in $O(n)$ has been proven and will be presented in a manuscript in preparation.

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...). Previous study on the histamin effect on its receptor H1(21) have been insert in the model too.

In the current state, we can now affirm that two important things 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 (22).

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 :

- An 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.

In addition to that, we have added the possibility of interfacing our application with the norm SBML (24). SBML allows the simplification of the model definition and provides the possibility to exchange data with the systems biology community.

Conclusion

We can now affirm that we have developed 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 a multi-model 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 organization (23). 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 multi-agent systems according to both the concept of organization and the chaotic asynchronous iterations.

Nowadays a large amount of articles in the scientific litterature talk about the necessity of an interdisciplinary research, the framework here proposed allows interdisciplinary modeling. Thanks to systemics way of thinking, it provides an interface able to collect the knowledge of experts in biology. These experts are researchers who may work in very different fields of biology and may not be used to communicate together. Thus, the application appears to be a great tool to centralize the data that have been collected by different biologists' teams to understand a phenomenon. Each biologist can complete the global model according to its speciality and its knowledge. It is an efficient communication vector between researcher, providing different viewpoint on the case of study. Furthermore, it was pleasant to realize the application great interest for teaching in order to understand complex phenomena.

From our standpoint, the *in virtuo* experimentation is design for the study of biological complex systems. The main reasons are:

- Environment and disturbances caused by it, on the system, is modeled.
- Random which is essential to reproduce biological processes, is simulated.
- Different modeling level are considered depending on the knowledge we have in the part of the system we are focused on (molecule, cell, organe, organism, ..., biotope).
- Different nature of model coexist in the same application. Chemistry causes mecanics and mecanics modifiy chemistry.
- Thanks to the autonomy principle: fuzzy expert system, neural network, rules-based system... can be embedded by the agents. This is interesting according to the suggestion of

the expert system methodologies review (Liao, 05) : different methodologies can be integrated into the same VR application.

- As a consequence we can mix qualitative and quantitative approach, depending on our knowledge and on the objective we have set.
- Hypothesis driven experiments can be performed at cellular or molecular level. Those experiments permit understand and to increase the model. We don't build a model of understood systems but we build model to understand systems.

We have design a toolbox to perform alternative experimentation on complex biological system. At the time where *in vivo* and *in vitro* research are more and more difficult to perform, owing to the statutory constraints, the simulations allowed by the *in virtuo* or *in silico* research, represents an interesting alternative. The construction of the model and the experimentations by using this toolbox may be quick and remain in very low cost in front of *in vivo* and *in vitro* experimentations.

Limitations/Perspectives

Computational :

The simulation size is currently limited by the power of computer. The multi-agent systems properties should make the application easily distributed. We are working on the distribution on several computers taking into account the generic model of interaction, organization and constituent. Some optimizations and improvements of the model are naturally planed such using adaptative grid for the molecular diffusion.

Biological :

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, retro action, and inhibition... which all are characteristic mechanisms of complex systems. We currently plan to test the effect of drugs such as anti-antihistamines which reduce the allergic response.

The model construction may be limited be the range of knowledge. But the lack of information is a part of the biologist everyday life. The experiment and modeling task being led together, the knowledge "holes" may be filled by producing new hypothesis. We are completing our urticaria model, producing new hypothesis and going to meet with another experts in different biology fields. Those meetings have given rise to new starting application: the modeling of the endothelium and the study of cardio-vascular risks; the modeling in toxicology and the study combinated effects of different molecular substances.

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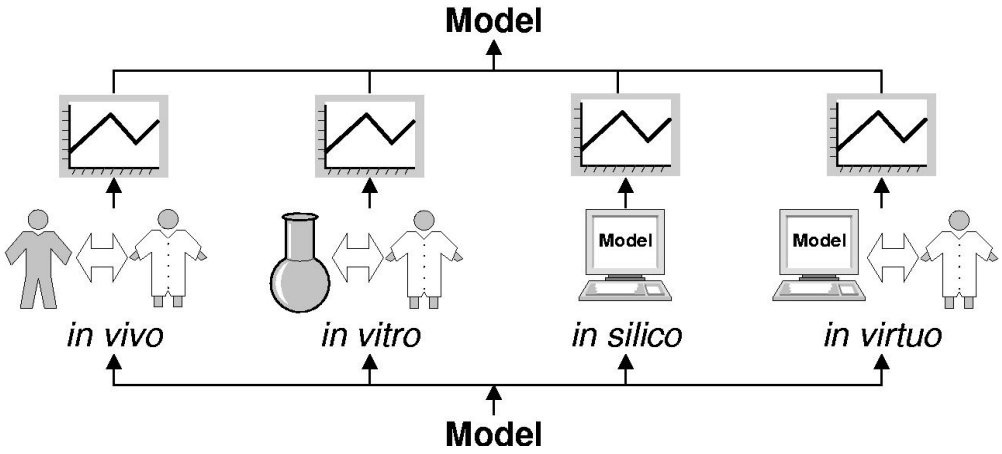

Figure 1:

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 theorical model.

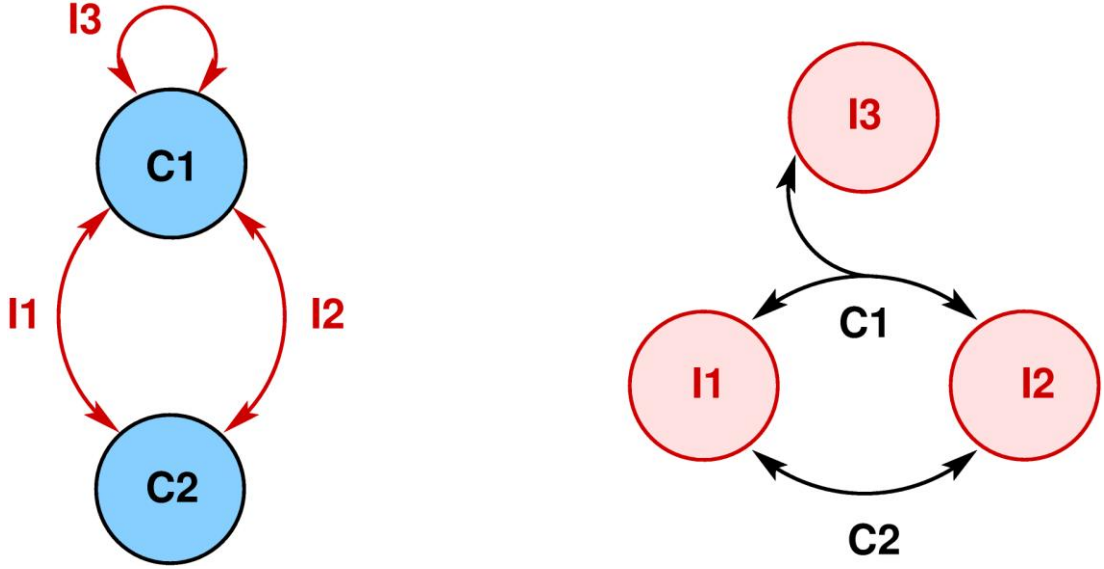

Figure 2:

Reification of interactions changes our vision of a system. This two dual graphs symbolize the reductionnist (left) and the systemic (right) modeling. Vertex/constituents are turned into links/constituents, and links/interactions into vertex/interactions.

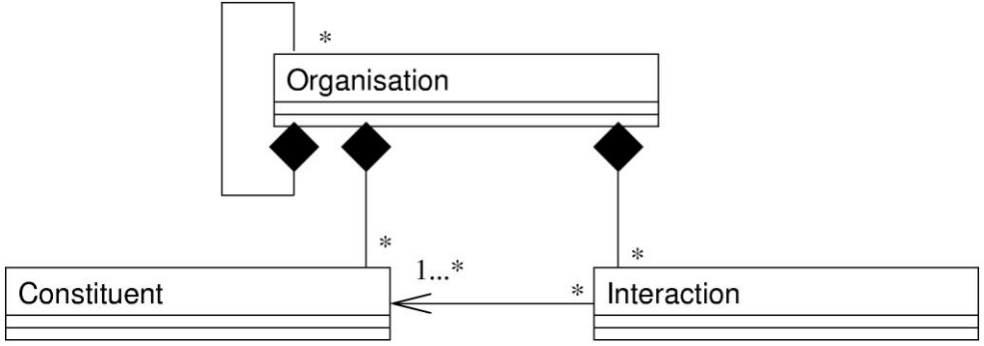

Figure 3:

The class *Organization* can be composed of passive objects *i.e.* the components, of active objects *i.e.* the interaction agents, and of sub-organizations. An interaction can take place on a single constituent or between several constituents.

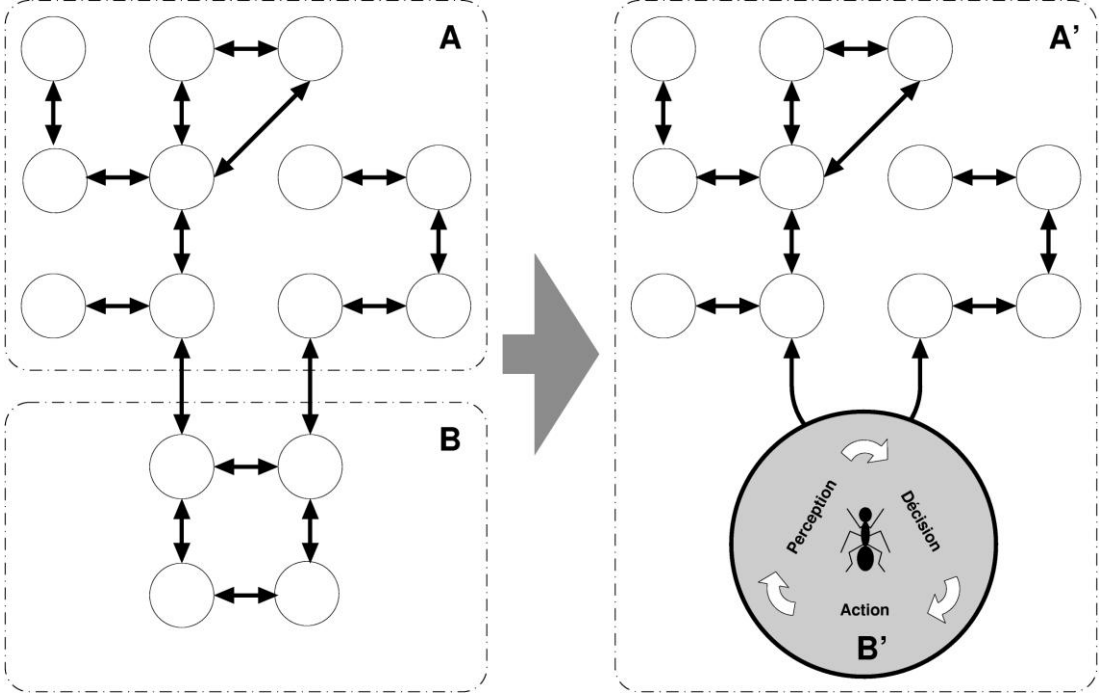

Figure 4: An autonomous sub-system (on the left) can be replaced by an interaction with the environment (on the right) that will have an equivalent behavior.

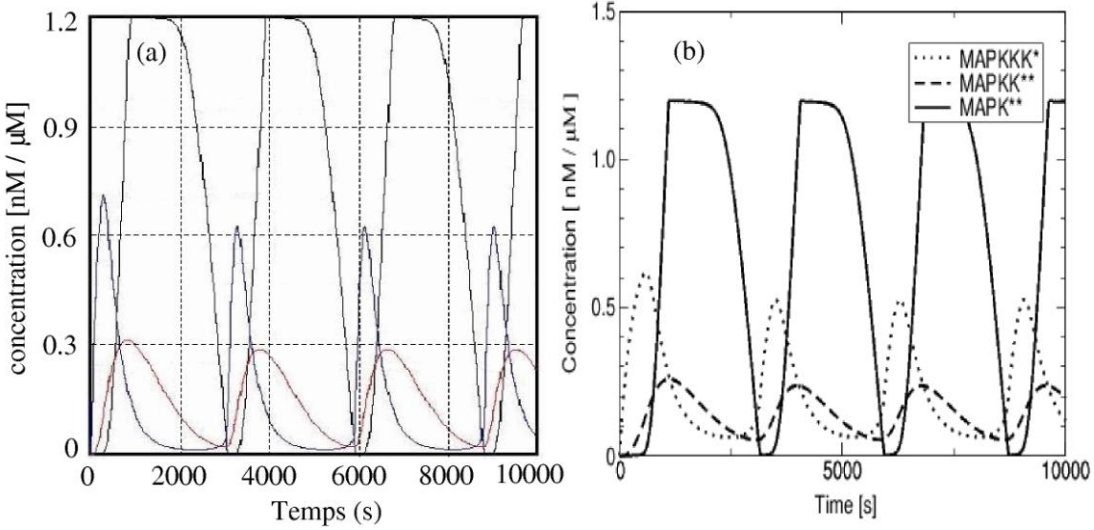

figure 5.a:

The right graph shows the kholodenko model of MapKinase transduction pathway solved by ODE. The left graph show the same model solved by the reaction agent method.

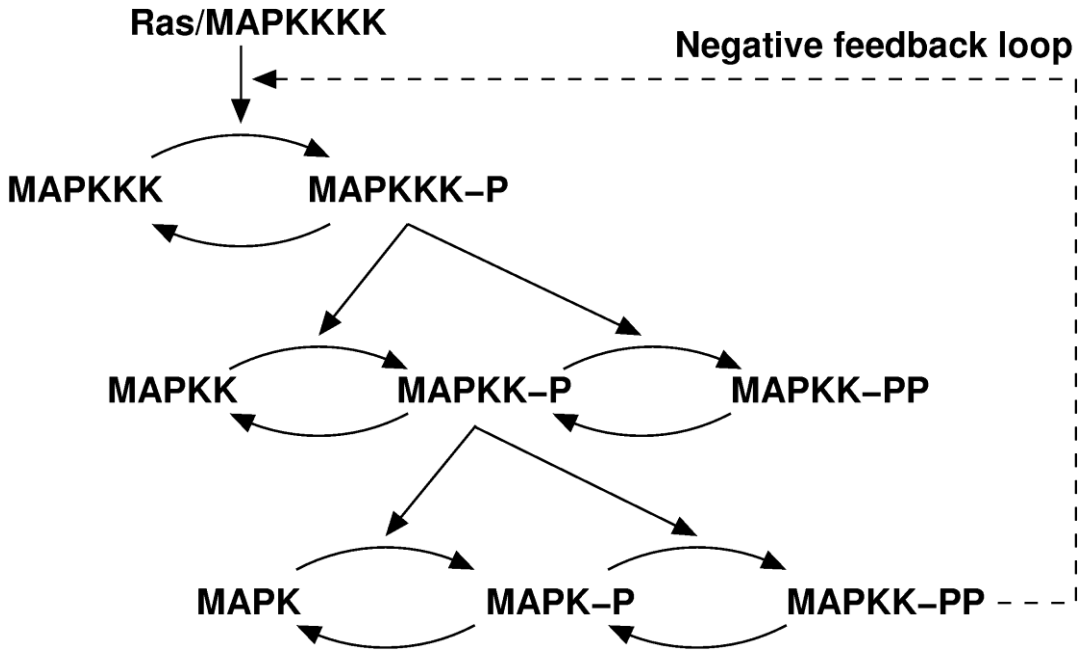

figure 5.b:

This is the kholodenko MapK pathway (kholodenko, 02).

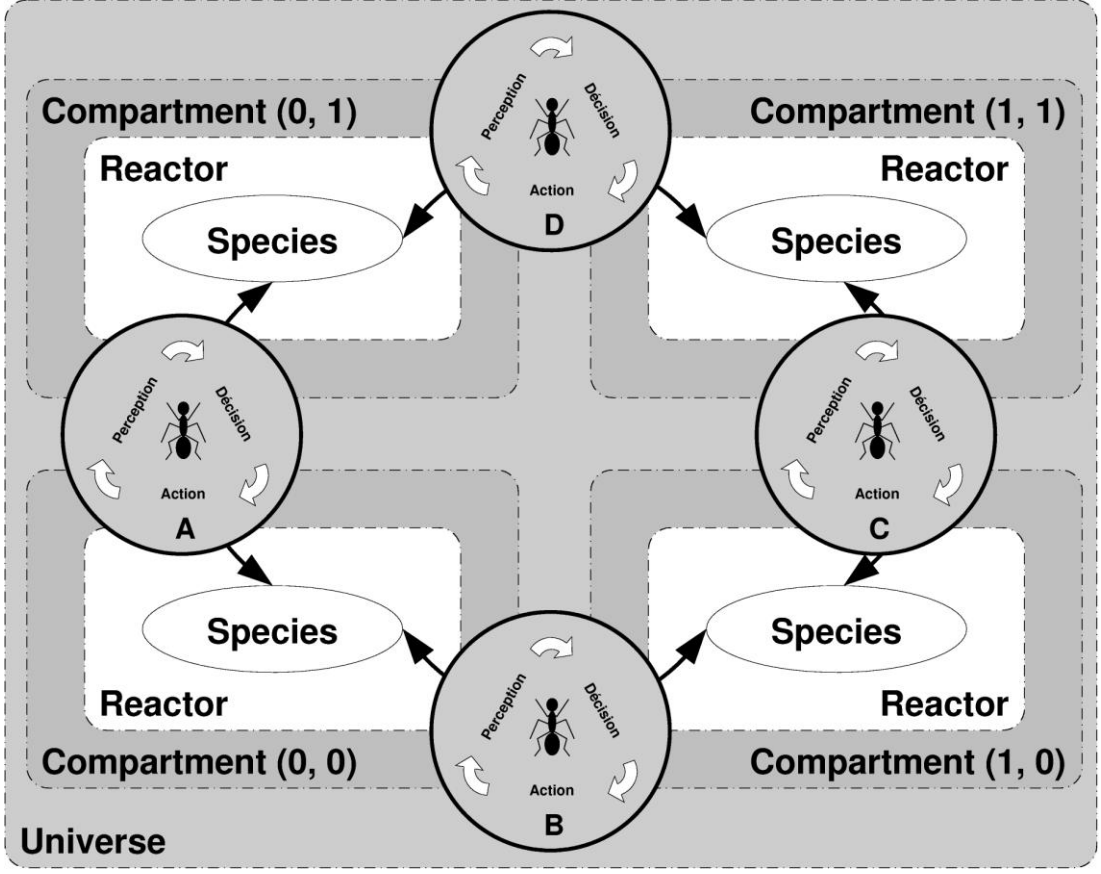

Figure 6:
The virtual 3D universe is partitioned in compartments. A chemical reactor without spatial dimension is associated to each compartment. *Diffusion* agents achieve the transportation of the chemical species from a compartment to another.

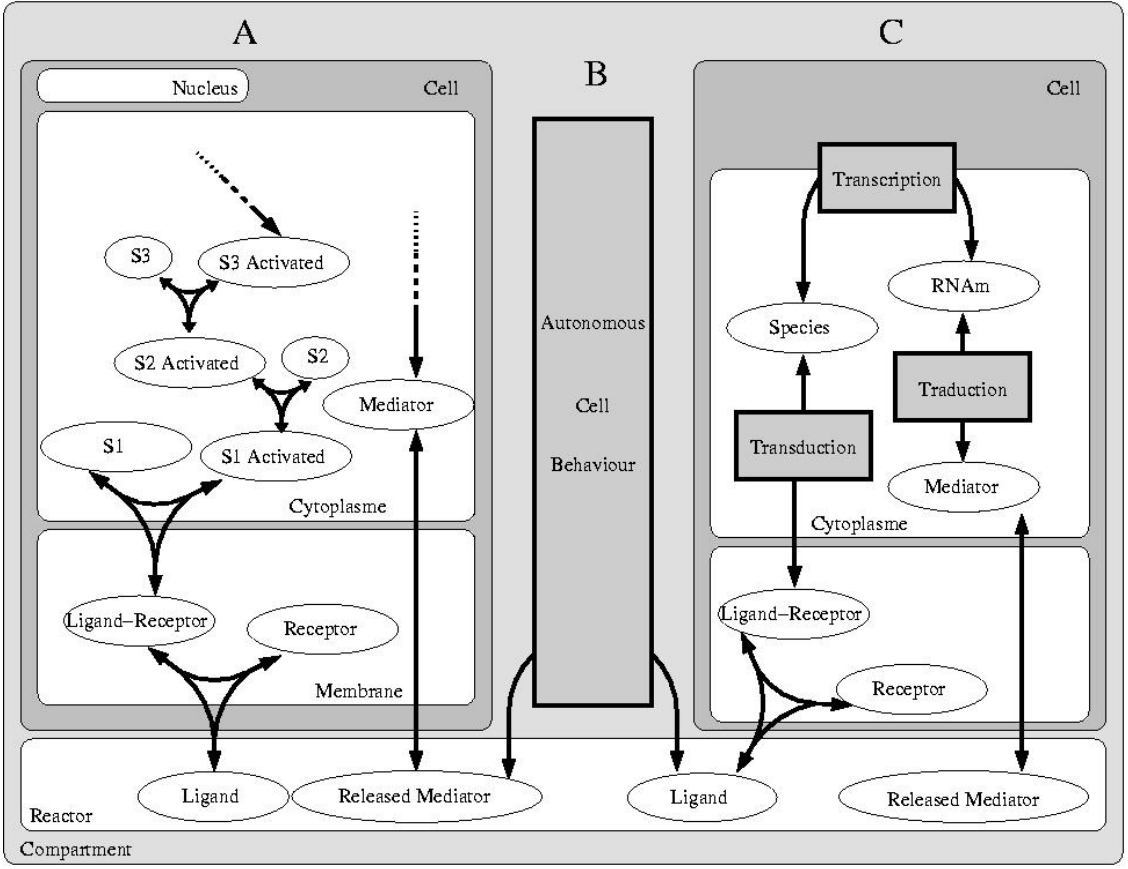

Figure 7:

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 modeling of the cell.

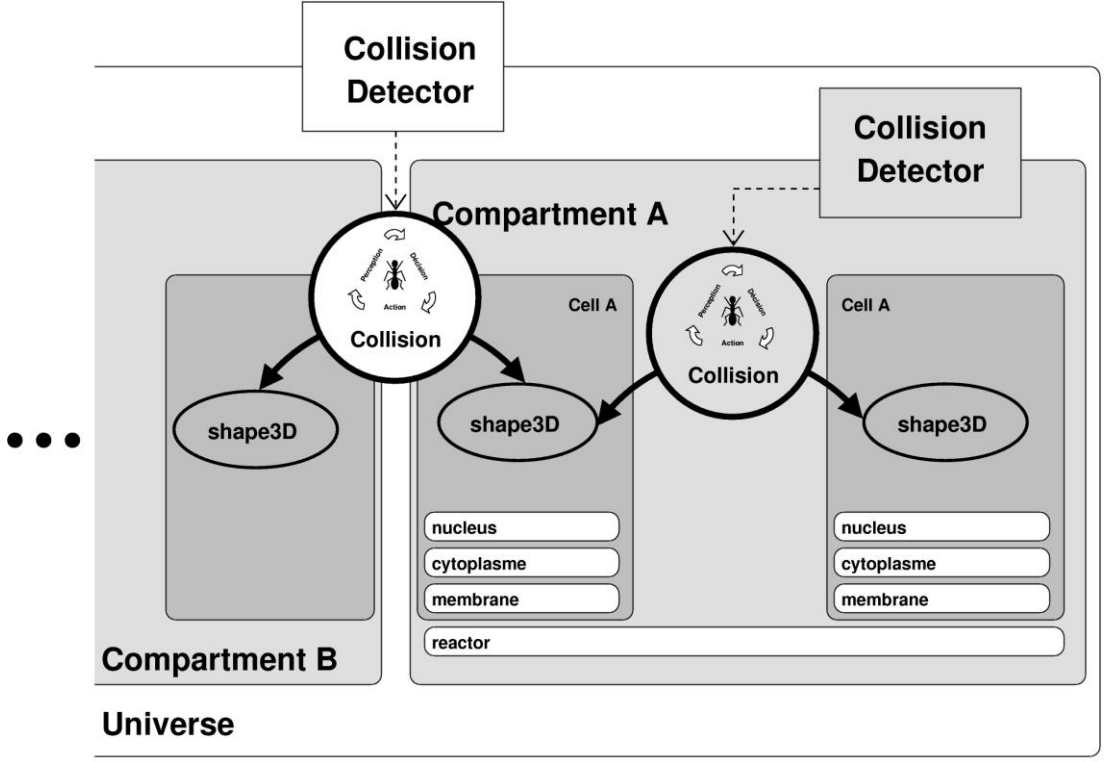

Figure 8:

CollisionDetector modules of the organization detect collisions between the *Shape3D* constituents and create *Collision* agents.

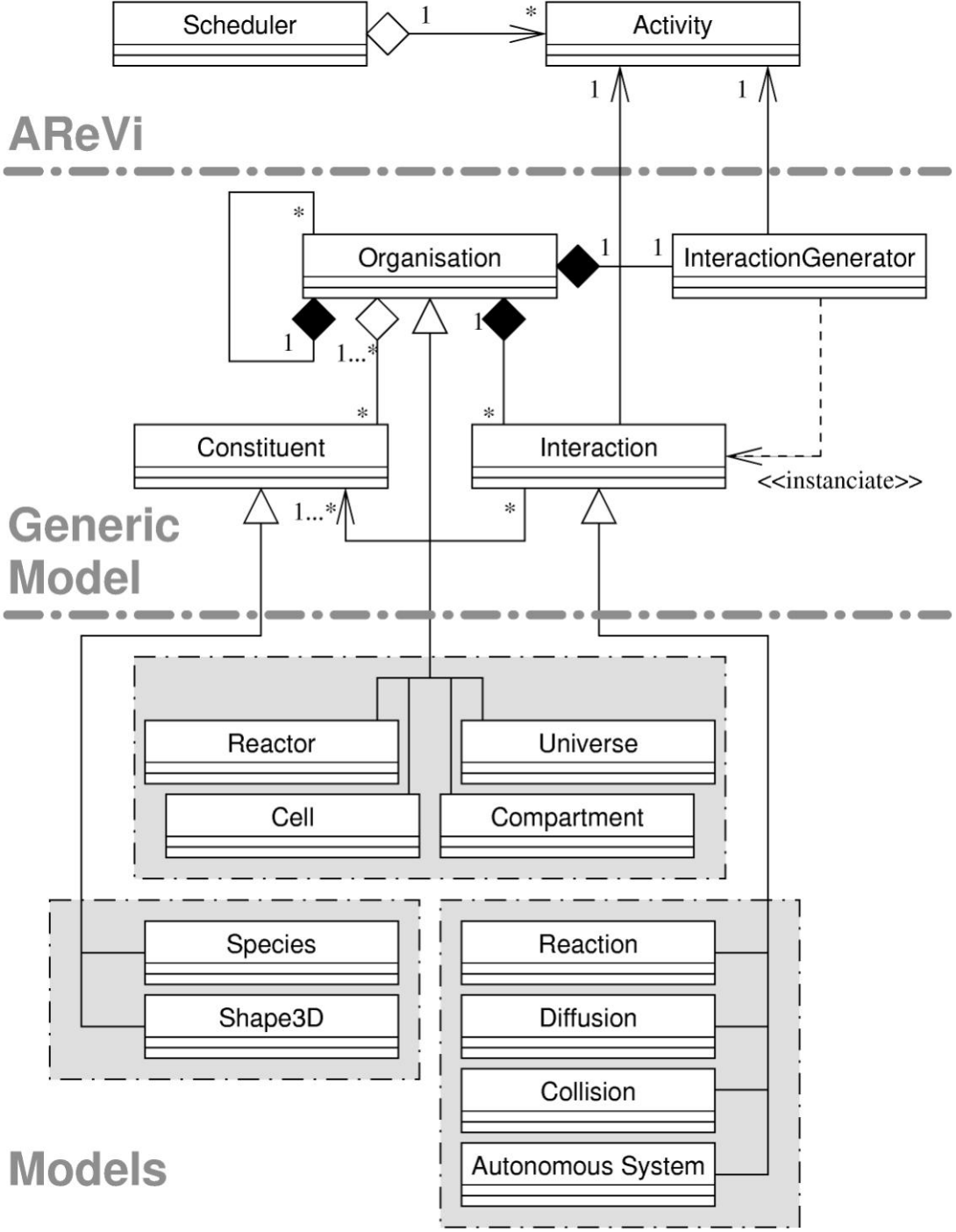

Figure 9:

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

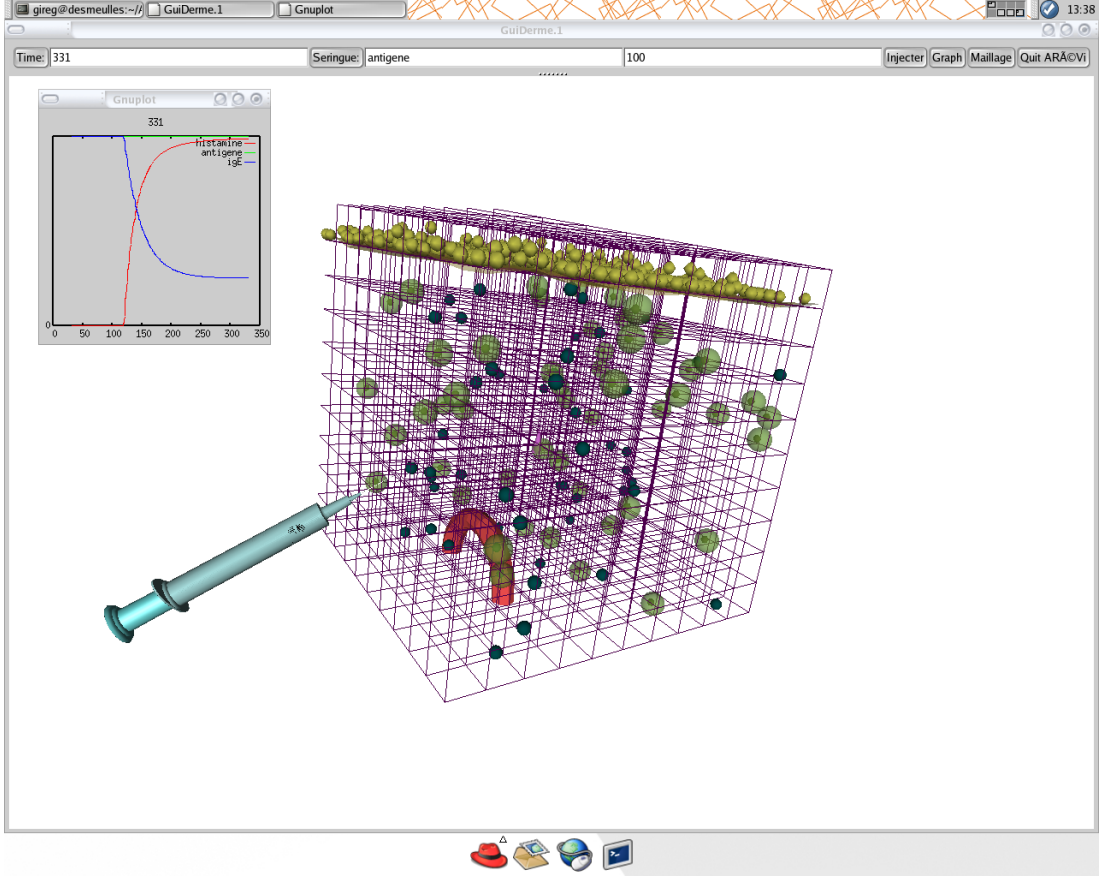

Figure 10:
A screenshot of the *in virtuo* experimentation of urticaria.