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In virtuo Experiments Based on the Multi-Interaction System Framework: the *RéISCOP* Meta-Model.

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Abstract: Virtual reality can enable computer scientists and domain experts to perform *in virtuo* experiments of numerical models of complex systems. Such dynamical and interactive experiments are indeed needed when it comes to complex systems with complex dynamics and structures. In this context, the question of the modeling tool to study such models is crucial. Such tool, called a virtuoscope, must enable the virtual experimentation of models inside a conceptual and experimental framework for imagining, modeling and experimenting the complexity of the studied systems. This article describes a conceptual framework and a meta model, called *RéISCOP*, that enable the construction and simulation of models of biological, chemical or physical systems. The multi-interaction conceptual framework, based on the reification of interactions, is built upon the concepts of autonomy, structural coupling and asynchronous scheduling of those reified interactions. Applications and virtual reality experiments described in the last section show the expressiveness of this approach and its capacity to actually formulate heterogeneous models in heterogeneous time and space scales, which is required for studying biological complex systems.

Keywords: Complex system modeling, autonomy, virtual reality,*in virtuo* experiments, multi interaction systems

1 Introduction

All research fields find themselves confronted with the problem of taking into account the complexity of the systems they are studying (Laughlin, 2005). This complexity stems first and foremost from the diversity of components, structures and interactions at work in the system. No theory capable of formalizing this complexity currently exists and, for this reason, there are no *a priori* methods for formal evidence as there are in highly formalized models. In the absence of formal evidence, one must rely on experimenting the system throughout its evolution in order to be able to conduct *a posteriori* experimental validations.

Virtual reality provides a conceptual and experimental framework adapted to imagining, modeling and experimenting this complexity. Users of virtual reality systems, immersed in real time within this space by the triple mediation of senses (perception), action (experimentation) and mind (modeling) are spectators, actors and/or creators of these virtual worlds (Tisseau, 2001b). Virtual reality places the user at the heart of a virtual laboratory and thus shares similarities with methods from experimental sciences: the user can therefore investigate the virtual world using various methods, e.g. numerical methods. Building a representation of a system and experimenting the resulting model enables experimenters to apply a scientific approach on an object as if it was a natural phenomenon. This type of investigation is known as "*in virtuo* experimentation" for its similarities with the expressions *in vivo* and *in vitro*. The "virtuoscope" thus refers to the virtual laboratory for studying complex systems, which is based on concepts, models and tools from virtual reality (Fuchs, Moreau, and Tisseau, 2006).

For the *in virtuo* experimentation of complex systems, the "virtuoscope" conceptual tool associates the virtual world with laws for creating the experimented systems. Thereafter, humans are directly engaged in the *in virtuo* experimentations of the numerical models within the virtual environment. Here, the experimentation refers to the dynamical building of a model by locally disrupting it, modifying one or another component of the model. The principle is to rely on the dynamical visualisation and experiment of the model to place the thematician[1] –domain expert– inside a virtual laboratory, which meets a modelers' need (Endy and Brent, 2001). The concept of virtual laboratory has already been proposed (Ramat and Preux, 2003; Amblard, Ferrand, and Hill, 2001), but not from the virtual reality's point of view. Classically, a virtual laboratory is seen as a tool to study representations. We propose to see it as the representation of a laboratory in which models, as natural systems, are built, experimented and studied.

Yet, such a tool requires more research and development. For instance, Baudouin, Chevaillier, Le Pallec, and Beney (2008) focus on the interaction between the learner and the virtual environment. In our case, the complexity led us to focus on the models' construction and the first issue we address is the dynamical experimentation of models, which requires a modeling framework for the models' description and modification. Such framework must therefore enable thematicians and computer scientists to build and interact with complex models together. More generally, modeling complex systems requires different roles (Drogoul, Vanbergue, and Meurisse, 2003), each of which is based on its own expertise. Various expertises mean various theoretical and methodological tools for the modeling ac-

[1] see Drogoul, Vanbergue, and Meurisse (2003) for a definition of the term thematician from the computer science simulation point of view.

tivity. It is therefore necessary to enable multi-modeling and the use of different modeling formalisms for studying complex systems (Bonneaud, Redou, Thebault, and Chevaillier, 2007). Hence, not only the "virtuoscope" must enable the building of models by both computer scientists and thematicians, but it must also enable the use of different modeling material by various thematicians and the building of heterogeneous models. The coupling of heterogeneous models was addressed in Bonneaud, Redou, Thebault, and Chevaillier (2007) and was achieved through the data: models are encapsulated in agents, which are in charge of the coupling. Ramat and Preux (2003) have proposed a simulation platform VLE which principle is to have a general and common formalism, based on DEVS (Zeigler, 1989), to express and couple all the other formalisms. We stress out the fact that those propositions do not try to address the dynamical building of the models within a virtual world. Moreover, those solutions do not ease the building of models by both thematicians and computer scientists.

The aim of this article is to describe the meta-model *RéISCOP* and the paradigmatic framework of *multi-interaction systems* that supports it. We argue that this meta model structures a "virtuoscope", i.e. gives thematicians and computer scientists the conceptual tools to build and dynamically experiment their models. Yet, because there is no general solution to manage the complexity of the models, such an instance of a "virtuoscope" must be constructed in confrontation with a specific field of application. Our proposal has been fulfilled in confrontation with the study of living entities. As we will see later on, the temporal multi-scale aspects and the heterogeneity of the phenomena brought into play in biology imply that the suggested solution extends to the simulation of physio-chemical phenomena in general.

More precisely, the individual-based modeling approach (DeAngelis, Rose, and Huston, 1994) along with the properties of the biological systems led us to suggest a shift of focus from "individual-centered" to "interaction-centered". Such shift of focus uncovers the conceptual means to build the meta-model *RéISCOP*. In section 2, we exhibit the paradigmatic framework which describes the concepts, method and point of view on which is built *RéISCOP*. We highlight the motivations which led us to adopt the principles of autonomy and reification of interactions. Section 3 then goes on to present the general *RéISCOP* meta-model. The notions of interaction, phenomena, organization and autonomous systems are developed in this section. Finally, the last section illustrates this proposition by describing a simulation platform based on the *RéISCOP* and working experimentations that were conducted with this platform.

2 Paradigmatic framework : multi-interaction systems

The arguments put forward in this section come from the two following contexts: the study of the living and virtual reality. These contexts enable us to explore two interpretations of autonomy which lead to the concepts of structural coupling, reification of interactions, chaotic asynchronous iterations and organization in autonomous systems. Those concepts structure the paradigmatic framework which supports the ReISCOP meta-model.

2.1 Autonomy for numerical models

First, we notice that the notion of autonomy as a principle for constructing numerical models in virtual reality is required (Tisseau, 2001a):

- In *essence*, as we aim to model systems made up of autonomous entities (cells of a living system, or individuals of a given species when modeling ecosystems, etc.).
- By *necessity*, so that the entities which make up the universe might adapt to modifications of exterior conditions in simulation (due to interactions, disruptions or other unforeseen modifications within the environment, particularly when Man and his free will are "in the loop"), thus enabling the experiment.
- By *ignorance*, as the absence of a model for the global dynamics of specific systems leads to the autonomization of their components' models. We would thus like to see the emergence of global behaviors out of individual behaviors.
- By *conviction*; by accepting to share the control of the evolution of virtual universes between numerical models which populate these universes and the users which participate in them.

Multi agent systems (MAS) are a bottom up approach and are based on the system's entities autonomy. The system dynamic emerges from the agents activities and interactions. In the literature, the MAS approach is considered as the most natural paradigm to implement autonomy[2] in numerical models (Wooldridge, 2001).

2.2 Autonomy for biological models

Biology is essentially a science more experimental than theoretical. The technical and theoretical contributions that physics, with Schröginger or Delbrück for

[2] As consequence, we will refer to MAS to build our proposition. But, we insist on the fact that the paradigmatic framework proposed does not necessary correspond to MAS.

instance, has made to biology have enabled the advent of molecular biology and genomics. The consequences of this revolution have included a huge increase in data for creating models as well as giving rise to biological complexity. Thus, much like the advances in physical sciences at the beginning of the last century, a change in paradigm (Capra, 1997) is today occuring in biology and giving rise to " theoretical biology", "systems biology" (Kitano, 2002) or "integrative biology". These new theoretical approaches are indistinguishable from modeling and call upon the concepts of systems, interaction, retroaction, regulation, organization, evolution, etc., in order to process the complexity of living entities.

Amongst those different theoretical approaches, the work of Maturana and Varela (Varela, 1979) is particularly relevant. Indeed, in addition to the significant epistemological advances made possible in biology by the definition of the autopoiesis principle and in cognitive sciences by enaction, Varela's work introduced a new definition for autonomy. In order to render biological mechanisms intelligible, Varela suggests modeling living entities as interwoven autonomous systems. These systems are dynamic and defined as units by their organization. He also suggests that a biological system must be operationally closed. Such a system therefore contains the means and the conditions to produce itself.

The aim of this article is therefore to unify this particular vision of biological autonomy with the autonomy principle for computerized entities in order to influence the way numerical models are built.

2.3 From structural coupling to reifying interactions

Structural Coupling. Consider that a system is characterized by its dynamics and structure. To an observer, structure is the current state of the system which is subjected to the actions of the immaterial dynamics of the system. The word "structure" here refers to a specific meaning linked to the modeling paradigm that we are outlining. Here, for computer models, the structure is defined as a set of elements that are, in the end, only numerical values when dissociated from the dynamic aspect of the system. Next, in order to understand the relationship between an autonomous system and its environment, Varela points out that we must reason in terms of structural coupling. That is to say that the environment's influence on a system is perceived by that system as a disruption of its structure. Therefore, an autonomous system has only perceptions of itself. It will not react to exterior commands on its dynamics (allonomy or reactivity) but can react in an autonomous manner to an alteration of its structure by the environment. It can therefore only perceive[3] other systems via the disruptions that they cause.

[3] A cognitive system such as this can only "know" the world by building up a representation of it through experience.

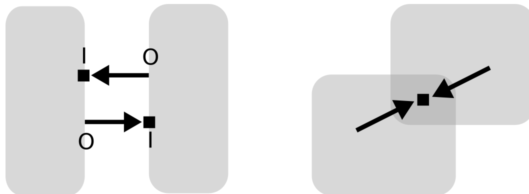

Figure 1: On the left are two systems communicating via inputs and outputs. On the right are two systems communicating via structural coupling.

For the model designer, focus is thus placed on the autonomy of what the dynamics of the different systems are doing rather than on the actions of their structures. This independence from systems' dynamics corresponds to the idea of autonomous processes directly implemented in multi-agent systems.

Opposition with the notions of input/output and of perception for computerized agents. The method, which consists in designing models as a juxtaposition of systems which mutually ignore one another and which communicate indirectly via structural coupling, must be translated into computer language. Usually, one models an elementary autonomous system as an agent (Ferber, 1999), using an object made of internal states, perceptions, behaviors and rules governing its dynamics. Here, we consider object-oriented modeling as a natural programing paradigm to build MAS (Odell, 2002; Hill, 1996). Communication with the environment and with other systems is traditionally governed by perception systems, by sending messages or by inputs/outputs. Perception and sending messages underlie the idea that one system "knows" the other systems. This idea conflicts with the point of view of structural coupling (figure 1). The same applies for synchronized communication via inputs/outputs between two systems that correspond more closely to the notion of command, causing a rupture in the independence of the dynamics of the two systems (for example procedure call). The traditional point of view therefore does not correspond to the application of structural coupling nor to the autonomy principle chosen here.

Reifying interactions. In order to implement structural coupling, systems need to be able to share their structures. The first consequence is the need to identify that which constitutes the system's structure. We considered a system to be the association of a structure and a dynamics. That which corresponds to the structure of an autonomous computer-based object is therefore the set of static data which makes up the system and which characterizes its current state. We can then no longer use the notion of composition between a system and its structure, as part of the structure can be composed of a number of other systems if it is involved in structural coupling. At the level of the system itself, it is also impossible to distinguish the structural elements which might be involved in structural coupling from the elements which are unique to it, without infracting the autonomy principle. From the point of view of software architecture, linking "systems" objects to their structures can therefore no longer be a compositional link nor an object/attribute relationship. All of the states of the system representing the structure must thus be extracted from the system.

Schematically, a MAS is made up of interacting autonomous entities with behaviors[4]. These behaviors can be perceived as the processes governing the interactions with the other agents or the environment. By means of numerous interactions, the global system can display complex behavior. We have already discarded the notion of perception. If we also remove the structural elements, all that remains to the agents are the processes underlying completion of the interactions. It therefore becomes natural to reify the interactions[5]. That is to say that rather than considering "autonomous individual" objects, we shall consider "autonomous interaction" objects. We notice that Mathieu, Routier, and Secq (2003) have worked on the RIO framework which focuses on the description of interaction protocols. Later on, Kubera, Mathieu, and Picault (2008) even proposed an architecture where interactions are reified regardless of agents: the goal is to enable reusability of MAS and separation of data from processing. Thereby, they adress the issue of MAS formalization which could be complementary to our approach. Yet, even though their point of vue on interactions is very close to ours, agents in their systems are still invididuals, where we propose to go even further in the interaction reification by fully deconstructing the individuals and focusing on structural coupling.

To summarize, we aim to construct a model as an assembly of active autonomous objects modeling interactions (or phenomena) between the passive structural elements which we refer to as constituents (figure 2). Interaction is therefore the autonomous elementary unit of the *multi-interaction system*. The constituents are the *medium* by which the interactions are linked. The couples *interaction / set of associated constituents* form systems. These elementary systems are thus structurally coupled to one another whilst the interactions act on the same constituents. This point of view offers a way of resolving the input/output approach.

[4] Of course, this definition of MAS is not complete, but in regards to the discussion, it is meaningful. More definitions can be found for example in Wooldridge (2001)

[5] At this level of thinking, we no longer consider an interaction as a non-instantaneous continual phenomenon in time. We shall later see how the suggested solution enables the implementation of this latter kind of interaction.

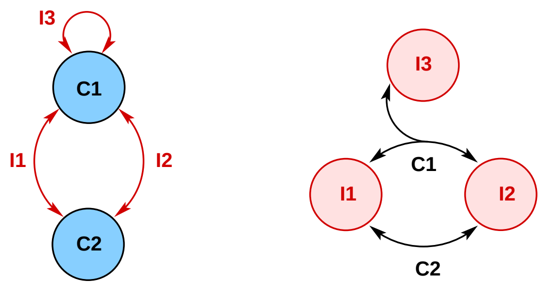

Figure 2: On the left, the traditional method for modeling a system with "component" nodes and "interaction" arcs. The right-hand diagram represents our approach, in which the arcs are transformed into nodes and vice versa.

It is also interesting to note that all theories studying complex systems lead us to focus on the relationships between components (Morin, 1990), which gives us yet another reason to clarify these interactions in order to give them equal importance to that of theoretical models, in their implementation.

It must also be noted that at this stage our proposition closely resembles blackboard architectures (Erman, Hayes-Roth, Lesser, and Reddy, 1980) and is compatible with research conducted in the field of stigmergy (Grassé, 1959). However, the semantics associated with autonomous processes differ from that which can be observed in simulations (González, Cárdenas, Camacho, Franyuti, Rosas, and Lagúnez-Otero, 2003), as the processes no longer model individuals, but phenomena. Furthermore, we expand our method by giving below a specific scheduler for executing these processes and by giving modeling organizational tools, which lead us away from the idea of a simple blackboard.

2.4 Asynchronism: a key element for temporal multi-scale

We have discussed until now active objects that model interaction phenomena taking place between structural elements that are numerical substrate. Therefore, these objects are active processes and they must be scheduled. In our case, each time a process is activated, the effect of the correponding interaction is calculated for the given time step and applied to the substrate. Choosing the scheduling method implies making a strong assumption as it calls time into question for the dynamical system simulation.

Asynchronism. Two main methods of scheduling are available: synchronous[6] and asynschronous[7]. In general the synchronous method is favored for numerical simulations. For example, it is well suited to the traditional tools used for resolving differential equations. However, the nature of the models that we are interested in means that we must take into account coupling phenomena acting on different time scales. The idea that we defend is that the scheduling of processes at different frequencies imposes heavy concessions on the hypothesis of synchronicity, thus limiting its significance. Indeed the notion of cycle, essential in the case of synchronous simulation, no longer holds when *offsets* and activation frequencies are commonplace. Even if synchronization solutions exist on a case by case basis, the synchronicity hypothesis makes the conception of a generic multi-scale method based on structural coupling difficult, without aligning the frequency of each process with the highest frequency, bringing everything down to the same level. We therefore chose to raise this hypothesis in order to assume a more appropriate asynchronous scheduling. At least three difficulties must be overcome in order to implement asynchronous scheduling: 1. sharing data; 2. defining the simulation current time; and 3. validating the calculations.

"Weak" asynchronism. In order to enable the sharing of data while guaranteeing its consistency, the execution of a time step for a given interaction is seen as an indivisible operation. Thus, two interactions cannot simultaneously act on the same resource. We can therefore refer to this asynchronism as "weak", where a "strong" asynchronim would have interactions executed on a multi-threaded system. For such a solution, traditional data sharing mechanisms (semaphores on structural constituents) should be used, which is a possible extension of this proposition.

Observer's time and global time. How should we determine the current global time of the simulation? Indeed, each interaction constitutes part of the global model. The current local time of an interaction goes from "*t*" to "*t + period*" at each activation. For each process, its period beeing possibly different, current local times of each interaction can differ at each instant. At a given moment, how can one date the global state of the system's structure? Rather than answering this question, we shall instead consider the time from the point of view of the observer.

[6] Synchronous: each process perceives the state of the system at instant t, calculates a modification of this state and applies its modification at t+1. Thus, there is no causality between the execution of processes within one cycle.

[7] Asynchronous: each process perceives and modifies the current state of the system prior to the following process being called. There is a causality between the successive calls even if simulation time has not been modified.

In virtual reality, the user is often modeled according to a particular model (avatar) amongst other models: in our case, the user is an entity in structural coupling with the system, which differs from the traditional approach, as the user is here reified as an interaction rather than an individual. Concerning the user's activation, in the case of real time simulation, the user does not question the time which has elapsed: the observer's time is function of the real time (that of a clock). However, if the constraint of real time is not applied, the user as a model must be scheduled in the same way as any other process, which enables him/her to maintain a consistent timestep. In conclusion, no process needs to know the current global time, not even the user.

Asynchronous and Chaotic Iterations. Asynchronous scheduling introduces a causal link between the activations of the processes which are supposed to intervene at the same time (for example if they are of the same period and *offset*). The order in which these processes are activated can introduce a bias into the simulation if they are in competition for the same resources (Michel, Ferber, and Gutknecht, 2001; Kubera, Mathieu, and Picault, 2009). In order to overcome this problem, it is possible to schedule these processes in a random manner, known as chaotic asynchronous iteration. On average, no one interaction is favored over another. Thus, the bias that may be generated, while a set of interactions are being executed, is limited if there are a great number of steps in the simulation. The bias is even negligible and algorithms converge in the case of chaotic and asynchronous iterations for the resolution of differential equations (Redou, Kerdélo, Le Gal, Rodin, Abgrall, and Tisseau, 2005). Thereafter, in physico-chemical biology, as most models are based on differential equations, they are validated. Otherwise, in the case of stochastic models, chaotic scheduling can be a source of random. Yet, in general, the bias must be known and the results validated *a posteriori*, which is the case in general for simulating complex systems (Sargent, 2004). And in any case, as shown above, we have argued that chaotic asynchronous scheduling is required for temporal multi-scale.

At this stage, we defined our models as multi-interaction models. These interactions are autonomous objects structurally coupled by means of the passive components which represent the ongoing state of the system. Finally these interactions are scheduled in a chaotic and asynchronous manner in order for them to be activated over different time scales. So far, we have not commented on the apparition or the destruction of interactions over time. This is the issue we shall now address.

2.5 Implementing complex dynamics

Phenomenon. The modeled system takes the form of a network of interactions possessing a specific topology. If, during simulation, the conditions for producing a new interaction are reunited, it must be introduced into the network. An interaction is a specific manifestation of a phenomenon. We can reify this notion of phenomenon in an object with the conditions and means for producing a new interaction. Thus, using phenomena, our multi-interaction system can dynamically enrich itself during the simulation. The conditions and means for destroying an autonomous interaction are left to the interaction itself.

Organization. Simulating complex systems can require the use of a huge number of interactions. In order to make models intelligible, model designers can call upon the notion of organization, which we propose to integrate to our framework. The notion of biological organization was introduced to virtual reality by Querrec, Bataille, Rodin, Abgrall, and Tisseau (2005), who inserted this notion within the context of systemic biology. Although this is one of the fundamental notions for the study of biology, it is difficult to find a widely accepted definition. That is why it must be defined broadly, to enable the model designer to adapt according to his/her epistemic orientations.

If there is one widely accepted idea, it is that an organization is more of a set of relationships between individuals than a set of individuals, which fits perfectly with the reification of interactions. An organization is therefore defined by a set of phenomena and associated interactions which concern part of the structure of the system as a whole (figure 3 illustrates the implementation of structural coupling with this definition of organization). The definition of the structural set on which the organization is based results from an arbitrary and subjective choice on the part of the model designer. Depending on the evolution of the system, this organization can change. For example, if a new component appears in the simulation and this component possesses the characteristics required to be inserted into the organization's structure[8], a mechanism must be available to stand in for the model designer and to update the topology of the organization. As the division of a model into organizations is the result of a subjective act[9], it is impossible to define a general method for managing the modification dynamics of this division. It is possible, however, to limit the conditions and the means of altering the structural topology of the organization to the organization itself (see section 3.2).

[8] During exocytosis, for example, "protein" components are transferred from the "cell" organization to the "surroundings" organizations.

[9] We do not aim, here to identify the origins of organization, but simply to organize the models.

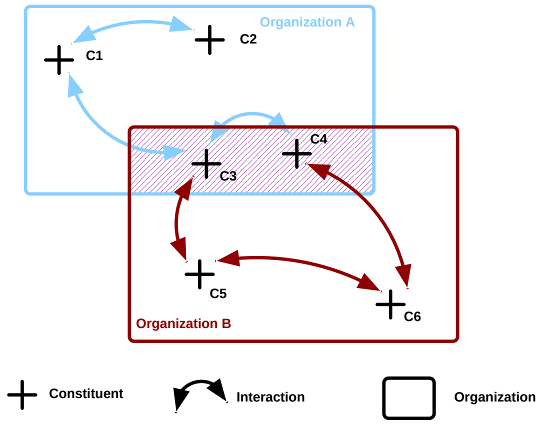

Figure 3: Two organizations, A and B, in structural coupling. The structure of organization A is the set of components $\{C1, C2, C3, C4\}$ and B $\{C3, C4, C5, C6\}$. The set $\{C3, C4\}$ is A and B's structural coupling.

Various agent-based organizational models exist. One can first cite OMNI (Vázquez-Salceda, Dignum, and Dignum, 2005), which is a framework that allows the description of both global organization requirements and autonomous individual agents: the question here is thus to enable the description of knowledge and constraints on the organizations and to have within them agents that follow such constraints while still being autonomous. In the same set of ideas, MOISE+ (Hubner, Sichman, and Boissier, 2007) enables the description of organizations within a platform that ensures agents will follow the organizational constraints. The point of view is organizational centered and a mechanism for dynamic reorganization, issued by agents, is supported. Those propositions, while focusing on the notion of organization, do not adress our issues: we do not want to express global constraints which are often inaccessible in the case of complex systems; our goal is on the contrary to build incrementally the complex model by describing it locally.

Autonomous systems. We started out with the idea that a system was a pair: *dynamic/structure*. We then went on to consider that the pair *reified interaction/associated constituents* is an elementary autonomous system. If we consider an organization as a set of interactions with the means and conditions required for the evolution of its topology, we can consider the *organization/associated constituents* couple as a higher-order system. The state of the system, the processes of interaction, phenomenon and modification of the organization's structure depend on one another recursively. The system holds the conditions and the means for its own production. Finally, it is linked by structural coupling to other systems with common structural elements (constituents). Here we refer to autonomous systems as they are understood by Varela. From now on it is possible to organize numerical models by juxtaposing autonomous systems. This multi interaction system (MIS) paradigm therefore combines our two initial perceptions of autonomy: interactions are agent-like autonomous processes and the composite models constructed using these interactions are also autonomous.

Thereafter, why didn't we use an existing agent meta model, autonomous systems being classically implemented using agents? For such a discussion let's consider three existing agent simulation platforms which are based on different agent conceptual models and different methods for building models of complex systems. First, CORMAS (Bousquet, Bakam, Proton, and Page, 1998) is a simulation platform focusing on exploited renewable resources. This platform's conceptual framework, which is essentially cellular automata based, is by definition limited to a cell-based and discretized description of systems and is also not compatible with our interaction-based approach. On the opposite, Repast (North, Tatara, Collier, and Ozik, 2007), based on SWARM (Minar, Burkhart, Langton, and Askenazi, 1996), is much more "generic" as the goal is to propose a multi-agent platform and toolkit. Because of this, the platform is not so much based on a precise framework. At last, MASCARET (Buche, Querrec, De Loor, and Chevaillier, 2004) is a simulation platform for developing virtual environments for training. Therefore, it addresses specifically social participatory simulations with social actors and pedagological agents, which is not our purpose.

From an epsitemologic point of view, we highlight again the fact that the biological autonomy principle used here stems from Varela's research in theoretical biology: models are operationally closed systems in structural coupling. The expansion of this area of research has given rise to a new cognitive science paradigm: enactionism (Varela, Thompson, and Rosch, 1992). We tried to articulate our proposition of autonomous processes –interactions– in the perspective of this paradigm, because we believe it favors modularity and incremental, thus interactive, modeling. It is in consequence a powerful means for enabling multi-modeling and temporal multi-scale. Thereafter, we argue that the method of cognition of our autonomous processes is closer, *in perspective*, to "enactive" agents[10], even though we do not address such issue in this article. Yet the classical agent approach is somehow in paradigmatic conflict with the underlying paradigms that structure our meta-model. In consequence, existing agent meta models are not relevant here. Furthermore, as discussed in section 2.2, the aim of this article is to unify Varela's vision of bio-

[10] Such agents would be our organizations and the sets phenomenon/interactions would be a type of behavior of such agents.

logical autonomy with the autonomy principle for computerized entities in order to influence the way numerical models are built.

3 Meta model: RéISCOP

This section describes the object-oriented meta-model based on the paradigmatic framework described in the previous section. The proposition implements the **Re**ification of **I**nteractions and the four following concepts: **S**tructure, **C**onstituant, **O**rganization and **P**henomena (RéISCOP).

3.1 `Interaction`, `Structure` *and* `Constituent` *classes*

The starting point for the meta model is the reification of interactions (see figure 4), an operation during which the notion of individual is broken down. The abstract `Interaction` class gives authority to active objects which each conduct actions of a particular relationship between "individuals" in the simulated system. Whilst we make maximum use of this point of view, everything which is involved in carrying out the dynamics of the simulation shifts from "individuals" to `Interactions` and thus, individuals become passive. In the end, they are a collection of variables — the numerical substrate — on which the interactions act. The `Constituent` class enables the representation of the state of these variables. The singleton `Structure` is therefore made up of the set of passive `Constituent` objects, thus defining the current state of the whole system at instant t. The active `Interaction` objects are organized in a chaotic and asynchronous manner.

3.2 The `Organization` *class*

First of all, the `Organization` class is designed as a container for constituents (its structural set) and is composed of interactions between these constituents. This container is also made up of `phenomena` (described below), enabling the creation of possible new interactions. The system as a whole is therefore interpreted as a layout of organizations which cause the global state of the system to evolve. In order to organize the models as a hierarchy, the `organization` object can contain sub-organizations. The significance of this approach is to be able to break down the functional, rather than the structural part (`Structure` being a singleton).

The default rule is that the structural set of a mother organization is composed of its own structural elements as well as the structural elements of its daughter organizations. Thus, the phenomena defined at the level of the mother class are also applied to the structures of the daughter classes. It therefore becomes possible to organize a global system according to multiple levels, each constructing one another (from the organelles, to the cells, to the tissues, to the organs and to the organisms...). Finally,

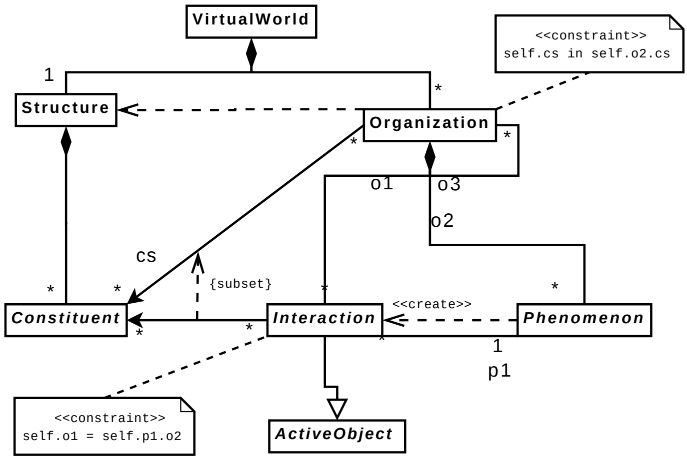

Figure 4: Diagram of the RéISCOP generic model.

hierarchical organization is only one of a number of possibilities. For example, the choice of a *middle-out* approach[11] would surely settle for simple juxtaposition, which is not a problem for this model. The model designer is free to arrange the organizations as s/he pleases using methods from the `Organization` class such as `add/deleteConstituent()`, `add/deletePhenomenon()` and `add/deleteOrganization()`.

Each class of the meta model possesses the means necessary to update the system at each intervening modification (dynamically or not) in the applicative model, which goes some way towards autonomy and modularity.

Finally, taking into account the autonomy principle, the update mechanism of the structural set on which the organization is based is isolated from the organization itself, and therefore implemented in the classes deriving from it. This is how we explain the association of the `Organization` class with the `Structure` singleton. The structural set's support algorithm is similar to that referred to below for phenomena (section 3.3). Management of topology via active waiting is to be avoided whereas a more passive, event-based system is more efficient. In order to do this, the organization subscribes itself to the `Structure` singleton and requests the reception of an event upon each creation of a certain type of constituent. But in general very few organizations have variable topology and when that does occur, the event-based mechanism suffices.

[11] The *middle-out* method, advocated by the S. Brenner Nobel prize Bock and Goode (1998) goes beyond the *top-down* and *bottom-up* oppositions, rather suggesting that systems modeling should be determined by the level of the available data.

3.3 *The* Phenomenon *class*

The `Phenomenon` class contains the interactions' rules of production. One instance of `Phenomenon` makes up one instance of `Organization`. As a result, the phenomenon concerns all of the constituents associated with the organization. Its role is to detect the creation conditions of new interactions and, if need be, to instantiate them[12].

The task of detecting the conditions for an interaction to appear is potentially costly in terms of calculation. Indeed, the ideal solution would be for each phenomenon to continually examine the structure's state. Unfortunately, the size of the considered simulations means that active waiting is not possible for all phenomena. Yet, all phenomena do not require the same detection mechanism. Such a choice of mechanism depends on the nature of the phenomena, which can encapsulate different mechanisms:

- **active waiting**. This is the least appropriate solution in terms of effectiveness. A phenomenon is an active object which, whenever called on to act, verifies the organization's entire structure;
- **event-based passive waiting on structural topology**. The phenomenon reacts to modifications to the organization's structural topology, that is to say, at each time a constituent is added or deleted;
- **mixed waiting.** a "mixture" of the two previous procedures. The phenomenon builds up a list of the constituents that might interest it, and proceeds through active waiting on these few objects. The list is thus updated chronologically as the topology changes;
- **event-based passive waiting on the constituents**. The phenomenon is part of a mechanism of events for detecting alterations in the state of the constituents which interest it.

Any combination of these mechanisms is possible. However, event-based mechanisms are favored[13], as they are less costly in terms of calculation time. They must nevertheless be used with precaution so as not to shortcut the autonomous nature of the processes by misusing callbacks. These have to remain local optimizations of the computational model, which do not impose restrictions on the rest

[12] It is possible to process the case of instantaneous interactions by replacing the instantiation of one interaction by the call of the function corresponding to the one action to be carried out, subject to appropriate scheduling.

[13] It must be noted that in all of the applications designed up to now, we have always managed to avoid the active waiting solution.

of the application. The use of phenomena thus facilitates the conservation of strong modularity.

3.4 Autonomous systems

Simulated systems are made up of `Structure` singletons and all of the organizations previously presented. It is possible to distinguish the sub-units created by each organization. The couple created by an organization and the structural whole to which it is associated thus makes up a sub-system. The same goes for the couple *interaction/set of associated constituents*. In thinking of the organization as a tree, the interactions would be its leaves. Organizations have all of interaction properties. Organizations can finally be defined as complex high-level interactions made up of other interactions. This point of view, associated with the idea of hierarchical composition between organizations enables variations of scale in describing phenomena.

Finally, the operational roles of interactions (modifying the state of the world), phenomena (creating interactions) and organization (managing topology) mutually influence one another. They are able to equip specific sub-systems associated to each organization with the means and conditions necessary to generate and to carry out its own processes. A system such as this displays the property of operational closure which Varela associates with the notion of autonomy (Varela, 1979). Using the approach put forward here, a model can be established through the juxtaposition of structurally coupled autonomous systems.

In summary, this section defines a meta model from five basic classes: `Organization, Phenomena, Interaction, Structure and Constituent`. It provides a modeling framework which is:

1. **multi-model:** by reifying interactions as autonomous entities, as each interaction can translate phenomena of entirely different natures, using various modeling tools (theoretical and computational).

2. **multi-time-scale:** implemented by the use of the real-time scheduling principle based on asynchronous and chaotic iterations.

3. **modular:** The arrangement of organizations representing structurally coupled autonomous systems.

In the following section, we shall present a number of examples demonstrating how this abstract model can be specialized in order to model complex systems. This will go some way to clarifying how this architecture might be implemented.

4 Results

Firstly, we shall quickly describe an implementation of the *RéISCOP* meta model. Then, we shall describe how the *RéISCOP* model branches out a first time to design generic tools for numerical modeling using three examples of chemical, mechanical and cellular phenomena. This illustrates how *RéISCOP* handles differential systems and how it supports multi-modeling. We shall then go on to show how it is possible to again adapt these tools in order to obtain concrete *in virtuo* experimental models stemming from thematic domains.

4.1 RéISCOP

RéISCOP is a library that implements the meta model described in the article. Figure 5 shows a UML diagram that sums up the RéISCOP toolbox. The classes implementing the meta model use the ARéVI (virtual reality workshop) library. The RéISCOP library also contains a certain number of classes derived from the meta model which model the phenomena presented in the following subsections. Finally, in order to create different applications, the RéISCOP classes can be used or specialized.

4.2 Resolving differential systems : example of chemistry phenomena

Modeling of differential systems like reaction diffusion systems is a major feature in the field of biological modeling. Thus, simulation of chemical phenomena using the RéISCOP model is necessary. To show how one can manage the modeling of such phenomena, let's consider the chemical reactions in play during spates of hematological coagulation and its modeling using *RéISCOP*. Based on Kerdélo, Abgrall, Parenthoën, and Tisseau (2002), the idea is that each chemical reaction corresponds to an autonomous process which carries out the kinetics of a particular reaction by acting on the concentrations representing molecule populations. By rendering the chemical interactions autonomous, this method operates the change in point of view of reifying interactions. The `Reaction`, `Species` and `ReactionPhenomenon` classes thus derive from `Interaction`, `Constituent` and `Phenomenon`, respectively. The `Diffusion` class, which also stems from `Interaction`, enables the simulation of diffusion phenomena. It therefore becomes possible to define an organization called `ChemicalOrganization`, which models the chemical environment subjected to reaction-diffusion phenomena (see figure 6).

The chemical models[14] defined by the `Reaction` interactions translate ordinary dif-

[14] In order to simplify the definition of biochemical networks, it is possible to use the SBML model (Systems Biology Markup Language) Hucka (Finney).

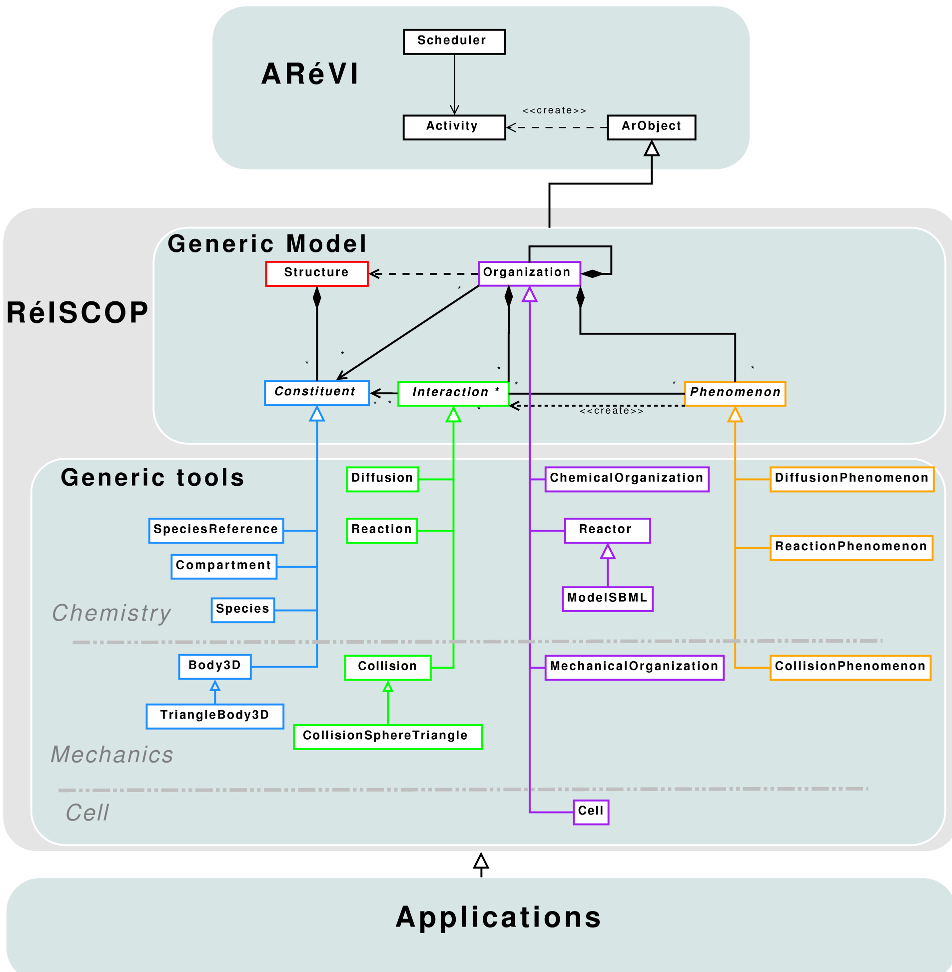

Figure 5: UML class diagram from the RéISCOP application

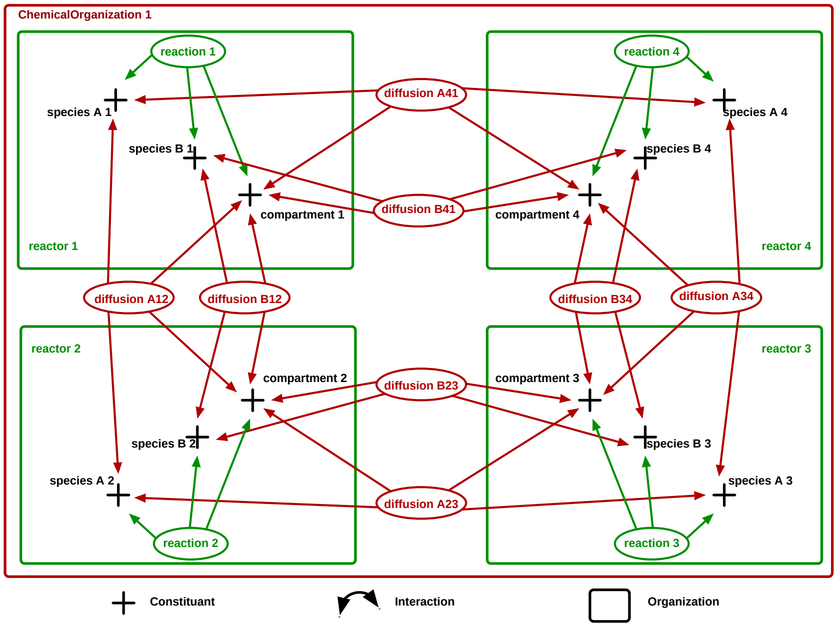

Figure 6: The `ChemicalOrganization` is made up of `Reactor` sub-organizations which are the site of chemical reactions. `Diffusion` interactions ensure the transport of materials from one reactor to another. The `Compartment` constituents represent the volume of each reactor and the `Species` constituents represent the quantity of reactants within that volume.

ferential equations (ODE). But, these systems are routinely processed using the traditional tools of ODE numerical resolution (Asher and Petzold, 1997) which adapt well to synchronous resolutions. Yet, chaotic asynchronous scheduling has been validated by Redou, Desmeulles, Abgrall, Rodin, and Tisseau (2007) who demonstrates the convergence of algorithms implemented by means of `Reaction` and `Diffusion` interactions.

This first case of application shows how the principle of reifying interactions allows us to integrate macroscopic knowledge on populations (concentrations of molecules) whilst retaining a bottom up approach. In this way, the online modification of certain settings or limited conditions, and the destruction or addition of new reactions pose no particular difficulties as they simply destroy or create new instances of `Interaction` without modifying the rest of the model.

4.3 Multi modeling

We have shown how we handle the classical modeling of differential systems. Yet, *RéISCOP* can also handle multi modeling : let's consider the construction of a second order model (a cell) and its structural coupling with other types of models (mechanical and chemical).

Cellular organization. The cell model is at a "higher" level of modeling (see figure 7). Being able to define a cell model, within the same framework that models chemical reactions, shows us that it is possible for multiple levels of organization to coexist. First of all, we consider the cell as a second-order system made up of chemical sub-systems, which is a good start as it is often the only chemical nature addressed in the literature. For the cell to chemically interact with the environment, it must be structurally coupled with it. This implies that the `Cell` organization must maintain its structural topology so as to include the chemical elements of its nearby environment. For example, in interrogating the `Structure` singleton it is possible to obtain a list of `Compartment` constituents and the `Species` present in close proximity to the organization. In order to do so, the `Cell` organization must be made up of a `position` state. Thus the cell's system can be coupled with a discrete chemical environment such as that described previously.

Mechanical organization. Rather than giving the cell a simple `position` constituent, it instead is preferable to give it a physical existence in the three dimensional universe. Therefore, we define a new type of constituent, the `Body3D`. A body is a three dimensional shape associated with a position, a reference mark and a mass. Through their bodies, the cells can therefore interact within a mechanical organization (see figure 8).

The mechanical organization retains its structural topology by adhering to the structure in order to receive an event upon the creation of each body. The mechanism therefore guarantees that all of the bodies in the virtual world are part of the organization. When the two encompassing spheres are close together, a `CollisionPhenomenon` creates an appropriate collision interaction. A mechanical collision interaction aims to repel two bodies if it senses that they are in contact. By the same principle, it is possible to establish adhesion (between bodies), or migration interactions (between a body and an "milieu" compartment). It therefore becomes possible to examine the role of spatial interactions in 3D, which is essential for conducting complex biological systems dynamics. It must be noted that, in general, processes linked to the mechanical aspects of the model require lower activation frequencies than for chemistry.

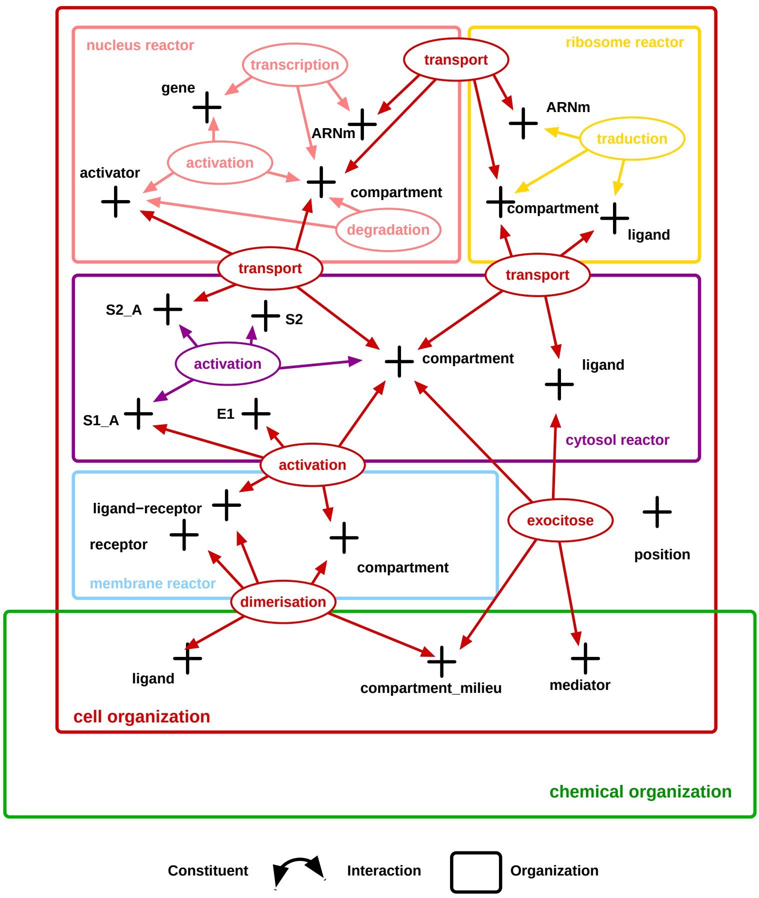

Figure 7: Illustration of `Cell` organization made up of `Reactor` sub-organizations modeling the cell's different compartments and organelles. Interactions are chemical reactions and the cell is in structural coupling with a chemical environment.

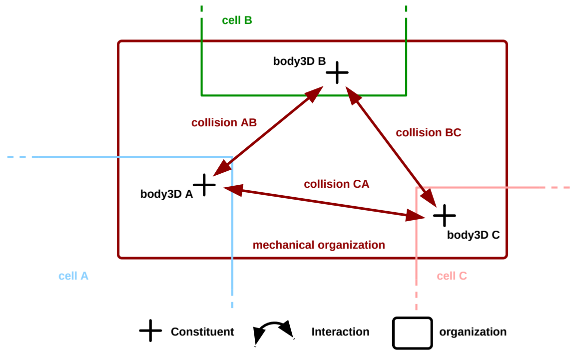

Figure 8: Mechanical organization makes the constituents of `Body3D` interact which could, for example, belong to `Cell` organizations.

4.4 Virtual Reality

RéISCOP has been used to describe models from various biological fields, *i.e.* hematology, oncology, dermatology or neurobiology. Two interdisciplinary modeling applications specifically address the perspective of the "virtuoscope" tool.

Firstly, the "*in virtuo* dermis" application takes place in the context of a scientific collaboration with doctors and biologists (Desmeulles, Rodin, and Misery, 2005). Through a model of allergic urticaria, the object of study is the interaction between the large complex systems of the human body: the skin, the vascular system, the nervous system and the immune system. The aim here is not to describe the biological model in detail. We can nonetheless specify that the application implements a model of one millimeter cubed of dermis. The model is arranged as a juxtaposition of autonomous systems simulating a discrete chemical environment, mechanical phenomena, mast cells, nerve fiber and a capillary. Figure 9 shows snapshots taken while experimenting the model[15] :

- 9.a) Using the syringe, a certain quantity of the allergen is injected into the environment;
- 9.b) The allergen activates the mast cells (color changes) which then release histamine into the environment, which activates the capillary's receptors;
- 9.c) The histamine activates the nerve fiber (which also changes color), it again releases a certain number of mediators which increase the activation of the mast cells which in turn again release more histamine;

[15] A film of this experiment can be found at `www.cerv.fr/en/activites/EBV.php`.

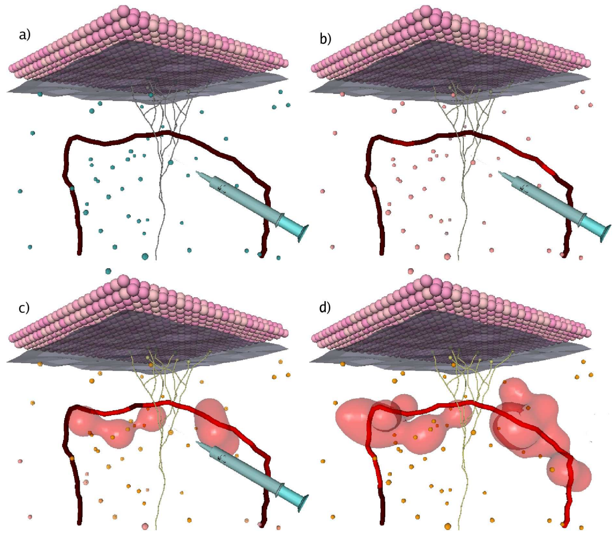

Figure 9: Snapshots of a simple *in virtuo* experiment with the application "dermis in virtuo".

- 9.d) As the permeability of the capillary increases, plasma flows into the tissue, which leads to a deformation of the basement membrane, thus forming an edema.

As shown above, it is possible to experiment interactively the model and observe the consequences without having predetermined these modifications. This application goes some way towards a full implementation of the "virtuoscope". Notice that in this example, we can observe the evolution of 400 organizations, 1,500 phenomena, 10,000 constituents and 40,000 interactions in real-time on a standard PC.

The second example of the meta model's application is the "EndoSim project" (Bourhis and Rodin, 2007). The aim is to model and simulate the vasorelaxation of arteries (that is to say muscular relaxation and adaptation of the size of the blood vessel according to both blood flow and various biochemical mediators present in the blood), focusing on the role of endothelial cells (see figure 10). As well as the biological aspect, this project aims to study the distribution of applications, in order to increase the size of the simulated models. Thus, the distribution is based on the RéISCOP models' organizations. It has been actually tested on a cluster of six standard PCs. Each PC is responsible for a simulated section of arteriole which has been sectioned off spatially. The whole simulation, with its 130 endothelial cells is conducted in real-time.

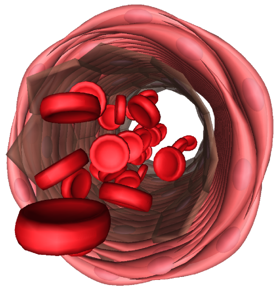

Figure 10: 3D view of a segment of a small artery (with red corpuscles, endothelial cells and muscular cells).

5 Conclusions

We propose in this article to implement the "virtuoscope" and enable the construction and "in virtuo" experiment of models of complex systems through the meta model *RéISCOP* which is based on the multi interaction paradigmatic framework.

The article first recalls what the "virtuoscope" is (§1). Then, it exhibits the paradigmatic framework that introduces the multi interaction concepts and point of view (§2). The starting point of this framework is the unification of the biological autonomy (§2.2) introduced by Varela with the autonomy principle for the building of virtual reality numerical models (§2.1). Such point of view leads to the concept of structural coupling wich enables the reification of interactions (§2.3). Those fundamental concepts make possible the building of modular heterogeneous models: models are reusable and multi-modeling can be achieved. Furthermore, a chaotic asynchronous scheduler (§2.4) enables the temporal multi-scale modeling. At last, the specification of the concepts of phenomenon and organization within the multi interaction framework enables the implementation of complex dynamics (§2.5) with autonomous models.

Thereafter, we formalize the multi interaction framework into the *RéISCOP* meta model (§3). We describe the five classes `Interaction`, `Constituent`, `Structure` (§3.1), `Organization` (§3.2) and `Phenomenon` (§3.3). With such classes, it is possible to build operationnally autonomous systems, as they are empowered with the conditions and means for their own production and destruction (§3.4).

Finally, we have implemented the meta model in the *RéISCOP* virtual reality modeling platform (§4.1), which has given way to various applications and experimentations. The first application (§4.2) shows that *RéISCOP* can integrate knowledge on populations, i.e. handle differential systems and thus classical models. Fur-

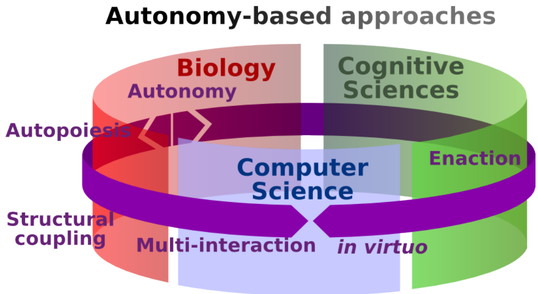

Figure 11: The figure shows how the meta model sits on top of concepts coming from the fields of computer science, cognitive sciences and biology. Thereafter, it shows the consistency of the multi interaction paradigmatic framework.

thermore, a mathematical validation demonstrates the convergence of the results. The second application (§4.3) shows that *RéISCOP* easily enables multi-modeling through the cell example. It also illustrates the modularity of this approach. At last, we exhibit two virtual reality research projects (§4.4) that were built in confrontation with the field of biology. They especially highlight how *RéISCOP* may implement the "virtuoscope".

The various results show that the meta model *RéISCOP* enables domain experts and computer scientists to formulate together models of various phenomena. The different points of view of the different research fields are thus consistently formulated within the same modeling framework. Indeed, our proposition is consistent from an epistemological point of view. As shown in figure 11 the involved paradigms can be understood as an evolution of the initial Varela's works through different fields.

Futhermore, we have shown how modeling, simulation and software engineering are imbricated to allow *in virtuo* experiment. One of the means to achieve this is to maintain the semantic of the models accessible at all times. This approach is anchored in the will to enrich the classical numerical modeling and simulation tools by considering a computer as more than a mathematical solver. It is an original aspect of the interdisciplinary practice of modeling and simulation.

The modeling pratice considers different levels of description (Fitzgerald, Goldbeck-Wood, Kung, Petersen, Subramanian, Wescott, and Source, 2008) : *quantum scale, molecular scale, mesoscale...* Interfacing those different levels is a quite chalenging question (see Chirputkar, Qian, and Source (2008) for an example of such a work). We have reported that our proposition has been designed to handle heterogenous models from a software engineering point of view (§3.4). Those sub-models might encapsulate algorithms that model different levels of description, and communicate *via* a structural coupling through the constituents. For a multi level purpose, constituents can be enriched to be accessed at different levels of description by the interactions. However, the meta model doesn't provide a magical solution to perform the multi level modeling that remains in most cases, theoretically and computationally impossible. *RéISCOP* can help to operationalize multi level models, but doesn't replace mathematical investigations. That is why the term "multi scale" has to be used carefully.

In perspective, how thematicians can experiment their models questions our ability to build an adapted user interface. Yet, such a perspective, opening on the fields of cognitive ergonomy and interface engineering, requires more experimental data and studies with thematicians. Indeed, interdisciplinary applications enable feedbacks that are necessary for enriching the experimental validation of the *RéISCOP* approach. At last, having operationally autonomous models enables the study of conceptually autonomous systems. Thus, we can envisage theoretical studies regarding autopoietic systems from a biological point of view or even regarding enactive systems from the cognitive sciences point of view.

References

Amblard, F.; Ferrand, N.; Hill, D. R. (2001): How a conceptual framework can help to design models following decreasing abstraction. In *Proceedings of the 13th SCS-European Simulation Symposium*, pp. 843–847, Marseille (France).

Asher, U. M.; Petzold, L. R. (1997): *Computer Methods for Ordinary Differential Equations and Differential-Algebraic Equations*. Éditions Médicales Internationales.

Baudouin, C.; Chevaillier, P.; Le Pallec, A.; Beney, M. (2008): Feedback on design and use of a virtual environment for practical lab work. In *Proceedings of the Virtual Reality International Conference, VRIC 2008*, pp. 117–125.

Bock, R.; Goode, J.(Eds): *The limits of reductionism in biology*, pp. 106–116. Eds. (Novartis Found. Sum., London, john wiley edition, 1998.

Bonneaud, S.; Redou, P.; Thebault, D.; Chevaillier, P. (2007): Multi-modelisation agent orientee patterns : Application aux ecosystèmes exploites. In *JFSMA07 - IN PRESS*.

Bourhis, M.; Rodin, V. (2007): A multiagent view of grid computing for biological simulations in virtual reality. In *The 21st annual European Simulation and Modelling Conference*, St Julian, Malte.

Bousquet, F.; Bakam, I.; Proton, H.; Page, C. L. (1998): Cormas: common-pool resources and multi-agent systems. *Lecture Notes in Artificial Intelligence*, vol. 1416, pp. 826–838.

Buche, C.; Querrec, R.; De Loor, P.; Chevaillier, P. (2004): MASCARET : A pedagogical multi-agent system for virtual environment for training. *International Journal of Distance Education Technologies (JDET)*, vol. 2, no. 4, pp. 41–61. ISSN 1539-3100.

Capra, F. (1997): *The Web of Life : A New Scientific Understanding of Living Systems*. Anchor.

Chirputkar, S.; Qian, D.; Source, C. (2008): Coupled Atomistic/Continuum Simulation based on Extended Space-Time Finite Element Method. *CMES: Computer Modeling in Engineering & Sciences*, vol. 24, no. 2/3, pp. 185.

DeAngelis, D.; Rose, K.; Huston, M. (1994): Individual-oriented approaches to modeling ecological populations and communities. In S.A., L.(Ed): *Frontiers in mathematical biology*, pp. 390–410. Springer Verlag.

Desmeulles, G.; Rodin, V.; Misery, L. (2005): In virtuo model for the allergic urticaria: Preliminary results. In *Journal of Investigative Dermatology*, volume 125, pg. A15.

Drogoul, A.; Vanbergue, D.; Meurisse, T. (2003): Multi-agent based simulation: Where are the agents ? In *Multi-Agent-Based Simulation II: Third International Workshop, MABS 2002, Bologna, Italy, July 15-16, 2002. Revised Papers*, pp. 43–49.

Endy, D.; Brent, R. (2001): Modelling cellular behaviour. *Nature*, vol. 409, pp. 391–395.

Erman, L. D.; Hayes-Roth, F.; Lesser, V. R.; Reddy, D. R. (1980): The hearsay-ii speech-understanding system: Integrating knowledge to resolve uncertainty. *ACM Comput. Surv.*, vol. 12, no. 2, pp. 213–253.

Ferber, J. (1999): *Multi-Agent Systems: An Introduction to Distributed Artificial Intelligence*. Addison-Wesley Professional.

Fitzgerald, G.; Goldbeck-Wood, G.; Kung, P.; Petersen, M.; Subramanian, L.; Wescott, J.; Source, C. (2008): Materials Modeling from Quantum Mechanics to The Mesoscale. *CMES: Computer Modeling in Engineering & Sciences*, vol. 24, no. 2/3, pp. 169.

Fuchs, P.; Moreau, G.; Tisseau, J. (2006): *Introduction à la réalité virtuelle*, volume 3: « Outils et modèles informatiques des environnements virtuels » of *Le Traité de la Réalité Virtuelle*, chapter 1, pp. 3–32. 3^e edition, 2006.

González, P.; Cárdenas, M.; Camacho, D.; Franyuti, A.; Rosas, O.; Lagúnez-Otero, J. (2003): Cellulat: an agent-based intracellular signalling model. *BioSystems*, vol. 68, pp. 171–185.

Grassé, P.-P. (1959): La reconstruction du nid et les coordinations inter-individuelles chez belicositermes natalensis et cubitermes sp. la théorie de la stigmergie : Essai d'interprétation du comportement des termites constructeurs. *Insectes Sociaux*, vol. 6, pp. 41–80.

Hill, D. R. (1996): *Object-Oriented Analysis and Simulation*. Addison-Wesley Longman Publishing Co., Inc., Boston, MA, USA. Translator-International, K.

Hubner, J. F.; Sichman, J. S.; Boissier, O. (2007): Developing organised multiagent systems using the moise+ model: programming issues at the system and agent levels. *Int. J. Agent-Oriented Softw. Eng.*, vol. 1, no. 3/4, pp. 370–395.

Hucka, M.; Finney, A.; Sauro, H.; Bolouri, H.; Doyle, J.; Kitano, H.; the rest of the SBML Forum: Arkin, A.; Bornstein, B. J.; Bray, D.; Cornish-Bowden, A.; Cuellar, A. A.; Dronov, S.; Gilles, E. D.; Ginkel, M.; Gor, V.; Goryanin, I. I.; Hedley, W. J.; Hodgman, T. C.; Hofmeyr, J.-H.; Hunter, P. J.; Juty, N. S.; Kasberger, J. L.; Kremling, A.; Kummer, U.; Le Novère, N.; Loew, L. M.; Lucio, D.; Mendes, P.; Minch, E.; Mjolsness, E. D.; Nakayama, Y.; Nelson, M. R.; Nielsen, P. F.; Sakurada, T.; Schaff, J. C.; Shapiro, B. E.; Shimizu, T. S.; Spence, H. D.; Stelling, J.; Takahashi, K.; Tomita, M.; Wagner, J.; Wang, J. (2003): The systems biology markup language (sbml): a medium for representation and exchange of biochemical network models. *Bioinformatics*, vol. 19, no. 4, pp. 524–531.

Kerdélo, S.; Abgrall, J.; Parenthoën, M.; Tisseau, J. (2002): Multi-agent systems: A useful tool for the modelization and simulation of the blood coagulation cascade. In *Bioinformatics And Multi-Agent Systems (BIXMAS'02)*, pp. 33–36.

Kitano, H. (2002): Computational systems biology. *Nature*, vol. 420, no. 6912, pp. 206–10.

Kubera, Y.; Mathieu, P.; Picault, S. (2008): Interaction-oriented agent simulations : From theory to implementation. In *Proceedings of the 18th European Conference on Artificial Intelligence (ECAI'08)*, pp. 383–387.

Kubera, Y.; Mathieu, P.; Picault, S. (2009): How to avoid biases in reactive simulations. In *Proceedings of the 7th International Conference on Practical Applications of Agents and Multi-Agent Systems (PAAMS'09)*, pp. 100–109. TODO : Editor, pdf.

Laughlin, R. B. (2005): *A Different Universe: Reinventing Physics from the Bottom Down*. Basic Books.

Mathieu, P.; Routier, J.-C.; Secq, Y. (2003): Rio: Roles, interactions and organizations. In Marik, V.; Müller, J.; Pechoucek, M.(Eds): *Proceedings of the 3rd International/Central and Eastern European Conference on Multi-Agent Systems (CEEMAS 2003)*, pp. 147–157.

Michel, F.; Ferber, J.; Gutknecht, O. (2001): Generic simulation tools based on mas organization. In *Proceedings of the 10 th European Workshop on Modelling Autonomous Agents in a Multi Agent World MAMAAW'2001*.

Minar, N.; Burkhart, R.; Langton, C.; Askenazi, M. (1996): The swarm simulation system: a toolkit for building multi-agent simulations. Santa Fe Institute Working Papers, 1996. available at `http://www.santafe.edu/projects/swarm/swarmdoc/swarmdoc.html`.

Morin, E. (1990): *Introduction à la pensée complexe*. ESF.

North, M.; Tatara, E.; Collier, N.; Ozik, J. (2007): Visual agent-based model development with repast simphony. In *Proceedings of the Agent 2007 Conference on Complex Interaction and Social Emergence*, pp. 173–192.

Odell, J. (2002): Objects and agents compared. *Journal of Object Technology*, vol. 1, no. 1, pp. 41–53.

Querrec, G.; Bataille, R.; Rodin, V.; Abgrall, J.-f.; Tisseau, J. (2005): Computer simulation of multiple myeloma in the context of systems biology. *Haematologica / The hematology journal*.

Ramat, E.; Preux, P. (2003): Virtual laboratory environment (vle) : An software environment oriented agent and object for modeling and simulation of complex systems. *Journal of Simulation Practice and Theory*, , no. 11, pp. 45–55.

Redou, P.; Desmeulles, G.; Abgrall, J.-f.; Rodin, V.; Tisseau, J. (2007): Formal validation of asynchronous interaction-agents algorithms for reaction-diffusion problems. In *PADS'07, 21st International Workshop on Principles of Advanced and Distributed Simulation*.

Redou, P.; Kerdélo, S.; Le Gal, C.and Querrec, G.; Rodin, V.; Abgrall, J.; Tisseau, J. (2005): Reaction-agents : First mathematical validation of a multi-agent system for dynimical biochemical kinetics. *Lecture Notes in Computer Science*, vol. 3808, pp. 156–166.

Sargent, R. G. (2004): Validation and verification of simulation models. In *Proceedings of the 2004 Winter Simulation Conference*, pp. 121–130.

Tisseau, J. (2001): *Réalité Virtuelle – autonomie* in virtuo –. PhD thesis, Habilitation à Diriger des Recherches, spécialité Informatique, Université de Rennes I, Rennes (France), 2001a.

Tisseau, J. (2001): Virtual reality – in virtuo autonomy. Accreditation to Direct Research, University of Rennes 1, 2001b.

Varela, F. (1979): *Principles of Biological Autonomy*. Elsevier/North-Holland.

Varela, F. J.; Thompson, E. T.; Rosch, E. (1992): *The Embodied Mind: Cognitive Science and Human Experience*. The MIT Press.

Vázquez-Salceda, J.; Dignum, V.; Dignum, F. (2005): Organizing multiagent systems. *Autonomous Agents and Multi-Agent Systems*, vol. 11, no. 3, pp. 307–360.

Wooldridge, M. J. (2001): *Multi-agent systems : an introduction*. Wiley, Chichester. GBA1-Z6596 Michael Woolridge.

Zeigler, B. P. (1989): Devs representation of dynamical systems: event-based intelligent control. In *Proceedings of the IEEE*, volume 77.