Multi-Agent Systems and Heterogeneous Scales Interactions. Application to Pharmacokinetics of Vitamin K Antagonists

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Abstract

The study of complex systems consists in considering entities submitted to interactions which define the dynamics of the system. Virtual reality opens the way to interactive simulation of complex systems, so called the *in virtuo* experimentation. For that purpose we use multi-interactions systems, based on the reification of interactions and multi-agent systems, in a phenomenological approach. Interaction agents represent the modeler understanding of the relations between the constituents of the system. Such descriptive models lead us to define parameters *a priori*. Moreover these parameters can be fluctuant, or even unknown, during a simulation in relation to the system dynamics or user interventions. To respond to this problem, we expose in this paper a redundant multiscale architecture which rests upon the fact that we can establish models of a same phenomenon at heterogeneous time and space scales. Heterogenous Multiscale Methods provide a general framework to mix levels of description of a system. Our intention is to implement this framework in multi-interactions systems by means of a *Scale-Interaction* agent. Then we illustrate our architecture through a pharmacokinetics application. Indeed biochemical kinetics abounds of parametric phenomena. Finally we discuss about some questions raised by this methodology, such as synchronicity, organization detection and genericity.

Introduction

The study of complex systems consists in considering entities in interaction. These interactions affect the entities behaviors and then change the system dynamics. The entities are most often heterogeneous by their natures, their interactions and their scales. Moreover, their great number is a major obstacle to their understanding. Thus we have to model these systems, even roughly, in order to get out some new knowledge. It's generally difficult formally to prove that a model is exact. That's why we need to experiment our models so as to compare simulations and observations.

Virtual reality enables us to manipulate these models (Fuchs et al., 2006). An expert can be immersed in real time within a virtual laboratory, mock up the system he wants to study and experiment it, without any danger or consequences. This is called the *in virtuo* experimentation by analogy with *in vivo* and *in vitro* methods. It allows the modeler to build his model incrementally, by successive additions of phenomena. This is a "phenomenological approach" for modeling (Parenthoën, 2004).

For that purpose we use multi-interactions systems (MIS), based on the reification of interactions and multi-agent systems. It consists in changing our point of view to describe phenomena just as we observe them. Thus agents are not the entities anymore but the interactions binding them. This method has been repeatedly successfully applied, validated (Redou et al., 2007) and today, there are several models and methodologies that can be used to experiment complex systems with multi-agent systems (Desmeulles et al., 2009).

In addition, this kind of modeling has the advantage of reducing the computation time because phenomena are described macroscopically with the help of ordinary differential equations (ODE). The price is that we often have to define parameters in models, like diffusion coefficients for instance. Moreover these parameters can fluctuate, or even unknown, during a simulation in relation to the system dynamics or user interventions (Béal et al., 2010).

To respond to this problem, we propose in this article to make maximum use of the knowledge we have about the phenomena. We expose then a redundant multiscale architecture which rests upon the fact that we can establish models of the same phenomenon at heterogeneous time and space scales. Parameters of a macroscopic model are in fact related to the system dynamics at microscopic scale. For instance, diffusion rate of a chemical concentration can be determined using brownian motion of molecules and statistical physics (Frenkel and Smit, 2001).

Therefore, our idea is to run parallel simulations of multiple description scales in order to parameterize phenomena. Interactions between the scales will be supported by agents, which is the core of this article.

We will illustrate our architecture through a pharmacokinetics / pharmacodynamics (PK / PD) model of the vitamin K antagonists (VKA). Chemical kinetics is indeed a perfect example of parametric phenomena. For this occasion we will discuss about some questions raised by our method.

Heterogeneous multiscales modeling

In the perspective of a phenomenological approach, we are interested in the effects of the phenomena over entities. These effects are usually described by differential equations at a macroscopic scale. This approach is very successful for large classes of problems but it favours efficiency over accuracy introducing empirical closures and parameters in equations that are often partially known or understood. Besides, the system dynamics can be unpredictable. So an acceptable closure or parameter at a given instant could become wrong at the next one. In the case of more complex systems it seems to be necessary to call upon different methods, particularly by coupling models with different levels of description in order to achieve a balance between accuracy and efficiency. We talk then about multiscale methods.

Multiscale methods have been existing for a long time, such as adaptative mesh refinement methods (Debreu et al., 2008). Their purpose is to mix different scales, solved separately, into a global simulation. Such an idea can be applied in the context of stiff ODEs resolution using splitting methods (Le Bris, 2005; Guibert, 2009).

Let us consider the example of a system z composed of C operators where A (resp. B) are non-stiff (resp. stiff) operators :

$$\frac{dz}{dt} = Cz = Az + Bz \tag{1}$$

We can solve z over each time step $[n\Delta t, (n+1)\Delta t]$ with

$$\begin{cases} \dfrac{dz^{**}}{dt} & = & Bz^{**} \\ z^{**}(n\Delta t) & = & z^{*}((n+1)\Delta t) \end{cases} \tag{2}$$

A different solver could be used for each part of the system in this way, potentially with a smaller time step for the stiff one.

Classical multiscale methods are extremely accurate but their cost can be huge. Indeed, their efficiency is closely dependent on the smaller time step used in the simulation.

That's why recently developed multiscale methods aim at one step further : in order to cut down the computing time, they try to capture the macroscale behavior of the system from local microscale simulations run over a limited time (Horstemeyer, 2009).

Heterogeneous multiscale method (HMM) (Weinan et al., 2007) relies on the following concept : coupling redundant scales in order to take into consideration possible variations of the system. In some cases, the macroscopic model is not explicitly available or is invalid in some part of the domain. The microscopic model is used then to supply the necessary data for the macroscopic model. Scale separation is exploited so that coarse-grained variables can be evolved on macroscopic scale using data that are predicted based on the simulation of the microscale ; see figure 1.

Figure 1: Schematics of HMM framework (Weinan et al., 2007)

We consider a macroscale with a state variable U. We have seen that this state depends on the system dynamics and / or parameters. We have at our disposal a microscopic model, such as molecular dynamics, that describes the microscopic state variable u of the same system. Let's not forget that we are dealing with different levels of description of an unique system.

The two scales are related one to each other by the use of reconstruction (Q) and compression (R) operators :

$$\begin{cases} Q.u & = & U \\ R.U & = & u \end{cases} \tag{3}$$

with the property $Q.R = I$, where I is the identity operator. The role of these operators is to translate the system structure and dynamics from a scale to the other. The main difficulty lies in the definition of these operators. Indeed it would be naïve to think that a macroscale phenomenon could be the result of an unique microscopic one. Most often we would be interested in a group of local interactions from which emerge a global behavior. This underlines one of primary interests of multiscale and complex systems simulation : we may increase our understanding of phenomena by observing their entanglements (Lesne, 2003).

Finally the idea is to make round-trips between the two scales regarding to the system dynamics. As soon as there is a lack of data in the macroscale ensued from a dynamics variation, we use Q to rebuild a microscale which we run and observe over a given duration. Thus we can make data estimations with the help of R so as to set new parameters in the macroscale.

HMM give guidelines on how to design redundant multiscale systems. It is a general framework which is lacking implementation. We intends in this paper to fill this lack by the use of multi-agent systems.

We saw that HMM deduce the macroscale behavior according to emergent processes and data from the microscale. Concept of emergence is one basis of multi-agent systems (Demazeau, 1995). Into such systems, autonomous entities evolve with only a partial knowledge

of their environment. The addition of their individual interactions results in a collective behavior. Then multi-agent systems appear as very good tool to model complex systems by the way of splitting the whole problem in smaller subparts. Today, it has been successfully applied to molecular dynamics for instance (Parisey, 2007). However, it implies to simulate each entity separately which is a very costly method. That's why we can say that classical multi-agent systems match much more to a microscale method.

As we have seen before, multi-interactions systems offer an original approach to model efficiently the links between entities. We can also discern that HMM operators could be considered as links between scales. That's why we propose in the following section to implement this process into multi-interactions framework which we use to perform *in virtuo* experiments.

Virtuo framework : MIS implementing HMM

Multi-interactions systems were first presented in the RéISCOP meta-model (Desmeulles, 2006). The motivation was to enable an expert to describe a system as he observes it in the nature, usually with the help of ODE. Subsequently, we pursued this work bringing the reification of numerical methods of solving used to make the system evolve during the simulation (Le Yaouanq, 2010). This allows us to keep control over the convergence and stability of the system. This modification and others prompted us to propose a new framework that implements MIS : we called it Virtuo.

Our will is now to take the advantage of redundant multiscale methods in order to parameterize macroscopic descriptions of phenomena. *In virtuo* experimentation puts interactivity first. It implies to consider some constraints such as real-time computing and reactivity of the simulation. In this context, we can not use classical multiscales methods which impose the choice of small time steps. That is where we join the HMM framework. Our idea is to simulate critical phenomena at a microscale selectively and for a limited duration so as to complete their description.

In this section, we detail Virtuo architecture and how it makes possible to model multiscale systems taking inspiration from HMM.

How to design the model of a given scale ?

As said above, we are interested in systems composed of numerous entities. They are represented by the *Entity* class in our model ; see figure 2. To fit reality, we introduce a concept of hierarchy between entities. Thus an entity can contain other entities. It is important to note that we are still talking about a same level of description. This ability is just a way of considering spatial organizations into a system. For instance, from a macroscopical point of view, a human body is composed of organs. But it doesn't mean that there are two different levels of description. The decisive element that will encourage us to consider multiple scales into a simulation is the time / spatial reach of interactions. This will be discussed thereafter.

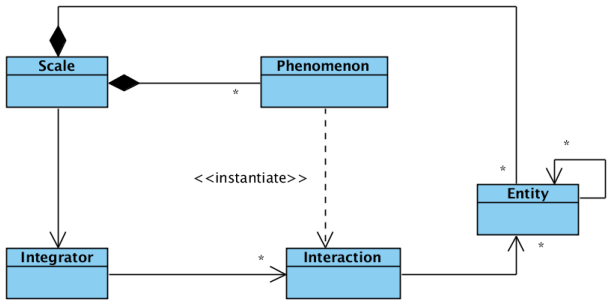

Figure 2: Class diagram focusing on Scale designing (Le Yaouanq, 2010)

Multi-interactions systems argue in favour of considering that active agents in the system are the interactions between passive entities. So an *Interaction* agent associates one or many entities and compute their local effects on each other. The systems's dynamics is the addition of these local modifications.

An *Interaction* computing consists in solving independently a part of an ODE system. For this we use numerical methods to make the system evolve on each time step (Ascher and Petzold, 1998). Even if they have been validated in the context of multi-interactions systems, they force us to take care of the system convergence and stability (Redou et al., 2010). Actually, if the time step is chosen too large, some interactions could induce an irreversible instability of the whole system. That is why we add the *Integrator* agent whose job is to manage the interactions. It would be able to control *Interactions* actions and order them to recompute more precisely if needed.

The desynchronization of interactions eases a modular and incremental building of the numerical model. Firstly, this is especially useful for online models building, since the modeller usually selects, subjectively, the phenomena that are most likely involved, and runs the model. If results are not correct enough, the model is incremented with other interactions, etc., until a satisfying model is obtained. Secondly, the need of *Interaction* instantiation could emerge from the system's dynamics. There we introduce the *Phenomenon* agent which will create or delete interactions in certain conditions. It leads us to consider that an interaction is the manifestation of a phenomenon.

Let us consider two empty compartments (*Entities*) A and B related by a *DiffusionPhenomenon*. If we add a concentration of a chemical species C in compartment A, the *Phenomenon* automatically instantiates a *DiffusionInteraction* between A and B to diffuse C. As soon as concentration of C is equal in the two compartments, the *DiffusionPhenomenon* destroys the *DiffusionInteraction*.

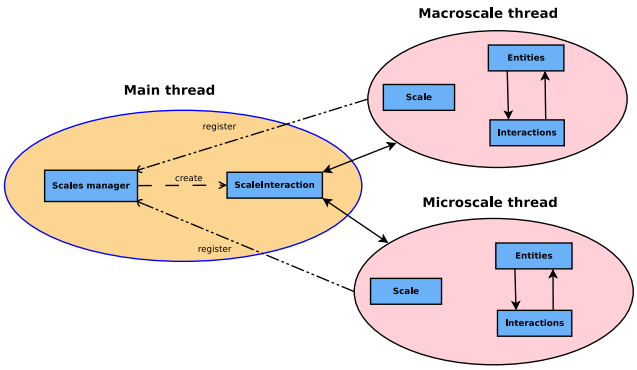

Figure 3: Diagram of threads distribution.

No useless calculation is done this way. Modularity makes this process natural and doesn't require to stop the simulation to modify the code of equations.

Until now, we detailed the different pieces we use to design a single *Scale* using the Virtuo framework. It is time to explain how we proceed to make multiple scales interact into a simulation.

Multiple interacting scales

Virtuo framework offers the possibility to build simulations composed of several *Scales*. Each one can be run independently in relation to each other. This allows us to improve performances by means of parallelization. As we can see it on figure 3, each *Scale* is distributed into separated threads. They are managed by the *ScalesManager* class that plays the role of a server on which a client *Scale* can log. Once again modularity enables this process to be done while the simulation is running.

We have seen before that multiscale modeling is a useful tool which may be used when a phenomena is not understood or when there is a lack of essential data in a macroscopical model. That is the point that leads us to make multiple *Scales* coexist. These *Scales* must of course be connected so that they can communicate. So we plan to implement this link thanks to a *Scale-Interaction* agent, as well as *Entities* are connected with *Interactions*

This new agent manages exactly two different *Scales*. It is in charge of doing translation work of structure modifications that may appear in each one. There we meet again HMM operators. A *Scale-Interaction* agent provides the two of them : compression from microscale to macroscale and reconstruction from macroscale to microscale. It does itself the translation and acts directly on the two *Scales* components, both *Entities* and *Interactions*.

Such a process requires to ensure data consistency. Indeed *Scales* are not paused and their structures still independantly change in course of the simulation. So we have to use locking mechanisms on *Scales* constituents such as any multi-threaded model. However, they can't guarantee the system's coherence alone. In fact the autonomy of *Scales* raises some questions about the *Scale-Interaction* action. The following exposes a first and non-exhaustive list of these questions and preliminary answers.

When should we introduce new microscales ?
As said previously, we need microscales because of a lack of data for solving interactions into the macroscale. This can appear further to a structural evolution induced by the system's dynamics or an intervention from the user. However, microscale simulation implies the choice of a very small time step in relation to spatial units and interactions intensities. Obviously, we can't simulate microscale permanently. So we would only introduce microscales selectively and for a limited time.

What should we observe to make data estimation ?
Given that a microscale is built from a need to explain explicit parts of a macroscale, the observation is inevitably directed. Thus the microscale's initial state does only contain *Entities* and *Phenomena* we choose to describe it. Though its dynamics could change and drive to take into consideration emerging behaviors then data estimation would mainly be done watching to the *Entities* states and their evolution through the observation duration. But in every instance, it seems that the rules and structure of the microscale must be defined *a priori* and on *ad hoc* basis, in the same way as the macroscale.

How long should we observe a microscale ?
Since microscales are simulated for a limited time, the observation duration must be short regarding to the macroscale time step. Additionally, the macroscale isn't turned off while the microscale is running. In most cases, the observation would be done until an equilibrium state which can be defined *a priori* or detected as a decrease of interactions intensity.

How and when to reflect the data estimation ?
Once data estimation is done, *Scale-Interaction* have to reflect it on the macroscale by affecting its structure. This process must be done carefully in order not to provoke instabilities in case of too brutal variations. Sometimes it would be executed progressively and at the right moment which could be difficult to identify.

We have explained principles and problems of the Virtuo framework, from "how to design the model of a scale ?" to "why and how to make scales interacting ?". In the next section, we illustrate our modeling method through a pharmacokinetics / pharmacodynamics application.

Application to PK / PD of VKA

Our objective on the long term is to provide a virtual laboratory for complex systems in which experts could

build models and conduct experiments. The domain of biochemical kinetics lends itself perfectly to this vision. Moreover, a lot of chemical phenomena involve multiple levels of description. That is why we chose to exemplify the Virtuo framework by means of a PK application.

Context

The development of a new medicine is very long process which requires clinical trials. They are divided into several stages and lead to identify pharmacokinetics properties of the substance :

- **Absorption** : how it enters the blood circulation
- **Distribution** : how it is disseminated throughout the fluids and tissues of the body
- **Metabolism** : how it is transformed by the body
- **Excretion** : how it is eliminated from the body

Pharmacokinetics may be simply defined as what the body does to the drug, as opposed to pharmacodynamics which may be defined as what the drug does to the body (Benet, 1984). Such practicals aim at measuring adapted dose which should be administered to the patient. They are very expensive and not totally safe. Thus biologists are more and more interested in numerical simulations. The *in virtuo* method allows to be ahead of classical *in silico* simulations thanks to the interactivity with model (Tisseau, 2001). Indeed, multi-agent systems used in the context of a phenomenological approach allows to add sense on phenomena to observe their individual and coupled effects on the system.

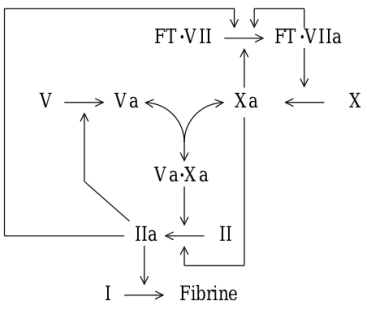

Figure 4: Simplified coagulation cascade (Kerdélo, 2006)

Our study focuses on vitamin K antagonists, a kind of medicine used to cure thrombosis. This work follows those done in the context of *in virtuo* blood coagulation in (Kerdélo, 2006). Blood coagulation, or clotting, is the outcome of a complex reactions cascade that implies coagulation factors ; see figure 4. Generally it arises when a blood vessel is damaged in order to stop the blood loss. Sometimes, this process can be thrown off balance due to a dysfunction of coagulation factors synthesis, which results in clots occuring without any necessity obstructing the flow of blood through the circulatory system (Abgrall et al., 2004). This synthesis should be regulated in another reactions sequence which can be affected by an excess of vitamin K (figure 5). VKA are prescribed in this instance so as to balance this problem. The chemical reactions entanglements and individual variations of patients make the right dose hard to define (Siguret, 2007). That's why biologists are looking for tools to simulate this process.

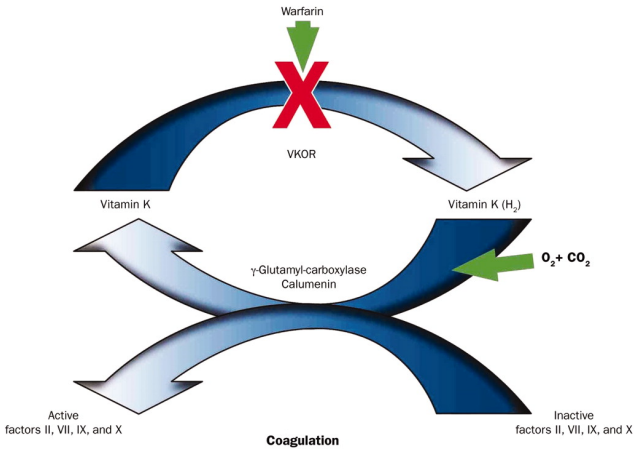

Figure 5: Coagulation factors synthesis (Siguret, 2007)

Macroscopic model

Classically, PK analysis consists in compartmental models which use kinetics to predict the concentration-time curve in each compartment. More complex PK models, called physiologically-based pharmacokinetics (PBPK) models, rely on the use of physiological information to ease development and validation ; see figure 6. The body is divided into linked compartments that can be associated with black boxes. Inputs and outputs are kinetics parameters which are most often identified by stochastic simulations (Brochot, 2006). It is therefore difficult to understand the various phenomena acting inside this boxes.

We proposed a first MIS implementation of PBPK models in (Le Yaouanq, 2010). We derived the Virtuo framework so as to be able to design chemical systems.

Each compartment is represented by an *Entity*. We linked them by *Diffusion-Phenomena* as in PBPK model. The first novelty of our model comes from the insertion of *Reaction-Phenomena* which operate between concentrations of chemical species inside the compartments. Relations between kinetics and dynamics are evidenced in this way. Our second contribution is based on a realistic identification of parameters of the model. This is where multiscale modeling gets involved. The idea is to simulate redundantly some phenomena in a microscale in order to parameter the macroscale. For the sake of clarity, we only outline our problems on the diffusion rate example.

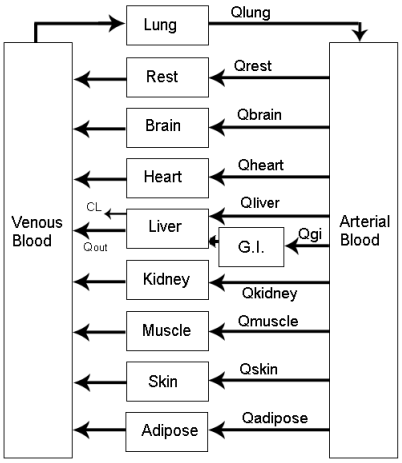

Figure 6: PBPK model (Igari et al., 1983)

Theorical elements Diffusion phenomenon is described by the Fick's laws of diffusion in macroscale (Fick, 1855).

Fick's first law

Fick's first law relates the diffusive flux to the concentration, by postulating that the flux goes from regions of high concentration to regions of low concentration, with a magnitude that is proportional to the concentration gradient. In the one dimension case we can write

$$J = -D\frac{\partial C}{\partial x} \tag{4}$$

where :

- J is the diffusion flux,
- D is the diffusion coefficient,
- C is the concentration,
- x is the position.

Fick's second law

Fick's second law predicts how diffusion causes the concentration to change with time, on the hypothesis of the matter conservation. Thus the diffused concentration can be computed with :

$$\frac{\partial C}{\partial t}(x,t) = D\frac{\partial^2 C}{\partial x^2}(x,t) \tag{5}$$

This gives rise to the following formula, in the biology perspective, considering two compartments separated by a membrane :

$$\frac{\partial C}{\partial t}(x,t) = \frac{D \cdot S}{L} \cdot \Delta C \tag{6}$$

where :

- D is the diffusion coefficient of a given chemical species at a given temperature,
- S is the surface area over which diffusion is taking place,
- ΔC is the difference of concentration across the membrane,
- L is the membrane thickness.

Implementation A *Diffusion-Interaction*, manifestation of a *Diffusion-Phenomenon*, operates between two compartments. It computes on each time step the diffused concentration from a compartment to the other and applies the modifications.

Let us consider two compartments A and B with the diffusion of a chemical species C from A to B. The concentrations of C in A and B from a given instant t to the instant $t+1$ will be altered in this way (using an explicit Euler method for numerical integration)

$$\begin{cases} [C]_A^{t+1} = [C]_A^t - d.\delta t \\ [C]_B^{t+1} = [C]_B^t + d.\delta t \end{cases} \tag{7}$$

where

$$d = \frac{D \cdot S}{L} \cdot ([C]_A^t - [C]_B^t) \tag{8}$$

is the diffused concentration. The figure 7 illustrates this simulation in the context of VKA diffusion.

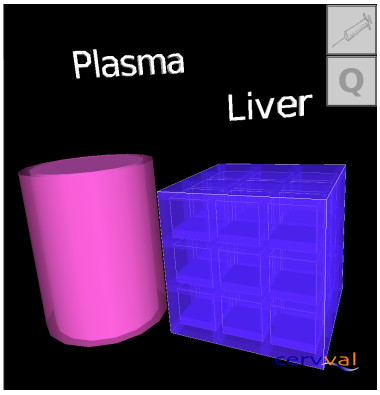

Figure 7: Physiologically-based simulation of VKA diffusion. Colors represent the medicine's concentration and goes from blue (lower) to red (higher).

In this equation, all the parameters can be measured in the simulation except the diffusion coefficient. This piece of data is generally determined with *in vivo* or *in vitro* experimentations for a given temperature and fixed conditions. It is therefore often a missing value in our models. That is why we would like to define this parameter automatically *in virtuo* by the use of a microscale simulation.

Microscopic model

Diffusion phenomenon at microscale is generally described with the help of stochastic processes (Karatzas and Shreve, 2000). There exist several methods more accurate than the one we expose in the following, but we chose to focus on the principle. We remind in this section some theoritical elements about the Brownian motion and how it is implemented in the Virtuo framework.

Theoritical elements Brownian motion, first observered by Robert Brown in 1827, is the random movement of particles suspended in a fluid. It is provoked by collisions of the considered particles with the molecules of fluid which are exposed to thermal agitation.

This random movement leads to a diffusion process which coefficient is given by the Stokes - Einstein law, in case of spherical particles :

$$D = \frac{k_B T}{6\pi\eta R} \tag{9}$$

where :

- k_B is the Boltzmann constant,
- T is the temperature,
- η is the fluid viscosity,
- R is the particle radius.

Thus the quadratic displacement of a particle on a x axis during a time interval Δt is denoted by :

$$\sqrt{\overline{\Delta x^2}} = \sqrt{2D\Delta t} \tag{10}$$

Implementation The *Brownian-Interaction* takes place within a fluid in which particles are immersed. We consider spherical *Entities* which are moveable. The interaction uses then a Gaussian distribution, with a null average and a variance $\sigma^2 = 2D\Delta t$, to randomly compute their displacement on each time step (Coulon, 2010).

Scale interaction

We now have two different levels of description of the diffusion phenomenon. Our aim is to observe the microscale in order to deduce the value of the diffusion coefficient we need in the macroscale. Here's how we proceed.

We introduce a new microscale, based on the state of the macroscale. We arrange randomly particles in a volume according to their concentration in the macroscale. It is the HMM reconstruction operator. We place side by side an empty volume. We add a *Scale-Interaction* agent between the two scales. It counts how many particles crossed from the first to the second compartment, estimates then a diffusion coefficient and sends it to the macroscale ; see figure 8. This is the HMM compression operator. We stop the microscale simulation and continue the macroscale's simulation with the new parameter.

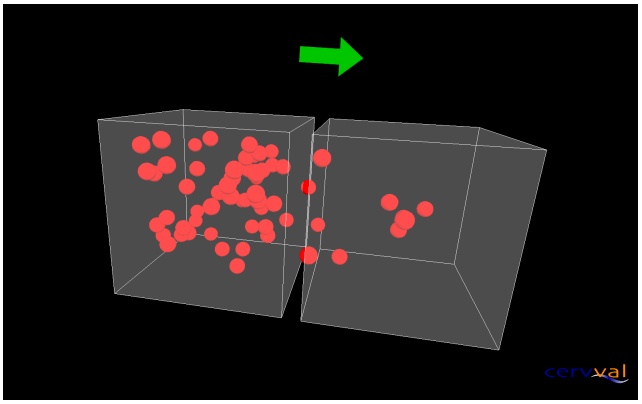

Figure 8: Microscale simulation of diffusion phenomenon using Brownian motion

Conclusions

We use *in virtuo* experimentation and multi-interactions systems, in the context of complex systems simulation. They enable us to describe phenomena and their actions on the entities composing the system always keeping interactivity with the simulation. This phenomenological approach induces the use of parametric models which parameters are often partially available. This assessment leads us to use multiple levels of description for the phenomena. Thus we simulate redundantely some phenomena at different scales in order to identify the missing parameters.

We propose to implement heterogeneous multiscale methods into the MIS by the introduction of a *Scale-Interaction* agent which plays the role of a translater between the simulated scales.

We illustrate our modeling method through a pharmacokinetics application and a diffusion coefficient identification process. This example points up some remarks and questions we have to answer more precisely in a future work.

Firstly, our will is to parameter a model from observations made on another model. Nevertheless, models aren't perfect by definition. Thus we should keep in mind that what we observe could be imperfect as well.

We can do the same comment about the observation method and data estimation. We inject the macroscale with estimated parameters which could introduce instabilities into the simulation. We need then to define a control mechanism or / and a more developped method to apply observation results.

Secondly, observations are made in the microscale on a very short time window. Indeed, it is generally impossible to run a microscale as fast as a macroscale due to the huge time step difference. But we need results almost immediately to meet the requirements of interactivity with the system. So we are often forced to infer that the observation remains valid for a larger period. It would be satisfactory for

some phenomena but we need to define another observation methodology to be more accurate. For instance, we could try to detect equilibrium states and organizations of *Entities* into the microscale (Ferber et al., 2003). Thus we should be able to partially generalize the observation process even if it seems difficult to define a totally generic method because of the nature of modeling.

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