# 3rd Workshop on MAS in Biology at meso or macroscopic scales

mercredi 16 juin 2010 - vendredi 18 juin 2010

LaBRI - Laboratoire Bordelais de Recherche en Informatique

# Recueil des résumés

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# Introductory talk: Biological programming

**Auteur correspondant** j.ramsden@unibas.ch

**0**:

Gergely Bándi and Jeremy J. Ramsden (Cranfield University, Bedfordshire, MK43 0AL, GB)

**Summary**:

Biology offers a tremendous set of concepts that are potentially very powerfully usable for the software engineer, but they have been barely exploited hitherto. Here we propose a fresh attempt to create the building blocks of a programming technology that could be as successful as life. A key guiding principle is to develop and make use of unambiguous definitions of the essential features of life.

**1**

# The Origin of Individuals

**Auteur correspondant** jean-jacques.kupiec@ens.fr

L'évolution des espèces (phylogenèse) et le développement des organismes individuels (ontogenèse) sont considérés comme deux phénomènes distincts. La biologie repose sur cette séparation qui pose l'espèce et l'individu comme principes premiers, réels et coextensifs, l'espèce étant une collection d' individus identiques. Dans sa version moderne cette ontologie s'appuie sur la théorie du programme génétique : une espèce est une collection d'individus possédant le même programme génétique et l'évolution des espèces est le résultat des mutations qui affectent leurs programmes (théorie synthétique de l'évolution). Cette conception est aujourd'hui mise en question par les données expérimentales. En effet, la théorie du programme génétique repose sur l'idée que les interactions des molécules biologiques excluent l'alea et qu'elles sont spécifiques. Au contraire, les données récentes montrent que les protéines manquent de spécificité. Elles peuvent interagir avec de nombreuses molécules partenaires. En conséquence, les interactions moléculaires sont intrinsèquement probabilistes, y compris dans la chromatine et l'expression des gènes est également un phénomène probabiliste. Cela contredit la théorie du programme génétique à sa racine. La prise en considération du manque de spécificité des protéines et du caractère intrinsèquement probabiliste des interactions entre molécules biologiques induit une nouvelle conception. La sélection naturelle agit non seulement dans la phylogenèse mais aussi l'ontogenèse. Celle-ci, au lieu d'être un processus déterministe dans lequel l'information génétique circule uniquement des gènes vers le phénotype (l'organisme individuel), est au contraire probabiliste et duale : les gènes fournissent les protéines, mais leurs interactions probabilistes sont triées par les contraintes sélectives produites par les structures cellulaires (et multicellulaires), qui sont elles mêmes soumises à la sélection naturelle. Au final, cette conception débouche elle-même sur une nouvelle ontologie : il n'existe qu'un seul phénomène d' ontophylogenèse expliqué par la seule théorie de sélection naturelle agissant en même temps sur l' ontogenèse et la phylogenèse.
J.J. Kupiec, L'origine des individus, Fayard, 2008. (The Origin of Individuals, World Scientific, 2009).

**2**

## A Reactive Multiagent Program using Stream Processing to Simulate Multicellular Systems.

**Auteur correspondant** pascal.ballet@univ-brest.fr

Programming multiagent systems for biological systems close to cellular scales require significant computational capabilities for different reasons: the studied systems include many interacting entities (usually more than 10^5), they have very different sizes (from 10^-8 for the macromolecules to 10^-4 for small organisms) and their behaviors are frequently complex. For example a cell changes its shape, migrates, orientates, divides, adheres, communicate by direct contact or at distance with others cells, etc.
The speed of microprocessors, in term of clock frequency, reaching its limits (around 4GHz), major manufacturers have chosen to develop multicore processors. This evolution is seen in Central Processor Units (CPU) but also in Graphic Processor Units (GPU). GPU contains stream processors allowing the parallel treatment of data (Single Instruction Multiple Data). Moreover, with the incoming of the openCL language, it is now possible to use he power of stream processing on different hardware (mother board and graphic cards for instance).
Thanks to this, we have developed reactive multiagent algorithms and a simple software architecture to simulate multicellular phenomena with many interacting entities (more than 10^5). We show different simulations like a simple random walk, a Belousov-Zhabotinsky like reaction, a prey-predator system and a multicellular morphogenesis system. The examples are detailed and their efficiencies and drawbacks are discussed.

**3**

## Development of the Cabbage Root fly in agricultural landscape : seeing agroecosystems from a fly point of view.

**0**:

Parisey N., Montagu R., Ezanic A., Cortesero A.M. and Le Ralec A.

**4**

## Com2 : to be chosen

**5**

## Com3 : to be chosen

**6**

## Stochasticity in gene expression, evolution and evolvability

**Auteur correspondant** jean-pascal.capp@insa-toulouse.fr

**Summary**:

Through the non-genetic heterogeneity it confers, stochasticity (or 'noise') in gene expression has been implicated in a wide range of biological phenomena, playing an active role in differentiation, appearance of cellular resistance to toxic molecules or stress, adaptability in fluctuating environments. The hypothesis of stochastic gene expression as a major source of phenotypic diversification important for population dynamics and evolution is now widely accepted. Moreover, recent works have shown how selection influences phenotypic fluctuations in evolutionary experiments. In these experiments, increase in phenotypic fluctuation through noise in gene expression is clearly a relevant evolutionary strategy. Using yeast as an experimental model, several hypotheses concerning the adaptation of industrial strains (versus laboratory strains) to stressful environments will be presented. Moreover, innovative theoretical works on the links between variability in gene expression and genetic variability will be discussed. In particular, the hypothesis of noise-driven heterogeneity in the rate of genetic-variant generation (RGVG) as a basis for evolvability provides opportunities to apply in silico experiments using multi-agent simulation to improve the model. By modulating environmental constraints on the agents, such simulations might provide indications on variations of the RGVG strictly driven by heterogeneity in the expression of DNA repair and maintenance genes and selection.

**7**

## A multi-scale agent-based model for the simulation of avascular tumor growth

**Auteur correspondant** guillaume.hutzler@ibisc.univ-evry.fr

**Summary**:

Agent-based paradigm for the simulation of complex systems is based on the modeling of the individual entities of the system. Given a chosen level of description, this implies modeling each and every entity of the system. When modeling biological systems at the cellular and/or molecular level, this results in the simulation of multitudes of agents, which raises performance issues. However, this is generally not necessary to have the same level of detail on every part of the system. In this paper, we propose to introduce dynamically an aggregated level in the simulation of avascular tumor growth. This model handles cells and PAI-1 molecules that are believed to play a key role in the amoeboid migration of cancerous cells. However, migratory events can only be triggered on the periphery of the tumor. The interior can therefore be modeled in an aggregated way, by replacing the individual cells and molecules by a global agent. We show that this can be done without changing the global dynamics of the system, and gaining

a linear increase of computing time, while the number of cells and molecules increases exponentially.

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## A Stochastic Model of cellular differentiation

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## Com4 : to be chosen

**10**

## Hydrodynamic simulation of ventral mesoderm invagination during Drosophila Melanogaster gastrulation

**Auteur correspondant** philippe.alexandre.pouille@gmail.com

The mechanical aspects of embryonic morphogenesis have been in most cases simulated using finite element models, which describe the tissue as a continuous medium. Here we develop a simulation of Drosophila embryo invagination of its ventral mesoderm during gastrulation, that allows access to both cellular and multicellular mechanical behaviours of the embryo. This model can be viewed as multi-agent where the individuals are the cell membranes characterized by an acto-myosin cortical tension and connected by apical and basal junctions and an acto-myosin contractile ring at the apical junctions. They interact with each other through hydrodynamic flow.
Behaviours observed in vivo, including apical junction movements at the onset of gastrulation, cell elongation and subsequent shortening during invagination, and the development of a dorso-ventral gradient of thickness of the embryo, are predicted by this model as passive mechanical consequences of the genetically and biochemically controlled increase in the apical surface tension in invaginating mesoderm cells.
In a second step, we also implemented the biochemical control system we investigated through experiments on the embryo. Here, a second set of individual agents are the cells and their gene expressions. We showed that ventral invagination initiation can be explained by a positive mechanical feedback. Under this hypothesis, the simulations account for the phenotypes observed in wild-type embryos and all the main mutants for invagination.

**0**:

Philippe-Alexandre Pouille

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## Exploring Hierarchical Evolution with an Artificial Protocell

**Auteur correspondant** barry.mcmullin@dcu.ie

**Summary**:

In this talk I will present an idealised model of an RNA-world “protocell”, and some of the evolutionary phenomena this gives rise to. In this model a protocell is simply a vesicle-like container carrying a well stirred mixture of “polymers” which can function as abstract analogues of certain (hypothetical) kinds of ribozymes - i.e., they function both as informational templates to be replicated, and as replicase enzymes to catalyse such replication. Replicases vary in the classes of templates which they can replicate (i.e., in the template motifs which they recognise and bind to). Some molecular species function as self-replicases. As the molecular population increases through replication, the vesicle grows until it reaches a critical size at which it fissions. The result is a system in which there are two distinct but coupled selectional processes: one at the molecular level, one at the cellular level. This is a (highly simplified!) model in which it might be possible to investigate some aspects of the evolution of cell signalling. In any case, I will illustrate some of the (perhaps unexpected?) consequences of this architecture.

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## Com5 : to be chosen

**13**

## A new ’hierarchical dynamic networks’ approach to multi-scale structure-function modeling of the kidney

**Auteur correspondant** srthomas@ibisc.fr

**Summary**:

I will present a dynamic whole-kidney modeling approach that aims to reproduce the clinically relevant input-output behavior of whole kidneys thanks to faithful representation of: the properties of individual nephron segments, nephro-vascular relationships in each kidney region, responses to hormones and renal nerve inputs, and relevant details of renal anatomy from the literature and also from recent structural reconstructions of rodent kidneys, which will provide new information on tubular characteristics and on the vascular organization of the human kidney. The legacy of renal modeling provides most of the needed quantitative descriptions of internal renal function (Thomas 2009), autoregulation of renal blood flow (Holstein-Rathlou & Marsh 1994), and much of the 3D anatomical structure (Zhai et al 2006; Pannabecker et al. 2008), but classic approaches are not well-suited to the dynamic whole-kidney integration sought here. We will thus use the hierarchical dynamic networks approach introduced recently (Moss 2009), starting with a published prototype model and building up to a complete model.

References:
Moss, R. et al. (2009). "A computational model for emergent dynamics in the kidney." Philos Transact A Math Phys Eng Sci 367(1896): 2125-40.
Nordsletten, D. A. et al. (2006). "Structural morphology of renal vasculature." Am J Physiol Heart Circ Physiol 291(1): H296-309.
Pannabecker, T. L., C. S. Henderson and W. H. Dantzler (2008). "Quantitative analysis of functional reconstructions reveals lateral and axial zonation in the renal inner medulla." Am J Physiol Renal Physiol 294(6): F1306-14.
Thomas, S. R. (2009). "Kidney Modeling and Systems Physiology." Wiley Interdisciplinary Reviews: Systems Biology and Medicine 1: 172-190.
Zhai, X.-Y., J. S. Thomsen, H. Birn, I. B. Kristoffersen, A. Andreasen and E. I. Christensen (2006). "Three-Dimensional Reconstruction of the Mouse Nephron" J Am Soc Nephrol 17(1): 77-88.

**14**

## Modeling high-frequency serial valvometry data of oysters: a kernel regression based-approach

The high-frequency measurements of valve activity in bivalves (e.g. valvometry) over a long period of time and in various environmental conditions allows a very
accurate study of the animal's behaviors as well as a global analysis of possible perturbations due to the environment. Valvometry uses the bivalve's ability to close its
shell when exposed to a contaminant or other abnormal environmental conditions as an alarm that indicates some possible perturbations of the environment. The modeling
of such high-frequency serial valvometry data is statistically challenging and here we propose a nonparametric approach based on kernel estimation. This method has the advantage to summarize the complex data into a simple density profile obtained for every animal and at every 24 hours period and then to make inference about the effect of time and external conditions on each animal's profile. The statistical properties of the estimator are presented. Through an application to a sample of 16 oysters living in the Bay of Arcachon (France), we demonstrate how this method can be used, first to estimate the normal biological rhythms of permanently immersed oysters and second, to detect perturbations of these rhythms due to changes in their environment. We anticipate that this approach could have an important contribution to the survey of aquatic systems.

**0**:

G. Durrieu

**15**

## Estimation of model parameters: application to the complex I of the respiratory chain

Developing dynamic models of metabolic pathways of the whole mitochondria could help in predictive or preventive medecine. But theses pathways are necessarily large and complex with lots of variables that can not be measured directly in vivo currently. Besides the different existing rates that describe the kinetic behavior of enzymes in this network are mostly non linear (in terms of parameters and variables) which leads to difficulties in adjusting the parameters.
That is why searching for a simple rate that describe the kinetic behavior of enzymes is useful. In this context, we derive an equation, called EMA (Extended Mass Action)
Next we studied our abilities to adjust the parameters of this new equation theoretically and numerically.
Finally we apply it to our experimental data derived from complex 1 enzymatic reaction.

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## Com6 : to be chosen

**17**

## Com7 : to be chosen

**18**

## Biological simulations : focus on 3D environment with multi-agent systems

**0**:

M Beurton-Aimar, R. Moussa, F. Vallée

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## Unsupervised learning to assist modeling of multilevel complex systems

The modelling by simulation of complex systems is a cyclic process: the modeller incorporates his/her knowledge into the model, runs simulations, discovers bugs or unwanted effects, corrects the model and eventually his/her knowledge, and the cycle restarts. The process ends when it is not possible to further improve the model because of technical or knowledge limitations. That cyclic process is particularly hard when modelling multi-level complex phenomena mainly because of the emergence of high level structures : the behaviour of lower level agents can be strongly influenced by the existence of emergent structures. Those structures must then be detected and considered as agents in simulations. The detection of structures is particularly difficult because of their dynamic nature. To consider the structures as agents implies to provide them with a behaviour. The latter is not an easy task because of the interdependence of the behaviours of agents that are placed at different levels. In this talk I propose to adress those problems by using automated learning mechanisms. In the first part of this talk I propose the use of statistical learning to discover the emergent structures. In the second part I propose the use of technics of automatic composition of programs to build the agents'behaviours.

**0**:

Javier Gil-Quijano

**20**

## Towards a Multi-Level Modeling Language to Represent and Specify Emergent Structures in Agent-Based Model

**Auteur:** VO Duc An[1]

[1] *UPMC Univ Paris 6*

**0**:

Vo Duc An, Alexis Drogoul, Jean Daniel Zucker

**Summary**:

Abstract. All modelers have come across, one day, one of these popular toy agent-based models : appearance of pheromone trails built by ants, evolution of social groups within human populations, formation of arches in granular media. Beside their exemplarity in terms of what can be achieved with ABMs, they are also representative of the way ABMs are designed: in addition to the individual entities employed to represent the system, modelers make implicit references to abstractions corresponding to the emerging structures they are looking after and want to analyze using simulations. Yet, these abstractions are not represented in the models themselves as first-class entities: they are either hidden in ex-post computations or only part of visualization tasks, as if an explicit representation could somehow damage the processes at work in their emergence. We claim that this deliberate choice constitutes an obstacle to the development of multi-level models, where emergence processes are known to occur at different levels of abstraction of the system. This paper describes a modeling language that allows a modeler to represent and specify emergent structures in agent-based models. Firstly, to ease the description, we present these emergent structures and their properties in four agent-based models: Schelling, Boids, Collective Sort and Ants. Then we define the operations that would be needed to represent and specify them explicitly without sacrificing the properties of the original model. An implementation of these operations in the GAML modeling language (part of the GAMA agent-based platform) is then presented. Finally, several simulations of the Boids model are used to illustrate the expressivity of this language and the multiple advantages it brings in terms of analysis,

visualization and multi-level modeling of ABMs.

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## Mobile Agents for Large Distributed Computing Systems

**Auteur correspondant** mosbah@labri.fr

The concept of mobile agents has been introduced recently as a novel and powerful paradigm to facilitate the design and programming of
distributed applications. However, while their popularity continues to grow, a uniform theory of mobile agent systems is not yet sufficiently elaborated, in comparison with classical models of distributed computation. In this talk, I present a model based on local computations to encode mobile agent algorithms. In doing so, we approach a general and unified framework for expressing mobile agent computations which is consistent with the classical theory of distributed algorithms based on local computations.

**0**:

Mohamed Mosbah

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## Invited talk To be announced (INRETS)

**23**

## Invited Talk

**24**

## Multi-agent System based on social agents: a GPU application

**Auteur correspondant** moussa@labri.fr

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## Collective discussion on MAS simulation frameworks