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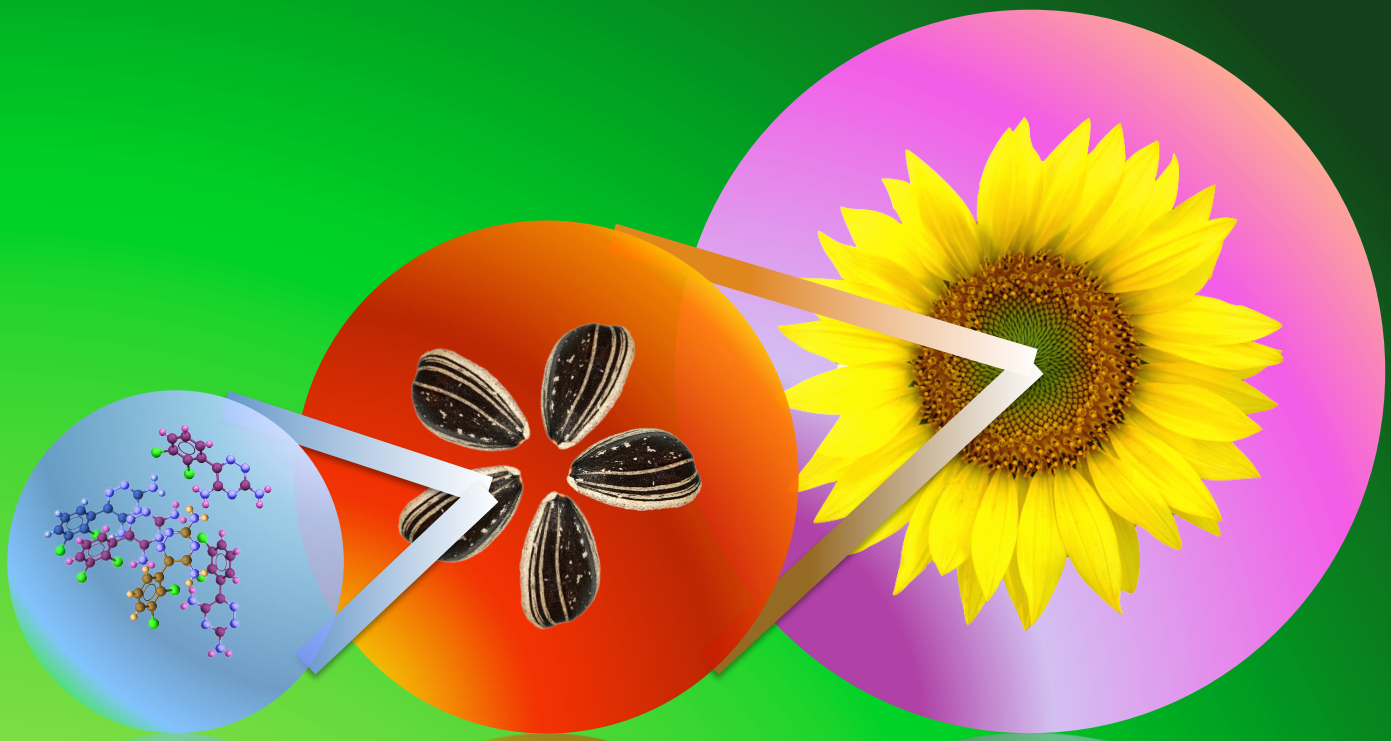
BIOMATH SPRING

LYON

EMS-ESMTB SPRING SCHOOL

“Multiscale Modeling in Life Science”



May 27-31, 2013

Labex MILYON

Mathématique et Informatique Fondamentale de Lyon

UNIVERSITÉ DE LYON

Supports

Organizing committee : **Vincent Calvez** (UMPA, ENS de Lyon), **Thomas Lepoutre** (INRIA, Lyon), **Vitaly Volpert** (Université Claude Bernard, Lyon 1)

Labex MILYON : **Bertrand Rémy** (Head), **Carine Sevestre** (Coordination)

Graphic design : **Laurent Pujo-Menjouet** (Université Claude Bernard, Lyon 1)

www : **Emeric Bouin** (ENS de Lyon)

SCHEDULE

	Monday	Tuesday	Wednesday	Thursday	Friday
09:30-11:00	Welcome	**THIEFFRY**	**VOITURIEZ**	**ERMENTROUT**	**CHAUVIERE**
11:00-11:30	Welcome	Coffee break	Coffee break	Coffee break	Coffee break
11:30-13:00	**RIBBA**	**DRASDO**	**ERMENTROUT**	**VOITURIEZ**	**DEGOND**
13:00-14:30	Lunch time	Lunch time	Lunch time	Lunch time	Lunch time
14:30-16:00	**DRASDO**	**THIEFFRY**	*FREE*	**DEGOND**	
16:00-16:30	Coffee break	Coffee break	*AFTERNOON*	Coffee break	
16:30-18:30		**POSTER SESSION**			

Abstract of lectures

Arnaud Chauvière (Université Joseph Fourier, Grenoble)

Introduction to lattice-gas cellular automata. Application to in vitro glioma growth and identification of invasion mechanisms.

In this lecture we introduce a discrete modeling approach for multicellular systems in biology, called cellular automaton. We present one subclass, the lattice-gas cellular automaton that originates from discrete fluid dynamics. In physical sciences, this approach has been developed because of its simple and intuitive description of the movement of particles, which has further been extended to model the movement of living entities such as biological cells.
We present an application of the method to model glioma, a particular brain tumor. The mechanisms of development and invasion of such tumors are still poorly understood. We use experimental data from the literature to develop a step-by-step modeling approach that reproduces the various features observed experimentally. By doing so, we show that our model allows for the identification of a set of cellular mechanisms leading to the reproduction of the experimental data. Our results suggest 1) that these mechanisms may be important during glioma development and invasion and 2) that further experimental investigation of these mechanisms should be performed.

★★★

Pierre Degond (Institut de Mathématiques de Toulouse)

Phase transitions and hydrodynamics of self-organized collective motion

Most living systems consist of a large number of discrete units or agents which interact and cooperate in order to ensure some functions. This interaction relies on very elementary rules involving only local interactions with neighbouring agents. In spite of the simplicity of these interactions, a coherent behavior is achieved which leads to large-scale structures and collective behavior. These large-scale structures, which are not directly visible or encoded in the agents' interactions, spontaneously emerge from the interaction of a large number of individuals: this is the 'emergence' phenomenon. The aim of these lectures is to review a certain number of challenges posed by the modeling of self-organization and to present models and approaches which allow to describe and understand it.

After presenting various examples, we will present a hierarchy of models used to describe self-organizing systems such as
- Rule-based agent models
- Kinetic models
- macroscopic models and their respective inter-relations.

We will then consider the emergence phenomena through the viewpoint of phase transitions and discuss one important example : the symmetry breaking phase transitions in self-propelled particle systems. Both phase transitions occur in animal swarms such as fish schools, bird flocks, or human crowds.

★★★

Dirk Drasdo (INRIA Rocquencourt)

Multi-scale modeling of tissue regeneration and tumor growth: from data to models and back

★★★

Bard Ermentrout (University of Pittsburgh)

Weak and slow: a tale of two epsilons

★★★

Denis Thieffry (Ecole Normale Supérieure Paris)

Logical Modelling of Cell Fate Specification

★★★

Benjamin Ribba (INRIA Alpes, Grenoble)

Analysis of efficacy data in preclinical and clinical oncology with tumor growth inhibition models

I will present issues in the development of oncology drugs, modeling techniques based on mixed-effect models, possible algorithms for parameter estimation of these models and several applications.

★★★

Raphaël Voituriez (Laboratoire de Physique Théorique de la Matière Condensée, Université Pierre et Marie Curie, Paris)

First passage times of random walks and search strategies

Course 1: First-passage statistics
-Mean first-passage times of discrete random walks in confinement
-Exact expressions involving pseudo Green functions and large volume asymptotics
-Splitting probabilities and occupation times
-Extension to Brownian motion and general Markovian scale invariant processes
-Beyond the mean : the distribution of first-passage times

Course 2: Optimizing search strategies
-Background : Levy searchers and the Albatross story
-Optimizing persistent random walks
-First example of intermittent search strategies : target location by proteins on DNA
-Animals looking for food and other examples
-Minimal model of intermittent search and its optimization

POSTER SESSION (MAY 28, 2013)

EMERIC BOUIN (ECOLE NORMALE SUPÉRIEURE DE LYON)

A KINETIC FISHER-KPP EQUATION : TRAVELING WAVES AND FRONT ACCELERATION

We analyze a kinetic model which describes the same situation as the Fisher-KPP equation. Thus, this model describes particles moving according to a velocity-jump process, and proliferating thanks to a kinetic reaction term of monostable type. We study existence and stability of traveling wave solutions. It turns out that we exhibit a critical speed for this existence, when the velocity space is bounded. Moreover, we recover the standard Fisher-KPP speed in the parabolic limit. The constructed fronts of minimal speed are linearly stable in suitable weighted L2 spaces. We also investigate the case of an unbounded velocity space and we are able to conclude that not only traveling waves can not exist, but also the equation induces an accelerated propagation behavior according to a scaling law, which depends on the stationnary Maxwellian.

★★★

ABDENNASSER CHEKROUN (INSTITUT CAMILLE JORDAN, UNIVERSITÉ CLAUDE BERNARD LYON 1, AND INRIA DRACULA)

TRAVELING WAVE FRONTS IN A NONLOCAL TIME-DELAYED REACTION-DIFFUSION HEMATOPOIETIC STEM CELLS MODEL

The production and regulation of blood cells is a very complex process, called hematopoiesis. It is located in the bone marrow before the mature cells enter the blood stream. This process involves a population of cells called hematopoietic stem cells (HSCs). They can be either in a proliferating or in a resting phase. We describe here the HSC population, taking account their spatial distribution. The resulting model is an age-structured reaction-diffusion population system. The method of characteristics reduces the age-structured model to an unstructured nonlocal time-delayed reaction-diffusion system. We study the existence of traveling wave front by using the classical monotone iteration technique coupled with the sub- and super-solutions method. Finally, we give some result about stability of this solution. Some numerical simulations are also carried out.

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STEPHAN FISCHER (INRIA BEAGLE)

STUDYING THE INDIRECT IMPACT OF INTRACHROMOSOMAL REARRANGEMENTS ON THE GENOME STRUCTURE OF MICROBES

Experimental evolution has shown that rearrangements within the chromosomes of bacteria occur at a very frequent rate. Indeed, several experiments show that fitness increases in a step-wise manner and that the first and most important steps of evolution are linked with chromosomal rearrangements, mostly deletions or DNA amplification.

These deletions are observed when experiments are repeated with independent populations, indicating that rearrangements must occur frequently spontaneously but also that they are essential for adaptation [Cooper et al., Journal of Bacteriology, 2001 ; Kugelberg et al., PNAS, 2006]. Obviously, such a high rate of rearrangement has a direct impact on the genome structure - e.g. gene order. Yet, it is also likely to strongly impact genome robustness and evolvability, leading to indirect effects that may be difficult to predict.

To quantify these effects, we developed computational and mathematical models to understand the impact of rearrangements on the evolution of genome structure. These models included local mutations but also inversions, translocations, duplications and large deletions, as well as competition for reproduction. Both simulations and theoretical analysis show that rearrangements not only play a major role in evolvability (by allowing for duplication/divergence or deletion of fragments of chromosomes), but also have an indirect impact on the genome structure. By using results of infinite Markov Chain theory, we showed that duplication and deletion rates impose a maximal genome size, even though there is no direct selective cost on the genome size or non-coding sequences. Simulations confirm that genomes converge towards a specific finite size and coding ratio that is strongly linked with rearrangement rates.

★★★

LENA FRERKING

A NEW MODEL FOR TRANSPORT IN AXONS

Axonal transport is responsible for the passive motion of several subcellular particles. Hence, it is crucial for many biological processes on the cell scale. Motor proteins like kinesins or dyneins act as transport vehicles for vesicles, mitochondria and proteins by binding to their cargoes and pulling them in a specific direction. Movement happens along tubelike structures called 'microtubules', which are located inside an axon.

We take a closer look to interactions between those motors. In this context, the protein dynactin plays an important role. Besides improving the processivity of dynein motors, it regulates their attachment and detachment behavior. This way, it prevents a dynein motor from pulling a cargo, if this already happens by a kinesin motor. Our macroscopic model considers this recent finding and shows its influence on the direction and on the velocity of axonal transport.

Some numerical simulation results will illustrate our findings.

★★★

MARKUS PIERRE KNAPPITSCH (UNIVERSITY OF MUENSTER)

DTI DATA BASED MULTISCALE MODELLING OF GLIOMA GROWTH

Gliomas are a class of rarely curable tumors arising from abnormal glia cells in the human brain. The understanding of glioma growth patterns is essential for both radiological therapy as well as surgical treatment. Currently, DTI is not only the preferred radiological method in glioma prognosis, but also allows to infer the white matter fibre structure of the brain in a noninvasive way.

Kinetic PDE theory provides an appropriate framework to include patient specific DTI data into a class of mesoscopic transport equation models for glioma growth. With the aid of scaling arguments corresponding macroscopic PDEs of advection-diffusion type are deduced for the evolution of tumor cell density, which is hence characterized w.r.t. the tumor diffusion tensor and the tumor drift velocity.

Our microscopic model for the receptor dynamics on the cell surface leads to an additional advection term on the macro scale. Some numerical simulations illustrate the predictions of the model w.r.t. glioma spread and show that the influence of the receptor dynamics is of high relevance.

★★★

Floriane Lignet (INRIA Rhône Alpes)

Computational Model of In Vitro Breast Cancer Cells Spheroid-Formation

The receptor HER2 is over-expressed in 20 to 30% of breast cancers and is associated with invasive phenotypes and poor survival prognosis. Treatments directed against this receptor or the downstream pathways exist but show low efficacy or induce resistance. The objective of this study is to develop a computational model that mimics breast cancer cells spheroid formation in order to better understand and optimize treatment action.

Based on data for wild and HER2+ mammary epithelial cells (MCF10A) grown in 3D Matrigel cultures, we developed a computational model of multicellular spheroids morphogenesis.

We used the modelling environment CompuCell3D (www.compucell3d.org/) to simulate, starting from one single cell, the evolution of epithelial cells depending of the contact interactions with the extracellular matrix, the lumen and in-between cells.

Depending on their position in the cluster, cells may proliferate, polarize orthogonally to the lumen or enter apoptosis, and their adhesion properties vary.

We first parametrized the model to reproduce the growth of normal spheroids, and then investigated the modifications of the cellular behaviours leading to the formation of tumorigenic-like structures.

To do so, measures of volume, lumen size and compactness were used for comparison to the experimental data. We performed a sensitivity analysis of the model parameters, estimating the values resulting in normal and mutated structures. We showed that the length of the contact to ECM triggering mitosis is of primary importance in normal spheroids. In addition, passage from a normal phenotype to a tumorigenic phenotype

includes a decrease of the apoptosis rate, a higher probability of proliferation, and a loss of polarization.

★★★

Cristina Martinez (Laboratoire de Physique, Ecole Normale Supérieure de Lyon)

Investigating cell dynamics with atomic forcemicroscopy

Atomic Force Microscopy (AFM) has become a widely used technique to measure mechanical properties of biological samples. Usually, a given load is applied to the surface, and the force is registered as a function of the indentation. This procedure can be complemented with other methods that are less intrusive and mainly, more relevant to the system's dynamics. We propose to combine these different approaches to measure the mechanical oscillations of living animal cells at different temporal and spatial scales.

★★★

Elissar Nasreddine (Université de Toulouse)

Well-posedness for a model of individual clustering

We study the model of individual clustering introduced by Grindrod in 1988: we are interested in the existence of the global solution in dimension 1 and 2, for two different choices of the rate of reproduction. We identify the long time behaviour of the solution. Finally, we study the behaviour of the solution in the case of vanishing diffusion.

★★★

Przemyslaw Pazdziorek (Institute of Mathematics of the Polish Academy of Sciences)

The modelling of the stochastic perturbation in the process of stem cells differentiation and tissue regeneration

Differentiation and self-renewal of stem cells are essential processes to maintain a supply of well-specialized cells for every tissue. The promising medical applications and the complexity of those processes encourages to implement numerical and mathematical methods to understand better the mechanisms which regulate stem cells behaviour. Environmental perturbations may have an influence on the death rate, proliferation rate and on the fraction of self-renewal at every stage of differentiation. We investigate the system of Ito stochastic differential equations with linear diffusion coefficients based on the deterministic model of multistage cell lineages proposed by Anna Marciniak-Czochra. We present some numerical simulations of the stochastic model for a different number of stages of differentiation. The interactions between the noises, added to the different stages, are characterised using numerical simulation. The long-time behaviour of the two-dimensional version of the model is well discovered,

asymptotic stability of the related Markov semigroup is proved using the theory of the Markov semigroups and the method of the Hasminski function.

★★★

Diane Peurichard (Institut de Mathématiques de Toulouse)

Modelling adipose tissue homeostasis

White adipose tissue (WAT) has long attracted attention because of its key role in energy homeostasis and obesity, prevalence of which is tremendously increasing. WAT acts as the main energy store of the organism and displays a great endocrine activity by which it can interacts with most of organs. Whereas the molecular pathways driving adipocyte differentiation are now well investigated and described, the spatial tissue organization and structure are poorly understood. The basis of WAT development, the lobule formation, was never investigated and no hypothesis on its determinants was proposed. Here,we present a numerical and theoretical model, which can explore the various factors intervening in lobule formation. We propose a two-dimensional IBM, which deals with the spatial organization of adipose tissue and the fate of the precursor cell. This first model may be useful in predicting how interactive cells with mechanical feedback between the fibre network and the dierentiated cells orchestrate the complex decision making of functional structure. Our model reveals that the self-organization of cells during adipogenesis into complex lobule-like structures can be obtained considering a mechanical feedback between fibres and adipocytes (free from chemical interactions) correlated to a reduced number of simple intern phenomena engaging few agents.

★★★

Sotiris Prokopiou (INRIA DRACULA)

Integrative modeling of sprout formation in angiogenesis: coupling the VEGFA-Notch signaling in a dynamic stalk-tip cell selection

In angiogenesis, new blood vessels headed by a migrating tip cell sprout from pre-existing vessels in response to signals. This is known to be regulated by two signaling pathways concurrently, vascular endothelial growth factor A (VEGFA) and Notch. VEGFA upregulates Delta-like 4 (Dll4; a Notch ligand) in endothelial cells (ECs) of a nearby blood vessel. The Notch signaling is responsible for cell fate decisions. In particular, for the interchange from the stalk to the tip EC phenotype leading to checkerboard (`salt and pepper') patterns along the vessel. Stalk cells selected to become tip cells are the ones with higher levels of Dll4.

Novel retinal angiogenesis data from embryonic mouse suggest that VEGFA might be secreted by macrophages (immune cells) located in close proximity to tip cells. Motivated by existing experimental observations and our novel results, we developed a cell-based, multi-scale mathematical model based on the cellular potts model framework. Our aim was to investigate the sprout evolution initiated from a parent blood vessel by integrating the two signaling pathways. The model incorporates three

level descriptions: 1) macrophage-mediated VEGFA activates Notch signaling in a nearby blood vessel, 2) tip and stalk EC phenotypes positioned along the sprout are dynamically interchangeable depending on their Dll4 level, and 3) sprout morphology and polarization depend on chemotaxis (cells move up VEGFA gradients) and the alignment of the extracellular matrix (ECM). The model reproduces phenomena in sprouting angiogenesis, including sprout morphology, tip competition, and explains and predicts perturbation experiments on Notch signaling pathway.

★★★

Christian Stinner (University of Kaiserslautern, Germany)

On a multiscale model involving cell contractivity and its effects on tumor invasion

Invasion of tumor cells is an important step for metastasis and is governed by several subcellular processes. A number of them affect the contractivity, by which we describe the ability of the cells to adapt their shape and orientation according to the surrounding tissue. We derive a multiscale model focusing on the influence of the cell contractivity on tumor cell migration. It takes into account both the subcellular level, where changes of contractivity are initiated, and the macroscopic level of the cell population. For this model we prove the local existence of a unique solution. This is a joint work with Christina Surulescu (Kaiserslautern).

★★★

Masoomeh Taghipoor (INRA PEGASE)

Mathematical modelling of digestion in the small intestine

The purpose of this study is to model the digestion in the small intestine: transport of the the bolus by the peristaltic waves, feedstuffs degradation according to the endogenous and exogenous enzymes and nutrients absorption. A mechanistic model based on ordinary differential equations is used to represent the digestion. The equations describe the evolution of the position and composition of the bolus of feedstuffs coming from the stomach. We prove by using the homogenization methods, that this model can be considered as a macroscopic version of more realistic models which contain the biological phenomena at lower scales of the small intestine.

★★★

Ariane Trescases (ENS Cachan)

Reaction-diffusion system approximation to a triangular cross-diffusion population model

★★★

CHRISTOPH WINKLER (UNIVERSITY OF VIENNA)

STOCHASTIC MODEL EXPLAINS THE FLATNESS OF LAMELLIPODIA

Many cells are pushed by thin sheets, called lamellipodia, that consist of a plasma membrane wrapped around an oriented actin filament meshwork. The filaments, growing by polymerization and being capped near the front, form a quasi two-dimensional network by preferably branching parallel to the substrate.

How the branching directions are chosen and thus the thinness of the lamellipodium is conserved remains unclear. We have developed a model that describes both the filament network and a fully deformable plasma membrane. In each time step the membrane shape is determined by minimizing an energy functional that takes into account the membrane's curvature, the filament ends as adhesive obstacles and biologically motivated boundary conditions. Our stochastic simulation uses the local geometric interplay between filaments and the membrane to determine the polymerization rate and the branch direction. The results show that this suffices to maintain thin lamellipodia and that no extra forces or restrictions acting on the membrane are needed.