Cell migration: Swimming versus Crawling

DySCo
Dynamique des systèmes complexes

Annual meeting 2019

March 18th & 19th, 2019
Hôtel Mercure Les Deux Alpes 1800

Invited speakers

- Vincent Calvez
  (ENS, Lyon)
- Rhoda Hawkins
  (U. of Sheffield, UK)
- Isabelle Maridonneau-Parini
  (IPBS, Toulouse)
- Daniel Riveline
  (IGBMC, Strasbourg)
- Olivier Theodoly
  (LAI, Marseille)

Coordinator: C. Misbah (LIPHY)

Steering committee: H. Bodiguel (LRP), C. Dapogny (LJK), C. Geindreau (3SR), G. Ghigliotti (LEGI) K. John (LIPHY), M. Léonetti (LRP), E. Maitre (LJK), L. Métivier (LJK), A. Millet (IAB), S. Rafaï (LIPHY) P. Récho (LIPHY), A. Stéphanou (TIMC)

Organizers: Abdessamad Nait-Ouhra (LIPHY) & Salima Rafai (LIPHY)

Registration and informations: https://dysco2019.sciencesconf.org/
Contact: dysco2019@sciencesconf.org

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Schedule

Monday		
10-10:55	**Rhoda Hawkins**	Theoretical models of cell migration
10:55-11:30	**Mohd Suhail Rizvi**	Simple overview on swimming
11:30-11:50	**Claude Verdier**	Transmigration de cellules cancéreuses
11:50-12:10	**Maxime Bonnefoy**	Cells and humans migration : crawling versus walking
12:10-12:30	**Arnaud Sengers**	Méthodes de diffusion-redistanciation pour le déplacement par flot de Willmore. Application à la forme d'équilibre des globules rouges
12:30-14:30	*Lunch*	
14:30-15:25	**Daniel Riveline**	Ratchetaxis
15:25-15:45	**Pierre Recho**	Force-induced repolarization of an active crawler
15:45-16:05	**Revaz Chachanidze**	Rigidity based margination
16:05-16:40	*Coffee break*	
16:40-17:35	**Olivier Théodoly**	Lymphocytes swim by molecular and not protrusion-based paddling
17:35-17:55	**Alexander Farutin**	Crawling in a fluid
17:55-18:15	**Ibrahim Cheddadi**	Modèle physique des tissus végétaux
18:15-18:35	**Marvin Brun-Cosme-Bruny**	Effective diffusivity of microswimmers in a crowded environment
Tuesday		
9:00-9:55	**Isabelle Maridonneau-Parini**	Macrophages open tunnels by mechanic and proteolytic actions to migrate in nanoporous environments
9:55-10:15	**Dag Dysthe**	Simultaneous measurement of intracellular actin dynamics and strain field of the extracellular matrix
10:15-10:35	**Philippe Peyla**	Interacting microswimmers and taxism
10:35-11:10	*Coffee break*	
11:10-12:05	**Vincent Calvez**	Biological waves at the mesoscopic scale.

Abstracts:

Theoretical models of cell migration

Rhoda Hawkins

E-mail of the corresponding author: rhoda.hawkins@physics.org

Migratory eukaryotic cells use a variety of mechanisms to move around. It is clear that the cytoskleton plays a key role in this, as does the environment the cell is moving in/on. In this talk I will review what is known about how the cytoskeleton produces the forces necessary for cell migration. I will present some minimal theoretical models developed by my own group and collaborators. I will discuss the important effects of interactions between the cytoskeleton and the nucleus and between the cell and its environment.

Simple overview on swimming

Mohd Suhail Rizvi

E-mail of the corresponding author: mohd-suhail.rizvi@univ-grenoble-alpes.fr

Motility is one of the crucial properties of the biological systems. It is responsible for the survival of microorganisms, immune response, embryonic development and also plays an important role in cancer metastasis. The biological mechanisms of cellular locomotion are quite diverse, ranging from swimming in a fluid medium to crawling in the presence of a substrate. The swimming mode of motility is usually achieved by the help of flagella/cilia or by shape deformations. On the other hand, the crawling cells take help of the adhesive or non-adhesive interactions with the underlying substrate. The microscopic nature of these systems presents some unique challenges in the study of the mechanics behind locomotion. In this talk I will present a basic overview detailing the physical principles of the swimming and crawling of the biological cells.

Transmigration de cellules cancéreuses

Claude Verdier

E-mail of the corresponding author: claude.verdier@univ-grenoble-alpes.fr

Nous nous intéressons aux mécanismes de migration de cellules cancéreuses au travers de l'endothélium. Cette étape est essentielle dans la formation de métastases. L'adhésion intervient au moment où les cellules cancéreuses se fixent sur l'endothélium et nous identifions les récepteurs et les liagnds. Puis les déformations cellulaires sont étudiées par micro-rhéologie (AFM). Nous proposons des mécanismes en relation avec le remodelage du cytosquelette pour expliquer la transmigration.

Cells and humans migration : crawling versus walking

Maxime Bonnefoy

E-mail of the corresponding author: bonnefoy.m@univ-grenoble-alpes.fr

This transdisciplinary research project proposes a synergistic collaboration between an interdisciplinary laboratory of physics and an architectural research laboratory. It is focused on the intricate spatial relations between a living being and the geometrical features of its environment. As both disciplines are facing similar questions, we explore the scientific purpose of analogous protocols. Our hypothesis is that the observation of these two differents living beings behaviors and especially the trajectories of their migration may provide us an understanding of their motion abilities and space perception faculties for both scales. In order to study the space perception of both living beings, we do a serial production of differentiated environments as corridors with folded borders either symmetric or not and morphological parameters changing as width, angles shapes or curvatures. Practically, keratocytes cells are cultured from Hypsophrys nicaraguensis scales and cell-adhesive micropatterns are designed with parametric modeling tools inherited from architecture and then generated by deep UV photo-patterning. Images of cells movements are captured by lensless microscopy and analyzed by homade ImageJ routines using especially tracking programs. Architectural environment are conceived with parametric modeling tools and built with digital-control machines. We aim to capture motion, do video tracking and image analysis of human beings experiencing these environments in accordance with biological protocol. The primary results of this ongoing research demonstrate our ability to combine parametric architectural design with experimental biology. We obtained clear defined micropatterns and captured clear images in which lensless microscopy gives an unprecedented acces to the dynamics of population of cells over hours or days.

Méthodes de diffusion-redistanciation pour le déplacement par flot de Willmore. Application à la forme d'équilibre des globules rouges.

Arnaud Sengers

E-mail of the corresponding author: arnaud.sengers@univ-grenoble-alpes.fr

Nous nous intéressons à la simulation du déplacement de membranes élastiques immergées dans un fluide, avec pour application la dynamique des globules rouges dans le sang. Différentes méthodes permettentde gérer le couplage entre le fluide et le solide, représentés respectivement par une formulation eulérienne et lagrangienne. Nous considérons ici la méthode des lignes de niveaux où la membrane est représentée implicitement comme la ligne de niveau 0 d'une fonction auxiliaire. Un des principaux avantages de cette méthode est l'utilisation d'un maillage unique pour le fluide comme pour l'interface. La stabilité des schémas de couplage représente un challenge important lors de la simulation de méthode de couplage fluide-structure. En effet, l'utilisation de schémas explicites est grandement limitée par une condition restrictive sur le pas de temps. Un schéma implicite, bien qu'inconditionnellement stable, nécessite la résolution d'un système constitué d'une équation de Navier-Stokes couplée à une équation detransport avec un terme source non linéaire, ce qui se révèle trop coûteux dans la pratique. Un schéma

semi-implicite a été proposé par Cottet et Maitre. Il consiste à ajouter une étape de prédiction de la position de la membrane et utiliser celle-ci pour calculer les forces impliquant la courbure dans l'équation de Navier-Stokes. Il permet d'obtenir la stablité inconditionnelle avec un coût algorithmique proche de celui d'un schema explicite. Cette étape de prédiction peut être rapprochée des méthodes de convolution-seuillage introduites initialement par Merriman-Bence-Osher. Conceptuellement, cela consiste à alterner une étape de diffusion d'équation de la chaleur et une étape de seuillage. Le principal avantage de cette méthode est son inconditionnelle stabilité. Initialement utilisée pour simuler le mouvement par courbure moyenne, cette méthode a été étendue pour simuler d'autres flots géométriques et plus particulièrement le flot qui intervient dans le cas des globules rouges : le flot de Willmore. Néanmoins, un défaut majeur des algorithmes de convolution-seuillage est que, sur maillage fixe, si la résolution est insuffisante, l'interface peut rester figée. Il faut alors recourir à un raffinement du maillageau niveau de l'interface, ce qui augmente fortement le coût algorithmique. Une solution alternative à ce problème est de représenter l'interface comme la ligne de niveau 0 de la distance signée plutôt que via une fonction caractéristique. Ainsi l'étape de seuillage, qui consiste désormais en une redistanciation, permet de mieux localiser l'interface numériquement. L'étape de redistanciation peut être réalisée efficacement avec par exemple une méthode de fast marching. Nous avons ainsi à disposition une méthode efficace pour simuler le déplacement par flot de Willmore. En effet, on enchaîne deux résolutions d'équation de la chaleur et une redistanciation. Pour respecter les contraintes de conservation de volume et de périmètre inhérentes au globules rouges, on ajoute une étape de correction avant la redistanciation qui consiste à déplacer légèrement l'interface en ne prenant pas la ligne de niveau 0 mais la ligne de niveau $\lambda + \mu\kappa$ (κ désignant la courbure moyenne). Les constantes λ,μ sont choisies pour récupérer le volume et périmètre initial. Le choix de cette correction est motivé par l'expression des premières variations du flot de Willmore avec multiplicateurs de Lagrange. Des simulations utilisant cette méthode ont été réalisées en dimension 2 et 3 pour obtenir la position d'équilibre d'une interface soumise au flot de Willmore.

Ratchetaxis

Daniel Riveline

E-mail of the corresponding author: riveline@unistra.fr

Tba

Force-induced repolarization of an active crawler

Pierre Recho

E-mail of the corresponding author: pierre.recho@univ-grenoble-alpes.fr

We develop a quantitative model of mechanical repolarization in a contraction-driven gel layer mimicking a crawling cell. We show that the force-velocity relations for such active crawlers exhibit multi-valuedness and hysteresis under both force and velocity control. The model predicts steady oscillations of cells attached to an elastic environment and offers a self consistent mechanical explanation for all experimentally observed outcomes of cell collision tests.

Rigidity based margination

Revaz Chachanidze

E-mail of the corresponding author: rdchachanidze@gmail.com

Margination can be described as the ability of certain suspended particles to travel from bulk flow to vessel walls. In blood this phenomenon of cell segregation plays a crucial physiological role. Additionally, in case of certain diseases when the mechanical properties of red blood cells were altered those cells show the affinity of lateral migration in a flow as well. Moreover, recent advances in targeted drug delivery arouse an interest in the margination of drug carriers. The mechanisms leading to margination are not fully understood and very few experimental studies have been performed. Our research is dedicated to a better understanding of how the rigidity of suspended particles leads to margination. For this purposes we observe and quantify a blood flow consisting of 2 populations of red blood cells: healthy and rigidified with a cross-linking agent (glutaraldehyde). We investigated cases of different hematocrit levels, wide range of velocities and different microvessel geometries.

Lymphocytes swim by molecular and not protrusion-based paddling

Olivier Théodoly

E-mail of the corresponding author: olivier.theodoly@inserm.fr

Mammalian cells developed two main migration modes. The slow mesenchymatous mode, like fibroblasts crawling, relies on maturation of adhesion complexes and actin fiber traction, while the fast amoeboid mode, observed exclusively for leukocytes and cancer cells, is characterized by weak adhesion, highly dynamic cell shapes, and ubiquitous motility on 2D and in 3D solid matrix. In both cases, interactions with the substrate by adhesion or friction are widely accepted as a prerequisite for mammalian cell motility, which precludes swimming. We show here experimentally and computationally that leukocytes do swim, and that propulsion is not fueled by waves of cell deformation but by a rearward and inhomogeneous treadmilling of the cell envelope. We model the propulsion as a molecular paddling by transmembrane proteins linked to and advected by the actin cortex, whereas freely diffusing transmembrane proteins hinder swimming. This mechanism explains that swimming is five times slower than the cortex retrograde flow. Resultantly the ubiquitous ability of mammalian amoeboid cells to migrate in various environments with or without adhesion can be explained for lymphocytes by a single machinery of envelope treadmilling.

Crawling in a fluid

Alexander Farutin

E-mail of the corresponding author: alexandr.farutin@univ-grenoble-alpes.fr

There is increasing evidence that mammalian cells not only crawl on substrates but can also swim in fluids. To elucidate the mechanisms of motility of cells in suspension, we propose a model which couples actin and myosin kinetics to fluid flow and solve it for a spherical cell. We also propose a model in which the actin flow is transmitted to the outside fluid by transmembrane proteins bound to actin, such as intergrins. The viscous friction of the fluid with a moving brush of transmembrane proteins creates a flow around the cell. We extract the transmission coefficient relating the outside flow to the actin velocity in terms of the geometrical parameters of the transmembrane protein brush. We solve the equations governing the actomyosin dynamics in order to find the conditions of motility onset and the distribution of the actin flow. We analytically find super- and subcritical bifurcations from a non-motile to a motile state and also spontaneous polarity oscillations that arise from a Hopf bifurcation. Relaxing the spherical assumption, the obtained shapes show appealing trends. Combining the two models allows us to extract the swimming speed in terms of the key parameters of the models.

Modèle physique des tissus végétaux

Ibrahim Cheddadi

E-mail of the corresponding author: ibrahim.cheddadi@univ-grenoble-alpes.fr

The growth of plant organs is a complex process powered by osmosis that attracts water inside the cells. This influx of water induces an elastic extension of the cell walls that, by resisting, build up pressure in cells, called turgor pressure. Above a certain stress threshold, cell walls yield to the turgor pressure and the cells grow. Based on Lockhart's seminal work, various models have been proposed of this synergistic coupling to describe the growth of plant tissues. However, these models have been developed in the context of single cell growth, more easily accessible to experimentation, or have focused on the description of wall mechanical properties, neglecting the role of water fluxes and osmosis. In this work, we propose a new multicellular model to study the interaction between osmosis and cell walls mechanics and how this impacts tissue development. We show that taking into account this coupling leads to new emergent properties at the level of the multicellular system, that can help interpret different aspects of morphogenesis in plant organs. In particular, the system can display a new type of lateral inhibitory mechanism that could contribute to the amplification of growth heterogeneities, essential for shape differentiation during morphogenesis.

Effective diffusivity of microswimmers in a crowded environment

Marvin Brun-Cosme-Bruny

E-mail of the corresponding author: marvin.brun-cosme-bruny@univ-grenoble-alpes.fr

The microalga Chlamydomonas Reinhardtii (CR) is used here as a model system to study the effect of complex environments on the swimming of micro-organisms. Its motion can be modelled by a run and tumble mechanism so that it describes a persistent random walk from which

we can extract an effective diffusion coefficient. In our experiments, the complex medium consists in a series of pillars that are designed in a regular lattice using soft lithography microfabrication, the cells are then introduced in the lattice. Their swimming is then tracked and analyzed within the pillars. The effect of the complex medium on the swimming behaviour of microswimmers is analyzed through the measure of relevant statistical observables. In particular, the mean correlation time of direction and the effective diffusion coefficient are shown to decrease when increasing the density of pillars. This provides some bases of understanding for active matter in complex environments.

Macrophages open tunnels by mechanic and proteolytic actions to migrate in nanoporous environments.

Isabelle Maridonneau-Parini

E-mail of the corresponding author: maridono@ipbs.fr

In vivo, immune cells migrate through a wide variety of tissues, including confined and constricting environments. In addition to the amoeboid migration used by all leukocytes, we showed in vitro that macrophages use the mesenchymal migration in dense environments (pores $< 3\mu m$) involving proteolysis of the extracellular matrix, compaction and ingestion of degraded matrix to create tunnels. In most cancers, the density and stiffness of the tissue stroma are enhanced. We found in mouse fibrosarcoma in vivo and in human breast cancer ex vivo, that tumor-associated macrophages (TAM) that help tumor progression, perform the mesenchymal migration using their own matrix metalloproteases (MMPs), and perform the amoeboid migration at the tumor periphery. As a proof of concept that targeting mesenchymal migration would be a novel therapeutic strategy, we showed that MMP inhibition correlates with decreased of both TAM recruitment and tumor growth. Podosomes are cell structures constitutively formed in a few cell types including macrophages that are involved in cell adhesion, mechanosensing, proteolytic degradation of the extracellular matrix and mesenchymal migration. We developed a technique called protrusion force microscopy allowing the estimation of the protrusive force generated by single podosomes. These cell structures present a submicron-size core of F-actin surrounded by an adhesion ring comprising integrins and proteins linking integrins to the actin cytoskeleton. We observed that talin is stretched in the ring revealing that the adhesion ring is a site of tension, possibly via lateral contractile cables, balancing protrusion at the core to form a unique two-module protrusive force generator. More recently, to reveal the distribution and dynamics of the forces of cells migrating in confined environments, we designed a device combining microchannels with integrated deformable micropillars serving as sensors of subcellular forces. Macrophages bended the pillars with average forces of 0.3 nN and applied higher forces at the cell edges than around their nuclei. When the degree of confinement was increased, we found that forces were redirected from inwards to outwards. Deciphering the architecture of podosomes and cell mechanics should provide new pharmacological targets.

Simultaneous measurement of intracellular actin dynamics and strain field of the extracellular matrix.

Dag Dysthe

E-mail of the corresponding author: dysthe@gmail.com

Before staring experiments on 3D cell migration in an ECM, we wish to focus on an experimental and methodological issue that is important to allow direct comparison between mathematical modelling and experiments: Simultaneous measurement of intracellular actin dynamics and strain field of the extracellular matrix. This is performed in a simplified setting where cell motion is restricted to 1D on the surface of gels of varying stiffness. The strain field of the gel is tracked by fluorescent beads and we test different techniques of inversion of the strain field to a stress field and compare this to the simultaneous actin dynamics of the cytoskeleton.

Interacting microswimmers and taxism

Philippe Peyla

E-mail of the corresponding author: Philippe.Peyla@univ-grenoble-alpes.fr

Moving toward a source of food, oxygen or light is a very widespread property among motile micro-organisms. This phenomenon is called "taxis". A large proportion of aquatic bacteria or planktonic cells swim to move, which is beneficial only in an inhomogeneous nutrient concentration or in an environment with a tropism. Here, we show and discuss the spreading of an assembly of interacting microswimmers during taxis.

Biological waves at the mesoscopic scale

Vincent Calvez

E-mail of the corresponding author: vincent.calvez@ens-lyon.fr

I will report on recent results concerning two case studies of traveling waves of biological populations: concentration waves of chemotactic bacteria, and dispersal evolution during species' invasion. The two problems share similar features, including a rich interplay between population local heterogeneity, and macroscopic transport properties. I will show that these two problems are amenable to analysis in the long time asymptotics.

List of participants:

1. Alexander Farutin (Liphy)
2. Marvin Brun-Cosme-Bruny (Liphy)
3. Pierre Recho (liphy)
4. Chaouqi Misbah (Liphy)
5. Olivier Théodoly (LAI Marseille)
6. Isabelle Maridonneau-Parini (IPBS Toulouse)
7. Arnaud Sengers (LJK)

8. Daniel Riveline (IGBMC-University of Strasbourg-CNRS)
9. Revaz Chachanidze (LRP)
10. Mehdi Abbasi (Liphy)
11. Dag Dysthe (Liphy)
12. Rhoda Hawkins (University of Sheffiled)
13. Claude Verdier (Liphy)
14. Ibrahim Cheddadi (TIMC-IMAG)
15. Emmanuel Maitre (LJK)
16. Mohd Suhail Rizvi (Liphy)
17. Swapnil Dalal (Liphy)
18. Alexander Erlich (Liphy)
19. Annie Raoult (MAP5)
20. Jocelyn Etienne (Liphy)
21. Philippe Peyla (Liphy)
22. Lourdes Monica Bravo Anaya (Liphy)
23. Arnaud Millet (IAB)
24. Salima Rafaï (Liphy)
25. Candice Rey (Liphy)
26. Abdessamad Nait Ouhra (Liphy)
27. Thibaut Metivet (IRMA Université de Strasbourg)
28. Mourad Ismail (Liphy)
29. Marc Leonetti (LRP)
30. Hai-Meng Huang
31. Anna Melnykova (LJK)
32. Hamid Yousefimashouf (3SR)
33. Angelique Stephanou (TIMC-IMAG)
34. Mete Demircigil (Institut Camille Jordan)
35. Georges Chabouh (Liphy)
36. Dimitri Balasoiu (LJK)

37. Vincent Calvez (ENS Lyon)
38. Maxime Bonnefoy (Cresson/Liphy)
39. Haythem Chelly (Liphy)