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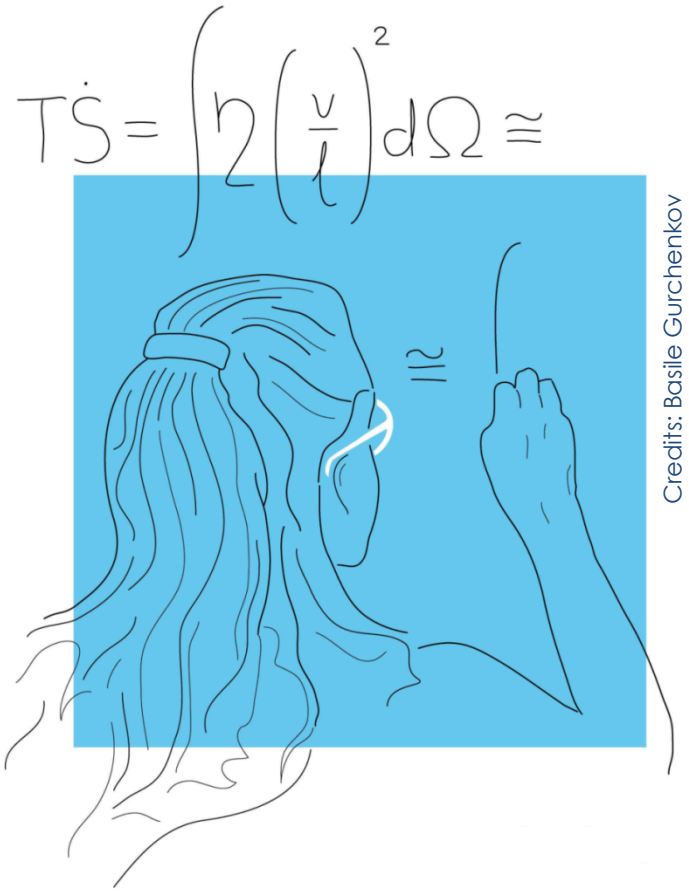


Credits: Basile Gurchenkov

From soft matter to cell biophysics: Be Simple!

GDR CellTiss 2018 Annual Days

& Workshop in honor of Françoise Brochard-Wyart

OCTOBER 1-3, 2018,
AT NOMADE LODGE,
LA CHAPELLE-GAUTHIER, FRANCE

Invited speakers

Jacques Prost (Inst. Curie), Jean-François Joanny (ESPCI & Collège de France), Nicolas Borghi (Inst. Jacques Monod), David Gonzalez-Rodriguez (U. Lorraine), David Hu (Georgia Tech), L. Mahadevan (Harvard U.), Tom Witten (U. Chicago), Erdem Karatekin (Yale), Claire Wyart (ICM, Sorbonne U., INSERM), Matthieu Wyart (EPFL), Pascale Brochard (Osha Liang)

Organization

Mathieu Coppey (Inst. Curie, CNRS, CellTiss), Olivia du Roure (ESPCI Paris, CNRS, CellTiss), Loïc Legoff (U. Aix Marseille , CellTiss), Cécile Leduc (Inst. Pasteur, CNRS, CellTiss), Pierre Nassoy (CNRS, U. Bordeaux, IOGS), Laurence Salomé (U. Toulouse, CNRS, CellTiss), Olivier Sandre (CNRS, U. Bordeaux, SFP), Marc Léonetti, (CNRS U. Grenoble Alpes, SFP), Marc Lefranc (U. Lille, CNRS, CellTiss)

Societe Française de Physique & GDR CellTiss CNRS,
Institut Curie, LabEx CelTisPhyBio, Sorbonne Universite,
Institut Pierre-Gilles de Gennes pour la Microfluidique,
LVMH Recherche, Michelin, Saint-Gobain, Zeiss Microscopy,
Alveole, JPK Instruments, IFP Energies Nouvelles

GDR CellTiss Annual Days 2018

& Workshop "*Be Simple*": From soft matter to cell biophysics

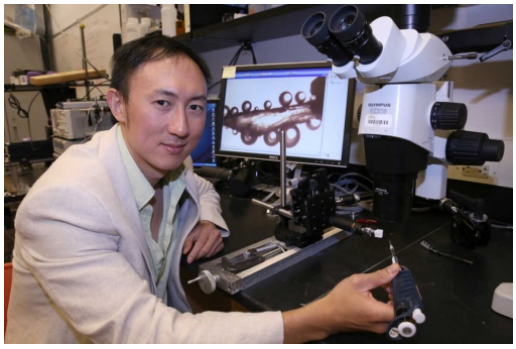
An international workshop entitled "*Be Simple*" will be organized to celebrate the distinguished scientific career of Françoise Brochard-Wyart and her contribution to our understanding of biological matter from the perspective of soft matter physics (liquid crystals, polymers, (de)wetting and hydrodynamics).
This meeting will be held from 1st to 3rd of October 2018 at the Nomade Lodge (La Chapelle-Gauthier, 1hour away towards East from Paris). This special event is organized in the context of the Annual Days of the GDR CellTiss, a national incentive from CNRS to foster research at the interface of physics, chemistry, cell biology, systems biology, and developmental biology.
The meeting will focus on current biophysical topics addressed at different levels, from molecular to cellular and tissue scales. Despite the complexity of living systems, some properties and behaviors can be explained with very simple arguments originating from concepts developed in soft matter physics or by analogy with other phenomena. This is typically the approach that has guided Françoise Brochard-Wyart since she started to orient her research activities towards biophysics, at the late nineties at the Curie Institute and can be summarized by her moto "*Be Simple*".
One day will be completely dedicated to Françoise, with presentations given by world-renowned physicist friends and by younger former students who have then made significant advances in Francoise's footsteps. These talks will cover themes like active biological matter, collective phenomena and self-organization and cell/tissue rheology, which are core themes of the GDR CellTiss. The rest of the meeting will allow PhD students, postdocs and researchers from the GDR CellTiss community to present their recent works related to the abovementioned topics or beyond, e.g. in systems biology, biomimetic systems, ...
Registration will soon be open on the GDR CellTiss website. More practical details, including transport, lodging, scientific programs, sponsoring, will also be found on the GDR website.

SOCIETE FRANÇAISE DE PHYSIQUE & GDR CELLTISS CNRS, INSTITUT CURIE, LABEX CELTISPHYBIO, SORBONNE UNIVERSITE, INSTITUT PIERRE-GILLES DE GENNES POUR LA MICROFLUIDIQUE,
LVMH RECHERCHE, MICHELIN, SAINT-GOBAIN, ZEISS MICROSCOPY, ALVEOLE, JPK INSTRUMENTS, IFP ENERGIES NOUVELLES

Plenary speakers - Special guests… *who will make a long trip to celebrate Françoise Brochard-Wyart*

Professor of Physics, James Franck Institute, University of Chicago, USA
Elected fellow of the American Academy of Arts and Sciences and of the American Physical Society.
APS 2002 Polymer Physics Prize
Tom Witten *is a theoretical physicist who looks for mathematical laws that govern unconventional forms of matter. He specialized in the study of polymers (found in Styrofoam cups), complex fluids (including coffee stain, paint and toothpaste) and aggregation phenomena (such as the way snowflakes clump together)*

Professor of Organismic and Evolutionnary Biology, Professor of Physics : Harvard University, USA
Elected member of the Royal Society of London
Genius Prize of the MacArthur Foundation
L. Mahadevan *is a mathematician who applies complex mathematical analyses to a variety of seemingly simple, but vexing, questions across the physical and biological sciences — how cloth folds when draped, how skin wrinkles, how flags flutter, how Venus flytraps snap closed*.



Professor of Mechanical Engineering and Biology at the Georgia Institute of Technology, USA.
Ig Nobel Prize in Physics in 2015
David Hu *has training in fluid dynamics from MIT. His research has generated broad interest across the fields of engineering, biology and robotics*

We warmly thank our sponsors:

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LVMH Recherche, Michelin, Saint-Gobain, Zeiss Microscopy, Alveole, JPK Instruments, IFP Energies Nouvelles

Monday, October 1st 2018

13:00 – 14:00 Welcome Buffet

14:00 – 14:15 Introduction: Laurence Salomé, Pierre Nassoy & Olivier Sandre

14:15 – 16:10 **GDR CellTiss Session 1**

Plenary talk: Jacques Prost (25+5')

Talk 1: Julien Pernier (10+5')
"A new actin depolymerase: a catch bond Myosin 1 motor"

Talk 2: Thomas Le Goff (10+5')
"Cluster formation of cooperative actin binding protein"

Talk 3: Alexandre Beber (10+5')
"Membrane reshaping by micrometric curvature sensitive septin filaments"

Talk 4: Morgan Delarue (10+5')
"Sensing without a sensor: When the biophysical properties of a cell control reaction rates"

Talk 5: Lorraine Montel (10+5')
"Designing high-throughput phagocytic assay to study the physics of phagocytosis"

Flash: Pierre-Olivier Strale (Alvéole) (10')
"Bio-engineering the cellular microenvironment"

16:10 – 16:40 

16:40 – 18:10 **GDR CellTiss Session 2**

Talk 1: Kaili Xie (10+5')
"Wrinkling instability of biomimetic cells"

Talk 2: Carles Blanch-Mercader (10+5')
"Buckling of epithelium growing under spherical confinement"

Talk 3: Maciej Lisicki (10+5')
"Autophoretic motion in three dimensions"

Talk 4: Claire Leclech (10+5')
"Control of the morphology and dynamics of migrating cortical interneurons by topographical cues"

Talk 5: Laura Alaimo (10+5')
"Collective cell migration under a 3D spatial confinement"

Talk 6: Christine Gourier (10+5')
"Flagellum beating and membrane remodelling for gamete fusion in mammalian fertilization"

18:10 – 19:30 **Poster session**

19:30 **Apéritif and Dinner. Posters' visit to be continued!**

Tuesday, October 2nd 2018

9:00 – 10:40 **FBW Session 1**

Plenary: Tom Witten (25+5')
"Chiral Phoresis"

Invited 1: Jean-François Joanny (15+5')
"Space exploration by dendritic cells"

Invited 2: Matthieu Wyart (15+5')
"The jamming transition as a paradigm to understand the loss landscape of deep neural networks"

Invited 3: Jean-Michel Vacherand (15+5')
"Dewetting and tire traction"

Flash: Fabrice Schmitt (Zeiss) (10')
TBA

10:40 – 11:15

11:15 – 13:00 **FBW Session2**

Plenary: David Hu (25+5')
"Cat tongues, frog tongues, and the cubed poo of wombats"

Invited 1: Ana-Suncana Smith (15+5')
"Frequency spectrum of the flicker phenomenon in membranes - why does it matter?"

Invited 2: Pascale Brochard (15+5')

"Patents, why it matters?"

Invited 3: Nicolas Pannacci (15+5')

"Soft Matter approaches at IFP Energies Nouvelles"

Contributed 1: Giovanna Fragneto (10+5')

"Structural Characterization of Biomembranes: the Role and Impact of Composition"

13:00 – 14:15

14:20 – 16:00 **FBW Session 3**

Plenary: L. Mahadevan (25+5')

"Collective physics and physiology in social insects"

Invited 1: Claire Wyart (15+5')

"Sensory signaling in the spinal cord: Roles during locomotion and organogenesis"

Invited 2: David Gonzalez (15+5')

"Permeability and fracture of cellular aggregates"

Contributed 1: Martine Ben Amar (10+5')

"*C. elegans* elongation: assessing the contribution of geometry, pre-stress and active stress"

Contributed 2: Xavier Noblin (10+5')

"Swimming zoospores and invasive fungal growth"

16:00 – 16:30

16:30 – 18:30 **FBW Session 4**

Invited 1: Nicolas Borghi (15+5')

"Mechanotransduction: from cell surface to nucleus"

Invited 2: Erdem Karatekin (15+5')

"Holey membrane! From simple bilayer pores to exocytotic fusion pores"

Invited 3: Atef Asnacios (15+5')

"Wetting inspired single-cell mechanobiology"

Contributed 1: Olivier Rossier (10+5')

"Deciphering the spatiotemporal regulation of integrins at the nanoscale"

Contributed 2: Marc de Gennes (10+5')

"Pattern formation in the drosophila wing"

Contributed 3: Laurent Bacri (10+5')

"Polymer chains in confined media"

Contributed 4 : Karine Guevorkian (10+5')

TBA

18:30 – 19:00 *Drawings of the day (Olivier Wyart) & Discussion (Françoise Brochard-Wyart)*

19:30 – 1h **Gala Dinner**

Bar and Dancing!

Wednesday, October 3rd 2018

9:00 – 10:40 **GDR CellTiss Session 3**

Talk 1: Antony Bazir (10+5')

"Measuring mechanical properties of spheroids with acoustic waves"

Talk 2: Lea-Laetitia Pontani (10+5')

"Biomimetic emulsions to probe the mechanics of tissues"

Talk 3: Nicolas Harmand (10+5')

"Merits and limits of surface and line tensions to understand the shape of epithelial cells"

Talk 4: Francis Corson (10+5')
"Fluid mechanics of amniote gastrulation"

Talk 5: Amit Kumar Singh (10+5')
"Substrate Dependent Self-Propulsion and Diffusion of active Enzymes"

Talk 6: Adrien Hallou (10+5')
"Theory of Turing pattern formation in active biphasic tissues"

Flash: Fréderic Eghiaian (JPK Instruments – Bruker) (10')
"Novel AFM methodologies for cell biophysics"

10:40 – 11:10 

11:10 – 12:40 **GDR CellTiss Session 4**

Talk 1: Satoshi Yamashita (10+5')
"Dividing a large deforming tissue into unitary regions"

Talk 2: Alexis Moreau (10+5')
"Microcirculation of Red Blood Cells in biomimicking splenic slits"

Talk 3: Revaz Chachanidze (10+5')
"Rigidity-induced margination"

Talk 4: Etienne Loiseau (10+5')
"The mechanical feedback between mucus and active cilia dynamics drives the self organisation of reconstituted bronchial epithelium"

Talk 5: Myriam Jory (10+5')
"Mucus rheology and cilia coordination of the human bronchial epithelium"

Talk 6: Kaori Sakai (10+5')
"Design of a full experimental microfluidic and microscopic toolbox for wide spatiotemporal study of plant protoplast development and physiology"

12:40 – 13:00 **Closing of the Meeting**

13:00 – 14:00 

and Departure (Bus leaving at 13:30 and 14:30)…

Notes:

Poster List

1. Laura Casanellas:
   “The role of adhesion on the microfluidic flow of biomimetic tissues”
2. Laroslava Golovkova:
   “Adhesive emulsions under pressure”
3. Emmanuèle Helfer:
   “Red blood cells in confined flows: structuration in bands and trains”
4. Joanna Podkalicka:
   “Caveolin-assisted sphingolipid transport to the plasma membrane”
5. Céline Bruyère:
   “Importance of morphological and mechanical properties of myoblasts in muscle cell differentiation”
6. Eléonore Vercruysse:
   “How cell-cell interactions modulate the collective migration of epithelial cells”
7. Marie Versaevel:
   “Epithelial closure over gradients of adhesiveness”
8. David Lacoste:
   “Selection Dynamics in Transient Compartmentalization”
9. Adria Sales Ramos:
   “Presentation of bone morphogenetic proteins to cells at their basal side reveals their role in the initiation of cell adhesion”
10. Léa Pinon:
    "Emulsion droplets as a new tool to study B cells polarization and mechanics"
11. Camille Simon:
    “Actin dynamics alone drive membrane deformations mimicking cellular processes”
12. Quang D. Tran:
    “Microfluidic study to investigate characteristics of collective and individual motions of swimming zoospores”
13. Nino Kukhaleishvili :
    “Physics of invasive fungal growth”
14. Sylvie Coscoy:
    “Formation and propagation of renal cysts: study in biomimetic tubular systems”
15. Elodie Couttenier:
    “Candida albicans on a chip”
16. Marc Lefranc:
    “A mathematical model of the liver circadian clock linking feeding and fasting cycles to clock function”

Program

	Monday, October 1st 2018	Tuesday, October 2nd 2018	Wednesday, October 3rd 2018
9h		**FBW Session 1** ***Tom Witten*** **Jean-François Joanny,** **Matthieu Wyart** **Jean-Michel Vacherand** Fabrice Schmitt (Zeiss)	**CellTiss Session 3** Antony Bazir, Lea-Laetitia Pontani, Nicolas Harmand, Francis Corson, Amit Kumar Singh, Adrien Hallou Fréderic Eghiaian (JPK– Bruker)
10h40 -11h10		*Coffee break*	*Coffee break*
11h30	1st bus leaves from Melun station	**FBW Session2** ***David Hu*** **Pascale Brochard** **Nicolas Pannacci (IFPEN)** **Ana-Suncana Smith** Giovanna Fragneto	**CellTiss Session 4** Satoshi Yamashita, Alexis Moreau, Revaz Chachanidze, Etienne Loiseau, Myriam Jory, Kaori Sakai
12h	1st bus arrives at Nomade Lodge		
12h30	2nd bus leaves from Melun station		
	2nd bus arrives at Nomade Lodge		***Closing ceremony***
13h	Welcome Buffet	Lunch	Buffet
14h	***Introduction:*** Laurence Salomé, Olivier Sandre, Pierre Nassoy	**FBW Session 3** ***L. Mahadevan*** **Claire Wyart** **David Gonzalez** Martine Ben Amar Xavier Noblin	13h30 1st bus leaves to Melun station 14h Arrival at Melun train station
14h15	**CellTiss Session 1** ***Jacques Prost*** Julien Pernier, Thomas Le Goff, Alexandre Beber, Morgan Delarue, Lorraine Montel Pierre-Olivier Strale (Alveole)		14h30 2nd bus leaves to Melun station 15h Arrival at Melun train station
16h10	*Refreshments*	*Refreshments*	
16h30	**CellTiss Session 2** Kaili Xie, Carles Blanch-Mercader, Maciej Lisicki, Claire Leclech, Laura Alaimo, Christine Gourier	**FBW Session 4** **Nicolas Borghi** **Erdem Karatekin** **Atef Asnacios** Olivier Rossier, Marc de Gennes, Laurent Bacri, Karine Guervokian	
18h30	***Posters***	***Drawings of the day: Olivier Wyart***	
19h30	Aperitif & Dinner	Gala Dinner Bar and Dancing	

Durations:

Contributions=10+5', **Invited talks=15+5'**, ***Plenary talks=25+5'***, Coffees=30', Sponsor = 10'

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A new actin depolymerase: a catch bond Myosin 1 motor

Julien Pernier[1,2,3], Remy Kusters[1,2], Hugo Bousquet[2,3], Thibaut Lagny[1,2,3], Antoine Morchain[1,2], Jean-François Joanny[1,2,4], Patricia Bassereau[1,2], Evelyne Coudrier[2,3]

1. Laboratoire Physico Chimie Curie, Institut Curie, PSL Research University, CNRS UMR168, Paris, France. 2. Sorbonne Universités, UPMC, Paris, France. 3. Institut Curie, PSL Research University and C.N.R.S. UMR 144, France. 4. ESPCI Paris, PSL Research University, France.

The regulation of actin dynamics is essential for various cellular processes. Former evidence suggests a correlation between the function of non-conventional myosin motors and actin dynamics. In particular, down- or overexpression of one of these myosins, Myosin1b, affects the organization of the actin cytoskeleton in the juxtanuclear region of HeLa cells and in growth cones of cortical neurons. We investigate the contribution of the catch-bond Myosin1b to actin dynamics using *in vitro* sliding motility assays and total internal reflection fluorescence (TIRF) microscopy. We observe that sliding on Myosin1b immobilized or bound to a fluid bilayer enhances actin depolymerization at the barbed end, while sliding on the weak catch-bond MyosinII has no effect. Our theoretical model supports that the catch-bond prolongs the attachment time of the motor at the barbed end due to the friction force exerted by the sliding filament; thereby this motor exerts a sufficient force on this end to promote depolymerization. This work reveals a non-conventional myosin motor as a new type of depolymerase.

T. Le Goff and A. Michelot
Aix Marseille Univ, CNRS, IBDM, Marseille, France

Abstract :

Cytoskeleton is a complex structure involved in different process like cell motility or cell division. One of the main ingredient of this system is the actin polymer. Depending on its function, the organisation of actin network in cytoskeleton takes various compositions and configurations. When motiled, some cells form a lamellipodium at the front where actin network is made of branched filaments with the presence of Arp2/3, an actin binding protein (ABP). In filopodia, which probe environment around the cell, the actin filaments are bound in parallel by the ABP fascin.

Each actin structure have a particular composition of ABPs and a specific localisation, there is a spatial segregation within the cell. Nevertheless, mechanisms underlying this phenomenon are still not well understood. We know that binding of some ABPs to actin is cooperative [1].
This effect implies the formation of clusters of ABPs [2] and could promote adhesion of one ABP instead of the others and so create the spatial segregation.

In this study we model and quantify the effect of cooperativity on the adhesion of ABPs depending on the spatial range and the intensity of the cooperativity. In particular, we characterize the structure and the length of clusters of ABPs.

References :
[1] E. Prochniewicz, E. Katayama, T. Yanagida, and D.D. Thomas, Biophysical Journal 65, 113 (1993).
[2] L. Gressin, A. Guillotin, C. Guérin, L. Blanchoin and A. Michelot, Current Biology 25, 1437 (2015).

Membrane reshaping by micrometric curvature sensitive septin filaments

Alexandre Beber, Patricia Bassereau

Laboratoire Physico-Chimie Curie UMR168 CNRS / Institut Curie / PSL Univ.

Septins are proteins able to form supramolecular structures such as filaments, networks and rings. They are found in eukaryote cells at specific locations including the separation between the mother and daughter cell during cytokinesis and the basis of cilial cells. While their specific function is still unclear, many studies show that septins are involved in the formation of diffusion barriers, allowing compartmentalization of cells and in the formation of a scaffold for the plasma membrane. Given their tendency to assemble in region of micrometric curvatures, we wanted to investigate the ability of septins to sense such curvatures. Using patterned supported lipid bilayers (SLB) and fluorescently labeled septins, we found that septin accumulate in region of positive curvature with a maximum around $2\mu m^{-1}$. We also got SEM evidence that septins organize with different orientation depending on the sign of the curvature. Secondly, to assay the possibility that septins have a role in membrane elasticity and deformation of the plasma membrane we used a micropipette assay to strain giant unilamellar vesicles (GUVs) and measure the effect that septins could have on membrane rigidity. We recorded no difference in the mechanical properties of septin-coated GUVs but were able to show that they can induce spike-like protrusion at high concentrations that have conserved features.

Sensing without a sensor: When the biophysical properties of a cell control reaction rates

Brittingham, G[1], Poterewicz, G[1], Holt, L[1], **Delarue, M[2]**

1. NYU Langone Medical Center, New York, USA
2. LAAS-CNRS, Toulouse, France

Any cell population growing in a limited space can generate mechanical compressive stresses. Tumors growing within tissues and microbes that are naturally confined by their environment both build up growth-induced pressure. While the impact of tensile mechanical stresses has been widely studied, much less is known about the effects of compressive mechanical stresses on cell physiology.

We developed various microfluidic devices enabling precise temporal control of mechanical and chemical conditions[1,2]. We found that a compressive stress can trigger specific pathways essential for cell survival, illustrating direct mechanosensing[2], but also that the rate of cell growth is affected by compressive stress: Cell growth decreased roughly exponentially with pressure[1]. In order to dissect the origin for such a growth decrease, we used genetically encoded multimeric nanoparticles[3] (GEMs) to assess the effects of a mechanical compressive stress on cell microrheology, along with other typical rheological probes, either located in the cytoplasm or in the nucleus of cells. We observe that the mobility of every particles, cytosolic and nuclear alike, decreases exponentially as cells experience increasing compressive stress.

We speculated that pressure-induced increase in crowding could lead to decrease mobility of every protein or protein complexes, implying a decrease of numerous cellular processes. Indeed, we found that the induction rate of a reporter gene decreases with decreased mobility (Fig. 1): macromolecular diffusion becomes rate limiting for growth under compressive stress, thus globally decreasing the rates of biochemical reactions.

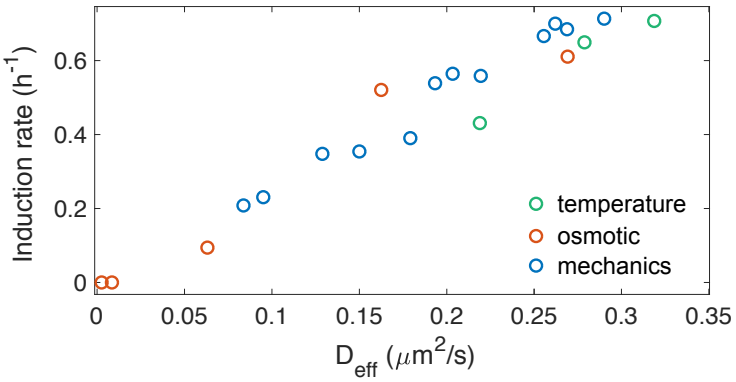


Fig. 1: Rate of induction of a non-mechano-sensitive gene, plotted as a function of the effective diffusion of GEMs, for cells subjected to either a mechanical stress or an osmotic stress.

While survival is regulated through specific mechano-sensitive pathways[2], compressive mechanical stresses could indirectly regulate cell physiology through a variation of molecular crowding. Interestingly, when cytosolic rheological properties are modulated through osmotic stress or temperature shift, we found that the induction rate of the reporter gene changed in a similar fashion as in a mechanical stress (Fig. 1). This led us to introduce the notion that cells can "sense" their environment without a specific sensor: while any stress will trigger the response of specific sensors, it will also have indirect consequences on the biophysical properties of the cell. Altered rheological properties can in turn affect reaction rates depending on the typical size of molecules involved, providing a novel possible mechanism on multiple aspects of cell biology.

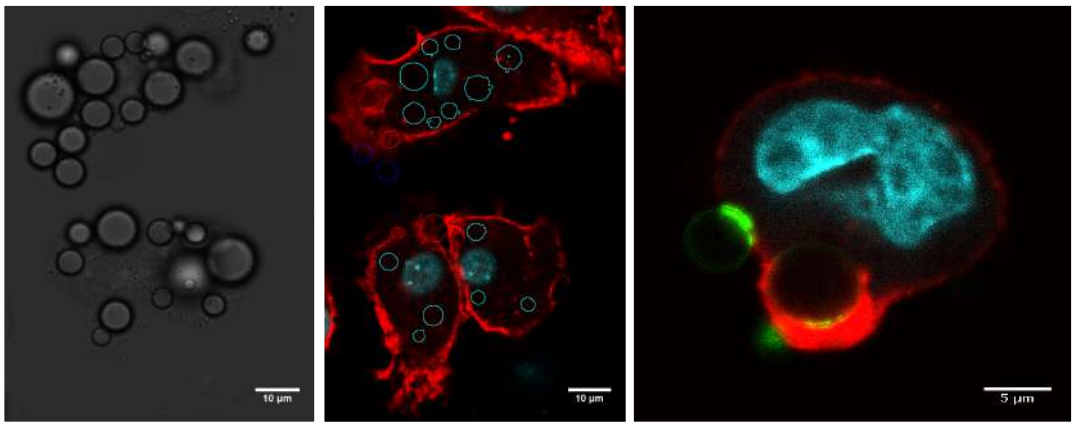
Bibliography

1. Delarue, M. *et al.* Self-driven jamming in growing microbial populations. *Nat. Phys.* **12,** 762–766 (2016).
2. Delarue, M. *et al.* SCWISh network is essential for survival under mechanical pressure. *Proc. Natl. Acad. Sci. U. S. A.* **114,** 13465–13470 (2017).
3. Delarue, M. *et al.* mTORC1 Controls Phase Separation and the Biophysical Properties of the Cytoplasm by Tuning Crowding. *Cell* **174,** 1–12 (2018).

Designing high-throughput phagocytic assay to study the physics of phagocytosis

L. Montel[1], L. Pinon[1], J. Fattaccioli[1]

[1] Ecole Normale Supérieure - PSL Research University, Département de Chimie, 24 rue Lhomond, F-75005 Paris, France



Left : Bright Field image of macrophages and oil droplets Scale bar 10µm. Middle: Confocal image of the same macrophages, with F-actin in red and nucleus in cyan. Circles represent segmented and classified droplets, cyan are internalized, red and blue are external. Right: Confocal image of a macrophage in contact with two droplets, F-actin in red, IgG in green, nucleus in cyan. The IgG cluster is visible on the droplet at the left, the actin cup closing on the droplet at the right. Scale bar 5µm.

Phagocytosis is the uptake, by cells of the immune system, of particles larger than 0.5µm. For the biggest particles, it involves a massive reorganization of membrane and actin cytoskeleton as well as an important intracellular deformation, all in a matter of minutes. Phagocytosis has mainly been studied using solid particles, as polystyrene beads, which are more rigid than biological targets, or biological particles, as zymosan, erythrocytes or inactivated bacteria, which are difficult to characterize. To assess the impact of the physical and chemical parameters of the objects on phagocytosis, we used functionalized emulsion droplets, which could be created with modular diameter, surface tension, internal viscosity and IgG surface density. On droplets, IgG form clusters at the contact of the cells, they can be extracted or reorganized throughout the phagocytosis.

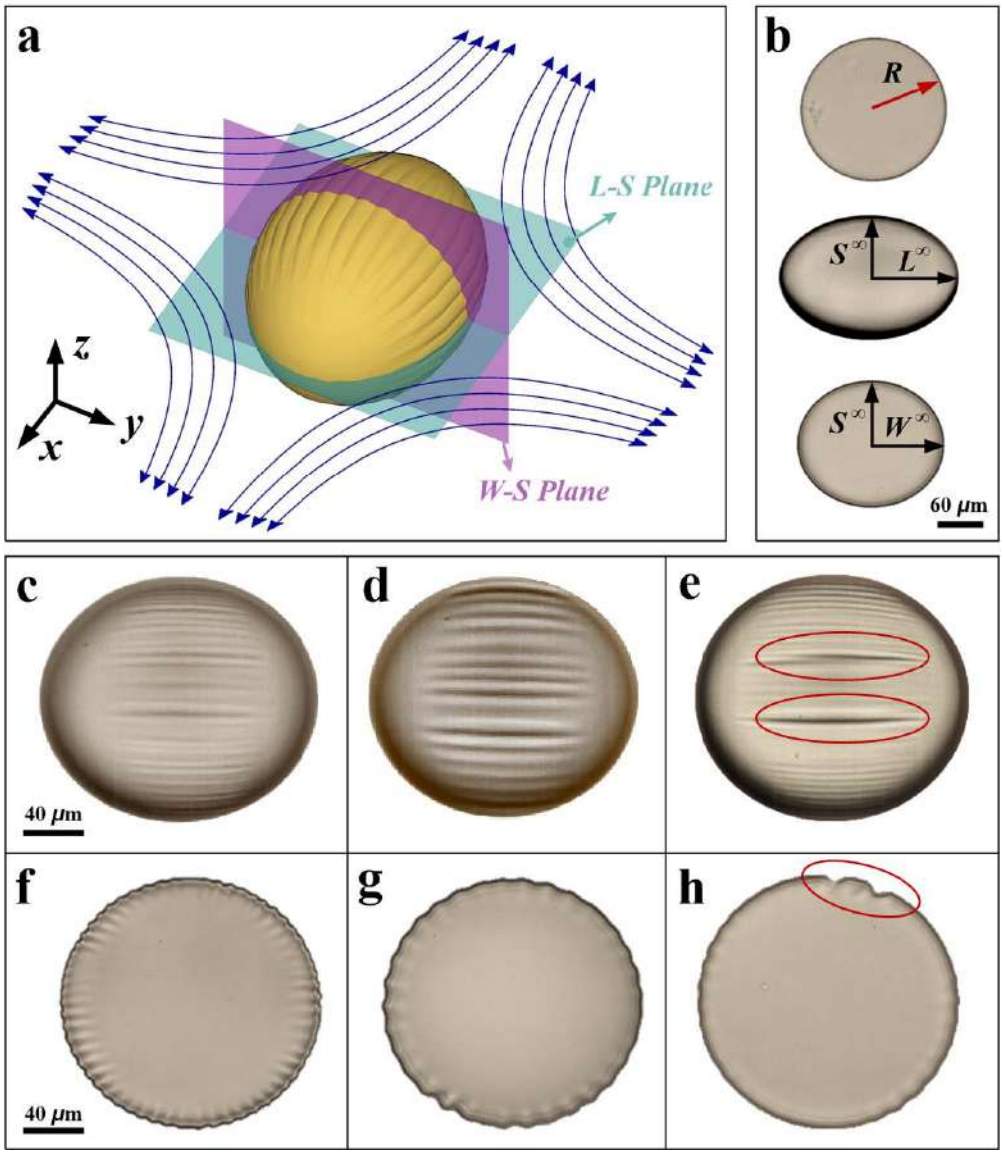
We designed a method using confocal microscopy, automated image analysis and databases for fast quantitative analysis of phagocytosis assays. It yields comprehensive data on the cells and targets geometric and fluorescence intensity parameters, automatically discriminates internalized from external targets, and stores the relationship between a cell and the targets it has engulfed.

Using both tools, we studied the influence of the size, surface tension and viscosity of targets on the efficiency of phagocytosis. The use of monodisperse droplets of several diameters reveals that the number of internalized objects is limited by the surface area needed to wrap the targets.

Wrinkling instability of biomimetic cells

K. Xie[1,3], C. de Loubens[1], F. Dubreuil[2], M. Jaeger[3], M. Leonetti[1]
[1]UGA, CNRS, G-INP, LRP, Grenoble ;
[2]UGA, CNRS, Cermav, Grenoble ; [3]AMU, CNRS, ECM, M2P2, Marseille
Contact: clement.deloubens@univ-grenoble-alpes.fr, marc.leonetti@univ-grenoble-alpes.fr

Red Blood Cells in flow present a wealth of dynamics of deformation that is governed by their shear elasticity and their bendability. Under flow, they can exhibit a buckling instability when rigidified. We quantitatively investigated the stability of biological soft particles in simple extensional flow by using biomimetic cells with controlled membrane elasticity and thickness. We observed the emergence of well-defined wrinkles driven by loop compression of the membrane when the cell is stretched by the flow. The threshold of wrinkles emergence is given by a single dimensionless number relating the effects of shear stress over shear membrane elasticity whatever the nature of the membrane and its bendability over four orders of magnitude. Our experimental set-up allowed us to observe the profile of the wrinkles by bright field microscopy and to analyse quantitatively the evolution of the wavelength with the membrane thickness. Near the threshold, the wavelength increases with the square root of the membrane thickness, in accordance with the scaling law developed by Cerda and Mahadevan (Nature, 2002).



Substrate Dependent Self-Propulsion and Diffusion of active Enzymes

Amit Singh Vishen,[1] Madan Rao,[2] and Jacques Prost[1]

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We model active enzyme as a deformable dimer with fluctuating forces acting on the colloids due to the nonequilibrium binding and unbinding of the substrate to the enzyme. Consistent with recent experimental observations, the activated dimer shows self-propulsion and enhanced diffusion whose magnitude depends on the substrate concentration. This is a consequence of the nonequilibrium fluctuations and the hydrodynamic interactions that introduces multiplicative noise in the description of particle positions.

Autophoretic motion in three dimensions

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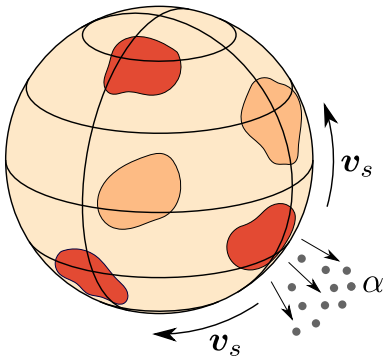
Catalytic particles are now well established as model system to address the properties of living and active matter. The mechanism of propulsion of individual catalytic particles relies on the phoretic motion in self-generated gradients. These may involve electric field (electrophoresis), temperature field (thermophoresis) or chemical concentration (diffusiophoresis). While the underlying formalism holds for all these types of motion, we focus our attention here on the latter case. The concentration gradients are typically produced by covering the surface of the body by a layer of catalyst. The non-uniform concentration field along the surface drives a diffusive flow, leading to an effective slip-flow on the surface of the particle. In result, motion of the particle itself is induced. The effectiveness of the catalyst is quantified by the chemical activity of its surface. The resulting surface slip flow is proportional to the local concentration gradient via a mobility coefficient, which is related to the details of the local particle-solute interaction potential. These two material properties – activity and mobility – fully characterise the flow generated on the surface.

The classical generation of motion by patterning can be achieved chemically in the so-called Janus particles by coating a cap of the spherical particle by a layer of catalyst. This idea has inspired a number of experimental realisations. To a certain degree, the particles can be controlled by external fields to mimic bacterial run-and-tumble motion, but typically their motion consists of straight paths with rotational diffusion being the dominant reorientation mechanism. The need for designing rotational phoretic swimmers has led to the idea of Janus particles conjoined in dimers capable of propelling on helical paths. Rotational motion, however, can also be achieved with a perfectly spherical particle, provided that an asymmetric coating pattern is used.

Inspired by recent experimental advances and ideas, we develop the mathematical formalism capable of predicting the translational and rotational velocity of a spherical phoretic particle with a given surface activity and mobility coverage. Following the classical framework, we model the surface activity by imposing a local chemical flux boundary condition on the surface of the particle. We assume that the diffusion of solute molecules is fast compared to advection and reaction rates and thus consider the limit of vanishing Péclet and Damköhler number for the solute. By expanding the activity and mobility in spherical harmonics, we calculate the resulting surface slip flow which drives the motion and the swimming kinematics. Next, introduce a conceptually simpler patch model in which the motion is induced by pairs of interacting patches of activity and mobility. Due to the bilinear mathematical nature of the flow generation problem and the associate boundary conditions, the interaction of patches can be superposed to predict the motion resulting from a given collection of point sources and patches of activity. Considering finite-sized domains instead does not change the qualitative picture but only modifies the quantitative characteristics of motion. We demonstrate the basic ingredients needed to program the particles to move along straight lines, circles, and arbitrary helical trajectories.



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Control of the morphology and dynamics of migrating cortical interneurons by topographical cues

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In mammalian embryos, cortical interneurons travel long distances among complex three-dimensional tissues before integrating into cortical circuits. Various molecular guiding cues involved in this migration process have been identified, but the influence of physical parameters remain poorly understood. In the present study, we have investigated *in vitro* the influence of the topography of the microenvironment in the migration of primary cortical interneurons released from explants dissected from mouse embryos.

We found that arrays of 10 μm PDMS micro-pillars, either round or square, influenced both the morphology and the migratory behavior of interneurons. Strikingly, most interneurons exhibited a single and long leading process oriented along the diagonals of the square pillared array, whereas leading processes of interneurons migrating in-between round pillars were shorter, often branched and oriented in all available directions. Accordingly, dynamic studies revealed that growth cone divisions were twice more frequent in round than in square pillars. Both soma and leading process tips presented forward directed movements within square pillars, contrasting with the erratic trajectories and more dynamic movements observed among round pillars. In support of these observations, long interneurons migrating in square pillars displayed tight bundles of stable microtubules aligned in the direction of migration.

Overall, our results show that micron-sized topography provides global spatial constraints promoting the establishment of two different morphological and migratory states. Very remarkably, both states belong to the natural range of migratory behaviors of cortical interneurons, highlighting the potential importance of topographical cues in the guidance of these embryonic neurons, and more generally in brain development.

Collective cell migration under a 3D spatial confinement

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The growth of epithelial tissues in confined microenvironment is essential for the development of lumens in the human body. However most of the prior studies investigating the role of physical cues on collective cell migration employed two-dimensional (2D) flat culture systems that do not replicate out-of-place spatial confinements encountered in complex physiological environments. To address this issue, we studied the coordinated migration of epithelial cell sheets in microchannels of widths ranging from 100 to 300 μm for mimicking three-dimensional (3D) microenvironments. We observed that the cell density decreases from the rear to the front of the tissue, whereas the mean cell area conversely increases, independently of the channel dimension. Our findings show that the migration velocity increases with the channel widening but drops significantly with time. Interestingly, we demonstrate that the jamming transition from a solid-like to a fluid-like state is not controlled by the cell density but rather by the strengthening of cell adhesions. Altogether, our findings provide insights into the emerging migratory modes for epithelial migration and growth under 3D spatial confinement, which are reminiscent of the *in vivo* scenario.

Flagellum beating and membrane remodelling for gamete fusion in mammalian fertilization

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In spite of increasing fertility troubles in modern society, gamete fusion mechanisms are still not elucidated. To date no protein has been identified yet as the bona fide fusogen in mammals, but three gamete membrane proteins –egg Cd9 membrane organizer, sperm Izumo1 and egg Juno adhesion proteins– have been proved to be mandatory for fusion. Moreover, performing individual in vitro fertilization assays on mouse (one sperm, one egg), we have recently discovered that gamete fusion is strictly correlated to an oscillatory constraint, imposed to the egg plasma membrane by the means of an oscillating up-and-down movement of the sperm head on it, this movement resulting from a specific beating mode of the sperm flagellum. Gamete fusion therefore appears to depend on a pool of factors –adhesion and organizer proteins and mechanical constraints–which play a role ahead of fusion, during the early minutes of the gamete encounter at their plasma membrane level, to control gamete fusion. Understanding the role of these factors and their interplay during fertilization require to image in real time and with high spatial resolution the gamete interface from the onset of their contact. This it is not an easy task because the high motility of sperm and the extended surface of the egg membrane make it unpredictable the location of gamete interaction. Performing Individual in vitro fertilization assays in a microfluidic device designed to lift these barriers, we have imaged fertilization in real time with submicrometer resolution from the onset of gamete contact to full sperm DNA decondensation into the egg cytoplasm. Following the dynamics of egg Cd9, we have identified a causal link between the mechanical constraint due to specific sperm oscillation and an increasing densification of Cd9 that leads to the formation of a micro platform highly enriched in Cd9 on which gamete fusion is initiated. Cd9 recruitment and subsequent fusion fail if flagellum has not the right beating mode or if Izumo1/Juno interaction is inhibited. These results suggest that gamete fusion is the culmination of a membrane interaction process during which, thanks to an accurate orchestration of these essential factors, membranes progressively acquire the configurations prone to fuse.

Structural Characterization of Biomembranes: the Role and Impact of Composition

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The structural characterizaton of lipid bilayers presents fundamental interest both in physics, for the study of thin fluctuating soft layers, and in biology, for the understanding of the function of biological membranes. This represents still a challenge: performing measurements on few nanometer thick, soft, visco-elastic and dynamic systems is close to the limits of the available tools and methods.

Neutron scattering techniques are rapidly developing for these studies. Since many biological processes occur at interfaces, the possibility of using neutron reflection to study structural and kinetic aspects of model as well as real biological systems is of considerable interest.

The most effective use of neutron reflection involves extensive deuterium substitution and this is becoming more and more an available option in biological systems in general and lipid bilayers in particular [1]. The use of deuterated lipid extracts presents relevant differences both with the hydrogenated counterpart and with synthetic systems [2,3].

The talk will review some progress made in the last few years by using neutron scattering at the ILL in the structural characterisation of biomembrane systems, efforts to build and characterize more and more complex systems [2-4], the impact in health related studies [4-6], and will provide perspectives for future developments [7]. It will aim at highlighting neutron reflectometry as a versatile method to tackle questions dealing with the understanding and function of biomembranes and their components. The impact of composition on the structure will be highlighted.

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C. elegans elongation: assessing the contribution of geometry, pre-stress and active stress

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The role of the actomyosin network is investigated in the elongation of *C. elegans* during embryonic morphogenesis. I will present a model of active elongating matter that combines pre-stress and passive stress in non-linear elasticity. Using this model we revisit recently published data from laser ablation experiments to account for why cells under contraction can lead to an opening fracture. By taking into account the specific embryo geometry, we obtain quantitative predictions for the contractile forces exerted by the molecular motors myosin II for an elongation up to 70% of the initial length. This study demonstrates the importance of active processes in embryonic morphogenesis and the interplay between geometry and nonlinear mechanics during morphological events. In particular, it outlines the role of each connected layer of the epidermis compressed by the apical extra-cellular matrix that distributes the stresses during elongation.

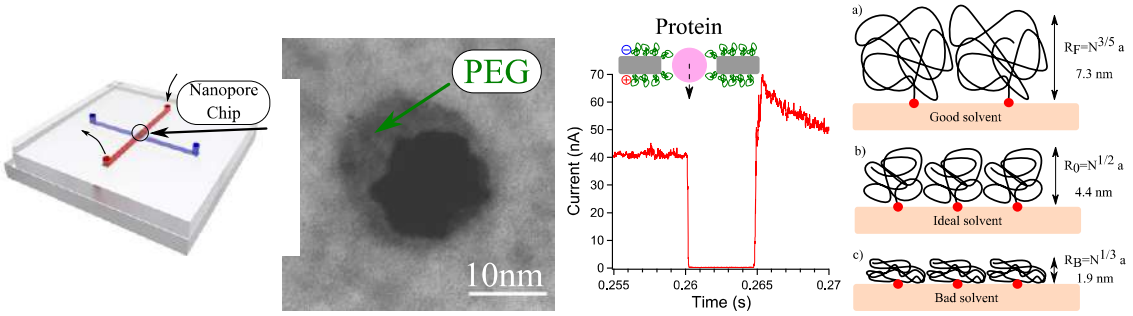
Polymer chains in confined media

Jean Roman, Olivier Français, Nathalie Jarroux, Gilles Patriarche, Juan Pelta, Bruno Le Pioufle and Laurent Bacri

Nanopores, coupled with an electrical detection method, represent a powerful tool to answer fundamental or applied problems in biology and biotechnology at the level of the single molecule. [1] This technique associated with a proteic channel holds great promise in fast DNA sequencing, [2,3] or peptide detections. [4,5]

In the same time, the design of biomimetic nanopores based on pierced solid state membrane is promising to develop new devices. [6–8] However, the control of these surfaces characterized by a high energy remains a challenge for biology applications. Then, we propose to graft a polymer brush on these membranes, integrated in a microfluidics device, to increase their life time. [9] The viability of these devices is demonstrated through the detection of nanoparticles and proteins, opening the way for new applications.

At the fundamental level, these devices allow to probe the dynamics of polymer chains, [10] polyelectroytes [11] or proteins [12] through confined media. Recently, we have characterized the conformations of polymer brushes in confined media governed by volume (ions) or surface (counter-ions) interactions according to the concentration and nature of the ionic solution and the quality of the solvent. [13]



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Measuring mechanical properties of tumour spheroids with acoustic waves

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Cellular spheroids have become important tool to study the mechanobiology of cancer. Their 3D structure allow describing *in vitro* avascularized tumors in a reductionist manner. Their complex structure (poroelasticity, metastability) yields an intricate frequency-dependent behaviour. The aim of our project is to use acoustic waves to investigate the mechanical properties of spheroids at various frequencies using a multi-scale acoustic probe.

My work in the first year of my PhD focused specifically on the intermediate ultrasonic range going from 10 kHz to 300 MHz by using laser-generated acoustic waves. In our experiment, the spheroid is sandwiched in-between two metalic plates. Following the absorption of nanosecond laser pulses in the bottom plate, the thermoelastic expansion generates a broadband acoustic pulse that propagates through the spheroid. The transmitted acoustic pulse is monitored in the top plate with an interferometer. We measured a speed of sound of 1642 m/s at room temperature in a HCT116 spheroid. We also determined the acoustic impedance and bulk modulus which were respectively 3.117 MRayl and 5.10 GPa. These values give access to the average stiffness and density of the spheroid.

The next step of our work will be to include temperature regulation in our experimental setup to make it more relevant from a physiological viewpoint, and compare with data acquired at quasi-static and hypersonic frequencies.

Biomimetic emulsions to probe the mechanics of tissues

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Emulsions are used for a wide range of applications: from the study of biomimetic tissues to directed self-assembly, or the investigation of jammed matter physics. In particular, we design biomimetic emulsions that are stabilized with phospholipids and functionalized with adhesive proteins in order to reproduce cell-cell interactions. The assembly of such droplets in 3D is mostly controlled by the balance between their adhesion energy, which can be tuned through the binders grafted on the surface, and the cost of their elastic deformation. For instance, adjusting the droplet interactions through carefully chosen DNA sequences allows for their self-assembly into structures with controlled geometry and sequence. Conversely, the pathways of droplet self-organization in 3D, according to their binding energy, can shed light onto the self-organization of cells in tissues during morphogenesis. We thus use those systems to study the mechanical behavior of tissues under mechanical perturbations. To this end, we apply external compression to adhesive emulsions and study their elasto-plastic response as a function of adhesion energy, packing or perturbation dynamics. Finally, because the emulsions are mechanically close to biological tissues, we also use them as probes for local cellular forces in developing tissues. Biomimetic emulsions are therefore a useful system to explore the pathways of biological self-assembly and quantify the forces at stake during morphogenesis.

Merits and limits of surface and line tensions to understand the shape of epithelial cells

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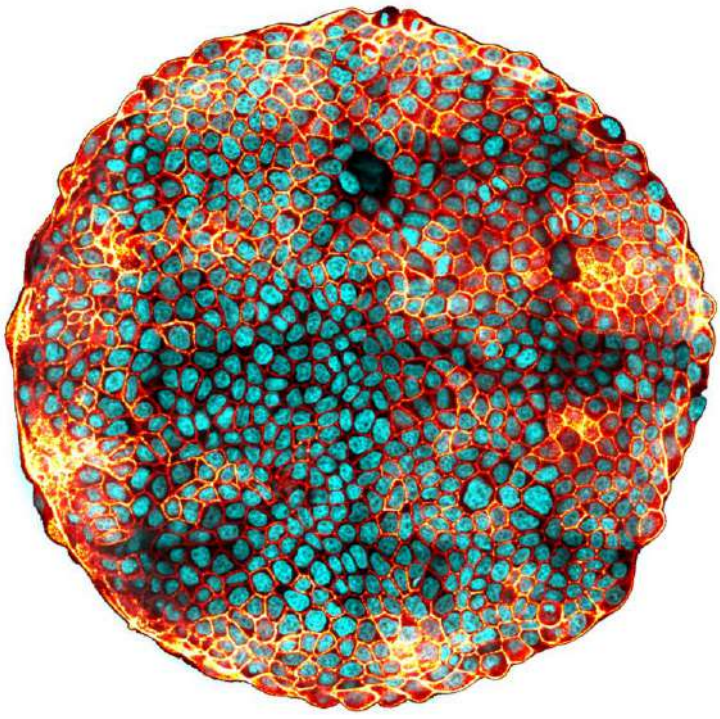
Building a physical framework to account for the shape of cells in epithelia is an important challenge to understand various biological processes, such as embryogenesis. As a PhD student, I aim to understand how surface tensions and line tensions shape epithelial cells using microstructured substrates, confocal fluorescence microscopy, force inference and theory.

I culture epithelial cells on either flat or curved substrates and I explore the influence of the curvature of the substrate on the shape of these cells, especially the resulting thickness of the epithelial sheet.

The model I propose to account for our measurements aims at computing the shape of individual cells within an epithelium using differentiated surface tensions for the different interfaces (cell-cell and cell-substrate surface tensions) and an apical line tension.

I combine these measurements with force inference within the tissue using both the shape of cells in the epithelial sheet plane and the shape of the intercellular junctions within the thickness of the epithelium.

I thus can infer which parameters determine the three dimensional shape of the cells and I can evaluate values for the different interfacial tensions by comparing the three-dimensional cell shape measurements with the prediction of the model and the prediction of force inference.



Fluid mechanics of amniote gastrulation

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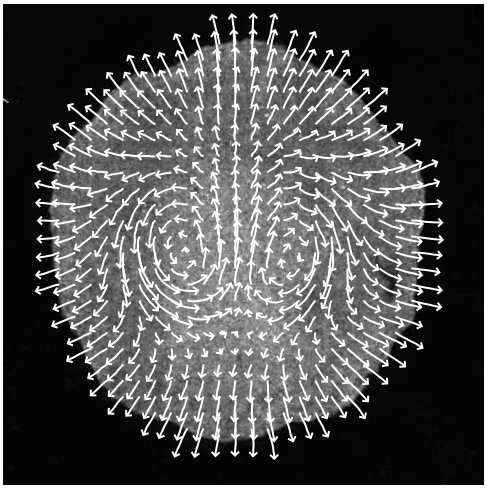
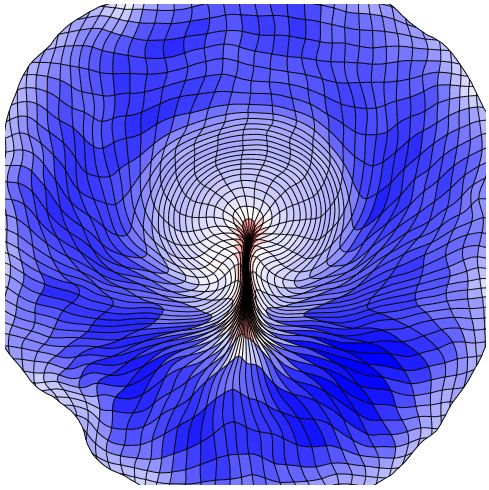
The early avian embryo exhibits vortex-like tissue movements, which lead up to the formation of the primitive streak. Although these movements are strongly reminiscent of fluid motion in a circular box, this was never pursued beyond analogy. Through live imaging, image analysis, and quantitative modeling, we now show that these large-scale movements are driven by graded contractile forces along the circular border between the embryonic and extra-embryonic tissues, both rendered fluid by cell division. This tensile ring is characterized by elongated cell shapes, enrichment of actin and myosin into supracellular cables, and revealed by laser ablation experiments. Remarkably, the model predicts, and experiments confirm, that the shaping of the embryo is largely independent of boundary conditions. Our results provide an integrated mechanical picture of amniote gastrulation, and set the stage for an investigation of embryonic self-organization, as evidenced by classic embryology experiments.





preprint: biorxiv:412767

Buckling of epithelium growing under spherical confinement

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Many organs, such as the gut or the spine are formed through folding of an epithelium. Whereas genetic regulation of epithelium folding has been investigated extensively, the nature of the mechanical forces driving this process remain largely unknown. It is generally supposed that mechanical heterogeneities drive epithelial invagination during development. Here we use a reconstituted system approach to show that growing cell monolayers on the inner surface of spherical elastic shells can spontaneously fold in the absence of local cues. By measuring the deformation of the shell and employing the mechanical properties of the cell-shell composite, we inferred the forces acting within the monolayer. Using elastic theory at different scales, we found that the compressive mechanical stresses arising within the cell layer quantitatively account for the observed folding, that is the geometry and statistics of monolayer morphology and the corresponding force distributions as a function of the spherical shell elasticity. Our study shows that forces arising from epithelium growth are sufficient to drive folding as during gastrulation or neurulation.

Theory of Turing pattern formation in active biphasic tissues

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The formation of self-organized patterns is key to the morphogenesis of multicellular organisms, although a comprehensive theory of biological pattern formation is still lacking. Here, we propose a biologically realistic and unifying approach to emergent pattern formation. Our biphasic model of multicellular tissues incorporates turnover and transport of morphogens controlling cell differentiation and tissue mechanics in a single framework, where one tissue phase consists of a poroelastic network made of cells and the other is the extracellular fluid permeating between cells. While this model encompasses previous theories approximating tissues to inert monophasic media, such as Turing's reaction-diffusion model, it overcomes some of their key limitations, permitting pattern formation via activator-inhibitor dynamics with equal diffusivities or any two-species biochemical kinetics thanks to mechanically induced cross-diffusion flows. Moreover, we unravel a qualitatively different advection-driven patterning instability which, in particular, allows for the formation of a single mode pattern scaling with tissue size. We discuss the relevance of these findings for morphogenesis.

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Dividing a large deforming tissue into unitary regions

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Within developing tissue, local variation of cell proliferation rage, cell motility, cell shape change, orientation of cell division and rearrangements, and other cell behaviors promote the formation of complex shape. However the spatial regulation of the cellular processes are not clear in many cases, and thus a major challenge is to define objective methods to find the different subregions of the tissue to study tissue-scale morphogenesis. The *Drosophila* notum offers a very nice model system to explore such questions as the tissue show high heterogeneity in term of cell dynamics and morphogenetic movement (Bosveld et al., 2012). Furthermore, we previously developed a framework to quantitate local tissue deformation rate and how cellular processes, including cell division, cell rearrangement, cell shape change, and cell delamination, contribute to the tissue deformation (Guirao et al., 2015). The framework allows to rigorously relate cell dynamics and overall tissue morphogenesis at each point in the tissue. Here we propose a method to divide a tissue automatically based on the local deformation rate and cellular processes, so that the obtained regions contain cells behaving more similar to each other inside the region than to those in other regions, i.e., homogeneous regions. This was achieved by combining several approaches including region growing algorithm of image segmentation, label propagation on a consensus matrix of cluster analysis, and cellular Potts model which simulates a dynamics of cellular tissue. Also, we evaluated the homogeneity of given regions by silhouette analysis, a tool of cluster analysis. By the quantitation of morphogenesis and the automatic tissue segmentation, developing *Drosophila* notum was divided into a large anterior, posterior, lateral posterior, and middle boundary regions with much higher homogeneity compared to grid regions given by tissue axes. The method therefore is an important step towards defining in an objective manner distinctive morphogenetic regions with in a tissue. This will greatly facilitate the analysis of complex tissue shaping and the biochemical and bio-mechanical cooperative regulation driving tissue morphogenesis.

Title: Microcirculation of Red Blood Cells in biomimicking splenic slits

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The blood circulation in the vascular system is a physical tour de force. Red blood cells (RBCs), the most abundant of the blood components, are responsible for distributing oxygen throughout the body. To fulfill this task RBCs are known to be highly deformable, a characteristics that allow them to pass through capillaries thinner than their size. RBC deformability is periodically monitored by the spleen: those unable to pass through the splenic inter-endothelial slits (IESs) are entrapped and destroyed by macrophages[1]. This can be considered as a *fitness test*. In sickle cell disease, RBC deformability is altered, this impaired deformability of sickled RBC promotes their trapping upstream in the open circulation of the spleen by the narrow IESs [2]. Thus RBC deformability may play a crucial role in splenic dysfunction and hemolytic anemia.

Nowadays, the mechanisms of the passage of RBCs through these IESs are still poorly understood. Thus our objective is to quantitatively study the dynamics of RBC circulation through IESs.

We recently developed a new on-chip PDMS device containing high aspect ratio slits with sub-micrometer width replicating the physiological dimensions of splenic slits [3]. This microfluidic device allows us to mimic the splenic slit geometry and flow conditions. By challenging RBCs through the chip, we observed novel modes of deformation. Moreover, we quantitatively study passage and deformation dynamics as function of physical parameters (slit dimensions, pressure drop) and biological parameters (hydration state). Finally, the experimental results are compared with a theoretical and computational study to investigate which parameters are crucial for an efficient crossing process.

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Rigidity-induced margination

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Due to their unique shape and mechanical properties, red blood cells (RBCs) undergo a so called *lift force* in the flow pushing them away from the vessel wall. It leads to creation of "cell-free layer" (CFL) at the periphery of the flow. The CFL has lower viscosity compared to the core of the blood flow which serves as a lubrication, facilitating the passage of blood in microvasculature. And while RBCs have tendency to move towards centerline of the flow, other blood components, such as white blood cells (WBCs) and platelets, migrate towards walls of blood vessels. This process is commonly referred to as *margination*. Margination in blood is a phenomenon of great physiological importance and can have applications in cell separation and targeted drug delivery. However, precise mechanisms involved in this process remain unclear. Margination appears to be a complicated process depending on many parameters such as size of the marginating particles, their shape, volume fraction of RBCs and etc.

In our research we study rigidity based margination in binary suspension of deformable and stiff particles. For this purposes we observe and quantify blood flow consisting of 2 populations of red blood cells – healthy and rigidified with cross-linking agent (glutaraldehyde) – in microfluidic channels in case of different flow rates, hematocrits and vessel geometries. Using such experimental model allows us to examine margination caused exclusively by rigidity contrast between to subpopulations of particles. In contrast to previously performed experimental studies where imaging of marginating particles was conducted by adjusting the focal plane in the middle of the microchannel, we used confocal microscopy to reconstruct 3D distribution of labeled cells across the section. In our work we accent following topics: (i) We investigate margination of rigidified RBCs in microchannels of different geometries and we demonstrate possible margination paths in rectangular channels, cylindrical capillaries and confined microchannels, imitating pseudo 2D blood flow. (ii) We show how distribution of rigid cells changes in the channels lengthwise and how margination reaches the saturation for different hematocrit levels. (iii) Effect of varying flow rate was studied for wide range of values and we conclude non-linear relationship between velocity and margination level.

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The mechanical feedback between mucus and active cilia dynamics drives the self-organisation of reconstituted bronchial épithelium

Despite a rich clinical corpus of the mucociliary clearance, the physical mechanisms underlying the transport of mucus remain poorly understood. Indeed, various intricate mechanisms are involved such as long-range hydrodynamic interactions, active collective ciliary motion, and the complex rheology of mucus. The whole system is complexified due to the mechanical coupling between the cilia and the mucus, and due to its multiscale nature: from the micrometric scale of the active cilia, to the centimetric scale of the transport of mucus.

Our work merges three seemingly diverse, thriving research areas in biomedical inspired physical science: active matter, topological soft matter and cell biophysics (1). Here we use an *in-vitro* reconstituted human bronchial epithelium which captures the phenotype of in-vivo tissues such as ciliogenesis and production of mucus. We present how active cilia self-organize and coordinate their beating in terms of directions and phases, to lead to the formation of deterministic and periodic fluid flow patterns, called mucus swirls, up to the centimetric scale. By considering the epithelium as a nematic material, i.e. which exhibits a long range orientational order, we present the spatiotemporal evolution of the nematic order during the ciliogenesis. Specifically we demonstrate how the mechanical coupling between the ciliated cells and the mucus drives the creation and annihilation of topological defects overtime and how this affects the efficiency of the mucus transport. We show that in absence of mucus the bronchial epithelium loses its orientational order. The creation or destruction of topological order and the resulting improvement/alteration of the mucus transport is of great interest in the context of wound healing and recovery from inflammation, which are both characteristic symptoms in severe chronic respiratory diseases.

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Mucus rheology and cilia coordination of the human bronchial epithelium

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The bronchial epithelium mucociliary function ensuring the lung continuous clearance relies on mucus rheological properties and cilia beating coordination. We focus on two points: first, the biochemical and physical parameters affecting the mucus viscoelastic properties; secondly, the cilia coordination and its coupling with the mucus.

We performed rheological experiments on mucus extracted from Air Liquid Interface cultures of bronchial epithelium reconstituted from bronchial biopsies. We combine standard macro-rheology to micro-rheology performed with optical tweezers, to quantify the mucus flowing behaviour at two scales: the mucus layer thickness and the cilia or bacteria scale.

Macro- and micro-rheology give different results: an elastic plateau (1-2 Pa) at the macro-scale; a viscous flow (10-3-10-2 Pa) at the micro-scale but with an important adhesion and elasticity at the interfaces. We also perform original experiments using optical tweezers directly on the epithelium, to access the viscoelastic response in the various mucus layers. We obtain an increased elasticity in the vicinity to the epithelium.

Finally, the study of the physical mucus properties coupled with the specific methodology we developed to quantify cilia activity, coordination and mucus velocity field, should help to evaluate the efficiency of the mucociliary function and to understand the mechanisms of clearance.

Design of a full experimental microfluidic and microscopic toolbox for wide spatiotemporal study of plant protoplast development and physiology.

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Because plant cells are encased within a pectocellulosic wall, plant morphogenesis cannot rely on cell migration inside the organism: differentiation of a plant cell depends more on its spatial positioning within the tissue than its clonal origin. Protoplasts are basic plant cells units in which the pecto-cellulosic cell wall has been removed, but the plasma membrane is intact. One of the main features of plant cells is their strong plasticity, which in some species, can be very close from what is defined as cell totipotency. In addition to mechanical and chemical constraints, cells experience hormonal and metabolic fluxes that can be both inhomogeneous and polar, and drive differentiation.

Culture methods and differentiation protocols used plant physiology and plant biology usually involve macroscopic vessels and containers that make difficult, for example, to follow the fate of the same protoplast all along its full development cycle, but also to perform continuous studies of the influence of various gradients. Thanks to their ability to recreate in-vitro environments at the cellular level that mimic a tissue, and also observing in real-time subcellular and cellular modifications that take place during growth or development, microfluidic devices have been used as culturing tools for insect, mammalian, and bacterial cells. In the plant science however, few microdevices have been developed so far. In this talk, I will present the complete microfluidic toolboxes we developed for the short-term and long-term study of protoplasts differentiation and moss physiology.

The role of adhesion on the microfluidic flow of biomimetic tissues

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The aim of this study is to design a biomimetic cohesive tissue with a tunable degree of internal adhesion, with the final goal of understanding the role of cellular adhesion on the flow of epithelial tissues. The artificial tissue is obtained by the controlled assembly of red blood cells [1] or giant unilamellar vesicles [2], which constitute two complementary model systems for cells. Intercellular adhesion is mediated by the inclusion of ligand-receptor complexes [3], which allows us to control the occurrence (or not) of cell-cell assembly, as well as the typical size of the formed aggregates. Aspiration experiments in microfluidic constrictions are performed in order to characterize the flow behavior of the designed tissues. Our velocimetry results show that, depending on the aspect ratio between the aggregate and the constriction size, the tissue adopts different strategies in order to advance through the constriction: aggregate reorientation, flow localization, or cell deformation.

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Adhesive emulsions under pressure

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We use novel tissue-mimetic systems to understand the physical basis of collective remodeling in biological tissues. In particular, we will study how the interplay between adhesion and forces controls the emergence of tissue architecture during morphogenesis. In order to work in a simplified framework, we design biomimetic emulsions that were shown to reproduce the minimal mechanical and adhesive properties of cells in biological tissues [1]. The adhesive properties of the system are controlled through depletion attraction forces between droplet surfaces, by tuning the concentration of SDS micelles in the continuous phase [2]. We study the mechanical behavior of such emulsions under lateral compression. To this end, we flow the emulsions in 2D through microfluidic constrictions with controlled geometries. Image analysis allows us to characterize the elasto-plastic response of the emulsions under such perturbations. We thus quantify the level of deformation of the droplets in the channel (elastic response) and monitor irreversible droplet rearrangements (plastic response). We characterize the emulsion behavior as a function of parameters such as the attraction forces between droplets or the volume fraction of the emulsion in the channel.

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GDR CellTiss 2018

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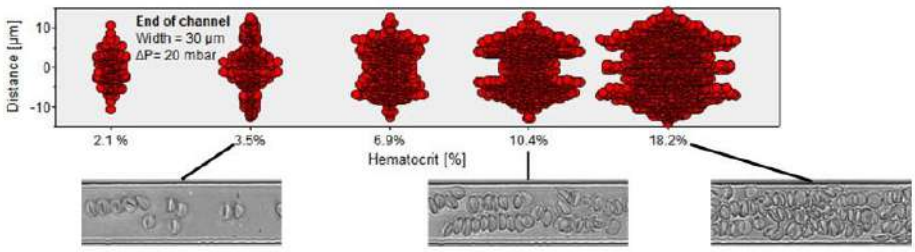
Red blood cells in confined flows: structuration in bands and trains

In the vascular microcirculation various organization processes occur: first, the blood flow displays a region devoid of red blood cells (RBCs) near the vessel wall, called the cell-free layer [1] ; second, the most rigid blood cells (e.g. white blood cells and platelets in healthy blood, and rigid malaria-infected RBCs in blood from malaria patient) segregate to the walls while flowing in wide channels, a process called margination. While the structure of the flow (fluctuation of the local RBC concentration, RBC radial distribution) has been studied theoretically [2], few experiments have been reported in which mostly one-dimensional channels were used, thus constraining RBCs to move in single files [3].
Here we study RBC suspensions in bi-dimensional microfluidic channels (10 µm in height) in which the cells are constrained in a single layer and submitted to controlled flow and hydrodynamic stress. RBC flow structure is investigated using ultrafast video-microscopy. We aim in determining which physical parameters, among RBC concentration (hematocrit, Hct), applied pressure drop, channel geometry, and RBC rigidity, are controlling the flow structure.
At the channel entrance, healthy deformable RBCs are initially scattered all over the cross-section. They then clearly organize while flowing through the channel: at the channel end (5 mm in length), RBCs are laterally distributed into *bands* parallel to the channel walls, with the expected cell-free layer; moreover, they form dynamic aligned clusters that we call *trains* (figure). On the other hand, RBCs rigidified with glutaraldehyde do not cluster, preferentially move close to the channel walls, and mainly display tumbling motion as predicted for rigid disks [4]. Additionally, the structuration is lost when the channel height is increased and RBCs are not constrained in 2D anymore. Our results emphasize the ability of deformable RBCs to organize under 2D-confined flow into parallel structures and aligned clusters and show that the RBC flow structure is highly sensitive to concentration and wall effects.

This work has been carried out thanks to the support of the A*MIDEX project (n° ANR-11-IDEX-0001-02) funded by the «Investissements d'Avenir» French Government program, managed by the French National Research Agency (ANR).



RBC organization in a 30-µm wide channel.
Top : lateral position of RBCs as function of RBC concentration (hematocrit, Hct). Bottom : Images of RBCs flowing in the channel at various Hct. Train clusters are visible for Hct ≤ 15%.

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Caveolin-assisted sphingolipid transport to the plasma membrane

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Lipid and protein sorting are crucial processes that maintain unique biophysical and biological properties of different organelles. Nevertheless, little is known about mechanisms behind lipid sorting. Sphingomyelin (SM) is synthesized at the trans Golgi network (TGN) and transported to the plasma membrane (PM) via an uncharacterized pathway. SM enrichment in transport carriers cannot be explained by a curvature-based mechanism of lipid sorting due to its property to form stiff membranes. A mechanism of protein-mediated lipid sorting has been proposed, taking advantage of proteins' affinity for curved membranes and specific lipids. One of the proteins enriched in the same secretory pathway is caveolin, which shuttles between the Golgi and the PM where it forms cup-shape, SM-cholesterol-enriched domains called caveolae. The assembly process is initiated by the export of caveolin-enriched vesicles from the Golgi but little is known about this first step except from a critical role of lipids in caveolin oligomerization.

The central goal of this project is to determine the role of caveolin in SM trafficking from the TGN to the PM and to decipher the molecular mechanisms behind caveolin assembly using a bottom-up approach. We purified caveolin 1 (Cav1) and reconstituted into small unilamellar vesicles, what was shown by density centrifugation and visualisation of proteo-liposomes by cryo-electron microscopy. Additionally, we analysed Cav1 reconstitution in presence of cavtratin – peptide disrupting Cav1 oligomerization. Without cavtratin Cav1 creates multilamellar, undulated structures, while in its presence unstructured lipids-protein aggregates are observed. In parallel ours *in cellulo* studies showed differential SM localization in MLEC Cav1 KO cells, indicating that Cav1 play a role in SM trafficking. Our ongoing studies aim to reconstitute Cav1 into giant unilamellar vesicles, where the recruitment of Cav1 and SM to curved membranes will be investigated, complemented by quantitative measurements of membrane mechanics.

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Importance of morphological and mechanical properties of myoblasts in muscle cell differentiation

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Myoblasts fusion is a key cellular process to form and repair the multi-nucleated muscle fibers that make up the skeletal muscle. Despite its importance, the mechanisms underlying this process are still not well understood [1]. The improvement of the contractile forces generated by skeletal muscles requires to better understand the role of the myoblast morphology and the spatial distribution of the cytoskeleton during the fusion process.

To address this challenge, we imposed different geometries to individual C2C12 myoblasts using protein micropatterns deposited on soft hydroxy-polyacrylamide hydrogels [2]. The orientation of the actin network was quantified with confocal microscopy, whereas myoblasts contractile forces were determined with traction force microscopy (TFM).

The maximal traction force increases with the distance between the cell extremity and the center of mass, leading to higher mechanical outputs for elongated myoblasts.

Moreover, our results demonstrate that the contractile properties of myoblasts are important in the process of differentiation. Indeed, by using blebbistatin and latruculin B, we show that a loss of contractility of myoblasts has an impact on the differentiation.

On the basis of these findings, we propose a conceptual framework for the mechanical regulation of myoblasts during their fusion.

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How cell-cell interactions modulate the collective migration of epithelial cells

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In a large number of epithelial tissues, cells migrate collectively within a compact cohesive monolayer. This characteristic is necessary to ensure the barrier role of epithelia and relies on the formation of cadherin-based intercellular adhesions. Deregulation of cadherin adhesions is largely associated with tumor progression and metastasis in a large number of cancers. However, the exact role of cadherin adhesions in motile forces, which are required for collective migration of healthy and tumor epithelial cells, remains unclear. By combining fish epithelial explants with adhesive microstripes (2D) and microchannels (3D), we develop an original experimental microsystem for studying the role of adhesive interactions of cadherin type in epithelial cell sheets. Adhesive microstripes (2D) and microchannels (3D), both functionalized with proteins involved in integrin (cell-matrix) or cadherin (intercellular) adhesions were used to decipher the individual role of cell-cell and cell-substrate interactions. We studied the migrating behavior of isolated keratocytes (without cadherin adhesions) and models of cellular aggregates (with or without cadherin adhesions). We observed by confocal microscopy the dynamics of migration of isolated epithelial cells and cell aggregates in the form of cell trains. Our results highlight the role of cell-cell adhesive interaction in confined 2D epithelium sheets.

Epithelial closure over gradients of adhesiveness

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The closure of gaps in epithelial tissues is a crucial step during developmental and repair processes. Gap closure has been widely studied using two-dimensional surfaces coated with an homogeneous layer of adhesive proteins. However, *in vivo* epithelial cells encounter gradients of substrate-bound adhesive molecules (haptotaxis) (1). Nevertheless, most of the previous works on gap closure did not consider the role of haptotactic mechanisms (2).

To address this issue, we used the PRIMO photopatterning technique distributed by ALVEOLE Company to create circular gradients of fibronectin (FN) that vary the adhesiveness over a distance of 700 microns. First of all, we observe that the spatial density of FN controls the spreading of epithelial cells (MDCK cell type). MDCK cells attach and spread preferentially on the higher density of FN, creating a circular gap over the lower density of proteins. Then, MDCK cells proliferate and spread towards the center of the gap over the decreasing gradient of FN.

We compare the dynamics of closure of an epithelial tissue over this surface covered with a linear gradient of protein to the dynamics of closure over a uniform fibronectin coating to show that the decreasing adhesiveness only slightly affect gap closure dynamics. The distinct roles of proliferation and spreading are studied at the different steps of the closure process.

Our study demonstrates that a gradient of adhesiveness of the culture substrate induces the formation of a gap in an epithelial tissue, but in a second time cells are able to close this gap by a combination of proliferation, migration and spreading.

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Selection Dynamics in Transient Compartmentalization

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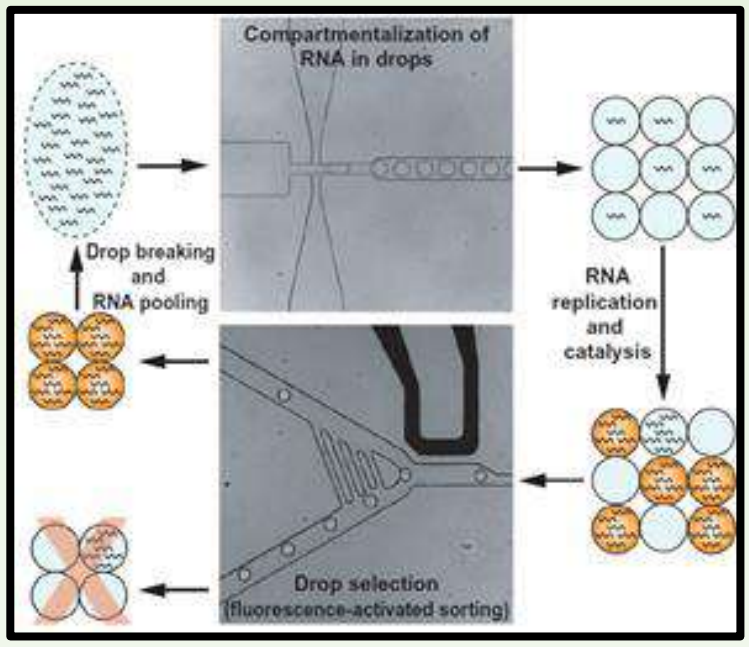
Introduction

Transient compartments have recently been shown to be able to maintain replicating functional molecules (ribozymes) and prevent a parasite takeover[1], in the context of origins-of-life scenarios. Motivated by this experiment, we show that a broad class of selection dynamics is able to achieve this goal. We identify two key parameters: the relative amplification of parasites (Λ) and the size of compartments (λ).

Protocol



Model

(I) Inoculation: Compartments are seeded with a total of n molecules, of which m are ribozymes, from a pool with ribozyme fraction x:

$$\boldsymbol{P_\lambda(n,x,m) = Poisson(\lambda,n) B_m(n,x)}$$

(II) Maturation: Initial exponential growth of ribozymes and parasites fixes the ribozyme fraction:

$$\boldsymbol{\overline{x} = \frac{m}{n\,\Lambda\, - (\Lambda - 1)\, m}}$$

(III) Selection: Full-grown compartments are selected as a function of their composition $\overline{x}$, according to a selection function $\boldsymbol{f(\overline{x})}$, which quantifies the odds of survival.

(IV) Pooling: Surviving compartments are pooled together, yielding a new pool composition x' (ribozyme fraction) which obeys a recursive relation:

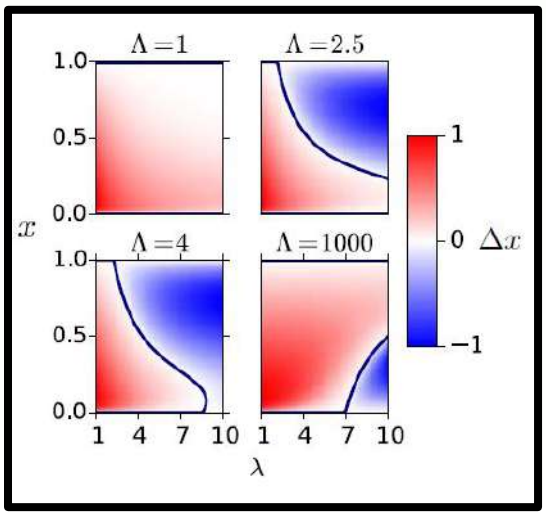
$$\boldsymbol{x' = \frac{\sum_{n,m} \overline{x}\; f(\overline{x})\; P_\lambda(n,x,m)}{\sum_{n,m} f(\overline{x})\; P_\lambda(n,x,m)}}$$

Contour Plots

We evaluate difference in ribozyme fraction:

$$\boldsymbol{\Delta x = x' - x}$$

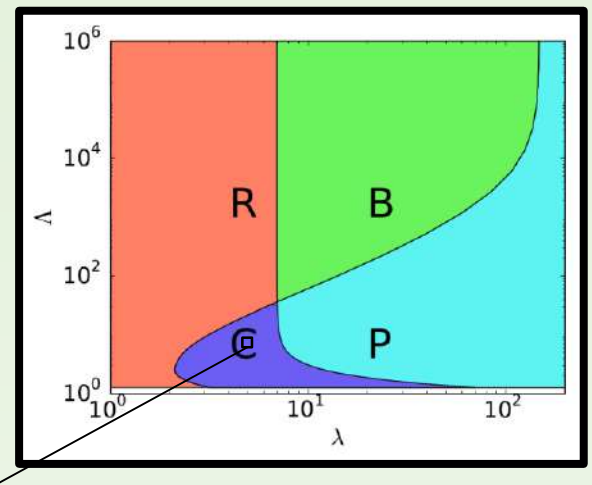
The relative amplification of parasites (Λ) and the size of compartments (λ) control the fixed point stability.

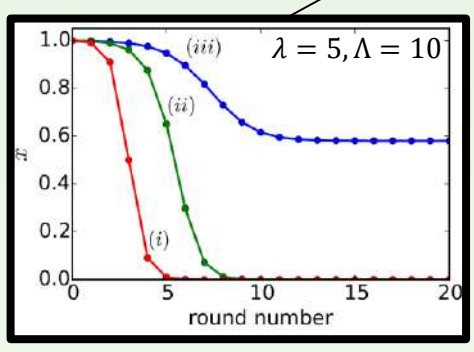


Phase Diagram

By evaluating the stability of the fixed points $x' = 0$ and $x' = 1$, we can find four phases for the selection dynamics.

- Ribozyme survival $x' = 1$ stable
- Parasite survival $x' = 0$ stable
- Bistable survival $x' = 0, x' = 1$ stable
- Coexistence $0 < x' < 1$ stable



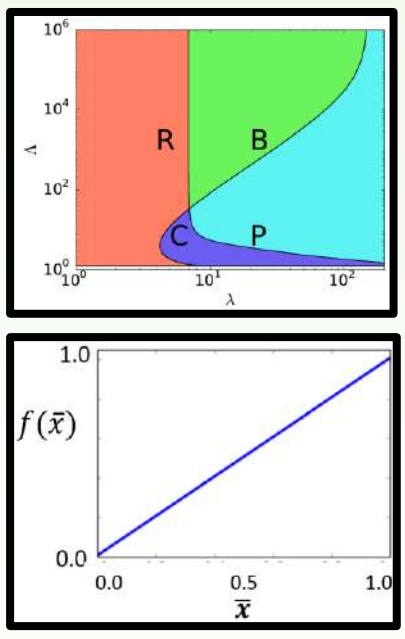


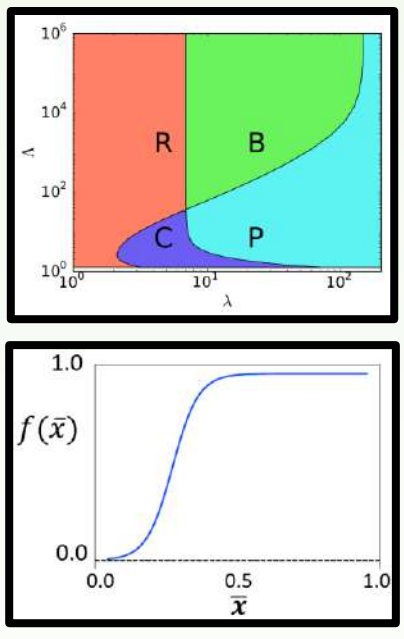
- Selection and compartmentalization
- Compartmentalization without selection
- Bulk without selection

The phase diagram shows the ultimate outcome of a selection over many rounds, exemplified here by a coexistence phase.

Universality in Selection

The asymptotes of the phase diagram depend only on the extremities of the selection function.





Outlook

- The framework can be used to study other scenarios: e.g. cooperating species
- Noise in growth can facilitate coexistence and ribozyme survival, the effect of different sources of noise may lead to rich selection behavior.
- The framework can be extended to study other selection experiments.

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Article

https://arxiv.org/abs/1802.00208

Presentation of bone morphogenetic proteins to cells at their basal side reveals their role in the initiation of cell adhesion

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There is a need to develop new biomaterials with tunable physico-chemical properties for the regeneration of large bone defects *in vivo* by inducing stem cell differentiation to bone cells. In particular, the use of bone morphogenetic proteins (BMPs) in combination with biomaterials offers promising possibilities in view of the key role of these proteins in bone regeneration [1]. Our team has already developed a thin biomimetic coating of a polyelectrolyte multilayer film made of hyaluronic acid (HA) and poly-L-lysine (PLL), which enables to physically trap the BMPs and present them to cells in a matrix-bound manner [2], meaning that the cells perceive the biochemical signal at their ventral (or basal) side and internalize the BMPs [3]. Biomaterials presenting BMP proteins in a matrix-bound manner enable to reveal so far hidden biological phenomena, notably a crosstalk between BMP receptors and adhesion receptors of the integrin family [4]. More specifically, we showed that BMP-2 physically bound to soft films induced cell adhesion and spreading through a cross-talk between integrin β3 and BMP receptor IA [4]. Recently, we developed an automated liquid handling system to deposit the layer-by-layer films in multiple well cell culture microplates. We showed using 96-well plates that the biomimetic film coatings are reproducible with >93% homogeneity inside each microwell and between microwells [5]. Taking advantage of the high throughput automated system to deposit the biomimetic films in a reproducible manner, we thought to study the effect of different matrix-bound BMPs on early cell adhesion and spreading, especially cell number and spreading area. We selected four major BMP proteins (BMP-2, 4, 7 and 9) that have important physiological roles in bone formation, eye and brain formation, fat regulation, gastrointestinal track development and cardiovascular physiology and pathology. We compared the matrix-bound BMPs loaded at increasing concentrations on the soft and stiff films for their ability to trigger cell adhesion of skeletal progenitors, the C2C12 skeletal myoblasts and human periosteum derived stem cells. We quantified the BMP-type dependency of cell adhesion and spreading and compared the different BMPs for their potential to activate the SMAD pathway, one of the hallmark of cell differentiation to bone. [6]. Our study reveals a so far hidden role of BMP receptors in the initiation of cellular adhesion.

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Microfluidic study to investigate characteristics of collective and individual motions of swimming zoospores

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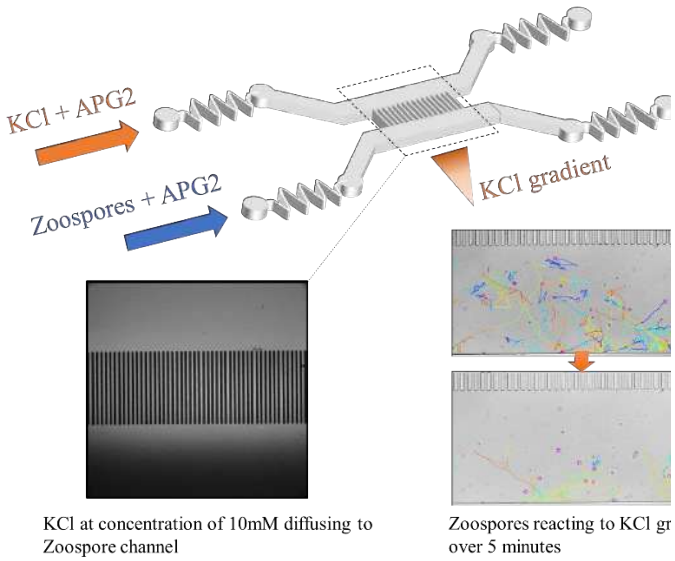
Abstract

Zoospores are flagellate swimming microorganisms that initiate pathogens and destroy plants, causing big threats to agriculture and eco-systems. Understanding their swimming mechanism and their interactions against gradients and surrounding environments becomes important. In this study, we develop a microfluidic system to investigate collective and individual motions of *Phytophthora parasitica* zoospores, a species that infects a broad range of host plants and represents most of the genus *Phythophthora*. Our system has the ability to generate a chemical gradient diffusing to a group of swimming zoospores and observe their swimming motions as well as the changes of the gradient at the same time. Our preliminary result shows that a group of *P. parasitica* react significantly against a gradient of potassium chloride. Low concentration of potassium helps reducing the speed of the zoospores and lure them away. High concentration of potassium (>3mM) causes the zoospores to change the swimming pattern to circulating around and stop moving. Moreover, when observing a single zoospore swimming in water, we achieved the characteristics of its beating flagella. The correlation between the zoospore velocity and its flagella motions can help us explain their reaction against the potassium gradient. The future work of this study will focus on the motions of an individual zoospore under potassium condition. We are also looking into the swimming behaviors of zoospores under constrained conditions with different obstacles.

a)



b)

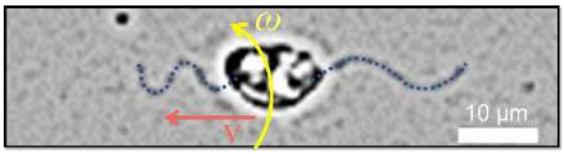


Figure: a) The microfluidic system to investigate the collective motion of zoospores under potassium gradient. b) A single zoospore captured swimming in water.

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Physics of invasive fungal growth

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The fungus *Candida albicans* is a commensal yeast that is found on mucosal surfaces of the gastrointestinal and urogenital tract in most healthy individuals. However, this organism can cause superficial as well as life-threatening systemic infections in response to alterations of its environment, and is particularly aggressive in immuno-compromised individuals. A switch from budding to filamentous growth is critical to invade host tissues [1], as well as to burst out of host macrophages.

The aim of this interdisciplinary project is to examine the biophysics of filamentous growth of this human fungal pathogen. The project uses a combination of micro-fabrication, live cell microscopy, physical measurements and modeling in order to understand how C. *albicans* adapts itself while invading.

To determine quantitative relationships between physical forces (due to turgor pressure) and cell growth, we are growing C. *albicans* in micro-chambers, composed of polydimethylsiloxane (PDMS), of different stiffness [2]. We are following C. *albicans* invasion as a function of substrate resistance, in order to study growth speed and tip shape. We are also mimicking C. *albicans* invasion by indentation of a macroscopic probe into the substrate [3], in order to understand rupture behavior (crack, friction, adhesion) of the PDMS. I have generated PDMS microchambers of different stiffness and measured their viscoelastic properties. By combining microscopic observations with rupture behavior, we will be able to quantify the internal pressure for wild type and several cell wall mutants.

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Formation and propagation of renal cysts: study in biomimetic tubular systems

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Tube geometry is altered in a wide range of diseases, from development to cancer, with cyst formation as a frequent type of deformation. We investigate the role of geometrical and mechanical determinants for cyst birth through the detailed study of renal hereditary diseases. Cyst formation in diseases such as autosomal dominant polycystic kidney disease (ADPKD) or nephronophthisis (NPH) remain imperfectly understood, in spite of their evolution towards end-stage renal failure and of the high prevalence of ADPKD. We study how diameter changes of renal tubules, initial cysts or/and disrupted flow impose continuous mechanical stress onto surrounding tissue, which locally increases the probability and frequency of new cyst formation. To that end, we developed new biomimetic systems of deformable tubes under controlled flow reproducing kidney-on-chip.

Kidney tubules exhibit a highly reproducible geometry, with conserved abrupt changes in diameter. Cysts in NPH are mainly located in this zone of change in diameter. We developed a microfabrication approach based on molding of etched tungsten wires, which can reproduce in a flexible way any change in diameter, and allows to study interconnected cell respond to differential constraints. In PDMS circular tubes with a transition between 80 μm and 50 μm diameters, we investigated the effect of the tube curvature and confinement on the morphology and orientation of renal MDCK cells, as well as the effect of shear stress simultaneously in both parts of tubes. These studies are now extended to cells models for NPH (collab. S. Saunier).

A key question in ADPKD is the exponential increase of cysts in patients, after a very slow progression from 0 to 30 years. Recent data suggest that initial cysts are the principal trigger for a snowball effect driving to the formation of new cysts in adjacent parallel tubules. We mimicked the dense packing of renal tubules in a multitube chip, built in collagen I, which consists in an array of parallel tubes of 80 μm diameter, with spacings of 200 μm. Tubes were lined with components of renal tubule matrix, and internally covered with cells, which could stay alive 1-2 months inside them. While MDCK cells formed a confluent layer which did not lead to tube deformations, first experiments with Proximal Convoluted Tubule cells models for ADPKD (collab. S. Somlo) suggested the occurrence of such deformations. Long-term imaging under different flows / compressions and theoretical modelling are being performed in order to study the physical mechanism of tube dilation and cyst formation.

Candida albicans on a chip

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The commensal yeast *Candida albicans* is an opportunistic pathogen of the mucosal surfaces causing severe infections in immunodeficient patients. It can form filaments called hyphae through an apical growth based on turgor pressure. Hyphae being capable of breaking through epithelial barriers, the reversible transition between yeasts and hyphae is thus mostly responsible for its pathogenicity.

Studying hyphae appears as an important challenge to understand the mechanisms of invasiveness. We aim here at characterizing the properties of individual hypha through a control of *C. albicans* microenvironment.

By using microfluidic devices including microchannels of various geometries, we implement confinement and guidance of hyphae in order to probe their elongation rate, article length, branching geometry and their response to obstacles.

In parallel, we specifically explore the mechanical properties of hyphae with: 1/ the development of a new technology using a pressure-controlled micro-piston moving inside a microchannel to measure the force-velocity characteristic of a growing hypha, 2/ the study of the bending rigidity of the filaments by measuring their deflection in response to hydrodynamic forces.

With the development of these microfluidic tools, we should be able to quantify various physical observables in different strains (knock-out or overexpression), and thus have a better understanding of the relation between the genotype and the phenotype of *C. albicans*, with a focus on the genes involved in virulence.

A mathematical model of the liver circadian clock linking feeding and fasting cycles to clock function

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To maintain energy homeostasis along the diurnal cycle, the liver relies on a circadian clock synchronized to food timing. Perturbed feeding and fasting cycles have been associated with clock disruption and metabolic diseases; however, the mechanisms are unclear. To address this question, we have constructed a mathematical model of the mammalian circadian clock, incorporating the intracellular metabolic sensors SIRT1 and AMPK [1]. The clock response to various temporal patterns of AMPK activation was simulated numerically, mimicking the effects of a normal diet, fasting, and a high-fat diet. The model reproduces the dampened clock gene expression and NAD+ rhythms reported for mice on a high-fat diet [2, 3] and predicts that this effect may be pharmacologically rescued by timed REV-ERB agonist administration [1]. However, it is known that besides intracellular factors such as AMP or NAD+, systemic factors such as insulin, glucagon, or free fatty acids (FFA) also can reset the clock. A natural question then is the relative importance of these different driving signals in synchronizing the clock hepatic clock. To address this question, we have constructed a simple 5-gene mathematical model driven by insulin, glucagon and FFA to study how well it can reproduce the clock phase shift observed when the feeding schedule is suddenly shifted by 12 hours [4]. We intend to eventually integrate all these stimuli in the same model to obtain a comprehensive mathematical description of how feeding/fasting cycles entrain the hepatic and other peripheral clocks.

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