Research Networking Programmes

Science Meeting – Scientific Report

The scientific report (WORD or PDF file - maximum of seven A4 pages) should be submitted online within two months of the event. It will be published on the ESF website.

Proposal Title: ***GDR Cell Tissue meeting: biology of complex system.***

Application Reference N°: **5470**

1) Summary (up to one page)

A GDR consortium (GDR = Groupement de Recherche) puts together french laboratories that are affiliated to the CNRS, the french national center for research, sharing a common scientific objective. GDRs are used to organize various types of meetings for their members in the purpose of scientific exchange and education; they are created for a period of 4 years, and can be renewed one or two times (for a 4 years period each time).

The purpose of the GDR CellTiss (Physique de la cellule au tissu), Physics from Cell to Tissue, is to rally physicists, chemists and biologists interested into developping new experimental approaches, scaling from a molecular level upto the pluricellular scale, including systemic biology. This GDR was created in 2007, and has from then on organized each year one plennary days workshop bringing together about one hundred senior and young scientists. Such workshop gives the opportunity not only to keep up to date with the last scientific advances in the field but also to start new collaborations in this naturally multidisciplinary field.

The present plennary days have put together 82 participants in total, and took place over five half-days, mixing longer oral presentations of 30-45 minutes duration, given by confirmed, invited speakers (international), and shorter talks (10-15 minutes) given mainly by young researchers, including PhD students (french laboratories). Poster sessions were also an important part of the workshop, giving the opportunity for numerous scientific exchange. Last but not least, the GDR plennary days took place, as usually, in a relatively isolated congress center, so to increase the exchanges between the participants : Mont Sainte Odile is a nice monastery on the top of a hill, at 45 km from Strasbourg.

2) Description of the scientific content of and discussions at the event (up to four pages)

The scientific program of the GDR CellTiss annual meeting aims at reflecting the relatively broad variety of thematics in which our community is concerned, namely :

1. *Mechanics, adhesion and cellular motility*
2. *Biologic nano-engines*
3. *Biological development and tissues*
4. *Membrane dynamics and cytoskeleton*
5. *Signaling and regulation*

Discussions took place after each oral presentation. Here are given some of the key subjects that were presented, and debated.

1. Mechanics, adhesion, and cellular motility :

Biophysical Studies of T-cell adhesion : T-cells play a central role in cell mediated adaptive immune response. They carry distinctive TCRs (T cell receptor), that are responsible for specific recognition of foreign peptides in the body, inducing cell adhesion and spreading accompanied by dramatic changes at molecular and cellular scale. This study reports how the usual behavior of a T-cell, i.e. a strong variability of both adhesion and spreading with the substrate nature, can be strongly reduced to almost no substrate-dependance, on blocking myosin-II or by inclusion of ICAM (ligand of LFA1 integrins) on the substrate. The discussion concerned the suitability of a model, inspired by earlier models of neuronal growth cones and filopodia, that links the dynamics of the leading edge of the spreading T cell to the friction generated at the surface by dragging or pinning of the ligands.

Deciphering the mechanisms of durotaxis in crawling cells : The mechanisms by which matrix stiffness determines motile cell behavior remain poorly understood. The mechanosensitive response of fish epithelial keratocytes, which are amongst the fastest moving animal cells, have been studied on different kinds of surfaces corresponding to a wide range of rigidities (from 1 kPa to 72 GPa). The results show, through the analysis of various morphological parameters (i.e. shape, aspect ratio, lamellipodial curvature, etc.), that the rigidity of the cell environment can be a valuable tool for controlling the natural phenotypic variability of keratocytes. The discussion concerned the expected close relationship between morphological and migrating parameters, suggesting that the substrate stiffness dictates the level of polarization and directionality of motile cells.

Micro-and macro-rheology of bronchial mucus : Bronchial diseases are often associated with mucus hypersecretion in the airways, but the distinctive roles of cilia beating and mucus properties and hypersecretion are still to be determined.

A multi-experimental approach, associating macroscopic cone-plate rheology and bead microrheology, was used to characterize mucus samples obtained from bronchial epithelium culture. The discussion concerned the preliminary results of this study, in particular the possible way to understand how cilia beating is coupled to the viscoelastic properties of the mucus, to generate mucus transport in lungs.

2. Biologic nano-engines

Combining SFA and FRET to monitor the progressive zippering of two biomolecules during force measurements : SNARE proteins are fundamental to membrane fusion during neuro-transmission. In order to fully understand their assembling process, a new device was designed, that associates a SFA (Surface Force Apparatous) and Förster Resonance Energy Transfer (FRET). This allows the investigation of the structural information on the SNARE complex assembly at a sub-molecular scale, in the narrow gap between the membranes. The discussion concerned the first measurements of FRET signal associated to force-distance profiles.

Energy lanscape of the hRad51 protein on a double stranded DNA : Homologuous recombination is a vital molecular process for the survival of any living organism. In the case of human beeing, hRad51 is able, on its own, to bind to the single strand of a broken DNA and to carry out the necessary rebuilding steps of the recombination. Model experiments involving the hRad51 alone, i.e. without its usual partners present *in vitro*, that measure the rate of DNA streching during this process, and the force and the torque involved, have been described and discussed.

3. Biological development and tissues

Single cell analysis of entry into replicative senescence in budding yeast : Budding yeast cells have an asymmetrical division pattern. Each mother cell produces a limited number of smaller daughter cells before entering senescence and eventually dying. The detailed mechanisms that govern entry into senescence are still poorly understood. The discussion concerned recent results obtained using a microfluidic system enabling to monitor the successive divisions of single yeast cells in real-time under the microscope, that show that cells undergo a sharp transition to senescence, which is not related to the loss of mitochondrial membrane potential, as previously proposed.

The role of cortical mechanics on the asymmetric division of mouse oocyte : Asymmetric cell division is crucial to ensure cell diversity, and mouse oocyte is a model system for its study. Micropipette aspiration was used to demonstrate that a decrease in cell cortical tension is necessary for proper asymmetric division, in opposition to mitotic cells where an increase in cortical tension ensures spindle positioning. This decrease in cortical tension is due to an Arp2/3-dependant cortical F-actin enrichment that results in myosin II cortical exclusion. The discussions concerned the so established relations existing between the architecture of the acto-myosin cortex and the outcome of cell division.

4. Membrane dynamics and cytoskeleton

Microtubule dynamics and mechanical forces in the one-cell C. elegans embryo : During mitotis, chromosomes are connected to a microtubule-based spindle. The displacement of the spindle poles and/or the activity of kinetochore microtubules generate mechanical forces that segregate the chromatids. The discussion concerned new experiments showing that neither of these mechanisms is necessary to achieve proper chromatid segregation, as shown from laser destruction of the centrosomes during C. elegans mitosis, while an outward force generated by the spindle midzone is sufficient for anaphase in mitotic cells.

Mechanism of membrane scission induced by ESCRTs-III complexes : Endosomal sorting complexes are required for transport (ESCRT) function in a number of important membrane remodeling processes, such as multi-vesicularbody (MVB) biogenesis at endosomal membranes, budding of some enveloped viruses, like HIV, from the plasma membrane and midbody abscission during cytokinesis. The discussion concerned the role of each of the 32 proteins of the human ESCRT pathway, that form five different complexes named ESCRT-0,-I,-II,-III and the ATPase VPS4 complexes, during MVB biogenesis.

Fluctuation-driven clustering of nanoparticles on lipid membranes : Clustering of proteins on the plasma membrane is an important step in a multitude of biological processes. Many proteins have been shown to aggregate in the absence of homophilic or cholesterol mediated interactions. Under these conditions, the mechanism of aggregation is enigmatic. The discussion concerned new results that show that clustering is driven by membrane interacting particle - induced perturbation of thermally - excited membrane shape fluctuations. In particular, a theroretical model as a form of Casimir force is shown to well represent the data.

5. Signaling and regulation

Fundamental constraints on the abundances of chemotaxis proteins : Flagellated bacteria, such as Escherichia coli, perform directed motion in gradients of concentration of attractants and repellents in a process called chemotaxis. Transmembrane chemoreceptors, which bind attractants and repellents, control the activity of the histidine kinase CheA, which phosphorylates the cytoplasmic response regulator CheY. Phosphorylated CheY binds to FliM in the flagellar motors. This binding controls the direction of the rotation of the motors, and hence the motion of the cell. E. coli chemotaxis is a model for signal transduction. The discussion concerned the strategies cell use to adapt the abundance of all the chemotaxis proteins as a function of the wealth of nutritiments in the medium.

Theory of cell signaling at adhesive sites : Integrin activation, integrin clustering and integrin organization into rosettes are the hallmarks of positive feedback loops generated by local phosphoinositide production. Integrin receptors mediate interaction between cells and the extracellular matrix. The discussion concerned a new reaction diffusion model where the conformational state of receptors is modulated by their lipidic environment.

3) Assessment of the results and impact of the event on the future directions of the field (up to two pages)

1. Mechanics, adhesion, and cellular motility :

Living cells are able to crawl, change their shape, and adhere with one another, to form tissues. Adhesion and cellular motility both imply complex reactions, starting at the level of individual bio-molecules, and ending at the cell scale. Understanding the ability of cell to control their mechanical properties in such a wide diversity represents a major challenge in nowadays research. In particular, understanding how cell dynamics couples to the different cytoskeletons is a major challenge where physics, biology and technological science can benefit from a strong interaction.

2. Biologic nano-engines

Biological nano-machines are proteins or protein assemblies that transform chemical energy into work. Recent years have been characterized by an important interest of physicists, chemists and biologists in this field, and we are able nowadays to observe and manipulate these molecules in their *in vivo* environment. Many open questions remain about for example the conformational changes with ATP hydrolysis, about what are the irreversible stages that impose the reaction directionality, but also about the nature of the processes that govern targeting strategies of these nano-engines, to name only a few.

3. Biological development and tissues

Biological tissues are dynamic, not only during embryonic growth, but all along the life of the host organism, and even apparently static tissues keep their integrity thanks to various homeostatic processes. One nowadays challenge is to relate the individual behavior of cells, including the interactions they are able to create with their exterior, to the collective behavior of the tissue they form. The GDR aims at putting together cell biologists, development biologists, physicists and theoreticians, in order to help us understanding these processes.

4. Membrane dynamics and cytoskeleton

Understanding at the molecular and supra molecular level the interactions between the membrane and cytoskeleton is one major challenge. We nowadays get a much dynamic view of living cells, down to molecular scales, thanks to important progresses in optical microscopy and detection devices. On the chemistry side, new molecular probes can be synthesized that enable fine observation of individual molecules and particles inside the cells. All these complementary methods can be associated to theoretical modeling, to understand the fundamentals of cell division, cell differentiation, and multicellular assemblies.

5. Signaling and regulation

Recent discoveries in the domain of signaling and regulation networks in living realms have unravelled how cells control and take advantage of the stochastic behavior of the elementary molecular events, in order to achieve their development, on both normal or pathological side. Nowadays very efficient optical microscopy techniques enable the observation of the activity of feedback loops in living cells. Thus, very promising results are expected from a strong interaction between the experimentalists and the numerical simulation community.

4) Annexes 4a) and 4b): Programme of the meeting and full list of speakers and participants

Annex 4a: Programme of the meeting

Monday November 3, 2014

11:30	*Check-In and Registration*
12:00-13:30	*Welcome lunch*
13:30-14:05	Felix Naef (EPFL Lausanne, Swiss) *Synchronization and resonances of cellular oscillators*
14:05-14:40	Daniel Riveline (Cell Physics Lab., ISIS/IGBMC, Strasbourg, Fr) *Active gels in vivo*
14:40-15:15	Mauricio Baptista (Chemistry Institute, Sao Paolo, Brasil) *Photosensitization reactions in health sciences*
15:15-15:50	Maxime Dahan (Institut Curie, Paris, France) *Target search of DNA-binding proteins in a mammalian nucleus: How to find a specific site in the genome?*
15:50-16:20	*-------- Coffee break --------*
16:20-17:40 (4 talks, 20' each)	Arumugam S. (Institut Curie, Paris, France) : *Fluctuation-Driven Clustering of Nanoparticles on Lipid Membranes* Campillo C. (LAMBE, Evry, France) : *The role of cortical mechanics on the asymmetric division of mouse ovocyte* Planade J. (ESPCI, Paris, France) : *Insight on the mechanical role of protein partners in yeast actin networks* Gonzalez Rodriguez D. (LadHyX, Palaiseau, France) : *Microindenteur Cellulaire pour Caractériser la Mécanique de la Rupture Membranaire*
17:40-17:50	Presentation of the team ***Physique et nano-micro bio-ingénierie pour le vivant,*** at CINM, Marseille.
17:50-19:30	"Poster minute" + Posters
19:30	*-------- Dinner --------*

Tuesday November 4, 2014

8:45-09:45	Frédéric Pincet (LPS, Paris, France) *Intracellular trafficking: compartimentalization, specifity and exchanges between the various organelles*
09:45-10:30	Thomas Neu (Department River Ecology, Magdeburg, Germany) *The matrix of interfacial microbial communities*
10:30-11:05	François Nedelec (EMBL, Heidelberg, Germany) *The Steady-state Organization of a Meiotic Spindle*
11:05-11:30	-------- *Coffee break* --------
11:30-12:50 (4 talks, 20' each)	Fourcade B. (ENS, Lyon, France) : *Theory of cell signalisation at adhesive sites : Integrin activation, integrin clustering and integrin organization into rosettes are the hallmarks of positive feedback loops generated by local phosphoinositide production* Bitbol A.F. (LSI IG, Princeton, Great Britain) : *Fundamental constraints on the abundances of chemotaxis proteins* Grammont M. (PhLAM, Lille, France) : *Epithelial morphogenesis in Drosophila: the genetics & the mechanics* Sorre B. (MSC, Paris, France) : *Model systems to study embryonic patterning*
12:50-14:00	-------- *Lunch* --------
14:00-15:00	Michel Labouesse (IGBMC, Strasbourg, France) : *Embryonic life under tension*
15:00-16:20 (4 talks, 20' each)	Nahaboo W. (ENS, Lyon, France) : *Microtubule dynamics and mechanical forces in the one-cell C. elegans embryo* Doonaruma D. (LCVN, Montpellier, France) : *Micro- and macro-rheology of bronchial mucus* Riaz M. (Faculty of Science, Mons, France) : *Deciphering the mechanisms of durotaxis in crawling cells* Dillard P. (Aix-Marseille Univ., Marseille, France) : *Biophysical Studies of T-cell adhesion*
16:20-18:00	-------- *Coffee break + Posters* --------
18:00-18:45	Luca Monticelli (IBCP, Lyon, France) *Molecular simulations of lipid membranes*

19:30 -------- *Dinner* --------

Wednesday November 5, 2014

08:30-09:05 Karen Perronet (Institut d'Optique, Paris, France)
Kinetics of mammalian translation by single molecule fluorescence microscopy

09:05-09:40 Erwin Peterman (University of Amsterdam, The Nederlands)
A single-molecule view of intracellular transport in living C. elegans

09:40-10:10 -------- *Coffee break* --------

10:10-11:30
(4 talks, 20' each)

Attwell S. (Institut Curie, Paris, France) :
Force et couple dans les pinces magnétiques :paysage énergétique de la protéine hRad51 sur ADN double-brin.

Wang Y.J. (LPS, Paris, France) :
Combining SFA and FRET to monitor the progressive zippering of two biomolecules during force measurements

Charvin G. (IGBMC, Strasbourg, France) :
Single cell analysis of entry into replicative senescence in budding yeast

Boselli F. (IGBMC, Strasbourg, France) :
Hemodynamic frequency content regulates valvulogenesis

11:30-12:00 Round Table : the next GDR.

12:00-13:45 -------- *Lunch* --------

13:45-14:20 Loïc Legoff (IBDM, Marseille, France) :
How mechanics shape growing tissues

14:20-14:55 Anne Cécile Reymann (MPI, Dresden, Germany)
Actin filament alignment by flow

15:00 -------- *End of the meeting* --------

Annex 4b: Full list of speakers and participants

ALAMEDDINE	Ranime	Master, PhD, Post-Doct.
ALIBERT	Charlotte	Master, PhD, Post-Doct.
ALQABANDI	Maryam	Master, PhD, Post-Doct.
ARUMUGAM	Senthil	Master, PhD, Post-Doct.
ATWELL	Scott	Master, PhD, Post-Doct.
BAPTISTA	Mauricio S.	Invited speaker
BASSEREAU	Patricia	Prof., permanent Researcher
BENARD	Emmanuelle	Master, PhD, Post-Doct.
BITBOL	Anne-Florence	Master, PhD, Post-Doct.
BLANCHOIN	Laurent	Prof., permanent Researcher
BOSELLI	Francesco	Master, PhD, Post-Doct.
CAMPILLO	Clément	Prof., permanent Researcher
CHARVIN	Gilles	Prof., permanent Researcher
CHIARUTTINI	Nicolas	Master, PhD, Post-Doct.
COMELLES	Jordi	Master, PhD, Post-Doct.
CRIBIER	Sophie	Prof., permanent Researcher
DAHAN	Maxime	Invited speaker
DAULOUDET	Olivier	Master, PhD, Post-Doct.
DILLARD	Pierre	Master, PhD, Post-Doct.
DONNARUMMA	Dario	Master, PhD, Post-Doct.
DREVON	Dorian	Master, PhD, Post-Doct.
DU ROURE	Olivia	Prof., permanent Researcher
DUPONT	Aurélie	Prof., permanent Researcher
FAGGIANELLI	Nathalie	Master, PhD, Post-Doct.
FORET	Lionel	Prof., permanent Researcher
FOURCADE	Bertrand Gabriel	Prof., permanent Researcher
GALLAGHER	Joseph	Master, PhD, Post-Doct.
GODEAU	Amélie	Master, PhD, Post-Doct.
GONZALEZ-RODRIGUEZ	David	Master, PhD, Post-Doct.
GRAMMONT	Muriel	Prof., permanent Researcher
GRUGET	Clémence	Master, PhD, Post-Doct.
GUEVORKIAN	Karine	Prof., permanent Researcher
GUILLOTIN	Audrey	Master, PhD, Post-Doct.
HELFER	Emmanuèle	Prof., permanent Researcher
HEUVINGH	Julien	Prof., permanent Researcher
HUET	Sébastien	Prof., permanent Researcher
ICHEVA	Téa Aleksandra	Master, PhD, Post-Doct.
KHELLOUFI	Mustapha Kamel	Master, PhD, Post-Doct.
KUMARI	Anita	Master, PhD, Post-Doct.
LABOUESSE	Michel	Invited speaker
LANTOINE	Josephine	Master, PhD, Post-Doct.
LE GOFF	Loic	Invited speaker
LE MAOUT	Emilie	Master, PhD, Post-Doct.
LEFEBVRE	Solène	Master, PhD, Post-Doct.
LEFRANC	Marc	Prof., permanent Researcher
LEXA-SAPART	Norik	Master, PhD, Post-Doct.
MARQUES	Carlos	Prof., permanent Researcher
MAYER	Claudine	Prof., permanent Researcher
MICHAUT	Arthur	Master, PhD, Post-Doct.
MOKHTARI	Zakia	Master, PhD, Post-Doct.
MONTICELLI	Luca	Prof., permanent Researcher
MORANDI	Mattia	Master, PhD, Post-Doct.
MORLOT	Sandrine	Master, PhD, Post-Doct.

MOTCHON	Yawovi	Master, PhD, Post-Doct.
MULLER	Pierre	Prof., permanent Researcher
NAEF	Felix	Invited speaker
NAHABOO	Wallis	Master, PhD, Post-Doct.
NEDELEC	François	Invited speaker
NEU	Thomas	Invited speaker
NIER	Vincent	Master, PhD, Post-Doct.
PARMEGGIANI	Andrea	Prof., permanent Researcher
PENEAU	Camille	Master, PhD, Post-Doct.
PERRONET	Karen	Invited speaker
PETERMAN	Erwin	Invited speaker
PINCET	Frederic	Invited speaker
PLANADE	Jessica	Master, PhD, Post-Doct.
REYMANN	Anne-Cecile	Invited speaker
RIAZ	Maryam	Master, PhD, Post-Doct.
RIVELINE	Daniel	Invited speaker
RUA FERREIRA	Rita	Master, PhD, Post-Doct.
SALOME	Laurence	Prof., permanent Researcher
SCHMATKO	Tatiana	Prof., permanent Researcher
SCHRODER	André	Prof., permanent Researcher
SORRE	Benoit	Prof., permanent Researcher
STEED	Emily	Master, PhD, Post-Doct.
TLILI	Sham	Master, PhD, Post-Doct.
VERMOT	Julien	Prof., permanent Researcher
VIALLAT	Annie	Prof., permanent Researcher
WAHL	Astrid	Master, PhD, Post-Doct.
WALTER	Jean-Charles	Master, PhD, Post-Doct.
WALTER	Vivien	Master, PhD, Post-Doct.
WANG	Yong Jian	Master, PhD, Post-Doct.