Research at ENS Lyon

2006

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- Jean-Louis Duclos 80 22
Communication - Virginie de Charentenay 88 16
Reservations Charles Mérieux Amphitheater
- Jocelyne Reynard 85 71

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The ENS Lyon: passion, innovation, openness

To research, discover, and innovate, one must be enthousiastic, enterprising and creative. Our aim is to share our passion for research through an education that is firmly anchored on initiative and openmindedness. The *École normale supérieure de Lyon* is a place of reactivity and innovation for teaching and research where researchers, faculty and students work side by side daily. Our academic programs, built with the *Université Claude Bernard* and other higher education institutions of the Rhône-Alpes Region, are in close interaction with the research conducted in a dozen internationally renowned laboratories located at the *École*. The guiding force of this interdisciplinary scientific education is the construction of tomorrow's science. Our students, after a thorough, high-level preparation, become privileged actors in teaching and research in public or semi-public organizations and in the private sector. Research innovation and daring, strong specialized knowledge and openness towards other disciplines for teaching are key words which accompany the commitment of those who study and work at the *École normale supérieure de Lyon*.

Philippe Gillet
Director

KEY FIGURES IN 2006

- **868** students including **185** Ph.D. students
- **278** researchers and faculty
- **85%** of the students obtain a Ph.D. and
- **51%** of the students obtain national teaching certification (*l'agrégation*) and a Ph.D.
- **1316** major publications in peer-reviewed international journals between 2003 and 2005 (958 between 1999 and 2001)
- **6** publications in the magazines Science and Nature in 2005
- **1.84** publications on average per researcher and faculty-researcher in 2005 (1.7 in 2002)
- **11** start-ups created between 1999 and 2006 - **153** jobs created
- **€9.6 M** in subsidies and research agreements in 2005 (€4.3 M in 2003)
- **46** doctoral theses defended in 2005 (29 in 2002)
- **40** cooperation agreements signed with universities outside of France
- **100** international students
- **72nd** in the top 200 universities (11th for citations per faculty score)*
- **4th** in France (behind 3 Paris-based institutions)*
- **21st** in Europe's top 50 universities*

**according to The Times Higher Education Supplement 2006*

Study and discover with us

The *Écoles normales supérieures* (ENS) are unique in the French system of higher education because they combine features of a *grande école* and of a university.

- Like the *grandes écoles*, they select some of their students through a highly competitive national examination. And because the ENS have an outstanding reputation they attract the top students who become *élèves normaliens* and are paid to study for four years. Another entrance competition is held by the ENS Lyon and is intended for students who have successfully completed two years in a French or European Union university.

- Like the universities, the ENS focus on pure science, with a strong link to research, whereas most of the French *grandes écoles* are schools for engineers.

The ENS Lyon ranks 72nd in the world's top 200 universities and 21st in Europe according to the World University Ranking in the 2006 *Times Higher Education Supplement*.
Every year about 200 students only are admitted, in the fields of mathematics, computer science, physics, chemistry, biology, and Earth and planetary sciences. Less than 900 students study at the ENS Lyon, including 185 doctoral students. As a result, ENS Lyon students benefit from individual attention and very well equipped laboratories.

This is why the ENS Lyon is a top choice for excellent students seeking a high level curriculum and a strong contact with research.

The ENS Lyon is an advanced study institution where the studies include not only standard courses, tutorials and lab classes, but also early exposure to scientific research. All teachers are high-level scientists and even at the *pre-master* level the students are involved in a two-month research internship. During studies for the *Master,* the importance of research internships grows in the curriculum. Moreover, throughout their studies at the ENS the students are embedded in the research laboratories.
While studying at the ENS Lyon is demanding, for those who love science it can be extremely rewarding because they have a chance not only to learn, but also to gain first hand experience in the school's excellent facilities. This approach to scientific education explains why diplomas from the ENS Lyon are so highly prized.

Michel Peyrard
Director of Studies

Study and discover with us

A diverse choice of programs

Programs leading to a bachelor's degree (university awarded), a master's degree (jointly awarded by the ENS Lyon and Lyon-1) and an ENS Lyon doctorate.

Five bachelor's-master's programs, organized in conjunction with the *Universté Claude-Bernard Lyon-1*

- Mathematics and Applications (Higher Mathematics track)
- Fundamental Computer Science
- Materials Science
- Molecular and Cellular Biology
- Earth Science

> double majoring is possible

Four educational tracks preparing for teaching certification *(aggrégation)*

- Mathematics
- Fundamental computer science
- Physical science, specializing in physics or chemistry
- Life science and Earth and planetary science

An edge for the future

Titles and degrees earned by *normalien* students

Statistics based on 1050 degreed *normalien* students between 1991 and 2000:

15 % Teaching certification (*aggrégation*) without a Ph.D.
51 % Teaching certification (*aggrégation*) with a Ph.D.
29 % Ph.D. without teaching certification
5 % Other (medical doctors, specialized engineers...)

85% of ENS Lyon students earn a Ph.D.

Professional situations

Statistics based on a sample of 500 students, 7 years after they completed their studies:

21 % certified teachers in secondary education
28 % certified teachers in higher education
28 % Public research
18 % Private or semi-private firms
5 % Other

Resources that live up to our high demands

Framework
Personalized contacts with faculty and researchers;
High-performance laboratory equipment with technical support;
Innovative projects carried out;
Foreign language classes;
Conferences and cultural activities.

Links to research
Educational programs closely linked to research activities;
Classes taught by faculty-researchers and researchers at the *École* or partner institutions;
Annual internships in research laboratories.

Scientific literature
Multidisciplinary library, regrouping research and teaching works;
Widely available internet access facilities.

Information technology tools
Integrated pedagogic space;
Online access to scientific and pedagogical resources for classes and labs;
Video conference broadcasting;
Forums and work groups.

Research at ENS Lyon:

one location that favors transdisciplinarity and gives access to high level technological facilities

Spanning the range of exact sciences, the ten laboratories at the ENS Lyon are all affiliated with major French national research organizations (INRA, INSERM, CNRS, INRIA) and some are also affiliated with the *Université Claude Bernard Lyon 1*. Indeed, these partners guarantee top-level quality.

Interdisciplinarity and openness to the world

It is in a spirit of exchange and interdisciplinarity–via research lead in a structure of a human scale–that, in 2004, the Joliot Curie laboratory (see page 43) and later, in 2006, the *Institut des Systèmes Complexes* (see page 85) were created.

Having an international scope, the ENS Lyon welcomes thirty-five researchers and faculty researchers, and approximately fifty postdoctoral researchers or long-term visitors from all over the world. The CECAM laboratory (*Centre Européen de Calcul Atomique et Moléculaire*) illustrates this openness well. Moreover, our laboratories participate in twenty-four networks and integrated European network programs (see page 88).

Scientific cooperation and involvement in nationwide scientific programs

Our laboratories join with other regional and national scientific and medical research institutes (*Institut Fédératif Biosciences Lyon Gerland, Institut de Médecine Théorique, programme dynamo avec l'ENS Paris et le CEA Saclay, Cancéropôle Lyon Auvergne Rhône-Alpes, Institut des Systèmes Complexes Rhône-Alpes*) to form high performance technological platforms (see page 86) in order to lead certain research projects in common.

Thus, in 2006 the ENS Lyon participated in important national scientific developments such as the creation of *Lyon Biopôle*, a world competitiveness cluster in the study of infectious diseases, and Axelera, a competitiveness cluster in chemistry. A theme based network of advanced research centered on innovations in the treatment of infectious diseases was also created the same year.

Finally, in 2007, the creation of the *Institut de Génomique Fonctionnelle de Lyon* will enrich Lyon's strong research potential in integrative and comparative biology.

A highlight on results

Research at the ENS Lyon has lead to industrial collaboration and transfer. Thus, ten companies have been created since 1999. Some of these companies, such as Genoway, Vivalis, and Varioptic are now well established and represent more than 150 jobs.

In four years, about twenty co-owned patents have been filed of which half have been licensed.

In the last four years, the ENS Lyon has published more than 1300 articles in international scientific journals. More than thirty researchers and faculty researchers have been awarded national and international prizes, and three have been elected to the *Academie des sciences*.

Jacques Samarut
Director of Research

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Astronomy Center of Lyon

Astrophysics Group of ENS Lyon

► **Team leader** ► *Gilles CHABRIER* ***Senior Researcher***
► **E-mail** ► *chabrier@ens-lyon.fr*
► **Partners** ► *CNRS, UCB Lyon 1*
► **Web** ► *http://www-obs.univ-lyon1.fr*

RESEARCH INTEREST:

The main research themes developed in the theoretical astrophysics group of the ENS Lyon include the physics of dense objects (dense plasmas, structure and evolution of dense objects, modeling of the atmospheres and spectra of cool and dense objects), galactic physics (gravitational microlensing, structure of the Galaxy, galactic dark matter), the hydrodynamics of compact objects (coalescence of white dwarfs and neutron stars, evolution of compact binaries, stability of stars) and the study of hydrodynamic processes in astrophysics (star formation, protoplanetary disks, instabilities and stellar pulsations, turbulence, MHD) with multi-dimensional numerical simulations.

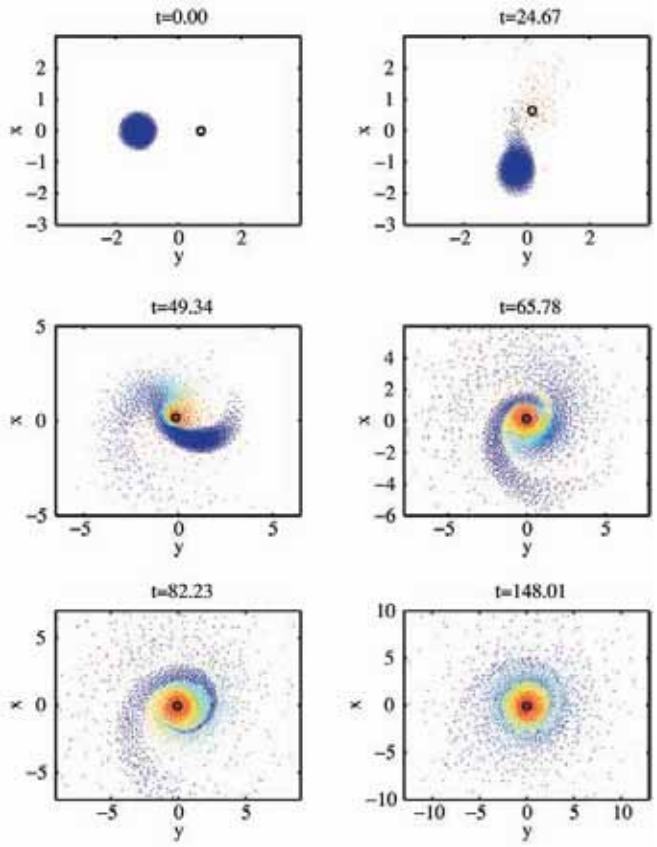
The underlying guideline in these different domains is the understanding of physical processes in astrophysics. These researches involve a variety of domains in physics, mainly statistical physics, atomic physics and hydrodynamics.

Along the years, different domains of research have been developed, chronologically:

- fundamental physics: hydrodynamics, statistical physics of dense matter, matter-radiation interaction,
- planetary and stellar astrophysics: structure and evolution of compact stars, brown dwarfs, solar and extrasolar gaseous planets, stellar seismology, star formation,
- galactic physics and cosmology: stellar initial mass function, gravitational microlensing, galactic structure, galactic missing mass, primordial stars.

RESEARCH TOPICS

- Physical processes in astrophysics
- Stellar and planetary physics
- Galactic physics
- Formation of stars and planets
- Hydrodynamics numerical simulations



◄◄◄ *Simulation of the merging of a white dwarf (compact star of about a solar mass for the radius of the earth) and a neutron star (about a solar mass for a radius of 10 km). This latter is modelized by a point mass at the center of the circle. The figure is the projection in the orbital plane (i.e. seen from above). The distance scale in x and y is 10,000 km. The colors indicate the temperature from the coolest (blue) to the hottest (red) regions.*

The indicated time is in seconds. All the coalescence takes place in about 148 secondes, i.e. less than 2 orbital periods. Such systems of white dwarf-neutron star pairs leading to a coalescence are expected in our Galaxy, producing highly energetic phenomena, as described in this simulation.

Astrophysics group of ENS Lyon

► **Team leader** ► *Gilles CHABRIER* ***Senior Researcher*** *- chabrier@ens-lyon.fr*
► **Team members** ► *France ALLARD* ***Associate Researcher*** ► *Marie-Christine ARTRU* ***Professor Researcher*** ► *Isabelle BARAFFE* ***Senior Researcher*** ► *Jean-Francois GONZALEZ* ***Associate Professor*** ► *Gerard MASSACRIER* ***Associate Researcher*** ► *Cedric MULET-MARQUIS* ***Assistant Professor*** ► *Franck SELSIS* ***Associate Researcher*** ► *Christophe WINISDOERFFER* ***Associate Professor*** ► *Jose GALLARDO, Benoit COMMERCON, Razvan CIOBANU and Guillaume LAIBE:* ***PhD students*** ► *Bernd Freytag, Christoffer Stoeckl:* ***Postdoctoral fellows***

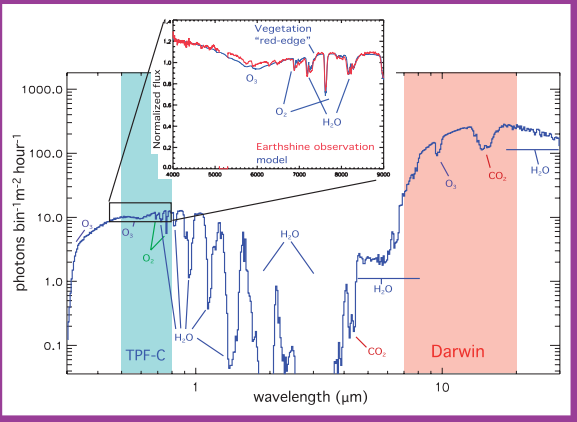
Recent scientific awards:
► Isabelle Baraffe (CNRS bronze medal 1999; German prize "Johann Wempe" 2004).
► Gilles Chabrier ("Miller Chair award" Berkeley University 1999; german prize "Johann Wempe" 2004; CNRS silver medal 2006).

A FEW HIGHLIGHTS

The ENS Lyon astrophysics group has particularly contributed to and has acquired an international reputation in the following domains:

- Equation of state and thermodynamic properties of dense astrophysical plasmas
- Structure and cooling theory of white dwarfs and neutron stars
- Structure, spectral synthesis and evolution of dense, low-mass objects: low-mass stars, brown dwarfs, solar and extrasolar giant planets. One of the papers published by the group in this field in 1998 (Baraffe, Chabrier, Allard & Hauschildt, 1998, Astronomy & Astrophysics, 337, 403) has been cited in the "Top 50 in Astrophysics" published by the monthly journal "LA RECHERCHE" two years in a row (LA RECHERCHE April 2000 and December 2000) and is still among the 100 most cited articles in astrophysics in 2003 (http://www.slac.stanford.edu/library/topcites/2003/eprints/astro-ph.topcites.2003.2.shtml).
- Determination of the stellar and substellar mass functions and of the baryonic mass budget in the Galaxy.

The new fields of investigation of the ENS Lyon group include (i) star and planet formation and (ii) the characterization of Earth-like extrasolar planets. The search for these objects represents presently a thriving domain of research, with several dedicated observational projects in a near future. The figure below illustrates the expected spectral energy distribution of an extrasolar Earth-like planet orbiting its Sun-like parent star, at a distance of 32 light-years. We can clearly see the contributions of the main elements to the spectrum and thus their expected observable signature as well as their relative contributions to the total flux. The reflected spectrum from the parent star in the optical part will be monitored by the American satellite Terrestrial Planet Finder (TPF-C) while the planet thermal spectrum in the infrared will be the goal of the European DARWIN mission. As seen in the smaller plot, the calculated reflection spectrum reproduces well the observed so-called Earth-shine spectum, an important test for the validation of the calculations. (Figure taken from J. Paillet thesis: "Spectral characterization of terrestrial exoplanets").



Chemistry
Laboratory

► **Director** ► *Phillippe SAUTET* ***Senior Researcher***
► **e-mail** ► *Philippe.Sautet@ens-lyon.fr*

► **Total personnel** ► ***80***
► **Partners** ► *CNRS, UCB Lyon 1*

The Chemistry Laboratory has a range of specialties in organic, inorganic, and physical chemistry, and develops research projects at the frontiers with biology, material sciences and physics. The research themes hence cover a large spectrum of expertise in chemistry, joining organic and inorganic syntheses together with a specific highlight on characterization and modeling.

The scientific project for development of the Laboratory is centered around four objectives:

• Creation of new molecules and materials with specific properties, in the domain of nonlinear optics, magnetism and porous solids

• Strategies to model catalysis, with a quantum or statistical simulation of elementary processes, and the synthesis of innovative catalysts using a bio-inspired approach

• Organic synthesis and intermolecular interactions, with a strong axis in supramolecular chemistry and a new action in bio-organic chemistry

• Characterizing structure and dynamics of complex molecules and solids: development of methods in solid state NMR for small molecules and for proteins, and computer simulations.

The laboratory published 78 papers in inter-national journals in 2005, including the following major scientific results:

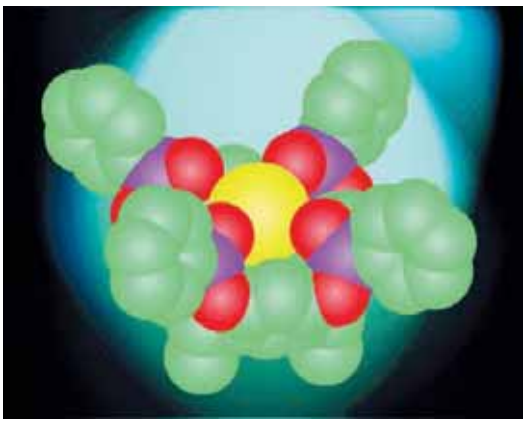
• First explanation of the origin of the molecular selectivity in the catalytic hydrogenation of unsaturated aldehyde.

• Synthesis of novel photoinitiators for radical polymerization sensitive to two photon adsorption, enabling the fabrication of smaller micro-devices for integrated optics

• Combination of experiment and modeling for the design of spin transition complexes, with applications in information storage

• New theory for the glass transition of a fluid confined in a porous media

• Innovative methods for the determination of the structure of disordered solids by high resolution NMR.



RESEARCH THEMES

• Molecules and materials with specific properties (Optical, Magnetic, Porosity) • Organic synthesis and intermolecular interactions • Modelling and Caracterization of molecules and interfaces: methods and applications

EXPERTISE

• Organic and inorganic synthesis • Physico-chemical characterization of molecules and materials • Separation of enantiomers • Theoretical Chemistry, quantum and statistical modelling • Nuclear Magnetic Resonance

AREAS OF APPLICATION

• Molecules for life sciences (Diagnostic, Imaging, Inhibitors) • Molecule-protein interactions • Separation of enantiomers for medecine • Molecules for physical applications • Analysis of complex molecules • Catalysis

EQUIPMENTS

• 200, 500 and 700 MHz Liquide and Solid NMR • EPR, Magnetometer • analytical: LCMS, HPLC • spectroscopy : IR, UV, DSV, Polarimetry, EFISH • parallel calculator

Bioorganic Chemistry group

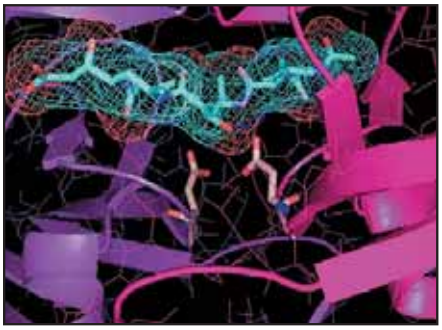
► **Team leader** ► *Jens HASSERODT* ***Professor*** *- jens.hasserodt@ens-lyon.fr*
► **Team members** ► *Philippe MAURIN* ***Assistant Professor*** ► *Delphine PITRAT*
► ***biochemistry technician*** ► *Mustapha ALLALI* ***Postdoctoral fellow***
► *Romain BARBE* ***PhD student*** ► *Yvon STORTZ* ***PhD student***
► *Pierre-Loïc SAAIDI* ***PhD student*** ► *Michael WAIBEL* ***PhD student***

Our group is engaged in fundamental and applied research at the nexus of Chemistry and Biology. Among our immediate aims are the following:

A. design of a line of contrast agents that allow the visualization of a specific enzymatic activity (such as expressed by a reporter gene) in the living animal by magnetic resonance imaging (MRI); B. design of a fluorogenic substrate for ultra-sensitive medium-throughput screening of weak aminopeptidase activity in bacterial expression libraries; C. introduction of a rare weak functional group interaction into molecule candidates and exploration of its capacity to confer on them inhibitory activity towards HIV-1 peptidase that is equal or superior to existing design strategies; D. investigation of this same interaction as a replacement for the donor-acceptor interaction found in the hydrogen bond for the design of a new biomimetic oligomer with superior folding properties over oligopeptides in physiological media; E. studies in physical organic chemistry with the aim of synthesizing a stable analog of a certain intermediate molecular species on the reaction coordinate of phosphoryl transferase activity.

Two major collaborations are currently underway: project A is conducted in close interaction with molecular biologists and radiologists/ imaging specialists at the imaging service and research center ANIMAGE of the Rhone-Alpes Genopole. Project C is carried out in close collaboration with the theoretical chemists at the Chemistry Laboratory of the ENS Lyon and the computational biologists at the Institute of Structural Biology IBS of the University of Grenoble.

We have recently obtained and characterized a first line of inhibitors for HIV-1 peptidase exhibiting the said weak functional group interaction and are currently designing the second generation with improved affinities by virtual screening of candidate molecules with a newly computed model of the target enzyme using hybrid potentials (QM/MM). For project A we are in the process of exploring with our partners an original approach patented by us that takes advantage of the phenomenon of electronic spin-state change upon encounter of the targeted enzyme by the candidate contrast agent.



Active site of HIV-1 protease complexed with Ac-pepstatine, a classic inhibitor (pdb_entry 5HVP)

Kinetics and Structure

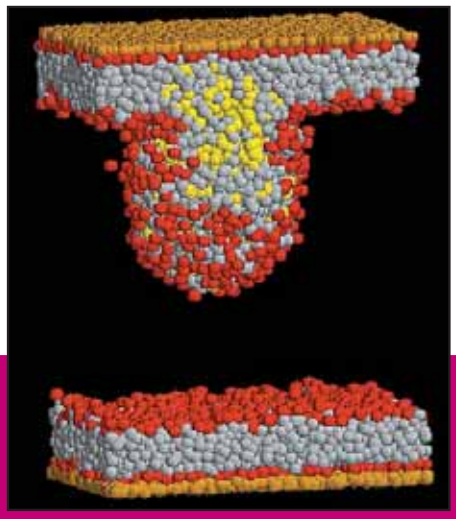
► **Team leader** ► *Wei DONG* ***Senior Researcher*** *- Wei.Dong@ens-lyon.fr*
► **Team members** ► *Max KOLB* ***Senior Researcher***
► *Vincent KRAKOVIACK* ***Associate Professor***
► *Shuangliang ZHAO* ***PhD student***

The research efforts of our group are devoted to the elaboration of theoretical approaches and simulations for studying complex molecular systems. Main current research themes are 1) porous media; 2) complex liquids and 3) surface reaction dynamics.

Our group has been working on fluids confined in porous media for many years and acquired rich experience in this field. Recently, we have made important progress in the study of glass transition and liquid-gas transition of fluids confined in random porous media. An approach based on mode-coupling theory was developed for studying very slow dynamics of dense confined fluids. To our knowledge, this is the first theoretical approach based on a microscopic description which allows for exploring diverse factors influencing the dynamic behaviours of confined fluids (e.g., structure of porous materials, nature of interactions, etc.). Gibbs ensemble Monte-Carlo method was extended for studying liquid-gas phase transition of fluids confined in random porous media. The main feature of the shift of phase equilibrium found from simulations is in good agreement with that observed experimentally.

The modelization of complex fluids meets often serious difficulties when many length and time scales are involved. This is typically the case for polymer solutions for which the relevant length scales go from that of a monomer to that of a whole chain. It is of tremendous interest to develop theoretical approaches which allow for linking the descriptions at different length scales. Recently, we have developed a computationally very efficient approach for determining the effective interaction potential between the centres of mass of polymers under various conditions. The results obtained with this approach are remarkable: all the tendencies observed in simulations (even the most subtle ones) can be reproduced. Our approach provides an efficient tool for investigating very complex polymer systems.

In the literature, quite few theoretical investigations have been made for studying the influence of surface temperature on surface reaction dynamics. Most previous works were based on a rigid surface model with a temperature maintained at T=0 K. This is obviously not the condition under which a real catalytic reaction takes place. The main difficulty is that ab initio molecular dynamics simulations are still out of reach when the motion of all the atoms (reactants and substrate) is to be taken into account. Therefore, one needs to find a simple way for accounting for the adsorbate-phonon coupling. Recently, we have proposed a simple approach based on a Langevin equation for describing the motion of the atoms of the surface layer. This approach has allowed us to elucidate the microscopic mechanism of the rotational excitation J = 1→3 of H_2 reflected by a Pd(111) surface and also to show the existence of a precursor state in the dissociative adsorption of H_2 on Pd(110).



Solute transfer from a micelle to a bilayer adsorbed on hydrophilic surface ►►►

HYBRID MATERIALS

► **TEAM LEADER** ► *Laurent BONNEVIOT* ***Professor***
► **TEAM MEMBERS** ► *Belen ALBELA* ***Assistant Professor***
► *Véronique DUFAUD* ***Associate Researcher***
► *Sébastien ABRY, Nicolas CROWTHER, Stéphanie CALMETTES, Reine SAYAH, Kun ZHANG:* ***PhD students***

Scope of research

Surface tailored multifunctional porous materials for heterogeneous catalysis, absorbents and chromatography toward more efficient and environment friendly chemical processes.

Topic

Since single sites and single chemical events are the solution to optimize both selectivity and activity, porous solids should contain specific surface sites, molecularly tailored in a given environment that controls both the reactants diffusion and the approach to the site. Therefore, the site accessibility has to be tailored taking into account molecular confinement, minimization of sequential events and low residence time. This implies molecular control at the subnanoscale and, structural control of the pores at the nanoscale (2 -10 nm) and above.

Approach of the MH group

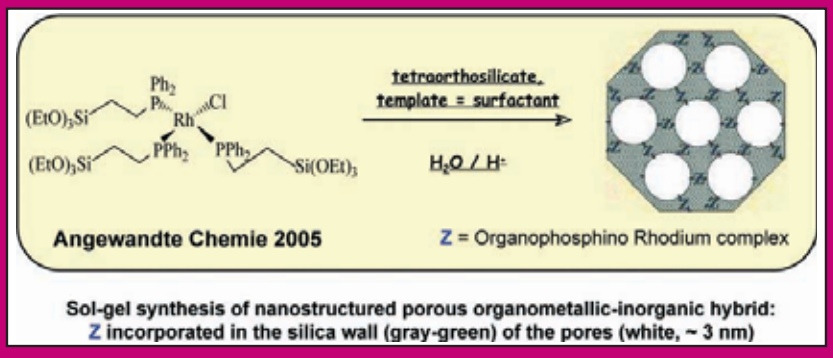
Porous silicates are designed taking advantage of the last advances in pore control and surface molecular functionalization. Molecules, micelle and/or beads of polymer are used as pore templating agents during the sol-gel synthesis of the materials to generate i) well define mesoporosity for confinement (monomodal pore size distribution) and ii) macroporosity for efficient diffusion in the solid. Molecular precursors (commercial or homemade organosilanes) for surface tailoring are introduced either during synthesis of the solid (direct synthesis) or after (post-synthesis modification). Chelated transition metal ions are active sites of choice.

Recent works

Hierarchical macro- and mesoporous silica have been developed (MMM 2003). Bifunctional catalysts were designed by surface grafting with molecular control of distance between functions (JACS 2003). Surface patterning using a molecular stencil on amorphous silica was developed as a new technique (CR Chim. 2005). The first structured porous organometallic-silica hybrid obtained by direct synthesis has been published by our group; its catalytic activity in hydrogenation is similar to that of its homogeneous analog (Angew. Chem. Int. Ed. 2005, see figure). Metalloproteins are now taken as bio-models for oxidation catalysts.

Some specific techniques

Liquid and solid state NMR, Electron Paramagnetic Resonance (EPR), magnetic susceptibility measurements and X-ray Absorption Spectroscopy (XAFS).



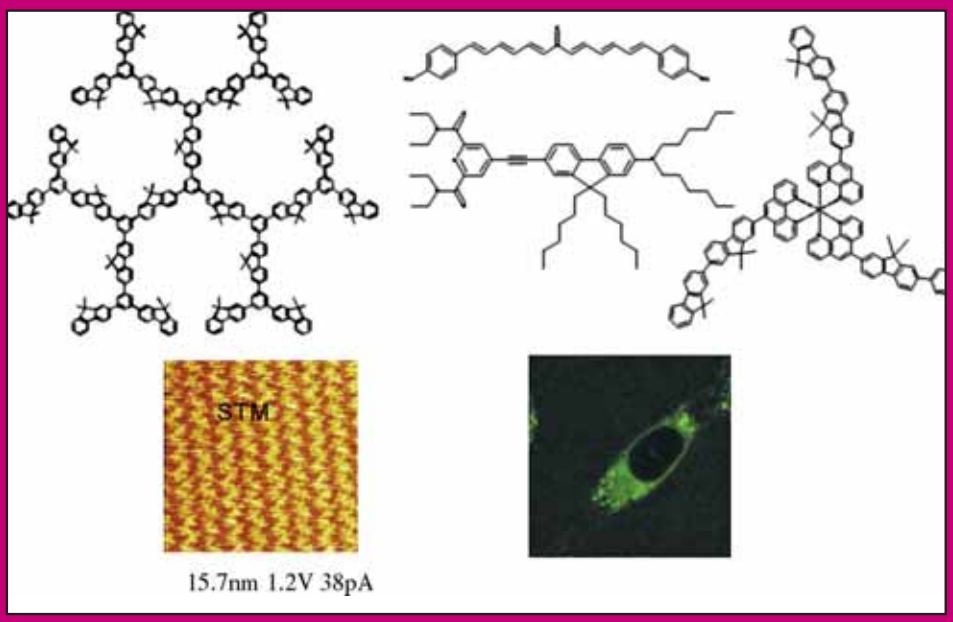
Sol-gel synthesis of nanostructured porous organometallic-inorganic hybrid:
Z incorporated in the silica wall (gray-green) of the pores (white, ~ 3 nm)

CHEMISTRY FOR OPTICS (CFO)

► **TEAM LEADER** ► *Chantal ANDRAUD* ***Senior Researcher*** *- Chantal.andraud@ens-lyon.fr*
► **TEAM MEMBERS** ► *Gilles LEMERCIER* ***Associate Professor*** ► *Yann BRETONNIÈRE* ***Assistant Researcher*** ► *Olivier MAURY* ***Associate Researcher*** ► *Cyril BARSU* ***PhD student***
► *Camille GIRARDOT* ***PhD student*** ► *Kamilla NOWICKA* ***Postdoctoral fellow***
► *François LUX* ***PhD student*** ► *Rémy BERNARD* ***Assistant Professor*** ► *Pierre-Antoine BOUIT* ***PhD student*** ► *Alexandre PICOT* ***Assistant Professor*** ► *Anthony D'ALLEO* ***Postdoctoral fellow***

The group develops a molecular engineering for different applications in optic and nonlinear optic (NLO): telecommunications (electro-optic modulation), nanotechonologies (3D microfabrication by photopolymerisation of objects such as microrotors in microfluidic, or microelements for integrated optics; nanoscopic light sources by self-assembling), biology (imaging of membranar potential variations in neurones, oxygen sensing in living cells, phototherapy), ocular and optical sensors protection by optical limiting. These applications involve the second harmonic generation (SHG) and/or two-photon absorption (TPA) processes with specific constraints for molecules due to the application or the laser wavelength.

Different families of molecules are designed in the group. Linear and dendritic oligomers, coordination complexes of transition metals or lanthanides, linear or octupolar conjugated push-pull molecules. In order to optimise molecules, theoretical calculations, interpreting or predicting their properties, are performed. For final devices, these systems can be grafted on different solid supports : mesostructured silicium, sol-gel matrices or metallic surfaces.
This research field at the interface of chemistry, physics and biology requires close collaboration with partners in France and in the world.

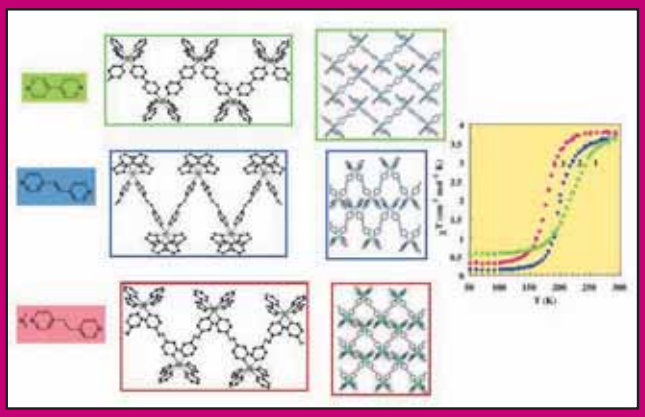


Example of molecular engineering in CPO

ELECTRONIC PHENOMENA IN INORGANIC COMPOUNDS

► **TEAM LEADER** ► *Serguei BORCHTCH **Associate Researcher** - borchtch@ens-lyon.fr*
► **TEAM MEMBERS** ► *Boris LE GUENNIC **Assistant Researcher** ► Vincent ROBERT **Associate Professor** ► Galina MATOUZENKO **Engineer** ► Caroline GENRE **PhD student** ► Maria CARVAJAL **Postdoctoral fellow***

The research in the group is focused on experimental and theoretical studies of inorganic compounds with open electronic shells. The open electronic shells result in macroscopic magnetic properties, which can be used in the treatment and storage of information. At the same time, the presence of the macroscopic magnetic properties gives an important tool for the deeper insight into the relationship between the electronic structure and physical properties. Our studies belong to the molecular materials science, which is a relatively recent and very active field on the interphase between physics and chemistry. The work of the team is oriented along two axes: experimental and theoretical. The experimental research deals with the synthesis and physico-chemical studies of spin transition compounds. The studies of magnetic properties and structures of new synthesized complexes must allow determining of the essential factors controlling the hysteresis, the critical temperature and the transition abruptness for creation of new magnetic materials with predictable properties. The experimental research of spin transition systems is accompanied by an important activity of the theoretical part of the group. Concerning the theoretical research, we are one of the rare theoretical teams exploring a large manifold of theoretical approaches of the electronic structure analysis, such as DFT, ab initio, and model Hamiltonians. This feature allows us to choose an adequate method for a particular chemical problem. We can mention as examples the modelisation of the NMR spectra of vanadium oxydo-phosphates and the characterization of electronic properties of complexes with non-innocent ligands. We also continue the analysis of the magnetic exchange in molecules and crystals.



A new family of spin crossover coordination polymers ►►►

Reactivity, Catalyse and Spectroscopy

► **Team leader** ► *Françoise DELBECQ - francoise.delbecq@ens-lyon.fr*
► **Team members** ► *Marie-Laure BOCQUET* ***Associate Researcher***
► *Henry CHERMETTE* ***Professor*** ► *Paul FLEURAT-LESSARD* ***Associate Professor***
► *David LOFFREDA* ***Associate Researcher*** ► *Philippe SAUTET* ***Senior Researcher***
► *Fabienne VIGNÉ* ***Associate Professor*** ► *Manuel CORRAL-VALERO, Céline DUPONT, Julian GARREC, Jérôme JOUBERT, Hervé LESNARD:* ***PhD students***

The main research field of the team is the theoretical description of the properties of the catalyst surfaces, of the structure and of the reactivity of the adsorbates on these surfaces. The catalysts can be pure metals, metallic alloys or metal particles and organometallic complexes grafted on supports like oxides. The studies of reactivity focus essentially on selective reactions with the aim of finding the origin of the catalyst selectivity to a given product. The major recent result is the detailed description of competitive reactions dealing with large molecules including the determination of the transition states. Among them one can cite the hydrogenation of acrolein on platinum and that of butadiene on platinum and palladium or the epoxidation of ethylene on silver oxide as well as reactions of grafted complexes on alumina in alkane metathesis or hydrogenolysis. An important aspect that is increasing is the introduction of the effets of temperature and pressure, which allows a more realistic description of the reactivity.

The simulation of surface vibrational spectra (IRAS, Infrared Reflection Absorption Spectrocopy, and HREELS, High-Resolution Electron Energy Loss Spectroscopy) or of STM (Scanning tunneling microscopy) images allows us to propose a theoretical interpretation (or a characterization) of the adsorbed structures observed experimentally with these techniques. The modeling of IETS (Inelastic Electron Tunneling Spectroscopy), that begins to be developed in our group, is a new tool for analyzing the chemical functions of an adsorbed molecule. This technique is still little studied but is promising. So this method applied to the dehydrogenation of benzene on copper has allowed the determination of the nature of the formed intermediate amongst the two possible radicals.

A new subject has recently emerged in the field of the biological systems. The first topic, in collaboration with the bio-organic team, is the design of inhibitors for the aspartic proteases, enzymes implicated in the HIV development and in the Alzheimer disease. Our contribution consists in the multi-scale modeling of these systems. On one hand, we use precise methods (quantum) on small models to define the important physical phenomena. On the other hand, we use less precise methods (molecular mechanics for instance) for modeling together the protease and the inhibitor. This will allow us to study the possible mechanisms and hence, to propose new inhibitors by virtual screening.

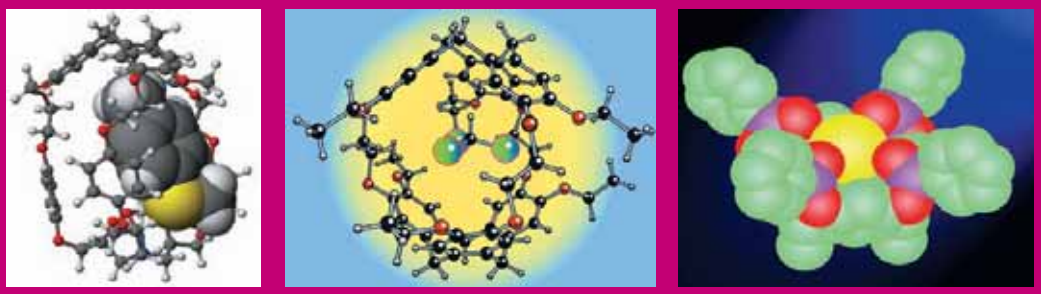
The team includes also a research axis in methodology: it takes part to the effort of several foreign teams to develop new methods for exploring the free energy surfaces. So it will be possible to optimize geometries at a fixed temperature, which means in conditions close to the experiment.

Example of a chemo-regioselective reaction in heterogeneous catalysis ►►►

Supramolecular chemistry and Stereochemistry

► **Team leader** ► *Jean-Pierre DUTASTA* ***Senior Researcher*** *- dutasta@ens-lyon.fr*
► **Team members** ► *Thierry BROTIN* ***Associate Researcher*** ► *Laure GUY* ***Engineer***
► *Béatrice DUBESSY* ***PhD student*** ► *Antoine STOPIN* ***PhD student***
► *Heather FOGARTY* ***Postdoctoral fellow*** ► *Alexandre MARTINEZ* ***Associate Professor***

Two main topics are developed in our group: the host-guest recognition processes and the investigations on fundamental aspects of molecular chirality. Research on host-guest systems is devoted to the synthesis and complexation properties of cryptophane and cavitand molecules. Phosphorus cavitands obtained by a stereoselective route are particularly interesting for the detection of various guests and the design of dynamic polymers. There is an increasing interest for the cryptophane chemistry since the discovery of xenon complexation in solution by these molecular hosts. Recent investigations in the functionalization and the resolution of cryptophane hosts, open the route to the preparation of new useful molecules, for example for the encapsulation of noble gas for bio-medical application in NMR imaging (MRI). Our group is deeply involved in a bio-sensor project for the recognition of biomedical targets by MRI. The chemistry of these molecules, their transformation, their functionalization, their complexation properties and their chiroptical properties are developed by our group. We are presently investigating new supramolecular assemblies with cavitands and (hemi)cryptophanes for their recognition properties and the study of the dynamics of encapsulated guests. Our group also develops fundamental studies on the stereochemistry of chiral systems. The resolution of enantiomers is actively developed in close relation with industry. Our specialty is the resolution by crystallization methods, a complementary tool to other available techniques, which is particularly interesting for pharmaceuticals. Research projects are devoted to chiroptical properties of specific molecules for observing parity violation at the molecular level and to the design of chiral molecules for application in supramolecular catalysis or physical optics.



Cryptophanes and cavitands

Solid-State NMR Group

► **Team leader** ► *Lyndon EMSLEY* ***Professor*** *- Lyndon.Emsley@ens-lyon.fr*
► **Team members** ► *Anne LESAGE* ***Engineer*** ► *Bénédicte ELENA* ***Engineer***
► *Guido PINTACUDA* ***Researcher*** ► *Sabine HEDIGER* ***Researcher***
► *Nicolas MIFSUD, Gwendal KERVERN, Julien SEIN:* ***PhD students***

Our research is related to the development of new experimental methods in Nuclear Magnetic Resonance (NMR) spectroscopy. NMR is a technique used by chemists, biologists, physicists and medical scientists to characterise the fine details of matter. It can be used to determine the identity of molecules and materials in analytical sciences (with applications ranging from the determination of stereochemistry essential for pharmaceutical molecules, to the analysis of metabolites in urine that can be used as markers for disease), or it can be used to determine the three-dimensional structure of the atoms and molecules that make up a wide range of matter. For example, today NMR is the method of choice for determining both the structure of proteins in solution and the structure of inorganic framework materials.

The ENS Lyon group is interested in developing NMR methods for applications in solid systems. This involves first developing our understanding of the dynamics of multi-spin systems undergoing time-dependent perturbations, using all the tools of statistical quantum mechanics. It also involves the conception of the pulse sequences that will extract exactly the information required for structural studies in different systems. Above all, it involves a major effort in the experimental implementation of these methods, on state-of-the-art equipment.

Recent results from this approach include the introduction of a range of homo- and hetero-nuclear NMR experiments which allow the characterisation of molecular materials at natural isotopic abundance, providing a new analytical tool for chemistry. These methods have been applied notably to the characterisation of pharmaceutically important polymorphs. We have also developed a range of techniques capable of studying solid proteins, to determine their physical chemistry (notably we have provided methods for studying protein flexibility and dynamics, as well as protein-water interactions). These properties are essential to understand their function. In another area we have provided methods that allow the detailed characterisation of catalytic processes occurring on surfaces, with an emphasis on understanding industrially important reactions such as metathesis. Finally, we are currently developing methods, for example, to characterise the fine elements of structural disorder in functionally important materials.

Much of our work is carried out in collaboration with leading groups in Lyon and around the world, in the USA, in England or in Italy for example.

►►► *New NMR experiments are developed from basic quantum mechanics to advanced applications*

Computer Science
LABORATORY

► **Director** ► *Frédéric DESPREZ - **Senior Researcher***
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► **Total personnel** ► *92*
► **Partners** ► *CNRS, INRIA, UCB Lyon 1*

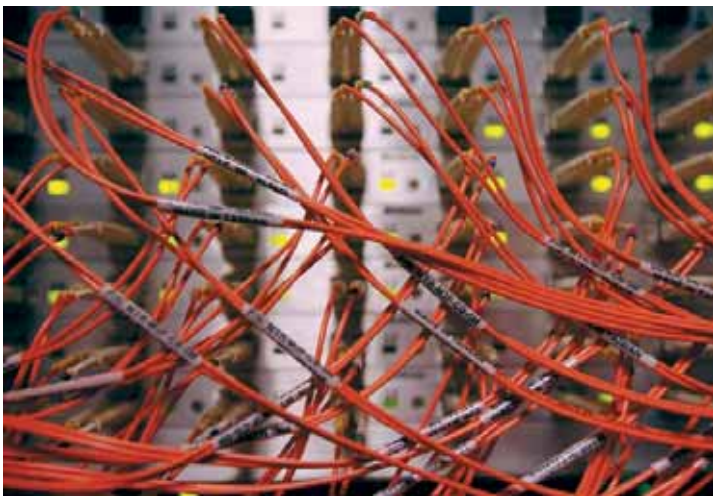
The LIP is the computer science laboratory of the ENS Lyon. It is associated with CNRS, ENS Lyon, INRIA and *Université Claude Bernard* (UMR CNRS - ENS Lyon - UCB Lyon - INRIA 5668). 92 people belong to the laboratory (20 professors or assistant professors, 19 researchers for INRIA and CNRS, 3 postdocs, 6 expert engineers, 35 PhD students, 4 engineers, and 5 secretaries. The laboratory has many international collaborations. It is made up of 5 teams:

- Arénaire (Computer Arithmetic), project leader Gilles Villard
- Compsys (Compilation and Embedded Computing Systems), project leader Alain Darte
- MC2 (Models of Computation and Complexity), project leader Jacques Mazoyer
- PLUME (Automated deduction), project leader Pierre Lescanne
- GRAAL (Algorithms and Scheduling for Distributed Heterogeneous Platforms), project leader Frédéric Vivien
- RESO (Optimized protocols and software for high performance networks), project leader Pascale Vicat-Blanc Primet

46 PhD students of the laboratory have defended their dissertation between September 2001 and October 2006. They have been recruited in the best research and/or faculty positions.

Examples of industrial collaborations: Sun-Microsystems, Myricom, France-Telecom R&D, ST Microelectronics, IBM, HP Labs, etc.

Examples of academic collaborations: University of Tennessee at Knoxville, University of California at Los Angeles, University of California at San Diego, University of California at Berkeley, University of Bergen, University of Southern Denmark, Japan Advanced Institute of Science and Technology, Novi-Sad University, University of Queensland, IMEC, University of Urbana-Champaign...



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RESEARCH TOPICS
• Computer arithmetic• Compilation and embedded computing systems• Models of computation and complexity• Automated deduction • Algorithms and scheduling for distributed and heterogeneous platforms• Optimized protocol and software for high performance networks

RELATED FIELDS
• Algorithmic
• basic and applied computer science

AREAS OF APPLICATION
• Life science applications (ex. Decrypthon)
• Design of safe systems• High performance numerical computations • Complex systems

EQUIPMENT
• PC clusters
• Grid'5000 and Decrypthon clusters

INDUSTRIAL PARTNERS
• Sun-Microsystems • Myricom
• France-Télécom R&D
• ST Microelectronics
• IBM • HP Labs
Etc.

Project-team Arénaire, Computer Arithmetic

► **Team leader** ► *Gilles VILLARD **Senior Researcher** - Gilles.Villard@ens-lyon.fr*
► **Team members** ► *Florent DE DINECHIN **Associate Professor** ► Claude-Pierre JEANNEROD **Researcher** ► Jean-Michel MULLER **Senior Researcher** ► Vincent LEFÈVRE **Researcher** ► Damien STEHLÉ **Researcher** ► Nathalie REVOL **Researcher** ► Nicolas BRISEBARRE **Associate Professor** ► Serge TORRES **Engineer** ► **8 PhD students***

Arénaire aims at elaborating and consolidating knowledge in computer arithmetic. Reliability, accuracy, and performance are the major goals that drive our studies. Our overall objectives are centered on the fundamental problems of computer arithmetic that are number representation, algorithm development, and implementation for arithmetic operators.

We contribute to the improvement of the available arithmetic, at the hardware level as well as at the software level, on computers, processors, dedicated or embedded chips. Improving computing does not only mean getting more accurate results or getting them more quickly: we also take into account other constraints such as power consumption, or the reliability of numerical software.

A main challenge for efficiency and quality in high performance computing is to combine hardware, algorithmic, and mathematical aspects, together with validation techniques. In this direction we especially:

• Study the interaction between the arithmetic operator design and problem solving constraints.

• Develop automatic tools for code generation and optimization, and for formal proof generation and checking. Normalization and validation aspects play here a central role.

• Emphasize software library developments and diffusion for validated computing.

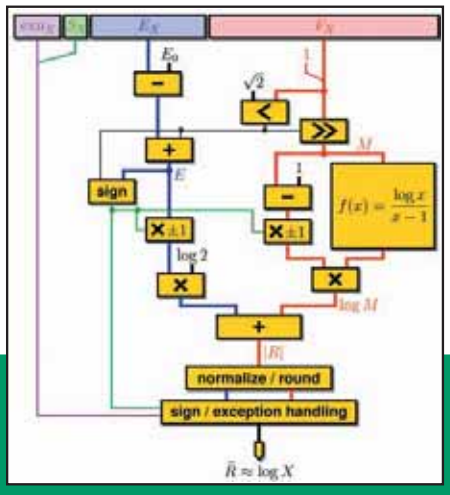
Our research is organized along three axes described below by keywords:

• Hardware arithmetic operators : VLSI and FPGA circuits, low-power operators, fixed and floating-point numbers. Finite fields in cryptography.

• Software arithmetic operators: fixed and floating-point numbers, elementary functions, intervals, large precision, exact computation. Software libraries for correct rounding, floating-point arithmetic on integer units, polynomial approximation under machine or mathematical constraints, handling of larger precisions.

• Properties of operators and validation: properties of floating-point arithmetic, correct rounding, rounding error, Taylor models. Error estimation and bounding, code validation, formal methods. Software libraries for exact or validated computing, algorithmic complexity, adaptative algorithms, exact and interval linear algebra, matrix polynomials in control, global optimization, lattice reduction and its applications.

Application domains: Our expertise covers application domains for which the quality of the arithmetic operators is an issue. It can be applied for instance to hardware oriented developments for designing arithmetic primitives that are specifically optimized (digital signal processing, embedded applications, etc.). It can also be applied to software programs when numerical reliability issues arise (critical application safety, reproducibility of computations, etc.).



►►► *Floating-point operator for the logarithm function*

COMPSYS: COMPILATION AND EMBEDDED COMPUTING SYSTEMS

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► **TEAM MEMBERS** ► *Paul FEAUTRIER **Professor** ► Antoine FRABOULET **Assistant Professor** ► Fabrice RASTELLO **Associate Researcher** ► Tanguy RISSET **Professor** ► Benoît BOISSINOT, Florent BOUCHEZ, Nicolas FOURNEL, Philippe GROSSE, Alexandru PLESCO and Clément QUINSON: **PhD students***

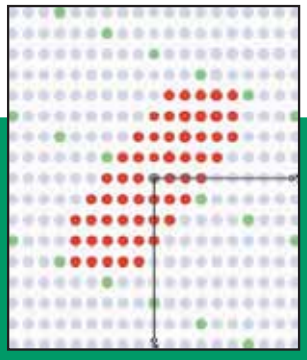
The objective of Compsys is to adapt and to extend some code optimization techniques, primarily designed for compilers/parallelizers for high-peformance computing, to the special case of embedded computing systems. In particular, Compsys works on micro-code optimizations for specialized processors and on high-level synthesis of hardware accelerators. The main characteristic of Compsys is to focus on combinatorial optimization problems (graph algorithms, linear programming, polyhedra) coming from code optimization problems arising in this field (register allocation, cache optimization, memory allocation, scheduling, optimizations for power, automatic generation of software/hardware interface, etc.) and to validate the developed techniques in compilation tools. The main new achievements and current developments of Compsys are:

• the study of a new approach for register allocation, in two steps, with a spilling phase (optimization of loads and stores) followed by an assignment phase including register coalescing (optimization of register-to-register moves); complexity study, developments of heuristics and algorithms, integration within the STMicroelectronics compiler.

• the introduction of new mathematical tools (related to critical lattices) to optimize the memory reuse for multi-dimensional arrays; theoretical and software developments (software tool Cl@k) with integration (in progress) in compilers for source-to-source program transformations.

• the development of methodologies for Systems-on-Chip: prototypes of high-level synthesis tools, developments of software/hardware interfaces, in particular for the SocLib platform, traffic analysis, power consumption analysis for embedded operating systems, etc.

Compsys publishes, among others, in conferences such as ASAP, CASES, CGO, IPDPS, DATE, and in journals such as Integration, the VLSI Journal, the Journal of VLSI Signal Processing, the Journal of Parallel and Distributed Systems, IEEE Transactions on Computers, the International Journal of Parallel Programming. The visibility of Compsys in the "embedded computing systems world" is acknowledged by the participation of its members in program committees of conferences such as ASAP, CASES, DATE, and in the editorial board of ACM Transactions on Embedded Computing Systems. Compsys is also member of HIPEAC, European network of excellence on High-Performance Embedded Architecture and Compilation. Our main French academic colleagues are the members of the Inria R2D2 and Alchemy projects, and the partners of the SocLib initiative (in particular, F. Pétrot); outside France, we have colleagues in the universities of Rice (J. Mellor-Crummey), Colorado State (S. Rajopadhye), UCLA (J. Palsberg), Urbana-Champaign (D. Padua), Michigan (S. Mahlke), at IMEC (F. Catthoor), and Leiden (E. Deprettere), etc. Our industrial partners are HP Labs and Synfora (CA), ST Microelectronics (both in compilation and high-level synthesis), and CEA.



Example of mathematical tool for code optimization: critical lattices and polyhedra for memory reuse ►►►

MC2 : Models of Computation and Complexity

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► *Eric RÉMILA* ***Associate Professor*** ► *Andreï ROMASCHENKO* ***Researcher***
► *Nicolas SCHABANAL* ***Researcher*** ► *Eric THIERRY* ***Associate Professor***
►*Olivier FINKEL* ***Researcher*** ► ***9 PhD students***

The team "Modèles de Calcul et Complexités" is interested in different computation models and in corresponding algorithms complexity notions and complexity classes in order to better understand complexity notions which appear in different fields.

Three kinds of computations are considered : sequential computation (on booleans, reals or complex) the essential problematics of which is the study of "P = NP", parallel computation (on cellular automata) which set down the question of knowing whether linear time is equal to real time and the quantic calculus where it is possible to give lower bounds in time. We have got new examples showing that quantic computation is more powerful than the former ones. It has to be noted that we have given a topological new definition of regularity unifying the regularity notions corresponding to the above models.

Such works cannot be led without algorithmics. Either one refines complexity of problems on reals or one designs new fast randomized algorithms. Concerning boolean computation, we have exhibited new factorization algorithms of sparse matrices and decision algorithms for finitely generated compact groups.

Besides time complexity we also study Kolmogorov complexity for which the complexity of a computation is expressed according to the length of programs performing it. We obtain new results on links between Kolmogorov complexity and Shannon information theory.

Other aspects of complexity naturally appear in Computer Science. Thus self-organization may emerge in evolution of some cellular automata as particles (cluster, agregats,...) or as moving borders between actions of subautomata. Studying these phenomena has led to partial formal definitions of emergence and to automata classifications whose structures we are finding. This too leads to algorithmics (synchronization, fault tolerant computations).

We are also investigating in social graphs (social relations, internet,...) whose best definition today is algorithmic (it is possible to very quickly -logarithmically- communicate relatively to the number of vertices). Besides design of new more efficient algorithms, we have begun their structural investigation (small worlds). We were wondering whether a given graph may be easily transformed into a small world: our first results show that it is the case for a wide variety of graphs. Main application domains are: internet, computer networks.

We have started the study of robustness of cellular automata on a one dimensional network (a local transition may occur or not following a probability law). We have experimentally identified robust cellular automata and proved the robustness of some of them. The main feature is that the probabilistic behaviour of robust automata is, in some cases, completely understood (fixed point and transitories). Such works need to be extended to more complex automata and to higher dimensions.

►►► *Orbit of a cellular automaton constructed from two others one*

PLUME : AUTOMATED DEDUCTION

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► **TEAM MEMBERS** ► *Jean DUPRAT, Philippe AUDEBAUD and Daniel HIRSCHKOFF **Associate Professors** ► Tom HIRSCHOWITZ **Assistant Researcher** ► Aurélien PARDON, Stéphane LE ROUX, Damien POUS and Dragisa ZUNIC **PhD students***

"The unreasonable effectiveness of logic" (P. Wadler) is at the heart of a rich interaction between two research fields, namely proof theory and the theory of programming languages, since the discovery of the Curry-Howard correspondence in the 1980's.

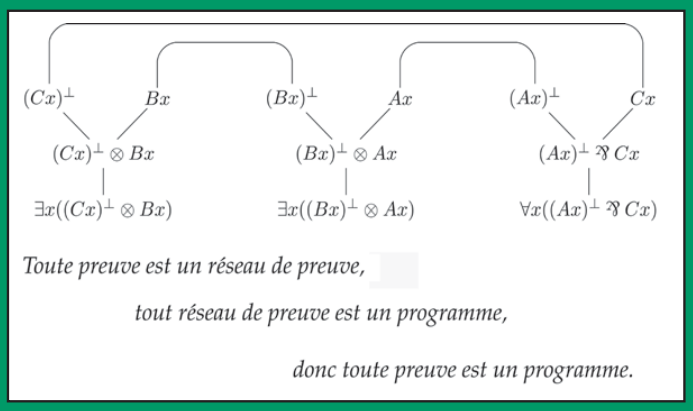
The Curry-Howard correspondence relates proofs and programs. Specifically, it relates the process of typing a program to the elaboration of a proof, and the process of putting this proof in canonical form to the execution of the corresponding program.

A deductive system is viewed as a programming language whose instructions have the shape "put this proof in canonical form". Reducing complex proofs to canonical form is computationally complex. So, the expressive power of the deductive system is directly related to that of the corresponding programming language.

Symmetrically, a typed programming language is viewed as a deductive system, in which proving a formula amounts to finding a program that has this formula as its type. The expressive power of the programming language is thus directly related to that of the corresponding deductive system.

The Curry-Howard correspondence gradually extends to new application domains, providing a logical meaning to new programming paradigms, or a computational meaning to logical theories.

The Plume team works primarily on:
the foundations of mathematics, following various approaches (Curry-Howard, but also categorical logic), the effective formalization of mathematics in the Coq proof assistant - based on Curry-Howard, and programming language design, especially concerning modularity, concurrency, and mobility, using methods inherited from the Curry-Howard tradition (static typing, operational semantics, observational equivalence, compositionality, etc.).



►►►
Each proof is a proof net,
Each proof net is a program,
Therefore each proof is a program

GRAAL: Algorithms and Scheduling for Distributed Heterogeneous Platforms

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► *Eddy CARON* ***Associate Professor*** ► *Frédéric DESPREZ* ***Senior Researcher***
► *Jean-Yves L'EXCELLENT* ***Researcher***
► *Yves ROBERT* ***Professor*** ► *Eric BOIX* ***Engineer*** ► *Aurélia FÈVRE* ***Engineer***
► *Abdelkader AMAR* ***Postdoctoral fellow*** ► *Lionel EYRAUD-DUBOIS* ***Postdoctoral fellow***
► *Emmanuel AGULLO, Raphaël BOLZE, Jean-Sébastien GAY, Loris MARCHAL, Jean-François PINEAU, Cédric TEDESCHI, Matthieu GALLET and Veronika REHN:* ***PhD students***

New computing platforms are no longer monolithic. They consist of collections of computers which can be scattered across an administrative domain, a country, or even the world. Such platforms can be built by the interconnection of computing centers, each holding clusters typically gathering several dozens of multi-processor nodes. They can also be made up by individual machines joining a Peer-to-Peer system. In all cases, the set of computational resources is heterogeneous: the processors have different computing speeds and memory capabilities. The computers from different sites are interconnected by wide-area network links and the platforms are often volatile: computers may join or leave them at any time, or may break down.

Deploying highly demanding applications on such platforms is called Grid computing. The efficient use of Grids poses new challenges. In this context, we address fundamental algorithmic and scheduling problems that have received little attention so far. An enormous effort has been devoted to enable Grid computing by addressing interconnection and security problems, or by building middlewares. However, we believe that many projects have failed to study fundamental problems such as the complexity of problems and algorithms, and scheduling heuristics. Also theoretical results are rarely validated on available (software) platforms.

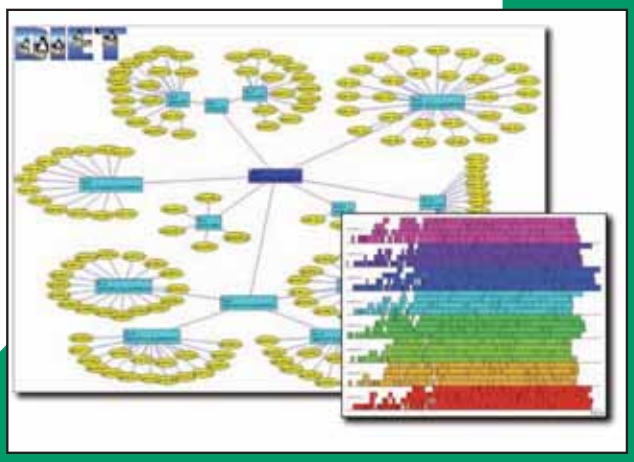
The GRAAL research team tackles two main challenges for the widespread use of heterogeneous distributed platforms: the development of environments that will ease their use (in a seamless way) and the design and evaluation of new algorithmic approaches for applications using such platforms.

The research work is organized in three themes:

• Scheduling strategies and algorithm design: communication-aware models of platforms, off-line and on-line scheduling, distributed scheduling, data and application mapping, performance evaluation.

• Parallel sparse direct solvers: scheduling under memory constraints, out-of-core solvers, functionalities for hybrid direct-iterative solvers. Research results are implemented in the freely-available MUMPS software.

• Network enabled servers: data management, performance analysis/prediction, scheduling, middleware deployment. Research results are implemented in the freely-available DIET middleware.



Scheduling applications on large-scale distributed platforms

RESO: OPTIMIZED PROTOCOLS AND SOFTWARE FOR HIGH SPEED NETWORKS

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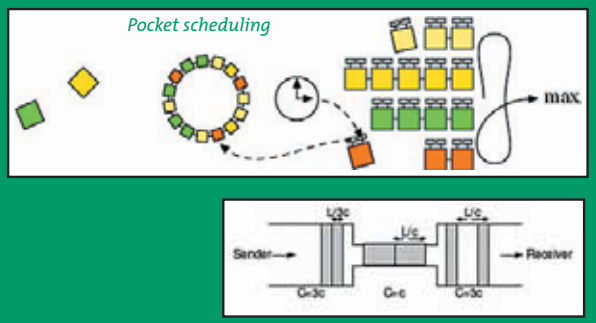
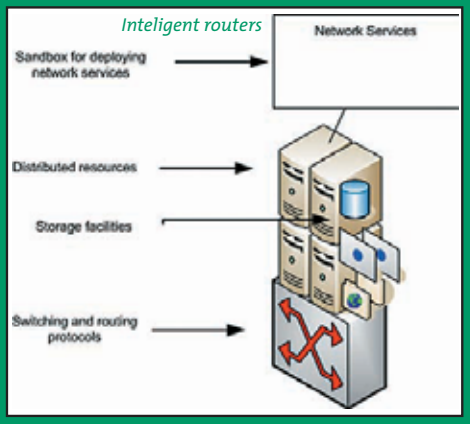
► **TEAM MEMBERS** ► *Olivier GLUCK* ***Associate Professor*** ► *Paulo GONCALVÈS* ***Associate Researcher*** ► *Laurent LEFEVRE* ***Associate Researcher*** ► *Jean-Patrick GELAS* ***Associate Professor*** ► *Isabelle GUERIN-LASSOUS* ***Professor*** ► *Narjess AYARI, Ludovic HABLOT, Patrick LOISEAU, Dino LOPEZ, Sébastien SOUDAN, Rémi VANNIER:* ***PhD students***

RESO studies protocols for very high speed networks and communication issues in Grids. Research areas concern new protocol design, communication software, performance optimisation, performance measurement, end to end quality of service studies, bandwidth sharing and reservation, high speed networks congestion control, traffic measurement and modelling. Approaches that we propose are based on protocol and function offloading, programmable and autonomous networks, data path shortening, flow and service differentiation, flow scheduling and virtualization. Very high rates (gigabits or 10 gigabits) induce a protocol processing power that is at the limit of the processor capacities. Bursty traffic of grids are not well modelled by classical statistical distributions. To better understand and model phenomenon and to validate our proposals, we adopt an experimental approach based on prototype development and large scale testbed deployment and evaluation. We are collaborating with industrials like France-telecom, Alcatel, Hitachi and Myricom. We are participating in the design and deployment of international and national grid plateforms (DataGrid, DataTAG, eToile, Grid5000) based on very high speed networks (VTHD, GEANT, RENATER4). We are participating in standard body like Open Grid Forum and IETF.





Reso is exploring and removing barriers that disable high performance computing applications to fully benefit from the huge capacities offered by high speed long distance optical networks in Grids

ENS LYON

Earth Science
LABORATORY

► **Director** ► *Bruno REYNARD* ***Senior Researcher***
► **e-mail** ► *bruno.reynard@ens-lyon.fr*

► **Total personnel** ► *50*
► **Partners** ► *CNRS, UCB Lyon 1*

The scientific activies of the Laboratoire des Sciences de la Terre can be described in four major themes:

- Formation of the Solar System
- Dynamics of the surface of the Earth and planets
- Dynamics of the Earth and planetary interiors
- Interactions of the mineral and the living

Various approaches are used : physics of natural processes, geology, remote sensing, analytical imaging and tomography, mass spectrometry, vibrational spectroscopy, experimentation based on instrumental developments on high quality equipment in the laboratory: multi-collection ICP-MS in geochemistry, high pressure presses and Raman spectrometers in mineralogy, computers for numerical modelling and image processing in geodynamics and tectonics, or on large instruments such as synchrotrons.

The LST is installed on two sites at the ENS and at the *Université Claude Bernard Lyon 1*, and its research activity is transferred to education through the implication of researchers in teaching at the Master of Earth Science level, and also through connexions with physics in the Master of Physics and Chemistry.

Outcrops of the most ancient rocks on Earth, age of about 3.8 billion years, in the Isua region, Greenland (courtesy F. Albarède). Early differentiation of the Earth's mantle in the first few hundred million years after the formation of our planet was demonstrated from the isotopic composition of Nd in these rocks using the plasma source mass spectrometer of the Laboratoire des Sciences de la Terre. The physics of this phenomenon and the thermal evolution of the Early Earth are currently being modelled by our geodynamics team. Search for traces of the earliest activity of life on Earth in these rocks is under investigation using isotopic and mineralogical techniques developed in the laboratory, in order to compare the Early environment on Earth and that of Mars our geomorphology team has reconstructed from remote sensing and image analysis of the Martian surface.

RESEARCH TOPICS
• Geochemical budget of planets
• Terrestrial material under extreme conditions
• Structure and dynamics of the lithosphere
• Planetology • Mantle dynamics
• Exobiology and origin of life
• Life under extreme conditions

RELATED FIELDS
• In situ characterization of materials
• Trace elements et isotopic analysis
• Numerical modeling and simulation
• Remote sensing

AREAS OF APPLICATION
•Properties and behavior of materials at high pressure and temperature
• Natural hazards
• Environment and energy (fossil fuel)

INDUSTRIAL PARTNERS
• St-Gobain • Risques naturels (Concrète)
• Cimentiers (Lafarge) • CNES, BRGM, CEA, IRD

EQUIPEMENT
•MC-ICP-MS and LA-ICP-MS
• Raman spectroscopy
• High-pressure presses

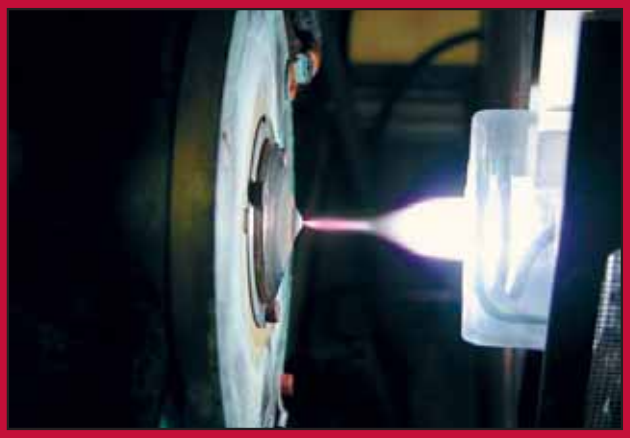
Geochemistry and Cosmochemistry

► **Team leader** ► *Francis ALBARÈDE* ***Professor***
► **Team members** ► *J. BLICHERT-TOFT* ***Senior Researcher*** ► *P. GILLET* ***Professor***
► *B. REYNARD* ***Senior Researcher*** ► *G. QUITTÉ* ***Researcher*** ► *G. MONTAGNAC* ***Engineer***
► *P. TELOUK* ***Engineer*** ► *E. ALBALAT* ***Engineer*** ► *C. DOUCHET* ***Engineer***
► *Tristan FERROIR* ***PhD student***

The oldest field of interest of our group is the long-term dynamics of the terrestrial mantle and the growth of continents, particularly the most ancient rocks on Earth. The last ten years have seen a revolution in the quality and throughput of isotopic data. Investigating the isotope compositions of neodymium, hafnium, and lead in mid-ocean ridge basalts and Hawaiian volcanoes provided us with an unprecedented map of the mantle reaching the surface and cast new light on the dynamics of mantle mixing. We dated the oldest objects of the Solar System, known as refractory inclusions, at 4568.5 million years, demonstrated that 30 million years after the birth of the Solar System, the Earth's core had formed and the upper mantle was largely molten (magma ocean). We also demonstrated that continental crust appeared in the first hundreds of millions of years and argued that the formation of the first continents and the appearance of life were companion events. We also revised the age of the Martian surface by dating Martian meteorites and obtained an old age of 4.0 billion years superseding the accepted age of 180 million years. Our original investigations on the isotopes of some elements (copper, zinc, nickel, iron) are opening new perspectives on the condensation of the Solar Nebula.

We are also developing new isotopic tools and concepts relevant to the environment, such as the stable isotopes of copper, zinc, iron and the uranium-series geochemistry of oceanic sediments, to biogeochemistry and to the dating of human fossils.

Our group is actively involved in analytical and instrumental development and is recognized as a CNRS national facility. We received the first commercial multiple-collector inductively-coupled plasma mass spectrometer in 1994 and are expecting a large radius ICP-MS due Summer 2007, the third mass spectrometer of that type in the world.

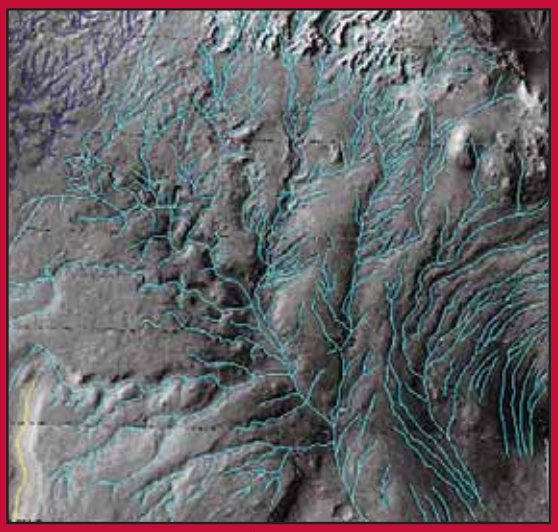


The ion source of the Plasma 54 from ENS Lyon. The plasma is produced by inductive coupling and reaches 8000°C, temperature which is necessary for the isotopic analysis of rocks, meteorites and biological samples

Dynamics of the surface of the Earth and planets

► **Team leader** ► *P. ALLEMAND* ***Professor***
► **Team members** ► *G. DROMART* ***Professor*** ► *H. LELOUP* ***Researcher*** ► *G. MAHÉO* ***Associate Professor*** ► *A. REPLUMAZ* ***Researcher*** ► *P. THOMAS* ***Professor*** ► *P. GRANDJEAN* ***Technician***
► *Caroline SASSIER, Johan KAPERSKY and Emilie GARDIN:* ***PhD students***

The surface of planetary bodies reflects the competition between the internal activity and the external one. The aim of this theme is to understand relationships between these two kinds of dynamics through remote sensing, field geology, geomorphologic analysis and measurements of sedimentary flux at various scales in space and time. The planet Mars has been investigated to understand the dynamics of the landslides of Valles Marineris. The geomorphology of the Red Planet is also used to build a climatic history and to reconsider the evolution of the atmosphere (figure). On the Earth, the uplifts of the French Alps and of the Himalaya are studied in terms of tectonic evolution. For example, the new tectonic model has been proposed for the uplift of the Mont Blanc massif. Sedimentary balances of carbonates are realized for various periods of the Mesozoic. These balances are used in models of CO_2 evolution. Finally, image correlation techniques have been developed to measure the displacement field of landslides from remote sensing data obtain by sensors onboard satellites or on unmanned radio controlled platforms. The resolution of these images ranges from 0.05m for drone platforms to 1 m for high resolution satellite data. These techniques permit us to evaluate a displacement as small as one tenth of a pixel to more than 100 pixels.



Valley network in Melas Chasma on Mars showing a density and order similar to similar scale pictures on Earth. They demonstrate the existence of a wet climate on Mars in relatively "recent" periods of its history, ca 3-3.5 billions years. Quantin et al. Fluvial and lacustrine activity on layered deposits in Melas Chasma, Valles Marineris, Mars, Journal of Geophysical Research Planets 110 (2005) E12S19

Dynamic of the Earth and Planetary Interiors

► **Team leader** ► *Yanick RICARD **senior researcher***
► **Team members** ► *F. ALBARÈDE **Professor** ► H. BERTRAND **Associate Professor** ► B. BRIAND **Associate Professor** ► J. BLICHERT-TOFT **Senior Researcher** ► F. CHAMBAT **Associate Professor** ► E. CHAMORRO **Associate Professor** ► N. COLTICE **Associate Professor** ► I. DANIEL **Professor** ► F. DUBUFFET **Researcher** ► J. MATAS **Researcher** ► B. REYNARD **Senior Researcher** ► P. TELOUK **Engineer** ► P. CAPIEZ **Engineer** ► H. CARDON **Engineer** ► C. DOUCHET **Engineer** ► G. MONTAGNAC **Engineer** ► Nadège HILAIRET, Julien MONTEUX, Mélanie CHOLLET, Nicolas FLAMENT, Ondrej SMAREK and Antoine ROZEL: **PhD students***

The "geodynamic team" studies the forces acting in the Earth's interior on geological time scales. Our main focus is the Earth's mantle that constitutes the outer 3000 km of our planet. The mantle is solid for all rapid phenomena, but behaves as a highly viscous liquid on the very long time scale of geological processes. This layer is stirred by convective motions that occur with velocities of a few cm/yr, and extract the heat stored at large depth or produced by the decay of radiogenic elements. The dynamics of the mantle is coupled with that of the liquid iron core in which the Earth's magnetic field is produced. The necessary conditions for this dynamo process provide information on the mantle thermal regime. Near the surface the mantle carries the lithosphere and the crust and controls the dynamics of plate tectonics. The forces that drive the mantle are responsible for the geological activity of the planet.

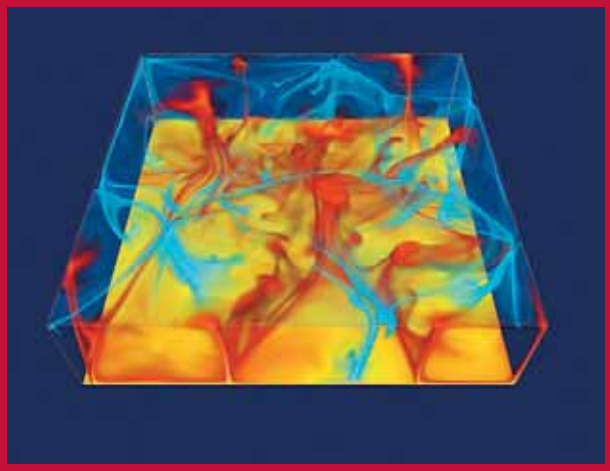
We try to understand the density structure of the mantle from the anomalies of the Earth's gravity field, from the distribution of seismic velocities, and from the confrontation with mineralogical data measured in laboratories at mantle pressure and temperature.

We model the present day dynamics of the Earth and its evolution during the last billion years using simple physical models as well as high performance numerical simulations.

We want to understand why plate tectonics is so specific to our planet by comparing the dynamics of the Earth to that of the other solid planets.

We also study the early stages of the history of the Earth when the primitive planet differenciated into mantle, core and early crust.

We have strong interactions with colleagues of Berkeley, Canberra, Minneapolis, Muenster, Yale, Zurich...

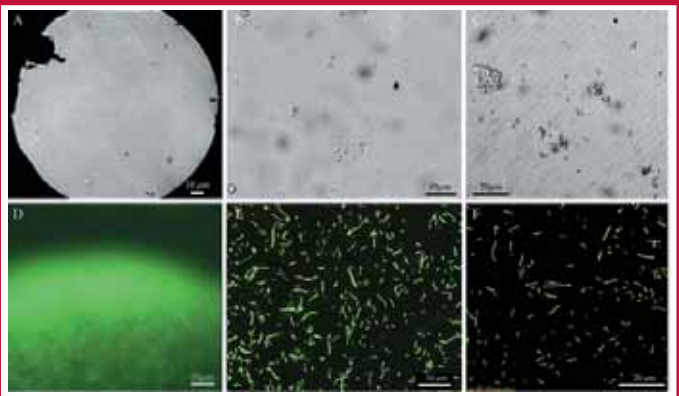


◄◄◄ *Model of convection in a box. The fluid is heated from the bottom and cooled from the surface. Thermal hot (red) and cold (blue) instabilities are rising from the bottom and sinking from the surface. The Earth's mantle undergoes this type of convective dynamics although it is not heated from its base but mostly cooled from its surface*

ORIGIN OF LIFE, AND INTERACTIONS BETWEEN MINERALS AND LIFE

► **TEAM LEADER** ► *I. DANIEL* ***Professor***
► **TEAM MEMBERS** ► *G. DROMART* ***Professor*** ► *P. GILLET* ***Professor***
► *L. LEMELLE* ***Associate Researcher*** ► *P. OGER* ***Associate Researcher***
► *S. PICHAT* ***Assistant Professor*** ► *B. REYNARD* ***Senior Researcher***
► *A. SIMIONOVICI* ***Associate Researcher*** ► *C. DOUCHET* ***Engineer***
► *Aude PICARD, Romain BASSET and Abel GUILHOU:* ***PhD students***

This theme is developed by a mixed group of biologists, geologists and physicists. We share our experimental skills to design and perform experiments dedicated to the recognition of the fingerprint of life in terrestrial and extra-terrestrial rocks. The case of extra-terrestrial rocks is of course related to the preparation of a spatial mission, which might bring back to Earth Martian rocks within the next decades. For instance, we use microscopic observations and spectroscopic methods such as fluorescence, or X-ray spectroscopy, to recognize bacteria at the surface of minerals, and to characterise the specific changes induced by the bacteria at the surface of minerals. In the frame of terrestrial issues, we attempt to estimate the limits for life within the depth of the Earth. Beyond the fundamental question, we also want to know how micro-organisms evolve with depth, and how important they are in the physical and chemical characteristics of rocks. This should help to recognize the early traces of life. Hence, we investigate by means of various spectroscopic tools the behaviour of live cells and of some cellular compounds of key interest as a function of pressure and temperature, in order to identify the changes that would affect the organic traces of life in the geological records. We also measure experimentally the isotope signature of selected elements involved in the metabolism of a large number of micro-organisms, in order to use that signature in rocks to reconstruct paleo-climates, and to look for biological signatures in old rocks. At a somewhat different scale, we also try to identify the relative role of micro-organisms in the porosity and permeability of carbonate rocks, which are key parameters to evaluate the quality of those rocks as oil reservoirs, and to infer the best process to recover as much oil as possible.



Progresses in imaging of microorganisms under high pressures in diamond anvil cells, from classical cells (left) to cells designed in the laboratory in classical (middle) or confocal (right) microscopie, in the visible (top) and in epifluorescence mode (bottom). Cell division can be followed in situ, as well as metabolism using X-ray or Raman spectroscopies.
Oger et al. Development of a low-pressure diamond anvil cell and analytical tools to monitor microbial activities in situ under controlled P and T BBA 1764 (2006) 434-442

ENS LYON

Human Virology
LABORATORY

► **Director** ► François-Loïc COSSET **Senior Researcher**
► **e-mail** ► flcosset@ens-lyon.fr

► **Total personnel** ► 72
► **Partners** ► INSERM

The Human Virology Department, a joint laboratory of the *Institut National de la Santé et de la Recherche Médicale* (INSERM) and the ENS Lyon, is pursuing basic research on the molecular biology of pathogenic human viruses, their interactions with the cellular factors that govern most aspects of their viral cycle, and the characterisation of pathologies associated to infection, such as chronic infections. These projects are particularly rich both in terms of scientific approaches and of the list of pathogens investigated (retrovirus, flavivirus, hepacivirus, gamma-herpes virus, filovirus, avian influenza virus and adeno-associated virus). They should strongly contribute to clarify the physio-pathological mechanisms of the viruses studied as well as to discover novel therapeutic targets or strategies.

These projects fall into four types of fundamental studies related to different aspects of virus/cell interactions: i) cell entry, ii) replication and gene expression, iii) virus assembly and iv) viral pathogenesis. Another category of projects, derived from the basic projects, aims to develop biotechnology applications using the viruses that have been studied as tools (e.g., transgenesis using vectors derived from lentiviruses) and to define antiviral strategies against some human pathogens (e.g., gene therapy, screening of antiviral compounds and vaccine development). The Human Virology Department is a partner of IFR128 - BioSciences Lyon-Gerland and is running the vector core facility that provides to other teams access to gene transfer technologies using viral vectors derived from retroviruses (MLV, HIV, SIV) and adeno-associated viruses (AAV).

RESEARCH TOPICS
• Virology
• Biotherapy

RELATED FIELDS
• Molecular biology
• Cellular biology
• Biochemistry
• Vectorology
• Vaccinology

AREAS OF APPLICATION
• Antiviral strategy
• Gene therapy
• Gene transfer
• Vaccines

Viral envelopes and engineering of retroviruses

► **Team leader** ► *François-Loïc COSSET* ***Senior Researcher*** *- flcosset@ens-lyon.fr*
► **Team members** *Assembly of viral envelopes:* ► *Bertrand BOSON* ***Senior Researcher*** ► *David BOUARD* ***PhD student*** ► *Christelle GRANIER* ***Engineer***
Cell entry and neutralisation mechanisms: ► *Birke BARTOSCH* ***Associate Researcher*** ► *Marlène DREUX* ***PhD student*** ► *Dimitri LAVILLETTE* ***Assistant Researcher*** ► *Géraldine VERNEY* ***Engineer*** ► *Judith FRESQUET* ***Engineer***
Vectorology, Gene therapy and Vaccines: ► *Caroline COSTA* ***Engineer*** ► *Pia DUPEYROT-LACAS* ***Engineer*** ► *emmanuel GAUTHIER* ***Postdoctoral fellow*** ► *Didier NEGRE* ***Associate Researcher*** ► *Judit SZECSI* ***Postdoctoral fellow*** ► *Els VERHOEYEN* ***Associate Researcher*** ► *Cécilia FRECHA* ***PhD student***

Research supported by: INSERM, EU, ANRS, AFM, VLM, Région Rhône-Alpes,
Team certified by the *Ligue Nationale contre le Cancer*

The manipulation of viral genomes and the engineering of viral particles lead to fascinating and powerful perspectives in several areas of biomedical research, pending a precise understanding of the molecular mechanisms of viral replication. Thanks to their capacity to integrate in host cell DNA, retroviruses allow the production of attractive tools for gene delivery. Furthermore, the flexibility by which different viral or cellular components can be assembled on/in viral particles allows to derive macromolecular platforms that display miscellaneous polypeptides of interest, an approach useful in the domains of vaccinology, gene therapy and compound screening. Hence, our projects focus on i) the investigation of the properties of the viral surface glycoproteins derived from retrovirus, flavivirus, hepacivirus and avian influenza virus, and ii) the development of novel gene transfer vectors and viral engineering techniques.

On a fundamental side, an important part of our objectives are to understand the function and the regulation of these proteins at the level of i) the assembly of enveloped viral particles, ii) their interaction with the external environment, notably the innate and adaptive immune system, and iii) the molecular processes governing the cellular entry of enveloped viruses and subsequent membrane fusion.

We are also pursuing our studies on the optimisation of methods allowing gene delivery in vivo, by direct inoculation of defective viral vectors. The specific objectives are: i) the development of gene transfer vectors, derived from onco-retroviruses and lentiviruses; ii) the investigation of strategies allowing a targeted gene transfer, restricted to cells expressing a specific cell surface receptor, through modifications of the viral surface glycoproteins. These studies will ultimately lead to the development of new tools, suitable for in vivo transgenesis and human gene therapy.

Finally, our studies on viral engineering and more particularly on the viral surface glycoproteins allow several therapeutic applications, particularly in: i) diagnostic, ii) antiviral compounds screening and iii) vaccine development. Some of these applications are being investigated, particularly in the field of hepatitis C and avian influenza.

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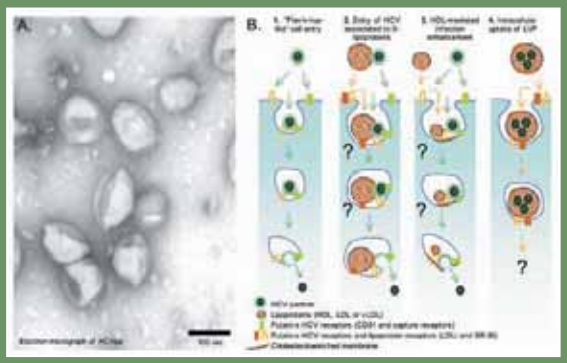


A. Assembly of HCVpp. Pseudo-particles displaying the E1E2 surface proteins of hepatitis C virus (HCV) from retroviral particles and can be used as a novel HCV vaccine candidate and as a flexible infection assay, allowing to investigate the factors that determine HCV entry into cells. B. Modulation of cell entry by HCV-lipoprotein interplay. 1. similar to cell entry of flaviviruses, HCV internalisation could be induced by interactions with receptors of its E1E2 glycoproteins, i.e., SR-BI, CD81 and other molecules, leading to membrane fusion in acidic endosomal vesicles and core release into the cytoplasm. 2. intracellular uptake of HCV particles associated to ß-lipoproteins could be induced via interaction of HCV-lipoprotein complexes with lipoprotein receptors, i.e., LDLr and SR-BI. Further interaction of HCV E1E2 glycoproteins with their receptors would be required to induce membrane fusion and core release. 3. the cholesterol transfer function of SR-BI from HDL enhances HCV infection, perhaps by promoting HCV internalisation or by increasing membrane fusion processes upon modification of lipid membrane composition. 4. intracellular uptake of HCV embedded into ß-lipoproteins, in the form of lipo-viro-particles (LVPs), via interactions with lipoprotein receptors, i.e., LDLr and SR-BI

Investigating replication of the human viruses HIV and HCV and their interaction with the cellular prion

► **Team leader** ► *Jean-Luc DARLIX **Senior Researcher** - jldarlix@ens-lyon.fr*
► **Team members** ► *Andrea CIMARELLI **Associate Researcher** ► Pascal LEBLANC **Associate Researcher** ► Delphine MURIAUX **Associate Researcher** ► Antoine CORBIN **Associate Professor** ► Valérie ATTUIL **Postdoctoral fellow** ► Sandrine ALAIS **Engineer** ► Caroline GABUS **Engineer** ► Christelle DAUDE **Technician** ► Roland IVANYI-NAGY **PhD student** ► Caroline GOUJON **PhD student** ► Boyan GRIGOROV **PhD student** ► Lise RIVIERE **PhD student** ► Vanessa ARFI **PhD student** ► José Luis GARRIDO **PhD student***

The overall objective of our ongoing research is the understanding of the structure and replication of the human viruses HIV and HCV that have worldwide impacts on health, economy and development. Another objective of our research is to exploit simple biochemical strategies to search for new anti-viral drugs aimed at inhibiting HIV and HCV.

LaboRetro has the following research program on HIV, HCV, Prions and anti-viral drug screening:

1) The understanding of the mechanisms by which HIV-1 and its close relative SIV replicate in dendritic cells (DCs), macrophages and CD4+ T cells since they are the primary targets for virus replication in vivo. We focus on identifying and characterizing the interactions and interplay between viral components and cellular factors during the early and late phases of virus replication. In that respect a new function of the viral protein VPX has been discovered (Cimarelli et al.).

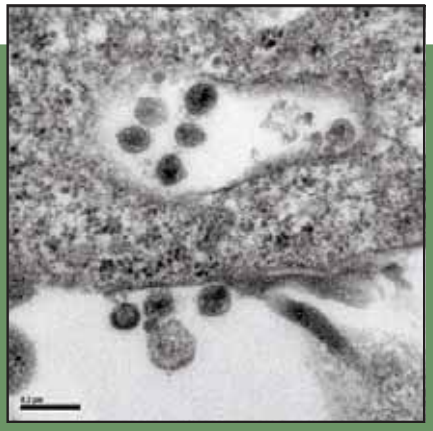
2) To understand how HIV-1 uses basic biological processes in the course of virus assembly, trafficking and production. In this respect, we recently found that HIV-1 can accumulate in intracellular vesicles before being released by exocytosis (Muriaux et al.).

3) To investigate the process of genomic RNA replication of the hepatitis C (HCV) virus. Our most novel findings show that the HCV genomic RNA can form dimers and that the viral Core protein controls RNA dimerization and replication with possible recombination events (Darlix et al.).

4) Prions are ubiquitous in higher eukaryotes and are strongly associated with the so-called prion diseases, also known as CJD, Mad-cow and Scrapie. We just discovered that ubiquitous endogenous retroviruses of mammals (MLV's) can function as effective vectors for the dissemination of the pathological form of the Prion (Leblanc et al.,).

5) We, in collaboration with EC (TRIoH), Biotech's and the faculty of Pharmacy of Strasbourg (Y. Mély), have an ongoing project to search for anti-HIV and anti-HCV targeting the viral RNA chaperones, namely HIV-1 NC and HCV Core.

For articles, references and citations, consult Darlix, J.L. at (http://www.scopus.com).



Electron Microscopy of HIV-1 infected cells reveal localisation of newly formed HIV in endosomes and at the cell surface

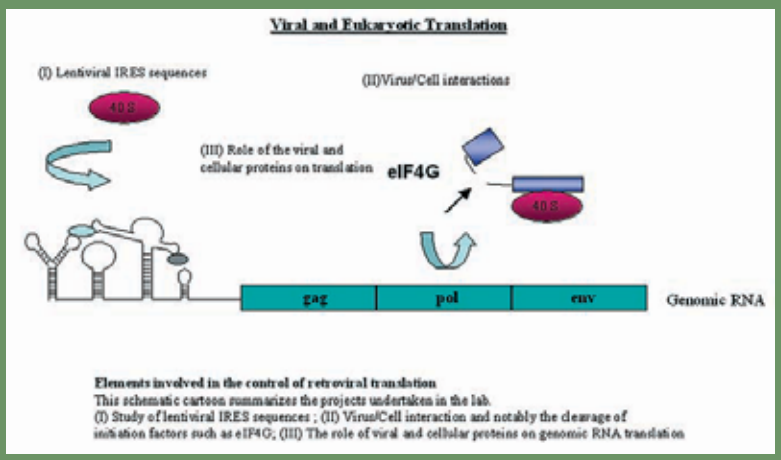
HUMAN VIROLOGY LABORATORY

Research Field: Virology and Biochemistry

► **Team leader** ► *Théophile OHLMANN **Associate Researcher** - tohlmann@ens-lyon.fr*
► **Team members** ► *Laurent BALVAY **Lecturer** ► Didier DECIMO **Engineer***
► *Olivier MONCORGE **Engineer** ► Valentina CAMERINI **PhD student***
► *Ricardo SOTO RIFO **PhD student** ► Emiliano RICCI **PhD student***

Translation is one of the last steps in the control of gene expression and plays critical roles in many important aspects of cell metabolism including cell growth, proliferation and development. One of the main advantages of translational control is the rapid response to stimuli in the absence of transcription. Translation rates can be controlled at three distinct steps: initiation, elongation and termination with the initiation phase being predominantly regulated. As such, controls impinging on initiation are exerted at the level of RNA structure by the intrinsic conformation of the 5' untranslated region that precedes the AUG initiation codon and by the subtle interplay of a set of proteins called eukaryotic initiation factors (eIF). These polypeptides are absolutely required for several critical steps such as bringing the Met-tRNAi to the 40 S ribosomal subunit (done by eIF2), bind the 40 S ribosomal subunit to the mRNA (achieved by eIF3 and eIF4F) and assist the scanning of the ribosome on its way to the correct AUG codon (catalysed mainly by eIF4F and eIF1).

The work carried out in our lab is aimed at improving our comprehension of the initiation step of protein synthesis from the assembly of the preinitiation complex, its attachement to the mRNA and its linear migration to the initiation codon. Retroviruses are single stranded positive RNA viruses that are both capped and polyadenylated as they are produced by the cellular RNA pol II polymerase. Interestingly, it has also been shown that retroviruses, and in particular lentiviruses (HIV-1, HIV-2, SIV and FIV) do possess one or several IRES sequences within their genomic RNA. In addition, lentiviral infection provokes cellular disorders such as the cleavage of the initiation factor eIF4G that has an impact on both cellular and viral translation. For all these reasons, lentiviruses are a good paradigm to study Eukaryotic translation initiation.

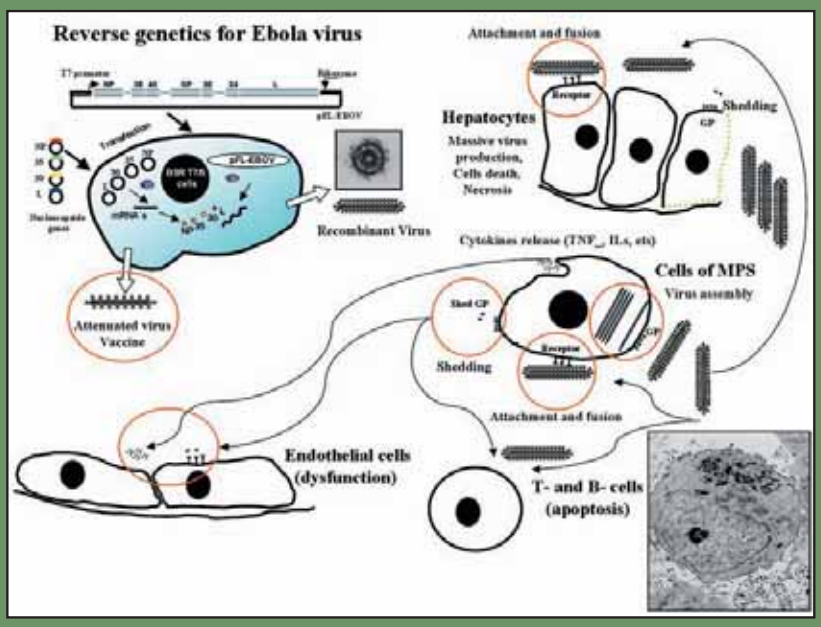


Elements involved in the control of retroviral translation
This schematic cartoon summarizes the projects undertaken in the lab.
(I) Study of lentiviral IRES sequences ; (II) Virus/Cell interaction and notably the cleavage of initiation factors such as eIF4G; (III) The role of viral and cellular proteins on genomic RNA translation

Filovirus Laboratory

► **Team leader** ► *Dr. Viktor VOLCHKOV* ***Professor*** *- volchkov@cervi-lyon.inserm.fr*
► **Team members** ► *Valentina VOLCHKOVA* ***Postdoctoral fellow***
► *Michèle OTTMANN-TERRANGLE* ***Associate Professor*** ► *Mikel MARTINEZ* ***Postdoctoral fellow***
► *Olivier REYNARD* ***research assistant, CDD*** ► *Yannik BOEHMANN* ***Postdoctoral fellow***
► *Sebastien DELPEUT* ***PhD student*** ► *Mathieu MATEO* ***PhD student***

The filoviruses, Ebola virus (EBOV) and Marburg virus (MARV), cause periodic outbreaks of severe hemorrhagic fever in humans with mortality rates from 40 to 90%. This extreme virulence has made EBOV and MARV of concern both as naturally emerging pathogens and as potential bioweapons. The molecular mechanisms leading to the severe pathogenesis of the filovirus infection have not as yet been completely determined. Understanding of the mechanisms contributing to the virus virulence is the overall goal of the Filovirus Laboratory. The main research areas include molecular and cell biology of the Filoviruses, anti-virus treatment and vaccine development.



During its life cycle filoviruses accomplish four major goals:
• entering the susceptible cells,
• replication of the viral genome,
• assembly of viral particles
• altering functions of the infected cells for dissemination of the infection.
A reverse genetics system for EBOV was first developed in our laboratory thus allowing recovery of recombinant viruses from cDNA clones and engineering mutations in their genomes. Recently, in collaboration with researchers from the Institute of Virology, Marburg (Germany) a similar system was generated for MARV. Using the systems we are investigating the role of viral proteins in pathogenicity. Studies are directed toward determining what protein domains and modifications are critical to virus assembly and replication in target cells

HUMAN VIROLOGY LABORATORY

Cellular and Viral Oncogenesis

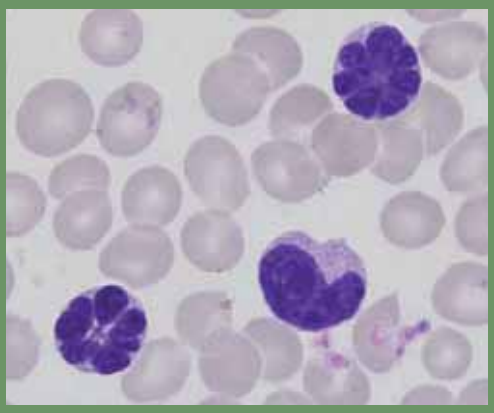
► **Team leader** ► *Marc CASTELLAZZI* ***Senior Researcher*** *- marc.castellazzi@ens-lyon.fr*
► **Team members** ► *Madeleine DUC-DODON* ***Senior Researcher***
► *Louis GAZZOLO* ***Senior Researcher*** ► *Oliver GUBBAY* ***Postdoctoral fellow***
► *Amélie SABINE* ***PhD student*** ► *Maya HOBEIKA* ***PhD student***
► *Mélanie WENCKER* ***PhD student*** ► *Soeren HANSEN* ***PhD student***
► *Anne-Sophie KUHLMANN* ***PhD student***

Our work is aimed at dissecting the molecular and cellular mechanisms, which control two distinct steps in tumour progression:

(i) an early step exemplified by the infection of human immature thymocytes and T lymphocytes by HTLV-1 (= Human T cell Leukemia/ Lymphotropic Virus, type 1), that is linked to the initiation and the development of Adult T-cell Leukemia (= ATL); our studies are focusing on the effects of Tax and HBZ, two major regulatory proteins encoded by the retrovirus, by determining how they interfere with or modify the expression or activity of transcription factors involved in the maturation and in the activation of T lymphocytes;

(ii) a late step, exemplified by the activation of endothelial cells, a complex process associated with cancer cell dissemination (metastasis) and angiogenic pathologies such as those found in HIV-1 (= Human Immunodeficiency Virus, type 1) -infected patients; this activation process remains poorly understood at the cellular level and has prompted us to investigate the transcription factors and critical target genes, that are involved in specific aspects of the pleiotropic response. Intriguingly, HIV-1 infected patients develop severe, vascular pathologies, which are likely to reflect excessive activation of certain types of endothelial cells. HIV-1 also contributes to the development of a particular type of highly aggressive, metastatic cancer, the Kaposi sarcoma, which likely results from the transformation of endothelial cells infected by HHV-8 (= Human Herpes Virus 8). However, for these pathologies, the endothelial cells do not seem to be infected by HIV-1, but rather activated indirectly by the viral regulator Tat acting as an extracellular chemokine. Therefore, experiments are also designed to analyse the effect of this viral chemokine in endothelial cells.
Both projects combine recent molecular biology and gene transfer techniques with the manipulation of human primary cell cultures.

see also our web site at
http://hvd.ens-lyon.fr/human_virology_dpt



►►►
Typical "flower cell" in the peripherical blood of an acute ATL patient. Leukemic cells contain multilobulated nuclei.

Molecular Biology of human gamma-herpesviruses

► **Team leader** ► *Evelyne MANET* ***Senior Researcher*** *- emanet@ens-lyon.fr*
► **Team members** ► *Alain SERGEANT* ***Senior Researcher***
► *Henri GRUFFAT* ***Associate Researcher*** ► *Fabrice MURE* ***Engineer***
► *Cahora MEDINA-PALAZON* ***Postdoctoral fellow***

Research themes:

1) In vitro, infection of quiescent (Go) B-lymphocytes by the Epstein-Barr virus (EBV) leads to their activation and long term proliferation (immortalization). Our objectives are to understand the early mechanisms involved in the activation of B-lymphocytes following the binding of the virus with its receptor, CD21, and to determine the function of viral genes expressed during latency in the immortalisation process, in particular EBNA-2, -3A et -3C.

2) EBV is quasi ubiquitous within the human adult population. After infection it persists (latency – reactivation balance) during the life-time of individuals who are subjected to phases of viral production and de novo infections. These phases are thought to be a risk factor for the emergence of certain cancers. We are interested in the study of several key steps of the productive cycle and in particular, the regulation of the expression of EB1, a viral transcriptional activator responsible for the induction of the viral productive cycle, in B-cells latently infected with EBV. We are also interested in understanding the function of an early viral protein, EB2, which is essential for virus production and which is involved in the efficient export of viral mRNAs.

Major recent results:

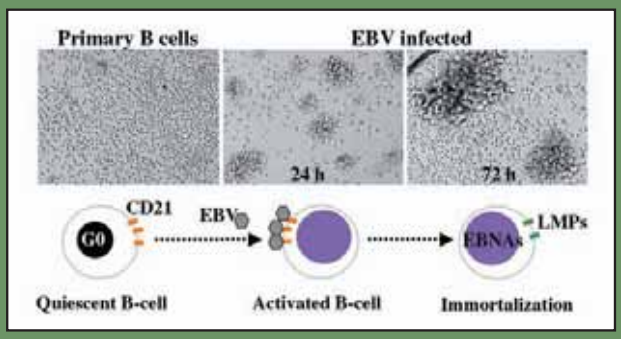
1) Demonstration that EB2 is essential for the production of EBV virions and characterization of its function in the export from the nucleus to the cytoplasm of some early and late viral mRNAs which are generated from intronless genes (via construction of an EBV recombinant deleted from the EB2 gene).

2) Characterization in EB2 of the domains responsible for the nucleocytoplasmic shuttling of the protein (NLS/NES), for its RNA-binding ability and for interaction with various cellular factors involved in mRNA export.

3) Characterization of a novel member of the Spen family of protein, OTT3, via its interaction with EB2. Demonstration that OTT3 inhibits the use of cryptic or «illicit» 5' splice sites.

Application domain: Human health

►►►
Activation and immortalization of quiescent B-lymphocytes by EBV
EBV infects quiescent B lymphocytes: the first step of infection is the interaction of the EBV gp350 glycoprotein with its receptor, the CD21. This induces a decondensation of the chromatin, a prerequisite for expression of a subset of the viral genes (latency genes) that cooperate to induce B cell proliferation



Control of Adeno-Associated Virus (AAV) life cycle by nuclear environment and use of recombinant AAV vectors as vaccines

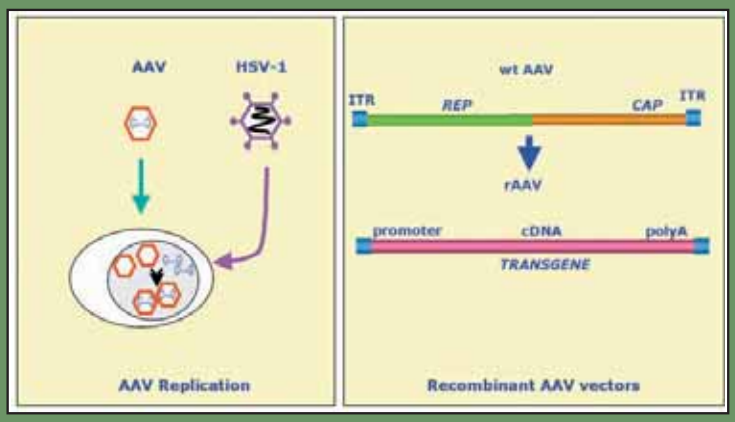
► **Team leader** ► *Anna SALVETTI* ***Associate Researcher*** *- Anna.Salvetti@ens-lyon.fr*
► **Team members** ► *Nathalie ALAZARD-DANY* ***Postdoctoral fellow***

► *Équipe Avenir* ***(team certified by INSERM)***

The Adeno-Associated Virus (AAV), a parvovirus infecting several animal species including man, is currently used as a vector for gene transfer. The research program of this new team will consist in:

1) The definition of the optimal nuclear environment for AAV replication. The specificity of AAV is to be able to replicate only in the presence of a helper virus, such as Adenovirus or Herpes Simplex Virus (HSV). Indeed, when AAV infects a cell alone, it enters a latent state characterized by the persistence of viral DNA in the nucleus of the cell. The objective of this research program is to precisely define the nuclear factors, of both cellular and viral origin, that constitute the optimal environment for AAV replication. The project is based on the proteomic analysis of AAV replication centers that arise in the nucleus of the cells in the presence of HSV-1. From the fundamental point of view, this project is designed to define the cellular and viral factors that contribute to AAV replication. From the biotechnological point of view, the identification of the factors critical for AAV growth will result in the definition of new strategies and tools for the production of recombinant AAV vectors (rAAV).

2) The evaluation of rAAV vectors as a tool for vaccination against viral infections. The aim of this part of our research program is to investigate the use of rAAV vectors as a tool against viral infections. Indeed, an increasing amount of experimental evidence indicates that these vectors can potentially be used to induce humoral and cellular responses against viral proteins. In this context, two collaborative studies will be conducted to evaluate the use of rAAV vectors to induce an immune response in vivo against Hepatitis C and Nipah virus glycoproteins.



◄◄◄ *Control of Adeno-Associated Virus (AAV) life cycle by nuclear environment and use of recombinant AAV vectors as vaccines*

Joliot-Curie
LABORATORY

► **Director** ► *Philippe BOUVET* ***Professor***
► **e-mail** ► *pbouvet@ens-lyon.fr*
► **Total personnel** ► *30 (maximum 60)*
► **Partners** ► *CNRS*

The *École normale supérieure in Lyon*, in collaboration with the CNRS wishes to reinforce pluridisciplinary approaches by creating a new laboratory, the Joliot Curie Laboratory (LJC). The aim of this laboratory is to favor the development of original approaches towards biological objects by researchers from other disciplines. The goal is not to create new research teams in the LJC, but rather to give the opportunity to independent researcher or to research team that have an idea of original approaches to study a biological object, to come in the laboratory for a limited time period (about 4 years) to set up these experiments, then to go back in there home laboratory or to another structure. The LJC is indeed an incubator for pluridisciplinary scientific projects.

The different projects developed within the LJC involved researchers from different teams, all present in the LJC. These projects need competences in biology, experimental and theoretical physics, and bioinformatics. Six main research areas are presently developed in the LJC:

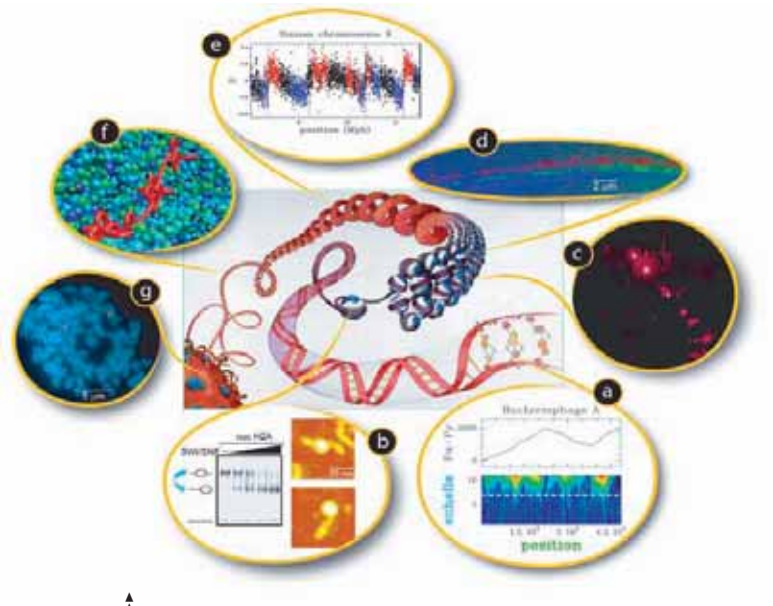
1) Structure and dynamics of nucleosome remodeling,
2) Chromatin and functional organization of the genome,
3) Effect of sequence on the structure and dynamic of naked DNA,
4) Dynamic of protein-nucleic acids interaction,
5) Activity and dynamic of conformation of proteins,
6) Interaction of the cell with its environment.

RESEARCH TOPICS

- Studies of biologycal systems using pluridisciplinary approaches
- Genome organization
- Chromatin structure
- Nucleolar organization
- Single molecule studies
- Protein folding
- Bioinformatic studies of the genome
- Laser-induced biophotonic chemistry of nucleic acids

EQUIPEMENT

- Cell culture rooms
- Atomic force microscopy (AFM)
- FPLC/HPLC
- Pulsed Nd: YAG picosecond laser
- Magnetic tweezers
- Micro colorimeter



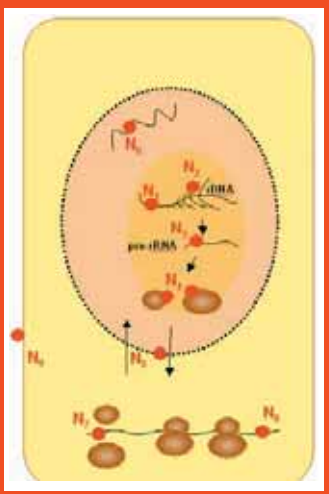
The main projects of Joliot curie Laboratory have for objectives to understand the structure and function of chromatin organization using a panel of biological, biophysical and bio-informatics techniques. Bio-informatics analysis of genomes (a), chromatin dynamics using Atomic force microscopy and biochemistry (b), chromatin organization using biophysics (c), chromatin combing (d), bioinformatics (e), modeling (f), and cell biology (g)

ASSEMBLY OF CHROMATIN AND RIBOSOME BIOGENESIS

► **TEAM LEADER** ► *Philippe BOUVET **Professor**- pbouvet@ens-lyon.fr*
► **TEAM MEMBERS** ► *Dimitar ANGELOU **Senior Researcher***
► *Fabien MONGELARD **Associate Professor***
► *Hélène DELAGE **Technician** ► Sébastien STORCK **Assistant Professor***
► *Hervé MENONI **PhD student** ► Sudheer KUMAR **Postdoctoral fellow***

Profound alterations of the nuclear compartment are found in cancer cells. In particular, hypertrophy of the nucleolus is one of the criteria used by pathologists to identify malignant cells. The nucleolus is the site of synthesis of ribosomal RNA (rRNA) and of the assembly of the ribonucleic particles involved in the synthesis of the proteins, the ribosomes. The biogenesis of the ribosomes is a very important process for the cell. Indeed, the synthesis of rRNA corresponds to about 40% of the transcriptional activity of the cell, and rRNA represents about 80% of total cellular RNA. The synthesis of ribosomes is very much linked to cell proliferation and is regulated during the cell cycle. The molecular mechanisms which regulate the assembly of ribosomes and their production in accordance with the needs of the cell are still largely unknown.

Our team studies this problem by characterizing a major nucleolar protein: nucleolin. It is a non-ribosomal protein which could represent as much as 10% of total nucleolar proteins. We study different aspects of the interaction between nucleic-acids and proteins, and their consequences for the transcription and the maturation of rRNA, and the co-transcriptional assembly of pre-ribosomes. This research is mainly focalized on two different aspects: the structural properties of variant nucleosomes (in particular of mH2A which is present in the nucleolus) coupled to the functional consequences on the structure and dynamic of chromatin, and to a functional study of nucleolin. We use a pluridisciplinary approach, using bio-physical approaches (pulsed UV laser cross-linking, imaging by atomic force microscopy, AFM) and biochemical and genetic approaches (knock out of mH2A in mice, interruption of nucleolin gene by homologous recombination in DT40 cells, RNAi, etc.). These studies should allow us to better understand the function of variant histones on the structure and dynamic of chromatin and in particular in the nucleolus, and to better characterize the function of nucleolin in cell proliferation.



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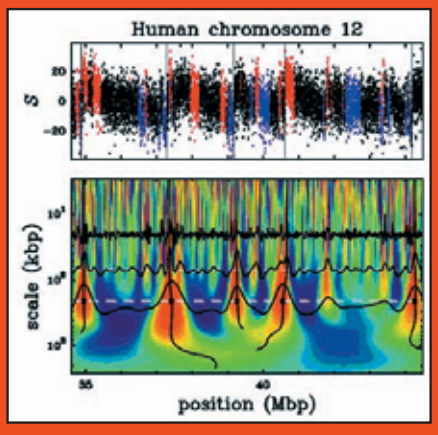
Genome organization and chromatin structure

► **Team leader** ► *Alain ARNEODO **Senior Researcher** - Alain.Arneodo@ens-lyon.fr*
► **Team members** ► *Benjamin AUDIT **Assistant Researcher** ► Brice JUANICO **PhD student***
► *Julien MOUKHTAR **PhD student** ► Yves-Henri SANEJOUAND **Associate Researcher***
► *Cédric VAILLANT **Associate Researcher** ► Lamia ZAGHLOUL **PhD student***

The "Genome organization and chromatin structure" group is composed of theoretical physicists with expertise in the study of multi-scale phenomena (turbulence, crystal growth, financial time series, etc.) combining the use of concepts from dynamical systems theory and statistical physics with the development of multi-resolution signal and image processing techniques (wavelet transform).

For about a decade, our group has been extending its field of research to the study and modeling of the structure and dynamics of biological molecules (DNA, proteins). In a first step, when using our wavelet-based methodology to analyze the scale-invariance properties of DNA walk profiles generated with some structural tri-nucleotide codings of DNA sequences, we have revealed the existence of long-range correlations (LRC), up to ~ 40kbp, in the fluctuations of the double helix local curvature. These LRC are the signature of the DNA-histone proteins interactions within the nucleosomes, the basic units for DNA compaction in eukaryotic cell nuclei, that constitute a regulatory factor for accessibility to genetic material. When further modeling DNA as a semi-fexible polymer explicitly taking into account the structural disorder induced by the sequence, we have provided some evidence that the observed LRC favor the spontaneous formation of small DNA loops which in turn are likely to facilitate nucleosome formation and dynamics.

Recently, we have broadened our studies of genomic sequences to encompass scales of the order of chromosome lengths (Mbp) while considering alternative codings with a clear functional significance. During evolution, DNA transcription and replication induce some compositional asymmetry (skew) along the DNA sequences. As illustrated below, deploying a multi-scale strategy of sharp upward-jump detection in noisy skew profiles, we have identified more than 1000 putative origins of replications in the Human genome. This number is quite large as compared to the 9 origins experimentally localized so far. When further investigating gene position, orientation and expression level in the neighborhood of our set of putative replication origins, it clearly appears that these origins are at the heart of the spatial organization (replication factories, chromatin tertiary structure) of the chromosomes in eukaryotic cell nuclei.



Detecting Human replication origins using a mathematical microscope. ►►►
(top) Skew profile S along a fragment of Human chromosome 12; S = (T-A)/(T+A)+(G-C)/(G+C) is calculated in 1 kbp windows. Dot colors indicate the nature of the underlying sequence: red (resp. blue) corresponds to sense (resp. anti-sense) genes; black to intergenic regions.
(bottom) Space-scale representation of S obtained with the wavelet transform (WT) using the first derivative of the Gaussian function as the analyzing wavelet; black: min WT values; red: max WT values; three cuts of the WT at scales 200 kbp, 70kbp and 20 kbp are superimposed together with the 5 maxima lines pointing at small scales to the 5 major upward jumps in the skew profile. Localizing these jumps provides the position of 5 putative origins of replication along this chromosome fragment. Note that sense (resp. anti-sense) genes are preferentially positioned to the right (resp. left) of the predicted origins suggesting that transcription and replication tend to be co-orientated

DYNAMICS OF BIOLOGICAL MOLECULES

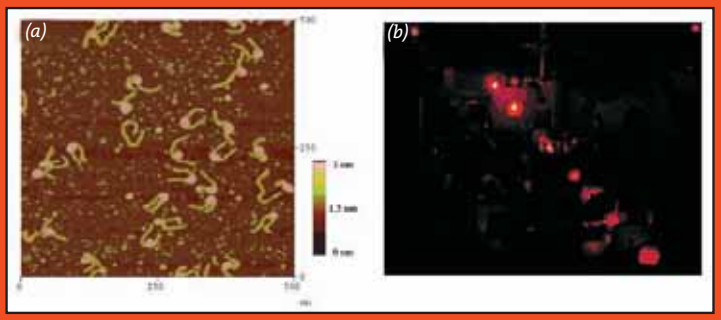
► **TEAM LEADER** ► *Françoise ARGOUL* ***Senior Researcher*** *- francoise.argoul@ens-lyon.fr*
► **TEAM MEMBERS** ► *Cendrine MOSKALENKO* ***Associate Professor***
► *Fabien MONTEL* ***PhD student***
► *Sanjun ZHANG* ***PhD student***

The "Dynamics of Biological Molecules" team is composed of experimental physicists using micromanipulation and visualization techniques (atomic force microscopy, evanescent wave optics) for single molecule imaging. We focus our efforts on the nucleosome, the basic unit for DNA compaction into chromatin inside eukaryotic cell nuclei, which plays the role of a regulatory factor for genetic material accessibility.

Recently our team has settled up physical approaches to address two different biological questions:

Nucleosome in-vitro formation and nucleosome sliding along a DNA fragment. These experimental studies are conducted in close collaboration with the biology teams of the Joliot-Curie Laboratory (P. Bouvet and S. Dimitrov) and aim at understanding on the one hand the various kinetic steps of nucleosome in-vitro reconstitution, and on the other hand how remodelling molecular motors exert mechanical action on nucleosomes. Our goal is to be able to visualize in real time, combining non-intrusive optical methods and high spatial resolution imaging (nm scale) the nucleosome formation dynamics and nucleosome sliding induced by remodelling complexes.

What is the role of the DNA sequence on the structure and dynamical properties of chromatin? This study is directly inspired from the theoretical results of Alain Arneodo's team, also present in the Joliot-Curie Laboratory. Their theoretical multi-scale approach of DNA sequences suggests that nucleosome thermal mobility is greatly affected by the existence of long range correlations in the structural disorder of DNA polymer (elastic properties induced by the DNA sequence). We study experimentally how these long range correlations influence the 2D thermodynamical equilibrium conformation of naked DNA fragments, as well as the formation and diffusion of nucleosomes. The goal of this project is to show the link between the DNA sequence and the structural and mechanical properties of the chromatin fiber for a better understanding of functional genome organization.



AFM and SSPM imaging for nucleosome dynamics study
(a) AFM imaging (atomic force microscopy in intermittent contact mode) allowing to visualise nucleosomes reconstituted on a 356 base pair positioning DNA sequence, and adsorbed on functionalised mica surface. The height of the objects is given by the 'false color' scale. (b) Photograph of the surface plasmon microscope (SSPM), that allows the measurement of the local optical index for a DNA monolayer confined close to a gold surface. This experimental set-up, when coupled to micro-fluidic injection system, allows to follow in real time the DNA monolayer dynamics with the injection of structural proteins

JOLIOT-CURIE LABORATORY

PHYSICS TO STUDY THE LIVING

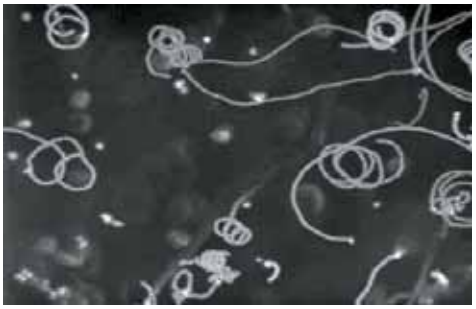
► **TEAM LEADER** ► *Christophe PLACE* ***Associate Researcher*** *- christophe.place@ens-lyon.fr*
► **TEAM MEMBERS** ► *Laurence LEMELLE* ***Associate Researcher***
► *Bertrand FRANÇOIS* ***PhD student***

Our objective is to lead projects at the interface of physics and biology by developing original technological approaches. Our main interest, covering different thematic areas, relates to:

1) the analysis of the single protein behaviours in interaction with immobilized DNA and, more precisely, on single DNA transcription by T7 RNA polymerase observed by fluorescence microscopy

2) the question of disentangling of long DNA, like the whole genomic DNA during mitosis, by studying the increase in disentangling velocity in the presence of topoisomerase II using high frequency rheometer and

3) the description and the hydrodynamic modeling of the behaviour of motile bacteria in the vicinity of a mineral surface using videomicroscopy and Total Internal Reflection Fluorescence Microscopy (TIRFM). The developed techniques are based on physics and rely on experiments in biochemistry, microbiology and cell biology.



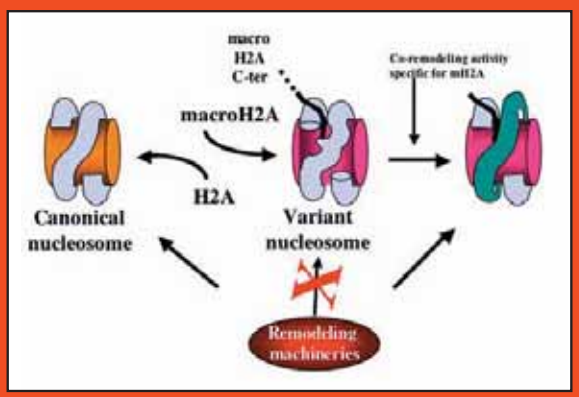
Trajectories of E. coli flagelled cells in the vicinity of a surface.

Biophysics of Chromatin

► **Team leader** ► *Stefan DIMITROV* ***Senior Researcher*** *- Stefan.Dimitrov@ens-lyon.fr*
► **Team members** ► *Mathieu BOULARD* ***PhD student*** ► *Manu SHUKLA* ***PhD student***
► *Syed Sajad HUSSAIN* ***PhD student***

Our research is focused on the structure and function of nucleosomes containing variant histones. In our studies we use a unique combination of physical methods (analytical centrifugation, optical tweezers, AFM and cryoelectron microscopy, UV laser protein-DNA crosslinking and footprinting, etc.) with the state of the art molecular and cell biology techniques. This allows us to obtain unique information, which is not accessible to the currently used approaches.

Recently, in a series of in vitro experiments and in collaboration with the team of Dr. P. Bouvet, we have shown that the nucleosomes containing the histone variant mH2A exhibited structural alterations, which interfered with both the binding of transcription factors and mH2A nucleosome remodeling by SWI/SNF and ACF. The presence of mH2A inhibited histone acetylation and PolII activated transcription. These data suggest that mH2A could be viewed in vivo as a major stopper of transcription by negatively regulating these two chromatin associated pathways. In contrast, our recent results on the histone variant H2A.Bbd point to a role of this protein in gene activation by a specific, but still unknown mechanism. Currently, in collaboration with D. Angelov (team P. Bouvet), we are developing a novel time-resolved UV laser based approach for studying the kinetics of protein-DNA interaction. This method will allow the detection of local movement (the "dance") of a transcription factor when interacting with naked or with nucleosomal DNA and an in depth analysis of the remodeling mechanism of both conventional and histone variant nucleosomes.



◂◂◂ *Schematics of the remodeling of macroH2A nucleosomes*

Molecular & Cell Biology
LABORATORY

► **Director** ► *Eric GILSON* ***Professor***
► **e-mail** ► *Eric.Gilson@ens-lyon.fr*

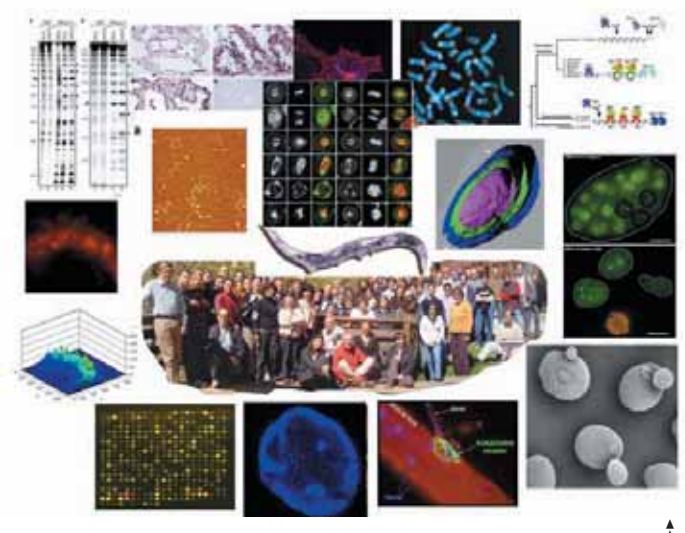
► **Total personnel** ► *158*
► **Partners** ► *CNRS* ► *INRA* ► *UCB Lyon 1*

The LBMC was founded in 1987 by Professor Jacques DAILLIE at the time of the creation of the *École normale supérieure de Lyon*. It is undertaking research aimed at clarifying the molecular basis for control of cell biology. The essential *raison d'ëtre* of the laboratory is to create a continuum of research in the field of cell biology, starting from the elucidation of the fundamental mechanisms of cell function to the comprehension of the dysfunctions encountered in human pathology.

The laboratory includes 14 research groups, which use various experimental systems, ranging from isolated molecules to cells, from yeast to man, via marine invertebrates, haematopoietic cells, nerve cells or embryos (chicken or mouse). The installation of various model systems within the LBMC was carried out with the specific desire to ensure complementarity in research themes, making it possible to cover the principal fields of eucaryotic cell biology (except plant biology): mechanisms controlling the expression of genes, biology of the nucleus, epigenetics, genomics, signaling, control of proliferation, differentiation, apoptosis and senescence, cell cycle, virology, endocrinology, immunology, neurobiology, evolution, development and oncogenesis.

The official *tutelles* of LBMC are the *École normale supérieure of Lyon*, the CNRS, the INRA and the *Université Claude Bernard*. Moreover, research partnerships exist between certain teams of the LBMC and the hospitals of Lyon (Hospices Civils de Lyon).
In the field of the public health, the LBMC possesses strong links with the hospital sector resulting in collaborative biomedical and clinical research programs.

On the socio-economic level, the LBMC has the policy to encourage the emergence of biotechnology companies based on discoveries and expertises of the laboratory. From the past, one can cite:
i) Genoway, involved in the development of transgenic animal models;
ii) Vivalis, which develops the technology of chicken embryonal stem cells for biotechnological applications;
iii) Aptanomics which uses the peptide aptamer technology to create novel therapeutic molecules against cancer;
iv) Phylogene, which develops methods of identification and authentification of food, using DNA and proteins.



«Biodiversity of LBMC»

RESEARCH TOPICS
• Molecular biology • Cellular biology
• Transcriptional control • Cell cycle • Differentiation
• Hormone nuclear receptors
• Telomeres, Heterochromatin • Ribonucleoproteins
• Cell culture • Genetic manipulations
• Yeast genetics • Nematode genetics
• Targeted inactivation of mouse genes
• Conventional and confocal microscopy
• DNA sequencing

AREAS OF APPLICATIONS
• Human and veterinary pharmacology
• Biotechnologies
• Agronomy

INDUSTRIAL PARTNERS
• GenOway • Mérial • Phylogène • Roche
• Aventis Pasteur • Vivalis • Sanofi
• Kaissei Pharmaceutics

EQUIPMENT (IFR 128)
• Cytometry • Microscopy • Animal Housing
• DNA Sequencer • Q-PR Machines

ASSEMBLY OF CHROMATIN AND RIBOSOME BIOGENESIS

► **DIRECTOR** ► *Philippe BOUVET **Professor** - pbouvet@ens-lyon.fr*
► **TEAM MEMBERS** ► *Dimitar ANGELOU **Senior Researcher** ► Fabien MONGELARD **Associate Professor** ► Hélène DELAGE **Technician** ► Sébastien STORCK **Assistant Professor** ► Hervé MENONI **PhD student** ► Sudheer KUMAR **Postdoctoral fellow***

Profound alterations of the nuclear compartment are found in cancer cells. In particular, hypertrophy of the nucleolus is one of the criteria used by pathologists to identify malignant cells. The nucleolus is the site of synthesis of ribosomal RNA (rRNA) and of the assembly of the ribonucleic particles involved in the synthesis of the proteins, the ribosomes. The biogenesis of the ribosomes is a very important process for the cell. Indeed, the synthesis of rRNA corresponds to about 40% of the transcriptional activity of the cell, and rRNA represents about 80% of total cellular RNA. The synthesis of ribosomes is very much linked to cell proliferation and is regulated during the cell cycle. The molecular mechanisms which regulate the assembly of ribosomes and their production in accordance with the needs of the cell are still largely unknown.

Our team studies this problem by characterizing a major nucleolar protein: nucleolin. It is a non-ribosomal protein which could represent as much as 10% of total nucleolar proteins. We study different aspects of the interaction between nucleic-acids and proteins, and their consequences for the transcription and the maturation of rRNA, and the co-transcriptional assembly of pre-ribosomes. This research is mainly focalized on two different aspects: the structural properties of variant nucleosomes (in particular of mH2A which is present in the nucleolus) coupled to the functional consequences on the structure and dynamic of chromatin, and to a functional study of nucleolin. We use a pluridisciplinary approach, using bio-physical approaches (pulsed UV laser cross-linking, imaging by atomic force microscopy, AFM) and biochemical and genetic approaches (knock out of mH2A in mice, interruption of nucleolin gene by homologous recombination in DT40 cells, RNAi, etc.). These studies should allow us to better understand the function of variant histones on the structure and dynamic of chromatin and in particular in the nucleolus, and to better characterize the function of nucleolin in cell proliferation.

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Biology of Cell regulations

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► **Team members** ► *Thomas LAMONERIE* ***Associate Professor***
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► *Francis BEBY* ***PhD student***
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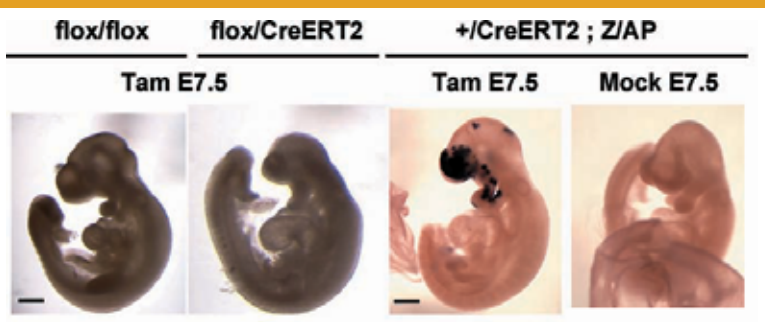
This group aims to understand the developmental functions controlled by the homeodomain transcription factor Otx2 in mammalian brain. Work is focused on the study of the late embryonic and postnatal mouse Otx2 functions that cannot be attained by classical genetic knockout, due to early embryonic lethality of null animals.

We have developed a new conditional invalidation method based on the knockin of the inducible CreERT2 recombinase gene into one of the two Otx2 alleles. The resulting heterozygotes have been crossed with an Otx2 floxed strain, yielding mice where Otx2 deletion can be triggered at any stage of development. The method has been validated and, when combined with cell lineage tracing, it provides a powerful tool to investigate the late developmental functions of Otx2. Specific windows of action of the gene have been identified, for instance, for proper cerebellum development and also for brain regulated post-natal survival and growth (Fossat et al., EMBO Reports 2006). This method is currently developed to provide a general insight on the embryonic developmental as well as on the maintenance of adult brain structures governed by this gene.

To understand the properties of the gene and of its product in neural cells we have also undertaken the characterization of its biochemical and molecular features. Unexpectedly, we have found that Otx2 expression is driven by three independent promoters. Activity of these promoters is modulated both at the spatial and temporal levels (Courtois et al., J Neurochem. 2003, Fossat et al., Dev.Dyn. 2005). Using GFP fusions with various deleted forms of the protein we have dissected its functional domains and we have found new serine rich determinants that could be central for regulation of the subcellular localization (Chatelain et al., J Mol Med. 2006).



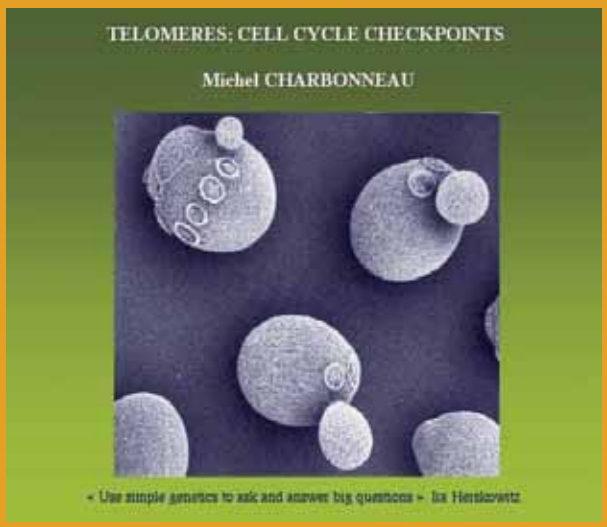
Conditional invalidation of Otx2 at E7.5 and lineage tracing of Otx2 expressing cells. Left: consequences of tamoxifen injection at E.75 in E9.5 embryos of indicated genotypes. Right : Alkaline phosphatase activity in E9.5 *Otx2*$^{+/CreERT2}$ *; Z/AP* embryos that received tamoxifen or solvent at E7.5. Scale bar: 500µm.

TELOMERES ; CELL CYCLE CHECKPOINTS

► **DIRECTOR** ► *Michel CHARBONNEAU* ***Senior Researcher*** *- Michel.Charbonneau@ens-lyon.fr*
► **TEAM MEMBERS** ► *Nathalie GRANDIN* ***Associate Researcher***

We currently study the maintenance of telomeres using a genetic model system, the yeast Saccharomyces cerevisiae. Studying telomeric functions has vast implications in both fundamental and applied research. Indeed, telomeric proteins have been uncovered only recently (over the last decade) and some of their functions known at the moment imply original, sometimes unexpected, mechanisms. Moreover, telomere biology is of major importance in the control of genome stability and, in tumor cells, of cell proliferation.

Recently, we have described a novel pathway of telomeric senescence which, unlike that resulting from telomere erosion provoked by telomerase inactivation, takes place in the presence of functional telomerase without telomere shortening. This telomere uncapping process can be induced by simultaneously, and partially, inactivating two telomere end protection complexes, Cdc13 and Yku. (Grandin and Charbonneau, Mol. Cell. Biol. 23, 3721-3734, 2003). We have also demonstrated (by analyzing telomere structure by Southern blotting) that the Cdc28-Clb2 complex (Cdk1-cyclin B) was required for efficient telomeric recombination, in telomerase-negative cells. Moreover, we have found that Cdc28-Clb2 controls a novel, minority, pathway of telomeric recombination that is independent of the two previously known pathways, Rad50-Rad52 and Rad51-Rad52 (Grandin and Charbonneau, Mol. Cell. Biol. 23, 9162-9177, 2003). Finally, in a recent research program, we have analyzed the checkpoint response to telomeric DNA damage by measuring the activation of various checkpoint proteins and analyzing cell cycle progression in various mutants. In particular, we have reported that the activation of Mrc1-Rad53 takes place during telomere erosion, but not during telomere uncapping. (Grandin, Bailly and Charbonneau, Biol. Cell 97, 799-814, 2005).



Telomeric and Epigenetic Regulations

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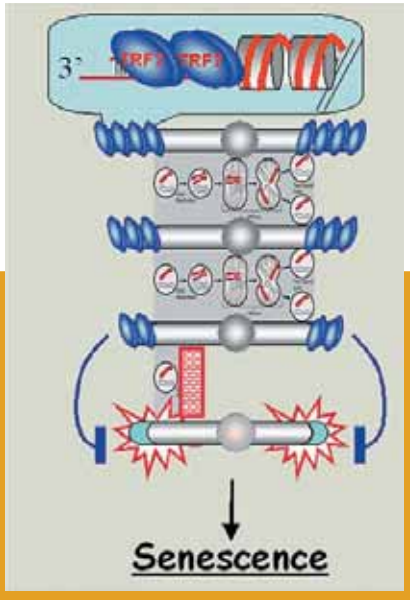
► **Team members** ► Pauline ABDALLAH **PhD student** ► Simon AMIARD **PhD student** ► Amadou BAH **PhD student** ► Serge BAUWENS **Engineer** ► Anne EUGSTER **Assistant Professor** ► Sylvie GERVIER **Assistant Researcher** ► Marie-Josèphe GIRAUD-PANIS **Associate Researcher** ► Béatrice HORARD **Postdoctoral fellow** ► Mélanie KOELBLEN **PhD student** ► Catherine KOERING **Engineer** ► Christelle LENAIN **PhD student** ► Frédérique MAGDINIER **Assistant Researcher** ► Alexandre OTTAVIANI **PhD student** ► Sébastien PINTE **Postdoctoral fellow** ► Delphine PONCET **Postdoctoral fellow** ► Jérémy SCARATO **PhD student** ► Teresa TEIXEIRA **Associate Researcher** ► Claire T'KINT DE ROODENBEKE **Engineer**

Telomeres are nucleoprotein structures found at the ends of all eukaryotic linear chromosomes. They play essential roles in the maintenance of genome integrity, in the epigenetic regulation of gene expression and in the control of cell proliferation. They specifically cap the ends of chromosomes such that they are not recognized by DNA damage checkpoints and repair systems. They are also involved in the control of gene expression and in the spatial and functional organization of chromosomes. Their structure is determined, at least in part, by the epigenetic state of the cell.

Telomeres have often been considered as DNA repeats of a certain length depending on the presence of a particular reverse transcriptase, the telomerase. In the past, the work of the Gilson team contributed to broaden this view by identifying the structure and function of various telomeric chromatin factors in yeast and human cells. The present objective of the team is to study the structure and function of telomeric and heterochromatin regions in yeast and in human cells. Two general approaches are developed: i) the elucidation of the role(s) of telomeric ligands in telomere length regulation, transcriptional silencing, DNA-damage response and various human disorders, including cancer and facioscapulohumeral muscular dystrophy (FSHD); ii) the exploration of long-range chromatin interactions in the creation or maintenance of functional chromosome domains. In addition, a new project is emerging that will address the exploration of telomere functions and the establishment of chromosomal-scale epigenomic maps of repetitive sequences of a cancer cell: B-CLL (B-cell chronic lymphocytic leukemia).

The team has extensive know-how and skill in molecular biology techniques, chromatin analysis, protein and tissue culture work, yeast genetics, immunological techniques, as well as in mammalian chromosome biology. In addition, a battery of DNA constructs, cell lines and antibodies are available for collaborative projects.



►►►
MODEL FOR TELOMERIC SENESCENCE
The number of TRF2 proteins associated with human telomeres decreases with cell division. If it reaches a critical threshold, telomeres signal senescence

Palaeogenetics and Molecular Evolution

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*► Marie PAGES **PhD student***

This team joined the IGFL (*Institut de Génomique Fonctionnelle de Lyon*) on 1 January 2007

Molecular Evolution

Our team is using the genetic information contained in preserved DNA molecules from ancient remains (bones, teeth, etc.) in order to reconstruct the evolutionary history of species and populations. In fact, until the emergence of paleogenetics, the ability to reconstruct evolutionary history was based on one hand on morphological and molecular data obtained from living species via comparative studies and on the other hand on the morphological data stored in fossils. The advent of ancient DNA studies allows us to confront scenarios based on these two types of data with the information stored in ancient DNA molecules. Three main topics are developed in our laboratory:

i) **the phylogeny of extinct species** (woolly rhinoceros, Megaloceros, Equids, rodents, Neandertal, etc.)

ii) the use of cave bear (Ursus spalaeus) as a model species to understand **the effect of climatic changes on genome evolution through time**

iii) the **domestication** and diffusion rates of sheep and goats at the Neolithic period in Europe.

Applied traceability

Our expertise in ancient DNA has allowed us to develop a project of industrial development in molecular traceability (food, forensic, etc.) as well as a unforeseen scientific development in archaeology.

Development of a national platform for paleogenetics

Due to the degradation and chemical modification of the DNA molecule through time and environment, studying ancient DNA is far from being routine and requires specific facilities and competences to really ascertain the authenticity of the obtained results. Our team is the head of a project of a national platform for paleogenetics, called **PALGENE,** that will allow the French and foreign community to carry out ancient DNA studies in good conditions. This platform will also set up new methodological developments devoted to paleogenetics.

◄◄◄ *The 100,000 year-old Neandertal mandibule from Scladina that gave rise to the oldest ancient human DNA sequence yet reported. The analysis of this sequence revealed that the genetic diversity of neandertals was much higher than previously believed*

Control of Gene Expression and Viral Oncogenesis

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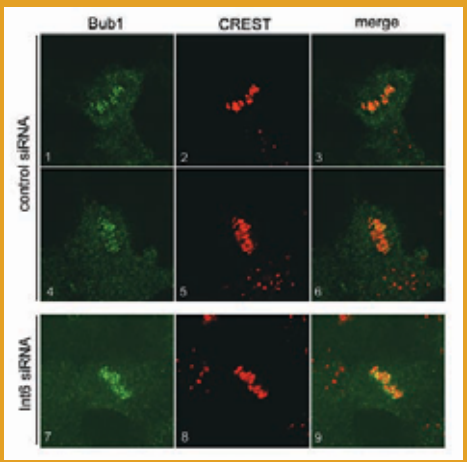
► *Jérémy SCARATO **PhD student***

Viral infection profoundly perturbs the normal cellular physiology and in the case of oncogenic DNA or RNA viruses can trigger cancerous transformation. For human oncogenic viruses this effect is achieved by expression of viral proteins which interact specifically with various cellular regulatory proteins. Hence, the study of such interactions is a way of deciphering the molecular mechanisms of viral oncogenesis, but also represents an interesting approach to identify new cellular regulatory pathways. In this perspective, our laboratory has been engaged for several years in the study of the interaction of the viral protein Tax expressed by the Human T-cell Leukemia Virus type 1 (HTLV-1) with cellular proteins. Infection by HTLV 1 is indeed associated with various degenerative or proliferative pathologies, including adult T-cell leukaemia. Identification of novel Tax cellular targets has been performed by screening a library of cDNAs prepared from human lymphocytes. We are currently studying two different types of Tax-interacting proteins: PDZ proteins and Int6. Proteins including a PDZ domain are important for signal transduction downstream of transmembrane receptors and represent targets of various viral oncoproteins. Alterations of the int6 gene are associated in mice with mammary tumour formation and the Int6 protein is important for stability of the genome, as well as of specific mRNAs. Our expertise in the use of the two-hybrid screening method has also been employed to isolate protein inhibitors owning the property of entering within cells from the extracellular milieu and of binding to a specific intracellular factor. This technology, which has been patented, is being developed for generation of inhibitors of viral proteins (Rev of HIV-1) and of cellular oncogenes (TAL1).



◄◄◄ *HeLa cells were transfected with either control or Int6-specific small interfering RNAs. Cells were fixed and stained using CREST serum (red) or Bub1 antibody (green). These images show an increase in the amount of Bub1 staining at the centromeres during metaphase when Int6 protein is suppressed. This correlates with chromosomes segregation defects due to the absence of Int6 and is indicative of a deficiency in the attachment of microtubule ends to centromeres*

BONE CELL BIOLOGY AND PATHOPHYSIOLOGY

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► *Marlène MAZZORANA **Associate Researcher***
► *Chantal DOMENGET **Engineer** ► Romain DACQUIN **Postdoctoral fellow***
► *Anne CHABADEL **PhD student** ► Anne GALLOIS **PhD student***
► *Petr VANHARA **PhD student** ► Geneviève DESPARS **Postdoctoral fellow***

This team joined the IGFL (*Institut de Génomique Fonctionnelle de Lyon*) on 1 January 2007

We are studying bone physiology through human and murine models using cell biology approach through osteoclasts. Bone is a dynamic tissue which will be formed during development, renewed during adult life and finally degraded when aging through the coordinated action of resorption by osteoclasts and formation by osteoblasts. Osteoclasts are cells of hematopoietic origin deriving from the monocytic lineage similarly to macrophages and immune dendritic cells (DC). We are interested in analyzing the relationship between these monocyte-derived cells but also in the specific actin cytoskeleton organization of osteoclasts allowing their unique ability to resorb bone mineralized matrix. We have defined three main topics:

• Osteoimmunology

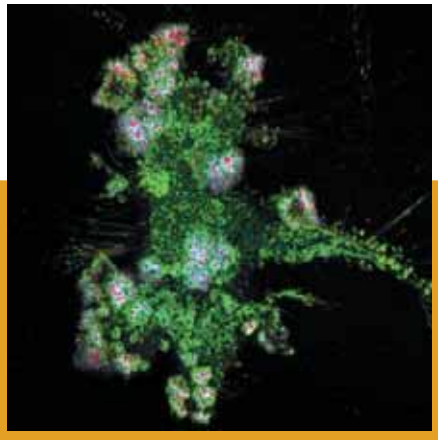
We have brought the first demonstration that DC can transdifferentiate into osteoclasts. Our results suggest that inflammatory conditions, such as in rhumatoid arthritis, potentiate transdifferentiation. Our goals are 1) to prove this hypothesis in rhumatoid arthritis murine models; 2) to determine the molecular mechanisms controlling the switch from DC to osteoclasts in comparison with the classical pathway from monocytes. In addition, with the availability of DAP12 mutant mice we are analysing the role of lymphocytes in the formation and function of osteoclasts.

• Cytoskeleton dynamics

By using osteoclasts constitutively expressing actin fused to GFP, we have deciphered the dynamic organization of the actin cytoskeleton of osteoclasts adherent either onto glass or apatite mineral. On glass, they exhibit podosomes whereas on apatite they form sealing zone induced by the mineral itself. We want to determine the role of these different actin structures, their molecular regulation (Rho GTPases,....) as well as the implication of integrin receptors in the recognition signals.

• Signaling molecules

Due to several observations we have postulated that signaling molecules such as semaphorins could be implicated either in the osteoclast differentiation pathway or in bone physiology. We are currently testing this hypothesis using mice with semaphorin gene inactivation.



Osteoclasts podosomes

STRUCTURE AND EVOLUTION OF NUCLEAR HORMONE RECEPTORS

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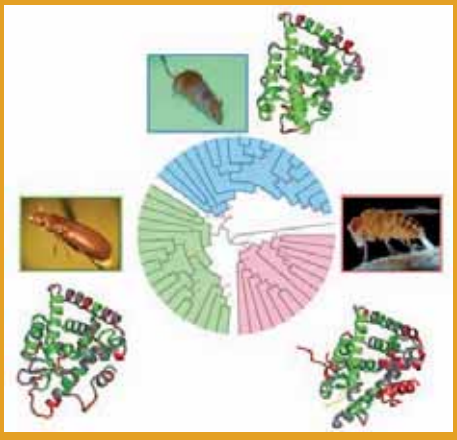
► *Pascale CHEVRET* ***Associate Researcher*** ► *Yann GIBERT* ***Postdoctoral fellow***
► *Ingrid MASSE* ***Postdoctoral fellow*** ► *Shin Ichi NISHIO* ***Postdoctoral fellow***
► *Sophie PANTALACCI* ***Postdoctoral fellow*** ► *Mathilde PARIS* ***PhD student***
► *Gilles PARMENTIER* ***Postdoctoral fellow*** ► *Juliette RAMBAUD* ***PhD student***
► *Emma RIBES* ***Engineer*** ► *Sana SASSI* ***PhD student*** ► *Michael SCHUBERT* ***Assistant Researcher***
► *Gérard TRIQUENEAUX* ***Engineer***

This team joined the IGFL (*Institut de Génomique Fonctionnelle de Lyon*) on 1 January 2007

Nuclear receptors (NRs) are transcription factors that play essential roles in embryonic development, cell differentiation and metabolism. Dysfunction of NR signalling leads to proliferative, reproductive, and metabolic diseases such as cancer, infertility, obesity or diabetes. The NR superfamily contains many liganded receptors (24 among the 48 known NRs in the human genome) but also "orphan" receptors, for which no ligand has yet been discovered. It is unknown whether all orphan receptors have the potential to bind natural or synthetic ligands or if they are "true" orphans that may be regulated by alternative mechanisms. Undoubtedly, the existence of orphan receptors constitutes both a major challenge for NR research and a potential opportunity for drug discovery. The question of the origin of orphan receptors and of their relationships with liganded receptors has become a central one in NR research with new data provided by ongoing genome projects.

Our group is interested in understanding the mechanisms that have led to the present diversity of NR genes during evolution. After having determined the main steps of NR diversification through phylogenetical analysis we are know focussing our interest on the evolution of the main functions of NRs such as the regulation of their transcriptional activity by ligand binding. Using an «Evo/Devo» approach, we also try to understand the main functions played by some NRs such as the retinoic acid receptors and the thyroid hormone receptors during evolution using zebrafish and the invertebrate chordate amphioxus as model systems. We also characterized functional shifts that occur in insects for RXR-USP, an essential partner of the ecdysone receptor (figure). Finally, from a purely functional point of view we are also interested in orphan receptors, such as Rev-erbs, in order to determine their biological roles. We believe that it is only through the integration of functional and evolutionary studies that we will have a clear view of the role played by NR genes in the development and evolution of metazoans, which constitutes our ultimate goal! This is why we plan to broaden our approaches to develop molecular zoology studies.



◂◂◂ *Three different functional forms of the same nuclear receptors, RXR-USP in various groups of metazoan. The comparative, structural and evolutionary analysis of this receptor in several model organisms (mouse, drosophila, beetle and amphioxus) allow to pinpoint major functional shifts that occur in terms of ligand binding during evolution*

EPIGENETICS OF PERICENTROMERES

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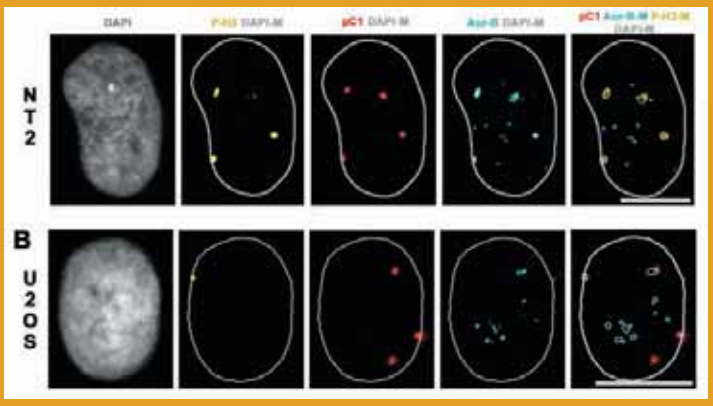
► **TEAM MEMBERS** ► *Sandrine MOURADIAN-GARCIA* ***Engineer***

Research in the team focuses on the interplay between epigenetics and cancer. In recent years, a tremendous excitement has come from the discovery that histone post-transcriptional modifications regulate essential cellular functions. Our emphasis is on pericentromeres, regions of heterochromatin made of satellite sequences surrounding centromeres. One function of pericentromeres is to prevent premature chromosome separation in mitosis via the maintenance of chromosome cohesion after DNA replication, ensured by cohesines. Another function of pericentromeres is to act as silencing domains in cis and in trans, mediated by the presence of epigenetic marks associated with a repressive chromatin state, like DNA methylation, tri-methyl histone H3-K9, heterochromatin protein 1 (HP1) and hypoacetylated histones. In the presence of these repressive epigenetic marks, we showed that histone H3-S10 phosphorylation, mediated by Aurora-B kinase accumulated most frequently at large human pericentromeres in G2 cells (Monier and Sullivan, in revision), while this accumulation was lost in cells exhibiting hypomethylated pericentromeres (Fig.).

Our current line of research is to determine whether the function of aurora-B kinase in G2 cells is linked to its latter functions in mitosis and cytokinesis, essential to maintain chromosome stability in the cell progeny. State of the art approaches of molecular and cellular biology associated with fluorescent imaging will be carried out to track changes in pericentromere composition upon Aurora-B recruitment and activity. The potential role of identified candidates will be evaluated on chromosome segregation and mitotic progression of human cultured cells by RNA interference approaches. Our research will help in understanding how misregulation of epigenetic status of pericentromeres during cell cycle can lead to chromosome instability and ultimately carcinogenesis. In the long run, our results will provide insights into how pericentromeres support centromeric function during chromosome segregation in mitosis.



◄◄◄ ***Figure :*** *Aurora-B is recruited to large pericentromeres of chromosome 1 (NT2 cells) providing cytosine methylation is not abolished (U2-OS cells). DAPI-M: DAPI mask, P-H3: phospho-histone H3-S10, pC1: pericentromeres of chromosome 1 detected by FISH, Aur-B: Aurora-B. Scale bars represent 10 µm*

Reference : *Monier, K., Mouradian S. & Sullivan, K. F., 2006, en révision. DNA methylation promotes preferential Aurora-B-driven phosphorylation of histone H3 in chromosomal subdomains*

Organization and Function of Repressive Chromosomal domains in Caenorhabditis elegans

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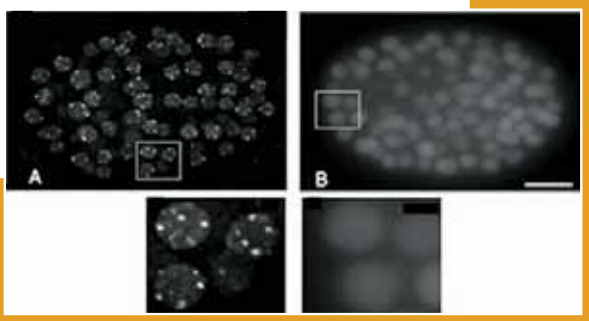
► **Team members** ► *Cécile BEDET* ***Postdoctoral fellow*** ► *Vincent COUSTHAM* ***PhD student***
► *Sonia SCHOTT* ***Engineer*** ► *Thomas SIMONET* ***PhD student***

We are using the nematode C. elegans as a model system to understand how the epigenetic regulation of gene expression influences metazoan development. As epigenetic modifications play an important role in cancer development, understanding the basic mechanisms of epigenetic gene regulation could contribute to a better understanding of pathologies like cancer. Furthermore, as cancer may be viewed as a developmental disorder, it follows that some of the molecular players involved in controlling development might also be implicated in cancer development, validating the use of simple genetic model systems like C. elegans.

Our studies are focussed on the highly conserved HP1 protein, an essential player in the dynamic organization of nuclear architecture and in chromatin remodeling and transcriptional silencing. We have shown that HPL-2, one of the two C. elegans HP1 homologues, acts in a transcriptional repressor pathway which includes homologues of the human Rb complex (Couteau et al., 2002). More recently, we have shown that HPL-2 forms a complex with the LIN-13 Zinc finger protein, another member of the Rb related pathway which includes HPL-2. LIN-13 is required for the recruitment of HPL-2 to chromatin and we have identifed potential targets for both genes. We believe that both proteins may act via Rb to bring about the repression of specific genes (Coustham et al, Dev. Biol. in press).

While deletion of hpl-2 results in sterility and growth defects, hpl-1 appears to be dispensable for both germline and somatic development. However, HPL-1 and HPL-2 are redundantly required for post-embryonic development, as hpl-1;hpl-2 double mutants do not develop past the larval stage. Our data provides the first direct evidence for both redundant and unique functions of HP1 family proteins in metazoan development (Schott et al, Dev. Biol. in press).

We have isolated SET1, the homolog of the human mixed lineage leukemia (Mll) gene, as a suppressor of hpl-2 mutant phenotypes. Chromosome translocations involving MLL are associated with aggressive acute leukemias and MLL is found in a histone H3 K4 specific histone methyltransferase (HMTase) complex associated with transcriptional activation. We have found that the nematode counterparts of other subunits of this complex also suppress hpl-2 mutant phenotypes, suggesting that an Mll related HMTase activity may antagonize HPL-2 repressor function. Understanding the different mechanisms of HPL-2 and Mll activities during C. elegans development may therefore contribute to a better understanding of mechanisms leading to the pathogenesis of leukemia.



HPL-2 recruitement to nuclear foci is dependent on LIN-13. HPL-2: GFP in wild-type (A) and lin-13 mutant (B) embryos at the 100 cell stage. Below each image is an enlargement of three nuclei

Differentiation and the Cell Cycle

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► Yindi DING **PhD student** ► Ambre SPENCER **PhD student**

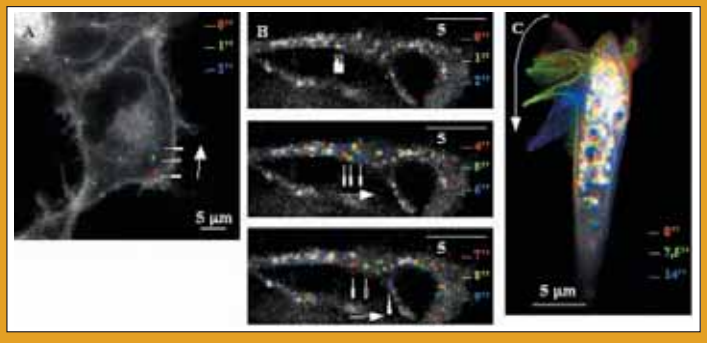
Our research focus is divided into two main areas – molecular and cellular neurobiology and cancer. Our research program has focused on cell cycle and signalling involved in the regulation of proliferation, differentiation and apoptosis in a model of neuronal differentiation induced by Nerve Growth Factor (NGF). Our team was the first to provide evidence for cell cycle phase-specific signaling of NGF. Further we have identified some of the key steps and players responsible for the anti-mitogenic effect of the NGF that accompanies differentiation.

The molecular analysis of the expression and fate of NGF receptors, TrkA and p75NTR, revealed that the surface expression of TrkA is regulated during the cycle. This is the first such observation for a neurotrophic factor receptor. It opens new prospects for the design of experiments to clarify the role of intracellular traffic on the signalling activity of such factors. We built and characterized TrkA-EGFP chimera allowing the observation of the intracellular traffic in quasi real-time. This remains a key facet of our research activities.

Another aspect of our work concerns small combinatorial protein tools called **«peptide aptamers»** for the study and perturbation of the NGF related signalling pathways. Peptide aptamers act as mini-antibodies, binding to specific sites on the target (e.g. Ras, Raf, Erk, etc.) selectively inhibiting certain functions. They consist of a protein scaffold (Thioredoxin) into which a variable sequence of fixed length is introduced in phase. The variable region was initially 20 amino acids. The peptide aptamers are selected against a specific target using two hybrid technology in Yeast.

Further, developments have been implemented, notably development of libraries for functional selection of biologically-active peptide apamers in bacteria (collaboration with the CEA), yeast and mammalian cells. The targets to which the aptamers were bound have been identified by yeast two hybrid, thus offering potential means of further studying key regulatory pathways.

We have been very active to transfer technology for the potential benefit of society and have coined the phrase "R2S" (Research to Society) to acknowledge this fundamental responsibility.



◄◄◄ *Time-lapse microscopy of TrkA-EGFP receptor chimerae.. A. Receptor internalisation. HeLa cells stably-expressing the chimerae, in the presence of NGF. One image per sec. B. Anterograde transport. PC12 nnr5 cells, expressing the TrkA-EGFP, in the presence of NGF. C. Mouvement of membrane (filipodia) and sortine in the growth cone. PC12 nnr5 expressing TrkA-EGFP, in the presence of NGF. The numbers in color represent the time at which each image was taken and corresponds to the vesicle or fillopodium of the same color*

Oncogenesis and Development

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► *Elodie BACHELARD **Technician** ► Anne-Marie BIROT **Engineer** ► Laurence CANAPLE **Engineer** ► Frédéric FLAMANT **Senior Researcher** ► Karine GAUTHIER **Associate Researcher** ► Sébastien GOUNEL **Technician** ► Romain GUYOT **Postdoctoral fellow** ► Elsa KRESS **PhD student** ► Fabrice LAVIAL **PhD student** ► Anne MEY **Associate Researcher** ► Guillaume MONTILLET **technician** ► Julien NADJAR **technician** ► Michelina PLATEROTI **Associate Researcher** ► Laure QUIGNODON **PhD student** ► Patrick RAVEL CHAPUIS **Associate Professor** ► Amélie REZZA **PhD student** ► Sandrine THENOT **Associate Researcher** ► Séverine VINCENT **Engineer** ► Virginie VLAEMINCK **Associate Professor***

Team certified by the *Ligue Nationale contre le Cancer*
This team joined the IGFL (*Institut de Génomique Fonctionnelle de Lyon*) on 1 January 2007

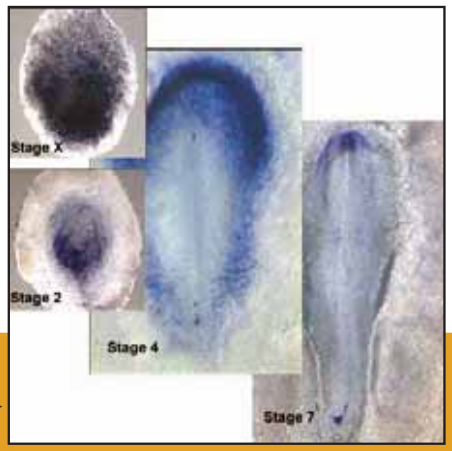
Role and mechanisms of action of thyroid hormone receptors in normal and pathological development.

Thyroid hormone plays a major role in the Vertebrates during development and tissue homeostasis. Its physiological effects are mediated through binding to nuclear receptors which are transcription factors. In mammals two genes, respectively THRA and THRB, encode several TRα and TRβ isoforms. Our group is dissecting the respective functions of these isoforms during development and homeostasis by generating isoform-specific TRα and TRβ mutant mice. From this work we could conclude that the TRα receptor plays a major role during the neonatal period in inducing the maturation of several organs like bone, brain, intestine, and spleen erythropoieisis. For example, in the neonate intestine TRα directly activates proliferation of epithelial cell progenitors through the transcriptional activation of the b-catenin gene. We also showed that before birth, the naturally unliganded forms of TRα control the functional development of the heart by repressing transcription of cardiac genes and slowing down the heart rate.

Focusing on specific organs, our future projects aim at identifying target genes regulated by TR isoforms during development and in adult homeostasis. In addition, we will also analyze the function of the different TR isoforms in the chromatin structure modification on the characterized target genes. An extension is the identification of the direct role of TR isoforms on human tumor development.

Molecular bases of development of embryonic stem cells.

Embryonic stem cells (ES cells) are pluripotent cells present at very early stages of embryonic development. Our group has been a pioneer in isolating ES cells from chicken embryo. This model is useful for addressing the question of the mechanisms controlling pluripotency and commitment to differentiation of these cells at the early stages of embryonic development. Our aim is to identify genes that are specifically expressed in ES cells and which might control their development. One such gene ENS-1 encodes a coiled-coil protein that interacts with proteins involved in chromatin organization. Using high throughput functional genomics we isolated sets of genes whose expression provides a signature for pluripotent ES cells, committed cells or early embryos. Some of these genes directly control pluripotency. In particular, for the first time, an avian homolog to the mammalian oct-3/4 gene was isolated and was demonstrated to be involved in the control of chicken ES cell pluripotency as well as germ cell lineage determinism. The role of these sets of genes in early embryonic development as well as germ line competency is being investigated by manipulating their expression directly in the living embryo. .



►►► *Expression of the Ens-1 gene in chicken embryos at various stages*

NEUROMUSCULAR DIFFERENTIATION

► **DIRECTOR** ► *Laurent SCHAEFFER **Senior Researcher** - laurent.schaeffer@ens-lyon.fr*
► **TEAM MEMBERS** ► *Evelyne GOILLOT **Associate Researcher** ► Katia ANCELIN **Assistant Researcher** ► Yann-Gaël GANGLOFF **Assistant Researcher** ► Dominique BAAS **Associate Professor** ► Valérie RISSON **Engineer** ► Jean-Luc THOMAS **Engineer** ► Claudine CORNELOUP **Engineer** ► Fanny PILOT **Postdoctoral fellow** ► Alessio ZANARDI **Postdoctoral fellow** ► Francis RAMOND **PhD student** ► Aymeric RAVEL CHAPUIS **PhD student** ► Caroline HUZÉ **PhD student** ► Sabine CAUSSANEL **PhD student** ► Alice FORNARI **PhD student** ► Frederico CALHABEU **PhD student***

Innervated skeletal muscle constitutes a model system of communication between two distinct cellular partners, and many general mechanisms have been elucidated through the study of the neuromuscular synapse, which remains an ideal tool to study the mechanisms by which a presynaptic neuron controls the differentiation and function of a post-synaptic cell.

RESEARCH THEMES

Epigenetic regulation of synaptic gene expression by motor innervation:

The different post translational modifications of the histone N-terminal tails constitute an epigenetic code that can be selectively recognized by transcription factors, therefore leading to a unique and specific answer at the transcription level.

We study the histone code in skeletal muscle and work to the identification of the chromatin modifying factors which control:

• The activation of synaptic genes expression by neural factors.

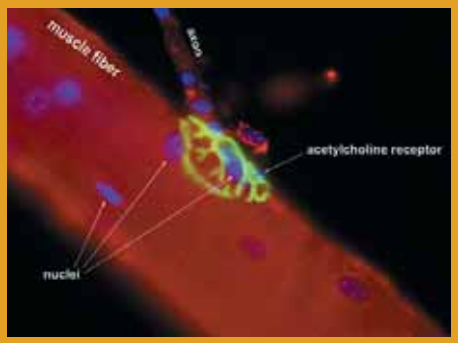
• The repression of synaptic genes expression in the muscle fibre extra synaptic regions by electrical activity elicited by the motor innervation (Mejat et al., 2005).

The PI3K pathway in skeletal muscle:

Study of the role of CKIP-1 (Casein Kinase Interacting Protein 1) in the response to promyogenic stimuli and at the neuromuscular junction. CKIP-1 is a pleckstrin homology domain signalling protein whose subcellular localization is controlled by the PI3 kinase pathway and whose expression is induced during muscle differentiation and is regulated by innervation (Safi et al., 2003). We study of the role of CKIP-1 during development, both in transgenic mice and zebra fish models.

Role of mTOR in muscle differenciation and plasticity

The serine/threonine kinase mTOR is a molecular integrator of different intra and extra cellular signals that performs numerous functions, including the control of translation at several levels. Many works suggest that mTOR signalling is involved in early and late muscle differentiation (regulated by motor innervation). We have generated a conditional knock-out of mTOR in mouse skeletal muscle. These animals develop a severe muscle dystrophy and constitute a unique tool to address mTOR functions in vivo.



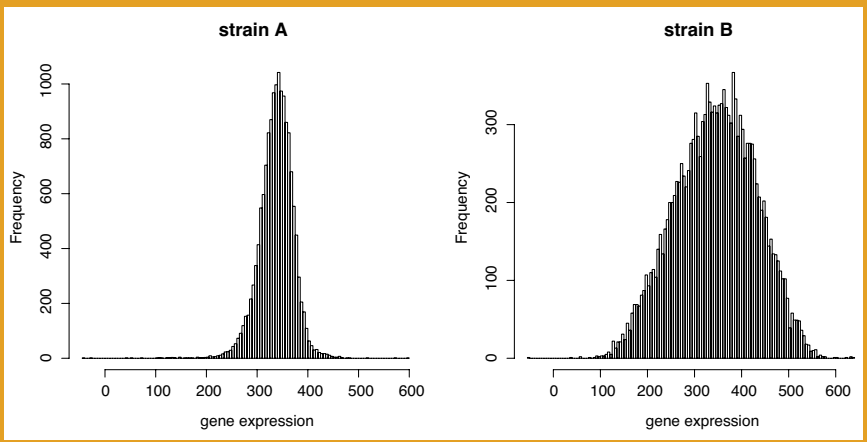
►►► *The neuromuscular synapse visualized by staining of the acetylcholine receptor with a-bungarotoxin (in green)*

Genetics of Intra-species Variation

► **Director** ► *Gaël YVERT* ***Assistant Researcher*** *- Gael.Yvert@ens-lyon.fr*
► **Team members** ► *Muniyandi NAGARAJAN* ***Associate Researcher***
► *Hélène BOTTIN* ***Technician***
► *Steffen FEHRMANN* ***PhD student***

Despite the exciting burst that genetics have experienced for the past decades, very little is known about the genetic architecture of common traits. This frustration is due to the complexity by which genotypic variation drives phenotypic diversity. Created in April 2005, our group mines into this complexity by studying molecular and cellular traits in a single-cell microorganism commonly used in laboratories : the baker's yeast Saccharomyces cerevisiae. This system offers numerous advantages: a very well annotated genome, a high recombination rate, easy manipulation of genes in their chromosomal context, and access to a large variety of strains from distant origins (from bread making to wine fermentations all over the world). In addition, the DNA microarray technology now offers the possibility to monitor thousands of molecular traits and to easily build dense genetic maps of natural allelic variations.

Using crosses between divergent strains, we are able to dissect the control of cellular morphology, epigenetic regulations or fermentation capacities of industrial strains. We also found a natural genetic variation in the level of stochasticity of gene expression: when the expression of a single gene is quantitated in individual cells, the cell-to-cell variability can differ from one genetic background to another (see figure). Applying quantitative genetics to a cross between such strains can reveal the regulators of this heterogeneity. Understanding this control is crucial to apprehend the emergence of cancer and the adaptability of a species to new environments.



Genetic variation of cell-to-cell variation in gene expression. The expression of a single gene (coding for a fluorescent protein) was measured by flow cytometry. Each panel shows the distribution of the expression levels in a population of isogenic cells, cultured together in a homogeneous environment. The cell-to-cell heterogeneity is higher in strain B (right) which has a distant genetic background from strain A (left)

Physics
LABORATORY

► **Director** ► *Jean François PINTON* ***Senior Researcher***
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► **Total personnel** ► *83*
► **Partners** ► *CNRS*

The spectrum of the research subjects of this laboratory is rather wide and ranges from theoretical and experimental physics to applications. Specifically we find research groups in soft matter, biophysics, non-linear physics, hydrodynamics, signal analysis, field theory and statistical mechanics. Among the on-going projects we can mention studies of the dynamo effect, of fluctuations in stochastic and dynamical systems, of Lagrangian turbulence, of the life time of materials under stress, of foam rheology, of the dynamics of biological macromolecules, of DNA sequences, of transport in granular media, of the traffic in networks, of the geometrical approach of conformal theory, of the spin-spin correlation functions in spin chains, of quantum phase transitions and of quantum decoherence.

This list is not exhaustive and is just a sample of the topics developed in the laboratory. Many of these topics are related by the common interest in the physics and in the statistical mechanics of out of equilibrium systems, such as turbulence, biological systems, granular materials, crack growth and rheology. The experiments performed in the laboratory are of small size and very flexible. This approach favors the interactions between theoreticians and experimentalists whose collaborations have been particularly fruitful in the last ten years. The members of the laboratory have many collaborations with other laboratories in France and abroad.

RESEARCH TOPICS
• Statistical physics • Soft matter
• Instabilities, crack growth • Aging
• Field theory • Fluid mechanics
• Turbulence • Magnetohydrodynamics
• Non-linear physics • Signal analysis
• Supersymmetry and supergravity
• Particles physics • Biophysics

RELATED FIELDS
• Acoustic as a detection system
• Rheology, electronics, optics,
Numerical calculation

AREAS OF APPLICATION
• Hydrodynamics, rheology • Granular media
• Liquid metals • Colloidal suspensions
• Polymers • Biological macro-molecules

INDUSTRIAL PARTNERS
• The Mathworks Inc(USA) • Canon
• ELF • Rhodia • BioMérieux

EQUIPMENT
• Wind tunnel • Light scattering apparatus
• Electro magnets • Spectrum analyzers
• Lasers • Rheometers • AFM • Optical traps
• High performance computer cluster

Picture of a region close to the tip of a crack slowly moving in a paper sheet. Crack dynamics is a non-linear phenomenon because during its propagation the fracture creates a new surface and continuously modifies its boundaries conditions. When a material is submitted to a stress smaller than the critical stress for rupture, which is intrinsic to each material, the failure may happen in a very slow way. We study experimentally the mechanisms of slow crack propagation, i.e. sub critical, and in parallel we develop statistical physics models to interpret the results and try to predict the time of the macroscopic failure

Soft Matter and Physics of Biological Systems

► **Team leader** ► *Patrick OSWALD **Senior Researcher** - patrick.oswald@ens-lyon.fr*
► **Team members** ► *Vance BERGERON **Senior Researcher** ► François CAILLIER **Associate Professor** ► Martin CASTELNOVO **Assistant Researcher** ► Alain DEQUIDT **PhD student** ► Jalal ERRAMI **PhD student** ► Bertrand FRANÇOIS **PhD student** ► Eric FREYSSINGEAS **Associate Professor** ► Hervé GAYVALLET **Associate Professor** ► Jean-Christophe GÉMINARD **Associate Researcher** ► Jean-François PALIERNE **Associate Researcher** ► Michel PEYRARD **Professor** ► Christophe PLACE **Associate Researcher** ► Patrick RIGORD **Assistant Professor** ► Valérie VIDAL **Assistant Researcher** ► Johannes-Geert HAGMANN **PhD student** ► Juliette LARBRE **Postdoctoral fellow** ► Thibaut DIVOUX **PhD student** ► Santiago CUESTA LOPEZ **Postdoctoral fellow** ► Sébastien MANNEVILLE **Assistant Professor** ► Niclolas TABERLET **Associate Professor***

This group studies a wide range of aspects in the field of soft condensed matter physics and biological systems, combining experimental work with theory and numerical simulations. Research interests are focused on the physics of liquid crystal materials, melted polymers, elastomers, emulsions, foams, granular materials, proteins, aspects of DNA molecular configuration and certain viruses and biological tissues. Emphasis is placed on understanding the transport properties of these systems (diffusion coefficients, thermal conductivity and thermo-mechanical coupling), in addition to their rheology (linear and non-linear), phase transitions, mechanical instabilities, interfacial properties, defects and aging. Both microscopic and macroscopic approaches are used to understand the structure-property relationships in these different systems. Continuum mechanics, combined with statistical physics, optics and non-linear analysis are some of the primary tools used by the group. A strong effort is placed on bridging the gap between fundamental studies and real-world applications. This later point is witnessed by the start-up activity within the group such as the recent creation of the company Varioptic (http://www.varioptic.com/en/) and the work concerning viruses and air purification using non-thermal plasma – collaborations in the public health sector being well established. Effort is also placed on understanding natural occurring phenomena such as volcanic eruption (acoustic and optical analysis of gas cavities moving through granular or viscoelastic materials) and snow ablation (creation of penitentes under controlled irradiation), studies conducted in international collaboration with volcanologists and glaciologists. Recent work has also addressed biomechanical aspects of the brain and trauma effects on biological tissue.

◄◄◄ *Bubble reaching the free surface of a non-newtonian fluid. The peculiar fluid properties are responsible for the elongated bubble shape and the cusp formation at its tail*

Physique non linéaire, hydrodynamique et Turbulence

► **Team leader** ► *Jean François PINTON **Senior Researcher** - jean-francois.pinton@ens-lyon.fr*
► **Team members** ► *Ludovic BELLON **Researcher** ► Francesca CHILLÀ **Associate Professor** ► Sergio CILIBERTO **Senior Researcher** ► Thierry DAUXOIS **Senior Researcher** ► Nicolas GARNIER **Researcher** ► Emmanuel LÉVÊQUE **Researcher** ► Antoine NAERT **Associate Professor** ► Philippe ODIER **Associate Professor** ► Artyom PETROSSYAN **Engineer** ► Loïc VANEL **Associate Professor** ► Denis MARTINARD **Assistant Professor** ► Romain VOLK **Associate Professor** ► Pierre-Philippe CORTET **PhD student** ► Cyril DUEZ **PhD student** ► Louis GOSTIAUX **PhD student** ► Sylvain JOUBAUD **PhD student** ► Pieromenico PAOLINO **PhD student***

This team studies experimentally, theoretically and numerically the role of the non-linear effects on the dynamics of several out of equilibrium phenomena. Among the recently developed subjects we find:

1) The aging of amorphous materials: several aspects of this phenomenon have been studied in polymers and gels, specifically the memory effects and the evolution of thermal fluctuations of these weakly but durably out equilibrium systems.

2) Reflections of internal waves: we study experimentally and theoretically the generation of internal waves by the tides and the reflection of an internal wave by an inclined bottom. These are two extremely important mechanisms to explain the mixing processes inside the oceans.

3) Statistical mechanics of out of equilibrium systems with long range interactions. We study the unusual behaviours, which may develop in these systems, such as the negative specific heat, the ensemble inequivalence, and very strange and unexplained dynamical behaviours.

4) Sub critical rupture of heterogeneous media. We study experimentally the mechanisms of the slow crack (i.e. sub-critical rupture) and we develop models to interpret the experimental results.

5) Fluctuations in out of equilibrium systems: we are interested in the dynamics of global quantities and in the fluctuations of the injected and dissipated power in dynamical and stochastic systems driven out of equilibrium.

6) Turbulent thermal convection (collaboration with the team SYSIPHE): we study the heat transport in turbulent thermal convection, which plays a crucial role not only in many natural phenomena but also in many industrial processes.

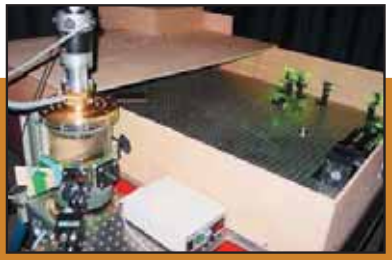
7) Magneto hydrodynamics: we study the induction of electricity in turbulent flows of conductive fluids with applications to dynamo effect. The experiments are performed in liquid gallium and in the CEA-Cadarache in liquid sodium in the context of the national collaboration VKS.

8) Lagrangian turbulence: we use original acoustic and optical techniques to follow particles transported by turbulent flows. The goal is to describe the dynamics of these particles and to make models of the forces acting on them.

9) Sub-grid models of the turbulent viscosity: In numerical simulations of the large structures in turbulent flows (Large-Eddy simulations) we study in details the effects of solid walls.

The goal of these researches is to understand the fundamental aspects of these phenomena, which have many important applications in several domains of engineering and geology. This team collaborates on several subjects with the other teams of the laboratory and with the other research teams in France and abroad (Germany, Spain, USA, Italy, Poland, UK and Russia).

More details about these researches may be found in:
http://www.ens-lyon.fr/PHYSIQUE/index.php?page=equipe2



Particle tracking in a turbulent flow: the new technique developed in our laboratory is based on the principle of the Laser-Doppler and is analogous to the ultrasound technique previously developed. It is applied to the study of the forces acting on either Lagrangian or inertial particles, i.e. particles with a density different than that of the fluid ►►►

SIGNAL, SYSTEMS AND PHYSICS

► **TEAM LEADER** ► *Patrice ABRY **Senior Researcher** - Patrice.Abry@ens-lyon.fr*
► **TEAM MEMBERS** ► *Pierre BORGNAT **Researcher** ► Bernard CASTAING **Professor***
► *Patrick FLANDRIN **Senior Researcher** ► Pablo JENSEN **Senior Researcher***
► *Stéphane ROUX **Associate Professor** ► John Mc BREEN **PhD student***
► *Mathieu CREYSSELS **PhD student** ► Mathieu GIBERT **PhD student***
► *Nicolas MALLICK **PhD student** ► Gabriel RILLING **PhD student***
► *Herwig WENDT **PhD student** ► Jun XIAO **PhD student** ► Edmundo PEREIRA DE SOUZA NETO **Researcher** ► Guillaume DEWAELE **Assistant Professor***

The SiSyPh, SIgnal, SYstems and PHysics, group is a statistical signal processing group within the Physics Department at ENS Lyon. The spirit of the researches conducted in the SISYPH group precisely lies in the interaction between the analysis of experimental data obtained from actual experiments and the development of solutions for theoretical signal processing issues, defined from the confrontation to real data.

The collaboration of the signal processing group with other research teams of the Physics lab, such as the Non-Linear and Hydrodynamic group, provides a perfect illustration of the way researches are conducted. From the study of the benefits brought by the use of wavelet transforms for the analysis of the energy cascade in hydrodynamic turbulence, has been devised the general research theme centered around "Scale Invariance, Multiresolution and Wavelets". Within this theoretical framework, the signal processing tools elaborated for the study of scaling have been applied to the analysis of computer network traffic scaling properties, before being again used in the context of turbulence.

SiSyPh organizes its research activities around two major theoretical directions:

- Non stationarity and time frequency analysis
  - Empirical Modal decomposition (with P. Gonçalvès, LIP, ENS Lyon)
  - Test of (non-)stationarity
  - Signal processing with deformation operators (with P.O. Amblard, INPG, Grenoble)
- Scale Invariance and Wavelets
  - Multifractal Analysis (with S. Jaffard, Département de mathématiques, Université Paris XII, and V. Pipiras, Department of mathematics, North Carolina University, USA)
  - Synthesis of Multifractal Processes (with P. Chainais, ISIMA, Université de Clermont-Ferrand, and R. Riedi, Department of Statistics, Rice University, Houston, Texas, USA)

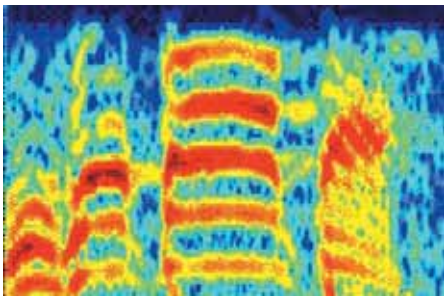
SiSyPh is involved in the analyses of various types of applications :

- Hydrodynamic Turbulence (in collaboration with the Non-Linear & Hydrodynamic group of the lab)
- Computer Network traffic (with D. Veitch, Melbourne University, Australia, and the French METROSEC project : Metrology for Security)
- Baro-reflex regulation (with the *Hospices Civils de Lyon*, French Public Hospital)
- Neuron Dynamics (with the *Laboratoire des Neurosciences et Systèmes sensoriels, UCB Lyon 1*)
- Analysis of waves in the Ionosphera (with the Department of Physics of Atmosphere, Praha, Czech Republic)
- Social networks modeling (with the LET, Université Lyon 2)

SiSyPh develops various Physcis experiments, implying the use of advanced Signal processing analysis:

- Granular medium,
- Non linear surface waves,
- Turbulent thermal convection (with the Non-Linear & Hydrodynamic group).

For more details, see
http://www.ens-lyon.fr/PHYSIQUE/index.php?page=equipe3



Time-Frequency Analysis for a Non stationary Speech Signal: It represents (with false colors) the evolution along time (Horizontal Axis) of the spectral energy content (Vertical Axis) of the data

Theoretical Physics

► **Team leader** ► *Jean Michel MAILLET **Senior Researcher** - maillet@ens-lyon.fr*
► **Team members** ► *Angel ALASTUEY **Senior Researcher** ► David CARPENTIER **Researcher** ► Pascal DEGIOVANNI **Researcher** ► François DELDUC **Senior Researcher** ► Laurent FREIDEL **Researcher** ► Krzysztof GAWEDZKI **Senior Researcher** ► Peter HOLDSWORTH **Professor** ► Etera LIVINE **Researcher** ► Marc MAGRO **Associate Professor** ► Edmond ORIGNAC **Researcher** ► Henning SAMTLEBEN **Professor** ► Véronique TERRAS **Researcher** ► Fabio TONINELLI **Researcher** ► Giuliano NICCOLI and Rafal SUSZEK **Postdoctoral fellow** ► Rafael CHETRITE, Karol KOZLOWSKI and Sébastien PAULIN **PhD Students***

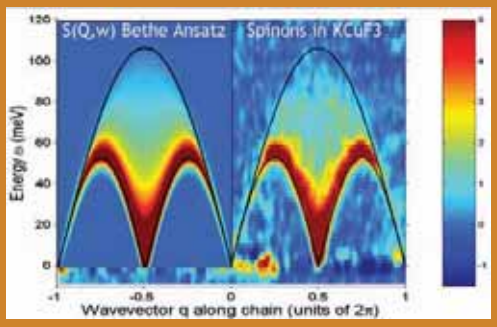
The Theoretical Physics team has a quite wide spectrum that encompasses several directions of modern theoretical physics. Beyond their diversity, these research activities enable to offer to the ENS Lyon students broad perspectives on the most recent developments in theoretical physics including field theory and fundamental interactions (string theory, quantum gravity, super-gravity and super-symmetry, etc.), mathematical physics, theoretical condensed matter physics, statistical mechanics and complex systems. Members of the Theoretical Physics team have collaborations both with other (more experimental) teams of the ENS Lyon Physics Laboratory and with other Laboratories or Institutes in France and around the world.

The research activities of the team can be described along three main directions: mathematical physics (in a wide sense), theoretical condensed matter and statistical mechanics and complex systems. These include various research (the list is certainly not complete, and subject to changes with time) :

Mathematical physics:
- Integrable models and applications (correlation functions, quantum groups,...)
- Quantum gravity (loop quantum gravity, spin foams,...)
- Quantum field theories and fundamental interactions (string theory, super-gravity, super-symmetric gauge theories, branes and boundary CFT, etc.)
- Exact methods in turbulence and disordered systems
- Quantum plasmas

Theoretical condensed matter physics:
- Quantum phase transitions: disorder, frustration and slow dynamics
- Dissipative dynamics of mesoscopic quantum systems
- Quantum transport

Statistical mechanics and complex systems:
- Stationary states for dissipative systems
- Global measurable quantitites
- Out of equilibrium systems



◄◄◄ *Dynamical structure factor S(q,w) as a function of momentum q and energy w for the isotropic Heisenberg chain in the disordered phase. On the left the result from the Bethe ansatz computation (J. S. Caux, R. Hagemans, J. M. Maillet) and on the right the measurements by neutron scattering on the compounds KCuF3 obtained by A. Tennant and his team in the Hahn-Meitner-Institut, Berlin. The value of the function S(q,w) is given according to the colours as indicated on the right of the picture*

Dynamics of biological molecules

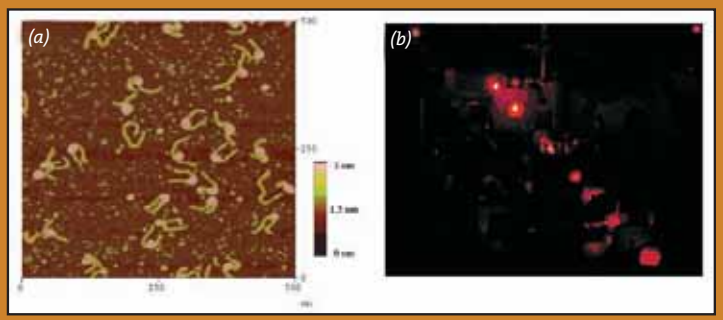
► **Team leader** ► *Françoise ARGOUL **Senior Researcher** - francoise.argoul@ens-lyon.fr*
► **Team members** ► *Lotfi BERGUIGA **Engineer** ► Emeline FONTAINE **Engineer***
► *Fabien MONTEL **PhD student** ► Cendrine MOSKALENKO **Associate Professor***
► *Sanjun ZHANG **PhD student***

The "Dynamics of Biological Molecules" team is composed of experimental physicists using micromanipulation and visualization techniques (atomic force microscopy, evanescent wave optics) for single molecule imaging. We focus our efforts on the nucleosome, the basic unit for DNA compaction into chromatin inside eukaryotic cell nuclei, which plays the role of a regulatory factor for genetic material accessibility.

Recently our team has settled up physical approaches to address two different biological questions:

Nucleosome in-vitro formation and nucleosome sliding along a DNA fragment. These experimental studies are conducted in close collaboration with the biology teams of the Joliot-Curie Laboratory (P. Bouvet and S. Dimitrov) and aim at understanding on the one hand the various kinetic steps of nucleosome in-vitro reconstitution, and on the other hand how remodelling molecular motors exert mechanical action on nucleosomes. Our goal is to be able to visualize in real time, combining non-intrusive optical methods and high spatial resolution imaging (nm scale) the nucleosome formation dynamics and nucleosome sliding induced by remodelling complexes.

What is the role of the DNA sequence on the structure and dynamical properties of chromatin? This study is directly inspired from the theoretical results of Alain Arneodo's team, also present in the Joliot-Curie Laboratory. Their theoretical multi-scale approach of DNA sequences suggests that nucleosome thermal mobility is greatly affected by the existence of long range correlations in the structural disorder of DNA polymer (elastic properties induced by the DNA sequence). We study experimentally how these long range correlations influence the 2D thermodynamical equilibrium conformation of naked DNA fragments, as well as the formation and diffusion of nucleosomes. The goal of this project is to show the link between the DNA sequence and the structural and mechanical properties of the chromatin fiber for a better understanding of functional genome organization.



AFM and SSPM imaging for nucleosome dynamics study
(a) AFM imaging (atomic force microscopy in intermittent contact mode) allowing to visualise nucleosomes reconstituted on a 356 base pair positioning DNA sequence, and adsorbed on functionalised mica surface. The height of the objects is given by the 'false color' scale. (b) Photograph of the surface plasmon microscope (SSPM), that allows the measurement of the local optical index for a DNA monolayer confined close to a gold surface. This experimental set-up, when coupled to micro-fluidic injection system, allows to follow in real time the DNA monolayer dynamics with the injection of structural proteins

Plant Reproduction and Development LABORATORY

► **Director** ► *Christian DUMAS* ***Professor***
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► **Total personnel** ► ***54***
► **Partners** ► *CNRS* ► *INRA* ►*UCB Lyon 1*

We are studying the biological processes through which plants develop and reproduce. We use model plants, such as Arabidopsis thaliana, to address fundamental questions of plant reproduction and development and we then apply the insights gained from these fundamental studies to cultivated plant species including maize and roses. In the longer term, our studies will help to improve such crop plants, particularly in terms of seed and flower quality. Members of our laboratory also play important roles in university-level teaching.

Our scientific programme covers all stages of reproductive development in plants from the initiation of the flower primordium to early embryo development. We are also studying the evolution of plant development by taking a comparative "evo-devo" approach. Several projects in our laboratory are concerned with cellular processes, including intracellular protein trafficking, intercellular signalling and cell differentiation. Further projects address the question of plant development by taking a "systems biology" approach, linked to the mathematical modelling of developmental processes. Our studies involve a combination of many different methods including genetics, genomics, transcriptomics, in vivo microscopic imaging and computer modelling. Increasingly, our work involves collaborations with groups of mathematicians and computer scientists, for which we take full advantage of the pluridisciplinary expertise available on campus.

Our laboratory is composed of six research teams, all supported by a common group of technicians. In addition to excellent general laboratory facilities for molecular biology, biochemistry and imaging etc, we are amply equipped with environmentally controlled plant growth chambers and a dedicated greenhouse facility. Our laboratory also has access to many technical platforms involving particularly high-cost equipment such as confocal microscopes, proteomic facilities etc, through its membership in the Federal Research Institute (IFR128) of Biosciences, Lyon-Gerland.

RESEARCH TOPICS
• Sexual organ differentiation
• Signal transduction
• Embryogenesis • Petal development
• Floral meristem

RELATED FIELDS
• Genetics •Physiology and biochemistry (proteins)
• Cell biology • In vitro culture • Trangenesis

AREAS OF APPLICATION
• Seed • Hybrid crops
• Trangenesis/plant regeneration
• Flower quality

INDUSTRIAL PARTNERS
• Biogemma

EQUIPMENT
• Controlled growth chambers • In vitro culture
• Confocal microscopy • Electrophoresis
• Sequencing

◄◄◄ *The figure represents ongoing research in the laboratory on flower development, ranging from flower initiation and growth to fertilisation and early seed development*

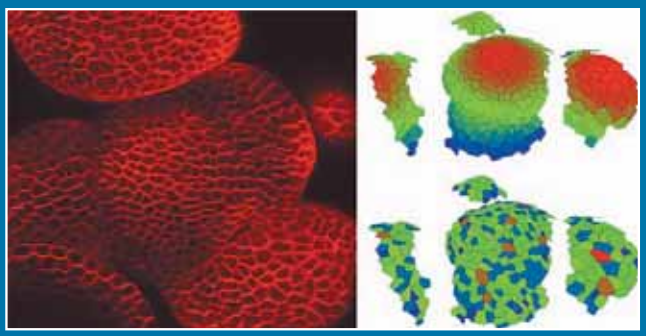
FLORAL MERISTEM FUNCTION

► **TEAM LEADER** ► *Jan TRAAS* ***Senior Researcher*** *- Jan.Traas@ens-lyon.fr*
► **TEAM MEMBERS** ► *Adeline BERGER* ***Engineer*** ► *Pradeep DAS* ***Postdoctoral fellow***
► *Olivier HAMANT* ***Postdoctoral fellow*** ► *Marianne SCHAEDEL* ***PhD student***
► *Teva VERNOUX* ***Assistant Researcher***

Plant architecture depends largely on the activity of stem cells located in the meristems. Since the meristems initiate and position all organs, they control traits of agronomic importance and a better knowledge of their function has important implications for agriculture. The main aim of our project is to unravel the mechanisms controlling the initiation and function of organs both in the inflorescence meristem and in the floral meristem, which generates the reproductive organs.

The initiation of organs is a complex process which includes drastic changes in gene expression profiles accompanied by cell growth and proliferation. We are using the model plant Arabidopsis to understand how the dynamics of these processes are coordinated and controlled. In this context we are primarily interested in cell-cell signaling. The complex function of the meristem requires coordinated behavior of individual cells. This involves cell-cell interactions mediated by the exchange of metabolites and signaling molecules. We are mainly focusing our efforts on one of the signaling molecules, the plant hormone auxin, which plays an essential role in organ initiation and positioning. The current hypothesis proposes that the precise accumulation of this hormone induces organ initiation at the periphery of the meristem. We are exploring the functional relationships between auxin, cell behavior and gene expression during organ initiation. To achieve this we use molecular genetics, genomics and in vivo imaging approaches to perturb auxin signaling and analyze the effect on organ initiation. We have also developed computer models of organ initiation that are used to help analyze our data.

In parallel, we are trying to obtain a more global understanding of the meristem function. For this purpose, we study a large set of parameters during flower development such as cell proliferation and differentiation patterns, signaling networks and transcriptional regulatory networks. In collaboration with mathematicians and computer scientists, we are creating a virtual floral meristem that integrates our results and use this model to generate new hypothesis concerning the initiation and function of floral meristems.



◄◄◄ *Shoot apical meristem of the model plant Arabidopsis visualised in the confocal microscope. At the left the orginal image, showing the individual cells. At the right two 3 dimensional reconstructions of the same meristem*

Flower Morphogenesis

► **Team leader** ► *Mohammed BENDAHMANE* ***Associate Researcher*** *- mbendahm@ens-lyon.fr*
► **Team members** ► *Philippe VERGNE* ***Associate Researcher*** ► *Annick DUBOIS* ***Assistant Researcher*** ► *Olivier RAYMOND* ***Associate Professor*** ► *Véronique BOLTZ* ***Technician***
► *Emilie VARAUD* ***PhD student*** ► *Marion MAENE* ***PhD student***

Research team at UMR5667 INRA-CNRS-UCBL-ENS LYON

Work in our group aims to understand factors that influence three commercially important traits: flower shape, longevity and scent. We use a combination of Arabidopsis thaliana, as a genetic tool, and the rose as a more applied model species. Petal is the major organ determining flower quality. The role of floral homeotic genes in the determination of petal identity is relatively well understood. However, very little is known about three important aspects that influence flower quality:

i) Flower shape: It is determined by petal characters such as shape and number. Specific final shape and size can be influenced by cell number or cell expansion or both. We focus our work on a novel petal-expressed transcription factor that we recently identified and showed to limit petal size by interfering with post-mitotic cell expansion (Szecsi et al., 2006 EMBO J 25, 3912-3920). A number of genes have been shown to control petal number mostly in Arabidopsis. We are studying the molecular interactions between these genes in order to control petal number in the rose.

ii) Flower longevity: The final stage of petal development, petal senescence, is particularly important as it has a major influence on the vase life and the quality of ornamental plants. Using a genetic screen, we identified an Arabidopsis mutant that is affected in flower senescence (early flower senescence). The functional characterization of the gene associated with this phenotype is one of our aims.

iii) Rose Scent (this part was developed in the group until September 2006 by Hugueney Philippe, now at INRA-Colmar): Flower scent is determined by a complex mixture of volatile molecules produced by petals. Using the rose as a model plant, we investigate the molecular, cellular and evolutionary aspects of scent production. Several genes involved in scent biosynthesis have been characterized and used to investigate scent evolution in the genus Rosa.

Petal final size is remarkably constant within a given species indicating the existence of checkpoints that control/terminate organ growth. One of our objectives is functional characterization of genes that control this process. The figure shows an example of an Arabidopsis thaliana mutant affected by a gene that controls final petal size (right) compared to the wild-type (left)

Flower Determinism

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► *Christophe TRÉHIN* ***Associate Professor***
► *Nathanaël PRUNET* ***PhD student***

Developmental plasticity in the flower meristem of Arabidopsis.

Meristems are proliferative structures which ensure a continuous growth capacity and a flexible architecture of the plant. They contribute to the modular organization of the plant body (axes). Therefore, organs are produced indefinitely. This is possible because meristems contain a stem cell niche. During ontogenesis, the meristems acquire different identities, from vegetative (axilary branches) to reproductive (inflorescence, flowers). This corresponds to phase transitions during development, controlled by several key chromatin factors. Such factors participate in the modulation of stem cell homeostasis.

Flower meristems are the exception in that they produce a finished number of organs due to the termination of the stem cell population. This repression is reversible. We are characterizing factors involved in this process which have been cloned following forward genetic screens. We are analysing these and several other components of the regulatory network (genetics, transcriptional regulation and epigenetic contexts, transcriptom profiling, protein complexes).

The project has a series of evo-devo implications, such as the study of the evolutionary origin of the flower, the identification of mechanisms driving biodiversity and domestication processes.

The project is a collaboration with John Bowman, Davis University.

◄◄◄ *Double mutant in Arabidopsis with an indeterminate flower phenotype resulting from a persistent stem cell activity in the flower meristem. Open carpel-stamen reiterations are visible along an inflorescence-type axis*

Cell Signaling and Endocytosis

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► **Team members** ► *Isabelle FOBIS-LOISY **Associate Researcher** ► Christine MIEGE **Associate Professor** ► Frédérique ROZIER **Technician** ► Rumen IVANOV **Postdoctoral fellow** ► Yvon JAILLAIS **PhD student** ► Mikael POURCHER **PhD student** ► Martina SANTAMBROGIO **PhD student***

The group has two main subjects of interest in the field of plant cell signaling and development, which are: (i) to decipher the molecular bases of self-pollen recognition and rejection that occurs during the self-incompatibility (SI) response in the Brassicaceae family, and (ii), to better our understanding of the regulatory functions played by endocytosis in plant development. SI in the Brassicaceae is controlled by a receptor-ligand interaction, which involves the S-locus receptor kinase (SRK) on the female side and the S locus Cysteine-Rich peptide (SCR, also known as SP11) on the male side. Recently, we have identified a Sorting Nexin-like protein (SNX1) as a novel interactor of the SRK kinase domain (Vanoosthuyse et al., Plant Physiology 2003). Interestingly, SNX1 also interacts with the kinase domain of other plant receptor kinases (e.g., SFR1 and CLAVATA 1), suggesting that SNX1 might play a general role in the regulation of plant cell signaling mediated by receptor kinases. In mammalian cells, SNX proteins play a role in receptor kinase down-regulation, intracellular trafficking of membrane receptors, and are essential to mouse embryo development. We are developing diverse genetic and cellular approaches to investigate the functions of plant SNXs and their interacting proteins in self-pollen rejection and plant development. We have recently shown that SNX1 defines a new endosomal compartment involved in the trafficking of carriers of the phytohormone auxin (Jaillais et al., Nature 2006). The ultimate aim of this work is to determine whether functions of the members of the very small (only three members) SNX family in plants are similar to those of their mammalian counterparts (30 members), or by contrast, whether plant SNXs exhibit unique features related to plant cell structural and physiological peculiarities.

This project requires tools of molecular genetics, cell imaging and proteomics, which all are available at the ENS Lyon and IFR 128 BioScience Lyon-Gerland.

A, The rejection of pollen grains on the stigmatic surface characterizes the self-incompatibility response. Rejection is associated with the arrest of pollen tube growth, which is here visible as white fluorescence plugs by fluorescence microscopy

B, Pollen rejection observed by scanning electron microscopy

C, Root cells of a transgenic Arabidopsis thaliana plant expressing a green fluorescent formed of SNX1, which localizes either in the cytosol (diffused green labelling) or in the SNX1 endosomal compartment (punctuate green labelling) observed by confocal microscopy

Flower evolution and development

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► *Sophie JASINSKI* ***Postdoctoral fellow and Associate Professor***
► *Géraldine BRUNOUD* ***Technician*** ► *Cédric FINET* ***PhD student***
► *Mathieu REYMOND* ***PhD student***

We are studying the evolution and development of the flower, the reproductive structure that characterises the flowering plants. In particular, we are interested in the mechanisms controlling the development of the flower's female reproductive organ, the carpel, and of the molecular events that shaped the anatomical evolution of this structure. We are following two main approaches:

1. We are comparing the structure, expression and function of genes that control carpel development in species whose lineages diverged early in the evolution of the flowering plants. This work takes us as far afield as the South Pacific in search of representatives of early-diverging plant groups, and involves the adaptation of laboratory methods for the investigation of these non-model species. Through this approach, we aim to identify the molecular changes that led to the closure of the carpel around the ovules in an ancestor of the flowering plants, over 150 million years ago, and thus to the evolution of the 300 000 species of flowering plants alive today.

2. We are studying the transcriptional control network that regulates carpel development in the model flowering plant, Arabidopsis thaliana. To achieve this, we are using micro-array analyses to identify genes whose expression is regulated downstream of numerous transcription factors with known phenotypic effects on carpel development. We are collaborating with other groups of biologists and mathematicians to combine the results of our analyses into a predictive model of carpel development: "The Virtual Carpel".

A female flower of Amborella trichopoda, a species endemic to the tropical island of New Caledonia and probable sister to all other flowering plants.
Our studies of Amborella indicate the gene CRABS CLAW to have conserved its role in carpel development since the common ancestor of the flowering plants (Fourquin et al., 2005).

Maize Embryogenesis

► **Team leader** ► *Peter ROGOWSKY* ***Senior Researcher*** *- peter.rogowsky@ens-lyon.fr*
► **Team members** ► *Vanessa VERNOUD* ***Assistant Researcher***
► *Nathalie DEPEGE* ***Associate Professor*** ► *Magalie COSSEGAL* ***PhD student***
► *Guillaume LAIGLE* ***PhD student*** ► *Sandrine PAINDAVOINE* ***Engineer***
► *Valérie MORIN* ***Engineer*** ► *Marie GAUTHIER* ***PhD student***

The Maize Embryogenesis Group headed by Peter Rogowsky employs both forward and reverse genetics to elucidate the function of genes involved in maize seed development. In the past the forward genetics approach focused on the embryo specific phenotype characterised by aberrant embryo but normal endosperm development. The phenotype of several embryo specific mutants has been described by classical and confocal microscopy, immunocytology and marker gene analysis and one of the underlying genes has been cloned (Magnard et al 2003 Plant Physiol 134: 649-663). Recently the scope has been broadened to include also the miniature phenotype characterised by a reduction in kernel size without developmental aberrations.

In the reverse genetics approach gene isolation and characterisation is based on differential methods allowing the isolation of tissue or stage specific genes. Several genes with specific expression patterns in the seed were isolated this way such as the ZmEBE (embryo sac – BETL – ESR) genes expressed in the basal part of the endosperm (Magnard et al 2003 Plant Mol Biol 53: 821-836) or the VPP1 (H+ translocating vacuolar pyrophosphatase) gene expressed in the aleurone layer (Wisniewski and Rogowsky 2004 Plant Mol Biol 56: 325-337). Another example are the 5 OCL (outer cell layer) genes that belong to the plant specific HD-ZIP IV family of transcription factors (Ingram et al 2000 Plant J 22: 401-414). All 5 genes show a specific expression pattern restricted to the outer cell layer of the embryo and some other tissues. The function of these transcription factors is likely the establishment and maintenance of the outer cell layer. Transgenic plants strongly expressing an Engrailed-OCL1 fusion exhibit a transient growth limitation of the seed at early developmental stages (Khaled et al 2005 Plant Mol Biol 58:123-139).

◄◄◄ *Transitory reduction of kernel size in the presence of the transgene Engrailed-OCL1. Immature ear at 15 DAP (days after pollination) of a transgenic plant expressing the chimeric Engrailed-OCL1 protein under control of the rice actin promoter (A) and of a wildtype sibling plant (B). After pollination by wildtype pollen a 1:1 segregation of normal sized wildtype kernels (wt) and smaller transgenic kernels (T) can be observed*

ENS LYON

Pure & Applied Mathematics Unit

► **Director** ► *Damien GABORIAU* ***Senior Researcher***
► **e-mail** ► *dirlab@umpa.ens-lyon.fr*

► **Total researchers** ► ***about 50***
► **Partners** ► *CNRS*
► **Web** ► *http://www.umpa.ens-lyon.fr*

The ENS Lyon mathematics department is an international-level research institution, in spite of its small size and of the young age of its members (half of whom are below 36).
Among its strong points, one can quote:
• a very strong participation of the CNRS (Centre National de la Recherche Scientifique), which employs about 60% of the permanent members;
• the wealth of exchanges between the various themes of research: many researchers belong to two different teams, many seminars and scientific activities are held together;
• as in all *Écoles normales supérieures*, the rich interactions between research and training, which benefits students as well as researchers.

Scientific activities are lively and training is personalized.
For instance, some courses are performed in small groups of 5-6 students around a researcher.

Mathematicians are not keen on splitting their laboratories into distinct "teams", so the UMPA lab only consists of three teams: "partial differential equations and modelling; geometry; and probability theory". It should be noticed that many members of these teams also belong to other teams. This is still another illustration of the great unity of mathematics in general, and of UMPA in particular!

Each has its own seminar, and its working seminars.
There is also a generalist internal seminar, which allows members of the laboratory to be well aware of the activity of their colleagues.
A fourth team, in algebra and number theory, is currently under construction.

RESEARCH TOPICS

• Riemannian geometry •Differential topology
• Dynamical systems • Global analysis on manifolds
• Algebra • Numerical analysis
• Systems of conservations laws
• Probability and its applications • Information theory
• Scientific computation • Kinetic theory of gases
• Modelling in fluid mechanics and in plasma physics
• Mathematical problems in fluid mechanics
• Modelling in medicine and biology

RELATED FIELDS

• FLuid mechanics • Complex chemistry
• Models in medicine • Geophysical fluids
• General relativity • Cryptography

Partial Differential Equations and Modelling

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► **Team members** ► *Emmanuel GRENIER* ***Professor*** ► *Cédric VILLANI* ***Professor*** ► *Stéphane DESCOMBES* ***Associate Professor*** ► *Olivier DRUET* ***Researcher*** ► *Marc BERNOT* ***Assistant Professor*** ► *Pierre BOUSQUET* ***Assistant Professor***
► *Guillemette CHAPUISAT, Valérie LE BLANC, Yaxin PENG, Rémi PEYRE, Paul LAURAIN and Tiansi ZHANG:* ***PhD students***
► **Other local collaborators** ► *Cédric BERNARDIN* ***Researcher*** ► *Albert FATHI* ***Professor***
► *Julien MICHEL* ***Associate Professor*** ► *Jean-Claude SIKORAV* ***Professor***

Rules : Art. 1. Participate in the PDE seminar on Thursday am. Art. 2. Interact with the teams Probability and Geometry of UMPA. Art. 3. To be at the international level in various topics. Art. 4. Be respectful of one's colleagues and maintain a warm atmosphere of work and friendship. Art. 5. Collaborations with external teams or researchers are welcome.

The most structured topic concerns the PDEs of non-equilibrium statistical mechanics, in particular the Boltzmann equation and its variants (Landau equation in plasma physics). We address regularity questions and convergence rate towards equilibrium. That leads to the study of logarithmic Sobolev inequalities, measure concentration (functional viewpoint), optimal transport and information theory. A key tool is given by the Wasserstein distances between probability measures. Interactions with probability and geometry (within singular spaces) are important. At the level of functional analysis, we have uncovered the notion of hypo-coerciveness, which unifies the notions of hypo-ellipticity and controllability. It provides regularity results as well as decay estimates towards the equilibrium.

Optimal transport is considered also from the point of view of colour images processing. For instance, one wants to form a single image (panoramic view) from two pictures having a zone in common.

The optimality of classical Sobolev inequalities is linked with so-called "critical" non-linear elliptic PDEs. These ones display a defect of compactness that leaves room for concentration phenomena. One shows that they arise in a quantized way. These PDEs have a strongly geometric contents and have had a prominent place since G. Perelman proved the Poincaré conjecture by following Hamilton's program through the heat flow for the Ricci curvature. The team is especially concerned with problems coming from conformal geometry. We also study the influence of the geometry of a Riemannian manifold on the spectrum of its Laplacian, and more generally the way the waves propagate on such a surface.

The analysis of systems of conservation laws and hyperbolic PDEs is one of the most developed topic in our team. We examine the symmetrization and the hyperbolicity, with application to well-posedness of the Cauchy problem. This remains a fruitful domain for realistic models in elastodynamics and magnetohydrodynamics. We continue our analysis of initial-boundary value problems. The case of a homogeneous boundary condition when the problem is given by a variational principle is promising. It ensures in particular that surface waves resembling the Rayleigh waves propagate in every direction of the boundary. An immediate application is to nonlinear elastodynamics.

Boundary layers arise for instance in oceanography, meteorology and magnetohydrodynamics. We determine their scales and characterize their linear or non-linear stability properties. We also study the existence of layer profiles for conservation laws, where the shock front plays the rôle of a free boundary. Such profiles appear when one quits the hyperbolic context. This may happen in presence of diffusion or dispersion. Viscous or viscous-capillar profiles are well known, though still the object of active research. The analysis of

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►►► discrete profiles, which is crucial in numerical analysis, involves deep notions of the theory of dynamical systems. Their properties (existence, localization and regularity) dramatically depend on the arithmetic properties of the ratio between the shock speed and the grid velocity.

Such profiles are particular cases of travelling waves. Other patterns of this family appear as well in our most applied research activity, the one that develops the fastest, with many exterior collaborations and new doctoral students. A lot of models in medicine involve PDEs (Krebs cycle, brain strokes, regulation of insulinemy, cell death, tumor development). In many cases, where the PDEs are parabolic and non-linear, it is the inhomogeneity (white versus grey matter) and the complexity of the geometry (circonvolutions) that are responsible for the complex behaviour of wave propagation. The goal is to identify the waves, then act upon the system (through medical or chemical means) in order to control them. Evidently, this is a major target for public health.

In complement to these modelling and theoretical approaches, we work on the Numerical Analysis of evolutionary PDEs, diffusive or dispersive. On the one hand, we study the approximation of semi-groups by splitting methods, where the order of the scheme with respect to the time variable may be high. A special attention is devoted to the stability with respect to stiff terms. On the other hand, we consider the implementation of artificial boundary conditions, for instance transparent ones. This requires the understanding of the coupling between finite volumes (for interior cells) and integral methods (for boundary meshes).

In the more specific area of fluid mechanics, we collaborate on the one hand on a research program about multidimensional phase transitions in van der Waals fluids. We study on the other hand the motion of rigid solids in a Newtonian fluid. In particular, we examine the (im)possibility of collision between two bodies or a body and the boundary. This leads naturally to the analysis of fluids where particles deposit. Another topic of ours is the propagation of density waves in a viscous compressible fluid.

Geometry

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Since the discovery of non-Euclidean and Riemannian geometries two centuries ago, the concept of geometry has undergone tremendous evolution, if only through the recent, revolutionary works of Gromov and Thurston. Some UMPA members have greatly contributed to this evolution and still work on as yet unfinished programs. Other types of non-Riemannian geometries e.g. symplectic, affine, projective, conformal, Lorentzian, holomorphic, etc, are still fascinating to mathematicians, including UMPA members, through their beauty and problems.

Topology is strongly linked with geometry. It deals with the study of properties of spaces which are invariant under deformations. This domain of mathematics is especially healthy and was deeply transformed in the last decades, in particular due to new tools, coming directly from a seemingly distant area: mathematical analysis.

The classical theory of dynamical systems emerged from a failure: it is not possible to solve all differential equations explicitly. Hence the interest, following Poincaré, of a qualitative study. At UMPA we work on hyperbolic (chaotic), holomorphic, Lagrangian, ergodic, etc, systems and also on extending the classical theory to arbitrary group actions.

This team has experts in these three fields, but one would try in vain to split it into three sub-teams. Interactions are numerous, there are plenty of working seminars, and collaborations arise in a natural way. It is impossible to present in such a restricted space some of the main results obtained by members of this team. As an illustration, we will only mention some examples, with no attempt at completeness. This may give a general idea of the activity.

In 2005, Jean-Yves Welschingher solved an old problem, dealing with "classical algebraic geometry". In 1856, Chasles established that given 5 conics in the plane (ellipses, parabolas or hyperbolas), there exist in general 3264 conics which are tangent to them, but he was dealing with the complex plane and many of these 3264 conics may be "imaginary". Welschinger developped a "real enumerative geometry" which implies in particular the following. Given 5 ellipses in the real plane whose interiors are disjoint, there exist at least 32 conics which are tangent to them (see figure)! It is remarkable that the proof of such a "classical statement" would not have been possible a few years ago, before the definition of Gromov-Witten's invariants, themselves strongly motivated by theoretical physics!

A good example of a "mixture" of geometry and physics is given by the mathematical study of relativistic cosmology. From a geometrical point of view, it deals with some Lorentzian manifolds, for which the metric tensor is not positive. The light cone defines some kind of dynamical system whose global structure yields fascinating questions, from the mathematical point of view, as well as from the physical point of view. One could ask for instance if it is possible to define some global "time functions" on the whole space, and one studies global causality conditions. In our team, Thierry Barbot and Abdelghani Zeghib contributed a lot to these questions. As a matter of fact, Thierry Barbot ran a "ACI-research project" on these questions.

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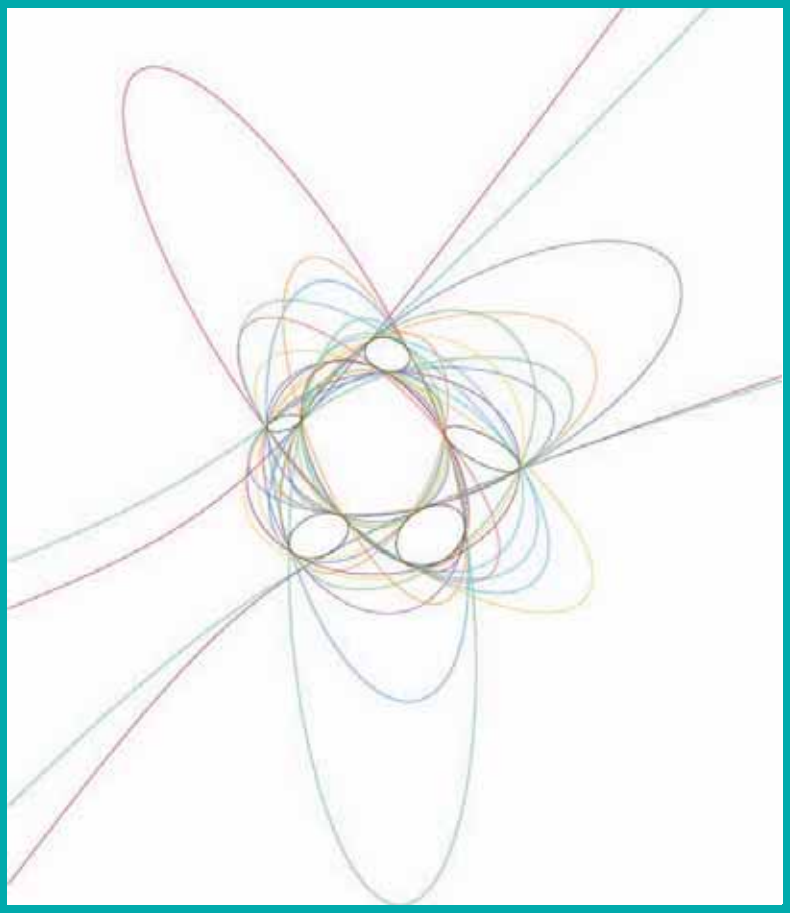
▸▸▸ One of the most abstract branches of dynamical systems is called "ergodic theory". It consists in the study of properties of dynamical systems which are independent of the topology of the ambient space and which only depend on the "measurable" properties. This theory originates from classical Hamiltonian mechanics, according to which Hamiltonian evolutions preserve measures (the so-called Liouville measures). Much more recently, this theory even became "time independent" and concentrated on the study of "measurable orbital equivalence", where the crucial role is played by orbits. Damien Gaboriau is one of the best experts of these questions. In particular, he introduced a powerful invariant, that he called "cost" and which deeply transformed the theory.

Finally, at the intersection of topology and dynamics, one could mention "contact topology". This theory also originates from classical mechanics, through the concept of "non-holonomic constraint". These "contact structures" took progressively a more and more important place in modern topology and dynamics. Emmanuel Giroux introduced new approaches to the theory of contact topology in dimension 3. In particular, his idea of using topological structures called "open book decompositions" enabled a completely new understanding of contact manifolds and generated a wealth of new classification theorems.

It is preferable to stop here this incomplete description of topics covered by this team. One should insist again on the richness of the interactions inside the team but also with the other teams: a pleasant feature of UMPA.



32 real conics tangent to 5 ellipses

Probability team

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► *Christophe SABOT **Researcher** ► Cédric VILLANI **Professor***
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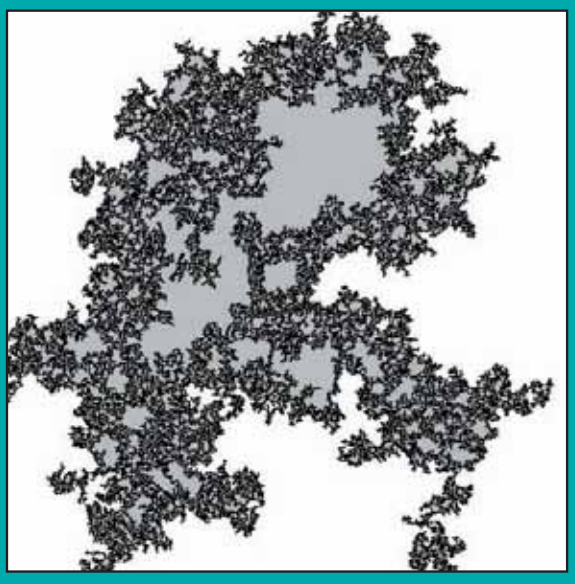
► *Damien GABORIAU **Senior Researcher** ► Katy PAROUX **Associate Professor***

The probability team is the youngest of UMPA; it flourished quickly after its creation in 2001. It is remarkable by its dynamism and the variety of the themes it is working on. Following the principle that nothing is ever completely knowable, probability theory reached into various domains during the last century. The activity of our team is a reflexion of this diversity. This makes it difficult to focus on a particular result to exemplify our production in these few lines, instead we present the main domains of our research.

Among the classical problems of probability theory, at the interface with statistical mechanics, we are interested in random walks in a complex medium, such as a fractal or a random environment. Another axis is the study of the critical behaviour of models from condensed matter physics, such as percolation and the Ising model.

In a symbiosis with the PDE (partial differential equations) team, we study questions of particular approximations of some of the equations of physics, and the dual question of the way to obtain these equations from a microscopic modelling (hydrodynamic limits). Also part of our preoccupations is the derivation of coercivity inequalities (of the Sobolev type), and the study of the long time behaviour of Markov processes.

Last but not least, a strong component of our team studies problems with a geometric taste to them, such as random geometries (the study of random shapes), random groups as introduced by Gromov, large random matrices and free probability, introduced by Voiculescu at the interface of probability theory and quantum mechanics.



Complex Systems Institute ISC

Michel MORVAN ***Director*** ►

The science of complex systems is orthogonal to the disciplines which study complex systems and develops from the theoretical questions that cross them. It corresponds to a deeply rooted reality in modern science which produces a rapidly growing quantity of sophisticated data about these very systems. Because it deals with the systems which live within us and in which we live, the science of complex systems also makes a lasting contribution to the reconciliation of science and social necessity. A trans-disciplinary movement exists today to attempt to reach a shared understanding of these systems. An international movement is causing research institutes to spring up all over the planet which are adapted to these new convergences.

The Rhône-Alpes institute of complex systems (ISC) is part of this movement. It is a multidisciplinary center for education and research in the study of large-scale complex adaptive systems, whatever their nature, whether they be macromolecular cell systems, neural networks, or economic, social, cultural, ecological and environmental systems. It also contributes to the elaboration of the complex system engineering which is necessary for any intervention within.

> www.ens-lyon.fr/LIP/ISC/index.html

European Center of Atomic and Molecular Computations CECAM

Berend SMIT ***Director*** ►

One can argue that the use of computers has induced a revolution in society: we are now living in the "information age". However, less visibly but no less importantly, a second computer-induced revolution is underway: computer-based modelling will fundamentally transform large fields of human endeavour, stretching from industrial manufacturing to medical science. At present, the groundwork for this revolution is laid in academic applications of computer modelling. Already, we see that computer simulations are used as a pre-screening tool to limit, or even eliminate, the use of experiments that are dangerous, expensive, or less desirable (e.g. animal testing). The increase in computer power now makes it possible to simulate, at the molecular level, systems that range from inorganic materials to complex biological systems.

The field of molecular simulations is one of the scientific areas in which Europe has a leading position. European research teams are internationally recognized for the development and application of novel molecular simulation algorithms. One of the factors contributing to this European success is the unique position of CECAM (European Centre of Atomic and Molecular Computations). CECAM is a top-level institute based in Lyon that is supported by 14 European research organizations. In addition to fostering ground-breaking research in the area of molecular simulation, CECAM aims at facilitating dissemination and networking activities in this domain. For example, each year, 20-25 workshops are organized at CECAM by world experts in computer simulations. Many of the ideas of algorithms that are now commonly used in molecular simulation software have originated from workshops that CECAM has organized over the last 30 years.

> http://www.cecam.fr/

Research and technical facilities

SHARED SERVICE:

• PSMN (Pôle Scientifique de Modélisation Numérique)

This center maintains and operates computing facilities acquired within the framework of the *Fédération Lyonnaise de Calcul Haute Performance* (FLCHP) with additional financial support from the ENS Lyon, the Rhône-Alpes region, and the *Ministère de l'éducation nationale, de l'enseignement supérieur et de la recherche* (MENESR).

The center's principal mission is to make flexible, high-performance computing resources--including software and assistance staff--available to research laboratories at the ENS and, more widely, the University of Lyon. The PSMN also provides training in high-performance computing for the personnel of these laboratories, including doctoral and postdoctoral students.

Equipment: about 200 cores/processors (AMD-Opteron)

TECHNICAL AND RESEARCH FACILITIES:

The ENS Lyon, as a partner in the *Institut Fédératif de Recherche* (IFR 128) *BioSciences Gerland-Lyon Sud*, has access to the IFR's different technical facilities.

The IFR128 is composed of nine departments, 67 groups, and a research staff of nearly 640 members on the Gerland and Lyon Sud sites. (http://www.ifr128.prd.fr)

The work carried out by the IFR covers the major fields of research in modern biology including cell biology, plant biology, protein biochemistry, bioinformatics, structural biology, molecular evolution, genomics, immunology and virology.

IFR BIOSCIENCES GERLAND-LYON SUD TECHNICAL FACILITIES:

• Genetic analysis: Three services are associated with this facility: a sequencing service, a real-time PCR service and a vectorology service.

• Fishery: This facility raises and keeps different strains of the zebrafish, a species whose embryo is used as a model in experiments principally involving microinjection, and in situ treatment and hybridization. Beginning in March 2007, the facility will also raise medakas, southern platyfish, green swordtails, and guppies.

• Protein microanalysis center: This facility comprises three services: peptide synthesis, sequencing proteins (Edman degradation), and mass spectrometry (instruments: API 165, MALDI-TOF Voyager DE-PRO, and Q-STAR XL).

• Flow cytometry: This facility is specialized in the multiparametric study of single cells suspended in a stream of fluid passing before lasers for analysis and high speed sorting along 4 paths (DiVa digital electronics).

• Imagery/microscopy: This center offers 9 systems of microscopy: confocal laser scanning microscopy, conventional fluorescence microscopy, video microscopy, stereo microscopy, and image analysis.
• P3/IFR128 Laboratory Facility: This high security laboratory permits the manipulation of level 3 pathogens. It is equipped to permit cell culture and the extraction of lipids (incubators, fume hood, ultracentrifuges, etc.)
• Production and analysis of proteins: This facility is composed of three services: the production of recombinant proteins (prokaryotic and eukaryotic expression systems), structural and functional analysis of proteins (apparatus: circular dichroism, florescence spectrophotometer, Biacore T100) and the IFR128 cell bank.

RESEARCH FACILITIES LOCATED ON THE ENS LYON SITE:

• Greenhouse type 2 (approved for the culture of transgenic plants): This transgenic greenhouse has 8 growth rooms/chambers for a combined usable area of 240 square meters and is equipped with an automated climate control system which controls the environmental parameters thanks to equipment including: an evaporative cooling unit, heating (circulating warm air), shading mechanisms, under bench heating, supplemental lighting (sodium), ferti-irrigation, wastewater treatment, etc.
• PBES (Plateau de Biologie Expérimentale de la Souris): This facility is specialized in the breeding, housing, and characterization of murine strains whether genetically modified or not. The facility currently houses approximately 200 specific pathogen free (SPF) strains, which translates into about 12,000 mice. Experiments can currently be carried out by researchers or as a service provided by the PBES under confinement conditions satisfying biosafety levels 1 and 2, with level 3 conditions possible in the very near future.
Other activities at the PBES include the rederivation of mouse lines produced in other laboratories, the creation of new lines of genetically modified mice, and genotypic and phenotypic characterization (bone, fatty tissue, and immunological markers).
The PBES also offers new services in collaboration with laboratories belonging to IFR128. Projects currently under development include the cryopreservation of embryos, transgenesis using a lentivirus, and genotyping using QPCR, as well as perfecting new methods of phenotyping.
The structural organization of the PBES makes it a high performance facility, allowing the introduction and rapid characterization of genetically modified murine strains.

Highlighting research

Eleven new businesses have been created benefiting from knowledge and know-how developed in ENS Lyon labs or benefiting from an incubation period at the time of their creation.

EXAMPLES:

- Varioptic: liquid lenses with electronically controlled focal length thanks to electrowetting technology. www.varioptic.com
- Genoway: development of animal models for therapeutic purposes. www.genoway.com
- Biotray: development, manufacture and sales of scientific and technical instruments specialized in the domain of micro-structured surfaces www.biotray.fr
- Edelris: Conception, production and sales of innovative, therapeutically relevant, natural product-mimetic screening compounds. www.edelris.com

In four years, over twenty co-owned patents have been filed, half of which have been licensed.

Awards and distinctions

- **Francis Albarède,** Professor, Earth Sciences Laboratory, Arthur Holmes Medal from the European Union of Geosciences.
- **Yannick Ricard,** Director of Research at the CNRS, Earth Sciences Laboratory, CNRS Silver Medal Winner–Sciences of the Universe, 2000.
- **Bernard Castaing,** Professor, Physics Laboratory, member of the French *Académie des sciences*.
- **Christian Dumas,** Professor, Plants Reproduction and Development Laboratory, member of the French *Académie des sciences*.
- **Etienne Ghys,** Director of Research at the CNRS, Pure and Applied Mathematics Unit, member of the French *Académie des sciences*.
- **Lyndon Emsley,** Professor, Chemistry Laboratory, CNRS Silver Medal Winner–Chemical Sciences, 2005.
- **Cédric Villani,** Professor, Pure and Applied Mathematics Unit, *Prix Louis Armand* from the French *Académie des sciences*, 2001.
- **Patrick Flandrin,** Director of Research at the CNRS, Physics Laboratory, Prix Michel Monpetit from the French *Académie des sciences*, 2001; Wavelet Pioneer Award from the SPIE, 2001.
- **Thierry Gaude,** Director of Research at the CNRS, Plants Reproduction and Development Laboratory, Prix Leconte from the French *Académie des sciences*, 2001.
- **Gilles Chabrier,** Director of Research at the CNRS, Astromy Research Center of Lyon, Prix Lalande-Benamin Valz from the French *Académie des sciences*, 1996; CNRS Silver Medal, 2006.
- **Emmanuel Grenier,** Professor, Pure and Applied Mathematics Unit, Prix Peccot from the *Collège de France*, 2000; European Mathematical Society Prize, 2000.
- **Philippe Sautet,** Director of Research at the CNRS, Chemistry Laboratory, Descartes-Huygens Prize from the Royal Netherlands Academy of Arts and Sciences, 1998.
- **Alain Arnéodo,** Director of Research at the CNRS, team leader at the Joliot Curie Laboratory and member of the ENS Lyon Physics Laboratory, Prix de *l'Académie Royale des Sciences, Lettres et Beaux-Arts de Belgique*, 2005.

EDITORS IN CHIEF OF INTERNATIONAL SCIENTIFIC JOURNALS:

- **Etienne Ghys,** *Les Publications Mathématiques de l'IHÉS (Institut des Hautes Études Scientifiques)*
- **Francis Albarède,** Journal of Geophysical Research (Solid Earth)
- **Michel Peyrard,** Journal of Biological Physics

EIGHT PROFESSORS FROM THE ENS LYON BELONG TO THE *INSTITUT UNIVERSITAIRE DE FRANCE*.

European contracts FP6

Project acronym	Scientist's name	Project title	Lab	Theme	Instrument
BIMAMOSI	B. SMIT	Materials Molecular Simulations	CECAM	Marie Curie actions	Excellence grants
CASCADE	V. LAUDET F. FLAMANT	Chemical as contaminants in the food chain	LBMC	LSH	NoE
CHROMOSOMAL CONTEX	A.ARNEODO	From the structural and dynamical chromosomal context to the functional organisation of genomes	JULIOT CURIE	Marie Curie actions	European Re-integration Grants
COMPUVAC	F.L COSSET	Ration design and standardized evaluation of novel genetic vaccines	VIROLOGIE	LSH	IP
CONCORDE	P.SAUTET	Coordination of Nanostructured Catalytic Oxides Research and Development in Europe	CHIMIE	NMP	Coordination action
CONSERT	F-L. COSSET	Concerted Safety & Efficiency Evaluation of Retroviral Transgenesis in Gene Therapy of Inherited Diseases	VIROLOGIE	LSH	IP
CONSTELLATION	I. BARAFFE	The origin of stellar masses	CRAL	Marie Curie actions	Research Training Networks
CORE GRID	Y. ROBERT	European Research Network on Foundations, Software Infrastructures and Application for large scale distributed, Grid and Peer-to-Peer Technologies	LIP	IST	NoE
CRESCENDO	J. SAMARUT V.LAUDET	Consortium for Research into Nuclear Receptors in Development and Aging	LBMC	LSH	IP
EUMODIC	J. MARVEL	«The European Mouse Disease Clinic: A distributed phenotyping resource for studying human disease»	PBES	LSH	IP
EU-NMR	L. EMSLEY	European Network of Research Infrastructures for providing Access and Technological Advancements in bio-UMR	CHIMIE	INFRASTR	Integrating activities implemented as Integrated Infrastructure initiatives
EUROSIM	B. SMIT	European Molecular Simulations Training Program	CECAM	Marie Curie actions	Early-stage Training
GEOBIOCHRONOS	F. ALBARED	Uranium-lead dating of phosphate minerals	LST	Marie Curie actions	Intra-European Fellowships
IDECAT	P.SAUTET	Integrated Design of Catalytic Nanomaterials for a Sustainable Production	CHIMIE	NMP	NoE
MATHLOGAPS	P.KOIRAN	Mathematical logic and applications	LIP	Marie Curie actions	Early-stage Training
MODELLING FLOWERS	J.TRAAS	Examining Arabidopsis floral organ number patterning using a dynamic computer model	RDP	Marie Curie actions	International Incoming Fellowships
MOLSIMU	B. SMIT	Molecular simulations	CECAM	Marie Curie actions	Conferences and training courses
MONET	M-L. BOCQUET	Molecular Networks at Phase Boundaries	CHIMIE	Marie Curie actions	Early-stage Training
MORFHEX	M.MORVAN	Morphogenesis and gene regulatory networks in plants and animals: a complex systems modelling approach	RDP et LIP	IST	STREP
NL-LOC-SOLID	M. PEYRARD	Nonlinear Vibrational on Solid Surfaces: Application to Catalysis	PHYSIQUE	Marie Curie actions	Intra-European Fellowships
NONREGWKAM	A. FATHI	Recherche relatives à la théorie KAM faible	UMPA	Marie Curie actions	Intra-European Fellowships
ODEON	C. ANDRAUD	Design and Fabrication of Optoelectronic Devices Based on Innovative Second-order Non linear Organic Nanomaterials	CHIMIE	NMP	STREP
ONCE-CS	M.MORVAN	Open Network for Connecting Excellence in Complex Systems	LIP	IST	CA
Psi-K	B. SMIT	Training in Computational Nanoscience	CECAM	Marie Curie actions	Conferences and training courses
RISK RAD	E. GILSON	DNA damage responses, Genomic instability and radiation induced Cancer : the problem of risk at low and protracted doses	LBMC	LSH	IP
TRIOH	J-L. DARLIX	Targeting replication and integration of HIV	LBMC	LSH	IP
X-OMICS	V. LAUDET	Xenopus Comparative Genomics: coordinating integrated and comparative functional genomics for understanding normal and pathologic development	LBMC	LSH	CA

Selected publications

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