CONTENT

2  25 YEARS OF RESEARCH AT THE CBS
4  THE CBS AT A GLANCE

DEPARTMENT OF STRUCTURAL BIOLOGY
6  Structure, Dynamics and Function of Biomolecules by NMR
8  Structure and Function of Highly Flexible Proteins
10 Multi-Scale Structural Biology
12 Nuclear Receptors as Integrators of Endogenous and Environmental Signals
14 Atelier de Biologie Chimie Informatique Structurale (A.B.C.I.S.)
16 Multi-Scale Biomolecular Modeling

DEPARTMENT OF BIOPHYSICS AND BIOENGINEERING
18  Mechanisms of DNA Segregation and Remodelling
20  Structure and Dynamics of Nucleoprotein and Membrane Assemblies
24  Single-Molecule Angular Dynamics
25  HemoPhysics
26  Synthetic Biology

PLATFORMS AND CORE FACILITIES
28  TEACHING, TRAINING, WORKING AT THE CBS
30  LIVING, STUDYING IN MONTPELLIER
34  ADMINISTRATION & CONTACT
35  INDEX
36  ACCESS
The Centre of Structural Biochemistry (CBS) in Montpellier was created in 1993, at the initiative of both CNRS and Montpellier University (UM), then joined by INSERM, in the context of the national IMABIO program designed to reinforce Structural Biology in France, in particular outside of Paris.

During 25 years, the CBS has grown and developed substantially. Originally located at the Faculty of Pharmacy, the CBS is now hosted by INSERM near the new campus of the Faculty of Medicine Arnaud-de-Villeneuve. Initially specialized in Nuclear Magnetic Resonance (NMR), X-ray crystallography and Bioinformatics, the CBS has extended its competencies to a wide range of methodologies including Atomic Force Microscopy (AFM), Electron Microscopy (EM), advanced fluorescence microscopies and spectroscopies, single molecule manipulation and synthetic biology. The diversity of the techniques and expertise present on the same site, together with the strong network of local, national and international collaborations built over the years have allowed the CBS to tackle more and more ambitious scientific projects that break the barriers between biology, chemistry, physics and computer science.

The general objective of the CBS is to carry out research at the forefront of Structural Biology, Biophysics and Bioengineering as a mean to describe and understand the fundamental physico-chemical mechanisms underlying biological processes, from the molecular to the cellular and tissue level. When possible this knowledge is exploited to develop new tools for research application or to design new therapeutic or diagnostic strategies for human health. The response to these challenges involves a multiscale characterization of both structure and dynamics of supra-molecular complexes, as well as a detailed comprehension of their assembly and regulation mechanisms.

To reach these objectives, the CBS research teams are strongly interacting with each other, bringing together their complementary skills to conduct the experimental studies and develop the state-of-the art technologies required to unravel the complexity of living systems using integrative approaches. The impact and dynamism of our research have attracted young scientists granted by ERC or ATIP-Avenir programs that contribute to the recognition of the CBS as a laboratory of excellence combining a critical mass of competencies and resources available to the scientific community through collaborations or facilities.

25 years of research at the CBS

Successive directors:
1993-1998, Jean-Marc Lhoste
1999-2006, Michel Kochoyan
2006-2013, Catherine A. Royer
2013-2015, Christian Roumestand
since 2015, Pierre-Emmanuel Milhiet
The CBS at a glance 2018

The CBS is an interdisciplinary center dedicated to academic research. It depends on three public institutions:
• Centre National de la Recherche Scientifique (CNRS-UMR 5048)
• Institut National de la Santé et de la Recherche Médicale (INSERM-U1054)
• University of Montpellier.

The CBS currently counts 91 people, 50 permanent employees (28 researchers and 22 technical and support staff) and 41 non-permanent members (Ph.D. students, post-doctoral associates, engineers and technical assistants). It is supported by national and European funding as well as contributions from private companies involved in specific research projects.

The CBS is organized in two scientific departments in charge of technological platforms and core facilities that provide research resources and expertise for combined structural and/or biophysical approaches.

DEPARTMENT OF STRUCTURAL BIOLOGY
• Structure, Dynamics and Function of Biomolecules by NMR
• Structure and Function of Highly Flexible Protein
• Multi-Scale Structural Biology
• Nuclear Receptors as Integrators of Endogenous and Environmental Signals
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DEPARTMENT OF BIOPHYSICS AND BIOENGINEERING
• Mechanisms of DNA Segregation and Remodeling
• Structure and Dynamics of Nucleoproteic and Membrane Assemblies
• Single-Molecule Angular Dynamics
• HemoPhysics
• Synthetic Biology

INTEGRATED PLATFORM OF BIOPHYSICS AND STRUCTURAL BIOLOGY
• Nuclear Magnetic Resonance
• X-Ray Crystallography
• Electron Microscopy
• Atomic Force Microscopy
• Advanced Fluorescence Microscopy
• Bio-Informatics
• Biophysical Characterization of Biomolecules
Plant Pathogens and Infectious Diseases
A. Padilla, K. de Guille, L. Mammi

The molecular details of plant immune receptors binding are elucidated in vitro and in vivo to validate structural models of fungi Avr effectors recognition and to investigate structure-function relationships. Plant diseases are among the most important problems in agriculture and the use of disease resistance genes is a key strategy for sustainable crop protection.

Plant resistance to microbial pathogens is a complex process relying on two major levels of resistance triggered by distinct types of plant receptors. Besides the first line of immunity, in which microbial molecules, such as bacterial flagellin or cell wall components of the pathogen are perceived, leading to plant resistance, the second layer of plant immunity relies on the recognition of certain pathogen-derived effectors by so-called plant resistance (R) proteins encoded by R genes. Effectors that are specifically recognized are called Avrproteins (AVR) and induce a plant effector-targeted immunity. We use the rice blast model system to investigate R protein function and AVR protein recognition. Rice blast caused by the ascomycete fungus Magnaporthe oryzae is the most important rice disease worldwide and as such is a serious economic problem and a major threat for food security and health care linked to pesticides usage. Our collaboration (INRA Montpellier) resulted in the generation of NMR structures for the M. oryzae effectors AVR1-CO39 and AVR-Pia and the project aims at identifying the structure of R rice immune receptors.

Main Collaborators: T. Koj, S. Cesari (INRA Montpellier)
References: Orz et al., Plant Cell 2017

Structure and Activation of G-Protein Coupled Receptors
H. Déméné, YS. Yang

G-Protein Coupled Receptors (GPCRs) represent the largest class of membrane surface cell receptors involved in signal transduction. We investigate on their structure-activity and conformational landscape.

Our research themes focus on the receptors of the vasopressin (V1R and V2R) and on the µ-opioid receptor (µOR), governing respectively key processes of organism water balance and pain management. In the past, we have deciphered the structural features of isolated intracellular loops of V1aR and V2R. They fold independently from the rest of the receptors. We now investigate on the structure-activity of whole GPCRs. In particular, we have shown that the ligand- and G-protein binding interfaces are weakly coupled in µOR, extending the concept observed before for the β2 adrenergic receptor by the Kobikia’s team. Based on the NMR spectral parameter changes upon interaction of µOR with various agonists as well as with a G-protein mimetic, we could propose a model of event propagation during activation. We now focus on the structural changes happening at the level of the whole receptor upon binding to different types of extracellular ligands and intracellular effectors.

Main Collaborators: S. Granier, R. Souver, B. Mouloua, C. Méndez (IGF Montpellier), N. Roquet (IBMM Montpellier), B. Kobikia (Univ. Stanford USA).
References: Souver et al., J. Biomol. NMR Assign 2017; Souver et al., Nature 2015
Structure and Function of Highly Flexible Proteins
Pau Bernadó & Nathalie Sibille

The main aim of the “Highly Flexible Proteins” group is to connect structure and dynamics in proteins displaying large configurational fluctuations with their biological function. To achieve this aim the group combines structural biology methods (NMR and SAXS), biological approaches and computational tools. Present projects include relevant intrinsically disordered proteins (IDP) involved in signaling and neurodegeneration.

Huntingtin: low-complexity regions at high-resolution
P. Bernadó, N. Sibille, F. Allemand, A. Urbanak, A. Morató, A. Fournet, A. Estaña, M. Popović

While most protein sequences are aperiodic and feature most of the 20 amino acids, many proteins harbor low complexity regions (LCRs), with a highly biased composition. LCRs are functionally relevant and, in some cases, are directly related with severe diseases. Despite their relevance, high-resolution structural and dynamic characterization of LCRs cannot be tackled with current methods placing them on the dark side of proteome.

Homorepeats, a subclass of LCRs that is characterized by stretches of the same amino acid, perform very specialized functions facilitated by the localized enrichment of the same physicochemical property. In addition, numerous severe pathologies have been associated with abnormally long repetitions eg. huntingtin (Htt). The N-terminal region of Htt, known as exon-1, contains glutamine and proline stretches, the poly-Gln tract is directly linked to Huntington’s disease (HD), a deadly neuropathy appearing in individuals with more than 35 consecutive Gin residues, the pathologival threshold. Present structural biology approaches do not allow high-resolution studies of Htt to investigate the origin of the pathological threshhold. Our group is developing chemical biology tools to enable the residue-specific labeling of Htt. This allows us for the first time to study Htt at the atomic level with NMR. The application of these approaches to several Htt constructs with Q tracts of different lengths will shed light on the structural bases of the pathological threshold of HD.

Molecular mechanisms of functional disordered C-terminal regions of GPCRs and impact on arrestin signaling pathways
N. Sibille, P. Bernadó, F. Allemand, A. Fournet, T. Cordeiro

This project aims to elucidate the details and principles of non-G protein dependent GPCR signaling. Arrestin-mediated and ligand-induced biased signaling is a hot topic currently in GPCR and drug research in general. By focusing on ghrelin, b2ar and V2 receptors, we have chosen varied GPCRs to investigate by state-of-the-art biochemical and biophysical methods the functional disordered regions of GPCRs with regard to their interaction with arrestins.

To design more effective drugs without side effects, it is essential to better understand the molecular mechanism of GPCR (G-Protein Coupled Receptors), which are targeted by one third of drugs on the market. Some crucial cell signaling pathways are mediated by the interaction of the cytoplasmic C-terminal part of the GPCR with β-arrestin. This functional interaction is modulated by GPCR-associated kinases (GRK). This project aims at revealing the link between C-tail phosphorylation patterns by the various GRKs, their structural dynamics and the different related arrestin «functional conformations». This will be achieved by combining solution spectroscopic techniques, such as NMR and SAS, on model systems of increasing complexity ranging from isolated peptides to purified signaling complexes into membrane-mimicking systems (nanodiscs). This study will reveal the structural and dynamic mechanisms necessary for the interaction of the C-terminal regions of GPCRs with β-arrestin and provide essential information to guide the rational design of peptide mimetics able to modulate specific signaling cascades.

Disentangling structural polydispersity in biological systems
P. Bernadó, N. Sibille, F. Allemand, F. Herranz-Trillo, L. Sémicourt, T. Cordeiro

The co-existence of multiple species in solution, also known as polydispersity, is an inherent feature of many biological systems that hampers the application of traditional structural biology methods. By combining SAXS with NMR and molecular modeling we address polydisperse systems such as amyloids and biomolecular complexes involving disordered proteins.

Low-affinity biomolecular complexes or amyloids are inherently polydisperse. In other words, the species present in a sample change or evolve depending on the experimental conditions. In vivo, these equilibria are finely tuned to precisely achieve specific biological functions, but in vitro polydispersity hampers the structural characterization of the relevant species. Our group develops tools to overcome present limitations and tackle the structural characterization of the species of interest. Using SAXS data measured in a time-dependent manner and analyzed using chemometrics approaches we have characterized the cytotoxic oligomeric species formed during amyloidogenesis. The software developed, which we call COSMiCS, can be applied to a broad range of biological problems. For other systems such as the regulation of nuclear receptors we decompose complex data by using integrative approaches. Following this strategy we built atomistic models of the species present in solution based on available information from multiple techniques to derive a general picture of the system.
Multi-Scale Structural Biology

Patrick Bron

The aim of the team is to decipher structure and dynamics of biological complexes by a multi-disciplinary approach mainly combining electron microscopy and X-ray crystallography methods in focusing on biological complexes of interest such as viruses, pathogenic complexes or membrane proteins. The team is also strongly involved in methodological developments and proposes its expertise through electron microscopy and crystallography platforms.

Structural investigation from molecular to cellular levels

The Multi-scale structural biology team aims to decipher structure and dynamics of biological complexes by a multi-disciplinary approach combining mainly electron microscopy (EM) and X-ray crystallography (X-Ray).

During the last years, a revolution occurred in the EM field. Indeed, the advances in detector hardware, in exceptionally stability of electron microscopes and image-processing software have led to a revolution in the use of cryo-EM to determine complex molecular structures at high resolution. Therefore, near-atomic-resolution cryo-EM structures can now be obtained for even the most challenging targets in structural biology: large macromolecular machines with dynamic composition and conformational and protein complexes with a mass (<100 kDa) previously considered too small to be suitable for cryo-EM investigation. We have then developed strong collaborations in order to investigate the structure of membrane proteins or pathogenic biological complexes.

For instance, we have determined the atomic structure of several viruses such as the Arabis Mosaic Virus (ArMV) or the Broad Bean stain mosaic virus strengthening the hypothesis of a key role of a pocket in the viral transmission specificity.

With the advent of electron tomography (ET), structural biology has taken a new dimension. Indeed, ET is a non-invasive, high-resolution imaging technique, which allows, when combined with a method of arresting cells in their momentary state of function, the visualization of the 3D organization of eukaryotic cells, with their dynamic organelles, cytoskeletal structures, and molecular machines in an unperturbed context. As a consequence, cellular structural biology is now becoming accessible by combining together different structural techniques. In this context, one of our goals is to investigate structure, dynamics, transmission and selectivity of viral complexes from molecular to cellular levels, in combining different approaches mainly based on EM, ET and X-Ray but also in integrating other in-house methods as light microscopy, small-angle X-ray scattering, atomic force microscopy and nuclear magnetic resistance. We are focusing on model viruses belonging to the animal, plant viruses or bacteriophages.

As we need to obtain structural information of biological complexes as viruses directly into intact cells, we determined culture conditions of different type of cell directly onto EM grid and defined acquisition conditions to perform cryo-ET on frozen-hydrated cells. In parallel, we have developed the cryo-correlation light and electron microscopy method allowing us to investigate region of interest previously localized by cryo-fluorescence microscopy.

Methodological developments

We investigate methods combining both electron microscopy and X-ray crystallography methods and novel approaches to gain structural information on biological molecules.

Micro electron-diffraction is a recently developed method in cryo-electron microscopy that allows the collection of high-resolution electron diffraction data from extremely small three-dimensional crystals that are in the range of 0.1–0.4 mm thick using a transmission electron microscope. We implemented this approach on the JEOL 2200FS transmission electron microscope and investigated its applications to membrane protein crystals.

Developments in EM 3D reconstructions: Fourier-space TEM reconstructions with symmetry adapted functions for all rotational point groups: a general-purpose and simple expression for the coefficients of symmetry adapted functions referred to conveniently oriented symmetry axes is given for all rotational point groups. The expression involves the computation of reduced Wigner-matrix elements corresponding to an angle specific to each group and has the computational advantage of leading to Fourier-space EM reconstruction procedures involving only real valued unknowns. Using this expression, a protocol for ab initio view and center assignment and reconstruction so far used for isosahedral particles has been tested with experimental data in other point groups.

New methods for cryo-EM single particle analysis. In collaboration with G. Bellot (CBS, Montpellier), we are investigating how to use DNA origami to bind proteins or complexes of interest at specific locations allowing at improving image processing and consequently structural information. Origami are nano-objects consisting of DNA that it is possible to precisely design and functionalize. We are designing various origami according to the investigated proteins.
Nuclear Receptors as Integrators of Endogenous and Environmental Signals
William Bourguet

Nuclear receptors are master regulators of gene expression in humans. Their biological functions depend on their ability to bind other molecules such as ligands (hormones, vitamins, etc.), DNA and coregulatory proteins. They are also the primary targets of many environmental endocrine disruptors that mimic the action of endogenous ligands and cause a wide range of diseases. A major interest of the group is to reach a detailed understanding of the mechanisms involved in the (de)regulation of nuclear receptor signaling.

Some nuclear receptors including retinoic acid (RAR) and thyroid hormone (TR) receptors act as transcriptional repressors by recruiting corepressor complexes to target genes. However, knowledge of the precise role of gene silencing still lags behind that of activation, and several diseases (e.g. acute promyelocytic leukemia and renal carcinomas) have been linked to aberrant interactions between modified forms of nuclear receptors and corepressors. The goals of this project are to (i) uncover the mechanistic aspects of the transcriptional repression mediated by wild-type and mutant RARs and TRs, (ii) decipher how this silencing activity could be modulated by natural and pharmacological ligands, and (iii) provide molecular tools to probe the importance of this repression in physiological, developmental and pathological processes. The strength of our project resides in the synergism and (patho)logical mechanisms.

The group of molecules acting as EDs is highly heterogeneous and comprises compounds that are often distantly related to endogenous ligands in terms of size or chemical structure. This group contains substances as chemically different as bisphenols, phthalates, parabens, dioxins, alkylphenols, organotins, benzophenones, or natural compounds such as the phytoestrogen genistein. This large structural diversity renders the interaction of EDs with their biological targets poorly understood and barely predictable. Our correlative analysis of structural, biophysical, cell-based and in vivo data allows revealing a variety of, sometimes unforeseen, mechanisms of action. Characterization of the interactions between nuclear receptors and environmental compounds at the structural and functional levels is important for the assessment of the harmful hormonal activity of a large number of chemicals, the rational design of safer substitutes, and the development of robust in silico screening methods.

Main Collaborators: P. Balaguer (IRCAM Montpellier), B. Demeneix (MNHN Paris), V. Lavedet (OBN Banyuls/Mer)
References: Delfosse et al., Nat Commun, 2015; Delfosse et al., PMAS, 2012; Le Maire et al., EMBO Rep, 2009

Lipid transport by Osh/ORP proteins
W. Bourguet, V. Delfosse, L. Héraud

Lipids, a group of more than 1000 subspecies, play critical roles in numerous cellular functions as precursors of a number of nuclear receptor ligands or as key components of cell membranes. Decrypting how cellular lipid homeostasis arises is essential to the understanding of many physio (path) logical mechanisms.

The endoplasmic reticulum (ER) is the major place of lipid synthesis. Newly made lipids are then transported to other subcellular compartments (Golgi apparatus, plasma membrane (PM), nucleus, etc.) by dedicated carriers, including the Osh/ORP family of proteins. In close collaboration with the team of Guillaume Drin, we discovered that Osh4p and Osh6p transport sterols and lipids, respectively, from the ER to their site of action by exchanging them with phosphatidylinositol-4-phosphate [PI(4)P]. As PI(4)P is prominent in the trans-Golgi and the PM but absent from the ER, we proposed a general mechanism by which Osh/ORP proteins use this unbalance to transport key lipids vectorially between organelles. Indeed, our structural and sequence analyzes suggest that all ORP/Osh proteins bind PI(4)P that can exchange with a second lipid, which is specific of each family member. Our current work aims at addressing key questions regarding the general scope of this mechanism and the nature of the lipids recognized by other Osh/ORP proteins.


DEPARTMENT OF STRUCTURAL BIOLOGY

A.B.C.I.S.
Atelier de Biologie Chimie Informatique Structurale
Gilles Labesse

Designing new drugs remains highly challenging. The group is developing an integrated approach for quicker design of drugs using structural bioinformatics, bioinformatics and chemistry. The corresponding techniques are implemented in a new platform for structure-based screening.

Structural bioinformatics and chemoinformatics
G. Labesse, J.-L. Pons, J. Gracy, V. Moreau, R. Salgado Ferreira

Structural bioinformatics aims at analyzing and predicting protein structure from sequences. We develop tools in order to improve the speed and the quality of the theoretical models one can build. In addition we are implementing an integrated interface connecting protein structure modeling and ligand screening.

Fold-recognition has been shown to be highly efficient to detect even weak similarities (15-25% of sequence identity). Nevertheless proper alignment and correct model building from distantly related templates still require significant expertise and work. Implementing new refinement approaches is necessary. In parallel, comparative docking has shown an unexpected robustness even at low level of sequence conservation and allowed functional annotation. We now focus our methodology development to improve ligand docking into multiple conformations.

References: Pons & Labesse, NAR, 2009; Martin et al., NAR, 2006

Fragment-based drug design
J.-F. Guichou, M. Gelin, G. Labesse, R. Rahimova, M. Schneider

The group is developing fragment-based drug design using X-ray crystallography, biophysics, chemoinformatics and soft/bio-compatible chemistry for therapeutics applications in virology, oncology and infectious diseases.

Designing new drugs remains highly challenging and complex with potential failure at each step. The group is developing an integrated approach for quicker and more rational design of drugs. Based on our expertise in ligand screening by X-ray crystallography, we have established a fully robotized platform for crystallization, crystal growth survey and diffraction in 96-well plates. This set-up is being used for the screening of fragment or more elaborate compounds generate by soft and/or bio-compatible chemistry. The group had also developed a fully automatic treatment for the resolution of the complex small molecule-protein (~150 structures per month). Combining all the structural information and the biophysics characterization (TSA, FT, ...), the group design new therapeutic compounds which are tested through collaborations for their biological effects.


Fine enzymology and target deep-characterization
C. Lionne, M. Gelin, G. Labesse

The goal of the group is to help the design of efficient and specific drugs by studying enzyme reaction pathways and drug-target interactions by the mean of fine enzymology, biophysical characterization and thermodynamic approaches.

Efficient and specific drugs directed against enzymes are much easier to design with a deep understanding of how the proteins work, and especially in which states they spend most of their time. Transient kinetics techniques (stopped-flow, quench-flow, cryoenzymology) are routinely used to measure protein-ligand kinetics (kon, koff), identify reaction pathway and rate-limiting steps, as well as to characterize the effects of inhibitors thereon. Beside, other biophysical techniques are used to characterize drug-target interactions: classical steady state enzymology, isothermal titration calorimetry, thermal shift assay, molecular docking and X-ray crystallography. Optimized inhibitors are designed and their biological effects tested (in collaboration for cellular and animal models).

The group focuses its research on new targets working on nucleotides for the design of innovative anti-infectious or anti-cancer therapies.


Grant: ANR-@RAction M4

Integrative molecular simulations of biological machinery

A. Barducci, R. Bailly, M. Paloni, C. Péan

Pushing the boundaries of biomolecular modeling toward a quantitative investigation of complex cellular processes at the molecular level.

Molecular simulations are today an essential tool for complementing experimental techniques in the characterization of protein structure and dynamics. However, proteins mostly accomplish their functions as part of large molecular machines through intricate regulatory networks of transient and/or stable biomolecular interactions, whose complexity greatly exceeds the current capabilities of canonical molecular simulations. We aim at alleviating this limitation by taking inspiration from integrative modeling approaches. Notably, we attempt to devise multi-scale simulation methods capable of incorporating information garnered from diverse sources, including biophysical/structural biology experiments and statistical analysis of protein sequence databases. Methodological development is tightly coupled to the investigation of intriguing biomolecular machines of great biomedical relevance, such as molecular chaperones and nuclear receptors, in close collaborations with experimental partners.

In our research we develop and apply a broad range of computational and theoretical methods for investigating the function of biomolecules. Particularly, we rely on supercomputers and advanced simulation algorithms to characterize protein behavior by integrating the results of experimental collaborators with bioinformatic tools and statistical mechanical approaches.

Researchers
Alessandro Barducci, INSERM
Non-permanent staff
Rémy Bailly, Post-doc
Matteo Paloni, Post-doc
Clarisse Péan, Post-doc

Multiscale Biomolecular Modeling

Alessandro Barducci

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Integrative molecular simulations of biological machinery

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Starting from atomistic simulations (left) it is possible to devise a coarse grained model (middle) which can be used to investigate complex cellular processes such as chaperone-induced expansion of substrate proteins (right: Hsp70 in red, substrate in blue)


Grant: ANR-@RAction M4
Mechanisms of DNA Segregation and Remodeling
Marcelo Nöllmann

The main interest of our group is the investigation of the mechanisms by which DNA is organized and segregated in the cell. We are currently carrying out two projects that touch upon different aspects of this general topic in prokaryotes and eukaryotes. In addition, we develop novel, state-of-the-art single-molecule and super-resolution methodologies to tackle these problems.

Chromosome organization in eukaryotes

The proper organization of chromosomes determines the manner in which the DNA sequence is interpreted in a large number of cellular processes, including DNA replication, repair and transcription. Understanding the organization of chromatin and the mechanisms involved is thus key to several research areas, such as developmental, stem cell, and cancer biology. We are interested in understanding the mechanisms and factors involved in the higher-order organization of eukaryotic chromosomes. To reach this goal, we use an array of interdisciplinary approaches, including physical, biochemical and biological methods. Particularly, we develop single-molecule and advanced microscopy methods to be able to resolve the structure of chromosome in single cells at the nanometer scale.

Mechanisms of DNA organization and segregation in bacteria

Bacteria grow and divide extremely rapidly, such that several cycles of replication are taking place concomitantly during each cell cycle. Thus, several mechanisms, such as DNA replication, cell growth and cell division have to be synchronized with the organization of the chromosome. Our main objective is to elucidate the factors and mechanisms involved in the coordination between chromosome segregation and other DNA transactions. To tackle this goal, we develop unique super-resolution, microfluidics, and advanced microscopy methods and combine them with chromosome conformation capture genome-wide approaches and analyses.

Molecular motors

DNA motors use the energy of ATP hydrolysis to processively translocate DNA between cellular compartments or within different cells, and belong to the large and diverse AAA+ family of enzymes. AAA+ motors form multimeric rings in which ATP hydrolysis and mechanical work are closely coupled. In general, we are interested in understanding the larger network of genetic interactions affecting the process of DNA transport in vivo. In particular, we want to understand the general mechanisms governing translocation directionality, transduction of energy into movement, and complex assembly. Over the years, we have worked on several motors involved in DNA segregation (SpoIIIE, FtsK, ParABS), DNA organization (SMC), transcription termination (Rho), or bacterial gliding (Agl-Glt). These are active subjects of research that we approach with a palette of single-molecule manipulation and advanced live microscopies.


Structure and Dynamics of Nucleoproteic and Membrane Assemblies
Emmanuel Margeat & Pierre-Emmanuel Milhiet

Our research aims at characterizing macromolecular complexes governing major biological processes, focusing on transcription regulation, signaling and remodeling of biological membranes. To achieve these goals, we develop, combine and use advanced single molecule biophysical methods (such as atomic force and fluorescence microscopies), as well as DNA nanotechnology.

Structure and Dynamics of Nucleoproteic Complexes

Our projects aim at bringing a quantitative and integrative view on molecular mechanisms of transcription regulation in bacteria, combining in vivo and in vitro approaches.

Prokaryotic transcription termination

N. Declerck, E. Margeat, C. Clerté, R. Vishwakarma

This work focuses on the two mechanisms used by bacteria to terminate transcription of a gene (intrinsic termination and Rho-dependent termination).

We use a combination of single molecule observation (smFRET, SPT-PALM & correlation spectroscopies), nano-self-assembly and structural biology to study the dynamics events that lead to transcription termination in bacteria. Specifically, our research focuses on:

1. LicT/SacY antitermination proteins from Bacillus subtilis, that prevent the premature arrest of transcription by binding to an antiterminator RNA hairpin that overlaps an intrinsic terminator.

2. The transcription terminator Rho, an ATP-fueled hexameric helicase and translocase, implicated in the dissociation of transcription elongation complexes.

Bacterial adaptation to environmental changes

N. Declerck, A. Bourges, C. Clerté

Our aim is to unravel the molecular mechanisms that underlie the adaptation of bacteria to rapid changes in their environment, from the atomic and single molecule resolution to the level of single cells and bacterial populations.

We particularly focus on the control of glycolysis/glucogenesis by the CggR and CcpN repressors from B. subtilis. We use highly sensitive and quantitative fluorescence fluctuation-based microscopy methods to measure directly the intracellular concentration, oligomerization state and diffusion properties of these regulatory proteins in live bacterial cells. Combined with in vitro experimental and modelling approaches, our studies provide an integrated picture of the adaptive response to a nutritional shift. We apply similar approaches for characterizing the Mrr endonuclease responsible for the activation of the SOS response in E. coli cells exposed to high pressure.

DNA nano-engineering

G. Bellot, E. Margeat, N. Aissaoui, A. Mills

We use DNA self-assembly methods that offer 3D-shape control at nanoscale resolution and programmable actuation. Our aim is to develop new bio-inspired intelligent systems to help solve problems of fundamental and medical interest.

DNA nanotechnology. DNA origami represents a major landmark as the first method to self-assemble megadalton scale nanostructures with arbitrarily-defined morphology. Our main objective is to explore new design principles for self-assembling molecular architectures for de novo fabrication of high-performing materials.

Membrane proteins. The understanding of the molecular mechanisms of the cell membrane requires new experimental tools at the nanometre level. We aim to develop DNA nanostructures to facilitate structural studies of membrane proteins by cryo-EM and single-molecule fluorescence microscopy.

Bio-inspired nanomechanics. Inspired by the biomechanical features of protein assemblies, our goal is to build nanometer-sized structures that exhibit controllable motions and functions. These man-made nanodevices can be used as sensors that respond to specific stimuli and may find applications in areas such as biosensing, biophysics and on-demand drug delivery.

DNA self-assembly of 3D nanostructures from 1.5 million of nucleobases.

Collaborations: S. Aymerich (INRA, Jouy-en-Josas), C. Royer (RPI, NY), O. Radulescu (UM, Montpellier)


Kinetic competition at a transcription termination/antitermination site. All-Bara S, Clerte C, Decleré N, Marguet E. RNA, 2017


Collaborations: Y. Ke, (Georgia Tech, USA), S. Granier (IGE, Montpellier), S. Bidault, (ESPCI, Paris).

Live cell imaging of a B. subtilis strain expressing a PcgR-GFP transcriptional fusion under repression on maltose.

Cartoon representation of the LicT antitermination protein dimer, bound to its target RNA hairpin that has been labeled with a pair of fluorophores to monitor its conformational dynamics in a single pair FRET experiment.
Structure and Dynamics of Membrane Assemblies

We explore the structure and dynamics of membrane assemblies, including mechanical properties, membrane proteins structure and interaction, and membrane remodeling mechanisms, on living cells or artificial membrane models, using single molecule experimental approaches such as atomic force (AFM) and fluorescence/super resolution microscopies.

Remodeling and partition of membrane components

L. Costa, P.E. Milhiet, C. Bénistant, P. Dosset, C. Doucet, C. Godefroy, L. Fernandez

We are interested in the molecular mechanisms of lipid-protein interaction within membranes and their spatiotemporal recruitment in different contexts, especially cancer and infection.

Structure and dynamics of tetranspanins. Tetranspanins are transmembrane proteins forming a network of protein-protein-lipid interactions at the plasma membrane of eukaryotic cells. They are involved in numerous cell functions and associated with several diseases. Using single molecule fluorescence microscopy and AFM we are exploring tetranspanin lateral segregation into micro- or nanodomains. We are especially investigating the dynamics and partitioning of the metastasis suppressor CD82 and its relationship to cell migration, and the role of tetranspanins CD9 and CD81 in cell infection by HIV-1 and influenza viruses.

Septin organization during membrane remodeling. Septins are conserved GTP-binding proteins involved in membrane compartmentalization and remodeling. Their ability to form functional filamentous structures depends on their binding to PIP2 lipids. Using supported lipid bilayers observed with high-speed AFM and correlative AFM-fluorescence microscopy, we explore at the meso and nanoscale how these proteins polymerize, recruit lipids and deform biological membranes.

Nanomechanics of cancer metastasis

C. Bénistant, L. Costa, C. Godefroy, P.E. Milhiet

Physical properties of the cancer cell microenvironment play important roles in promoting cell invasive migration phenotypes and can constitute an obstacle for therapy accessibility. We aim at analyzing how biomechanics impact the formation and progression of cancer by measuring physical properties of cancer cells and tissues, using AFM (force spectroscopy and force mapping).

Mechanical properties of colorectal cancers in transition to metastasis. We measure and correlate the rigidity (Young Modulus) of a bank of colorectal cancer tissues with genomic and patient’s survival data in collaboration with clinicians of the Montpellier Cancer Research Center. CD82 metastasis suppressor functions. CD82 regulates several membrane remodeling events such as adhesion, migration, endocytosis… by unknown mechanisms. As membrane organizers, tetranspanins could influence membrane nanomechanics. We test the influence of CD82 on membrane tension, a key parameter in membrane remodeling.

Mechanisms of nuclear pore complex assembly

C. Doucet, L. Costa, P. Dosset, P.E. Milhiet, A. Vial

Nuclear Pore Complexes (NPCs) are the only gateways between the nucleus and cytoplasm. In dividing cells, the number of NPCs doubles during interphase. New pore insertion in the nuclear envelope requires the local fusion of inner and outer nuclear membranes. This implies exquisite coordination between membrane remodeling and nucleoporins recruitment and assembly. We aim at understanding the mechanisms involved in early steps of interphase NPC formation, in particular nuclear membrane deformation, following 2 main axes:

1. Identify the sequential involvement of molecular players in membrane deformation. We combine AFM and Single Molecule Localization Microscopy on isolated nuclei, to correlate the recruitment of specific proteins with nuclear membrane deformation and pore assembly.

2. Understand the peculiar deformation of the nuclear envelope. Membrane binding agents suspected to intervene in pore formation induce convex deformations on synthetic liposomes while pore intermediates are concave. We investigate determinants of the pore membrane leading to this discrepancy.

Structural dynamics of single metabotropic glutamate receptors

E. Margeat, C. Clerté, R. Quast

Using a combination of advanced single molecule microscopy methods, we investigate the activation mechanism of G-protein coupled receptors.

Metabotropic glutamate receptors (mGluR) are members of the class C G-protein coupled Receptors (GPCR family). Each subunit is composed of an extracellular domain that binds orthosteric ligands such as glutamate, and a heptahelical transmembrane domain responsible for G-protein activation. We study mGluR structural dynamics by a combination of site-specific labeling, receptor purification and solubilization, and smFRET with multiparametric fluorescence detection (MFD).

Methodological developments

L. Costa, E. Margeat, P.E. Milhiet, C. Clerté

Our research requires the development of new methodological approaches in the fields of fluorescence spectroscopy, microscopy and atomic force microscopy, such as:

Correlative Atomic Force with super-resolution fluorescence microscopy (STORM and Light Sheet Microscopy (LSM))

Non-contact, atomic-based near-field probe microscopy

One- and two-photon scanning fluorescence fluctuation microscopies

Two-spot correlation spectroscopy coupled with rheometry

Photonic structures for high resolution single molecule FRET

Collaborations: E. Crapez and A. Turtoi (IRCM, Montpellier)

Mechanical properties of colorectal cancers in transition to metastasis. We measure and correlate the rigidity (Young Modulus) of a bank of colorectal cancer tissues with genomic and patient’s survival data in collaboration with clinicians of the Montpellier Cancer Research Center.

Correlative AFM and fluorescence microscopy

Cartoon representation of a metabotropic glutamate receptor dimer in a lipid bilayer
DEPARTMENT OF BIOPHYSICS & BIOENGINEERING

Single-Molecule Angular Dynamics
Francesco Pedaci

Our research aims to develop novel tools in single-molecule manipulation and detection to unravel new dynamics in biological systems. We focus on angular manipulation at the single-molecule level using novel optical and magnetic tweezers. In particular, we use these and other techniques to study the biophysical origins of rotation in the Bacterial Flagellar Motor in E.coli.

Optical angular manipulation and the biophysics of the Bacterial Flagellar motor
F.Pedaci, AL.Nord, Z.Santybayeva

Our research, in the field of single-molecule manipulation, is defined along two lines where rotation and torque are the relevant parameters: 1) technical development of “angular optical tweezers”; and 2) the study of the rotary Flagellar Motor in bacteria.

In our first line of research, we develop a novel optical manipulation technique termed Optical Torque Wrench, which extends the possibilities of standard Optical Tweezers towards the control and measurement of torque at the single-molecule level. This is achieved by optically trapping microscopic birefringent particles with a controlled geometry, which we produce in the IES cleanroom in Montpellier. Possible applications are in the field of single-molecule force- and torque-spectroscopy, as well as in new scanning microscopy, micro- and nano-rheology, and cell membrane fluctuation-spectroscopy.

Collaborators: B. Chaurot (IES Montpellier), C. Callot (I2C Montpellier), M. Abkarian (CES Montpellier)

Our second line is focused on unraveling the physical principles responsible for the dynamic function of the Bacterial Flagellar Motor, which actively rotates the flagella in many motile bacteria. We study this large and powerful rotary motor (which can rotate in the KHz regime) by single-molecule force- and torque-spectroscopy, as well as in new scanning microscopy, micro- and nano-rheology, and cell membrane fluctuation-spectroscopy.

Collaborators: B. Chaurot (IES Montpellier), C. Callot (I2C Montpellier), M. Abkarian (CES Montpellier)

HemoPhysics
Manouk Abkarian

Our group explores the physics of blood rheology with a multi-scale approach, tackling problems linking red blood cells (RBCs) membrane mechanics to their flow in complex microcirculatory situations both in health and in diseases. Our team uses high-speed video-microscopy, sate-of-the-art force measurement techniques (micropipettes, optical tweezers, rheometer, and AFM), as well as microfluidics to produce both biomimetic flow conditions and textured lipid vesicles.

A new look at blood shear thinning
Manouk Abkarian, Luca Lanotte, Viviana Claveria

Blood viscosity decreases with shear stress, a property essential for an efficient perfusion of the vascular tree. Shear thinning is intimately related to Red Blood Cells (RBCs) dynamics and mutual interactions.

We performed experiments and simulations in microcirculatory flow conditions that reveal rich RBC dynamics governing shear thinning. In contrast to the current paradigm, which assumes that RBCs align steadily around the flow direction while their membranes and cytoplasm circulate, we show that RBCs successively tumble, roll, and adapt highly diverse deformed polylobed shapes for increasing shear stresses. Our results suggest that any pathological change in plasma composition, RBC cytosol viscosity, or membrane mechanical properties will affect the onset of morphological transitions and should play a central role in pathologies.

Main Collaborators : S. Mendez and F. Nicoud (IMAG, Montpellier, France), D. Fedosov and G. Gorpper (CES-2, Julich, Germany).

Flow geometry and sickle cell anemia vaso-occlusion
Manouk Abkarian, Viviana Claveria

Sickle cell anemia is a blood disorder of the microcirculation and is characterized by painful vaso-occlusive crises (VOC) in deep tissues.

Using microfluidic devices, we showed that the flow of a suspension of sickle red blood cells around acute corners or bifurcations, leads to the enhanced deposition and aggregation of cells. We found that aggregates morphology changes dramatically to filamentous structures when using autologous plasma as a suspending fluid. Such structures could play a major role in vaso-occlusive events.

Main Collaborators : Philippe Connes (LIBM, Lyon), S. Mendez (IMAG, Montpellier)
Synthetic Biology
Jerome Bonnet & Martin Cohen-Gonsaud

Our first field of research is synthetic biology, the rational design and construction of new biological systems and functions. We are particularly interested in engineering genetic circuits allowing us to “program” cellular behavior, and to apply these tools to healthcare challenges, starting with diagnosis of disease. Our second field of research aims at using structural biology approaches to understand Mycobacterium tuberculosis pathogenesis, in particular to decipher the host-pathogen interactions.

Systematic design of programmable cellular biosensors.

Living cells have evolved to detect and process various signals and can self-replicate, presenting an attractive platform for engineering scalable and affordable biosensing devices. Microbes are perfect candidates: they are inexpensive and easy to manipulate and store. Our goal is to engineer microbial biosensors with unprecedented capabilities.

Microorganisms present a robust chassis for engineering whole-cell biosensors or microbiome therapeutics, yet scalable technologies to engineer receptors detecting novel ligands are lacking. Our work focuses on engineering artificial receptors that can be tailored to detect many ligands of interest, with a particular focus on biomarkers of clinical interest for diagnosis. We are deploying these artificial sensing pathways into different systems, including bacteria, yeast and cell-free systems. These scalable and versatile detection systems will support many translational applications of synthetic biology, including sophisticated low-cost diagnosis, environmental monitoring and remediation, and targeted cellular therapeutics.

Mycobacterium tuberculosis structural biology
M. Cohen-Gonsaud, A. De Visch, P. Barthe

The first M. tuberculosis (Mt) structure was elucidated at the CBS in 2002. Since then, many structures have been solved in the lab either using NMR or X-ray crystallography. Structural biology approaches are key to understand the mechanisms at play behind the virulence and persistence of the tuberculosis agent.

Tuberculosis is directly linked to the tight interplay between the host immune response and the persistence of Mt. The Tuberculosis bacilli need to be efficiently phagocytised, block phagosome maturation, escape from the phagosome and subvert the host immune response. Despite their importance in virulence, the functions of most secreted proteins regulating these processes are still largely unknown.

Our main project is focused on the investigation of secreted mycobacterial proteins, identification of their host partners, and understanding how they promote Mt infection. To do so, we use our strong expertise in mycobacterial proteins biochemistry, and a well-established model organism for host-mycobacterial interaction studies, Dictyostelium discoideum/M. marinum structural and combine biochemical approaches with cellular biology.

Scalable composition frameworks for genetically encoded logic
J. Bonnet, S. Guiziou, P. Mayonove, A Zuniga, V. Moreau.

Reprogramming the response of living cells to chemical or physical signals is a key goal of synthetic biology that would support the development of complex manufacturing processes, sophisticated diagnostics, or cellular therapies. Our aim is to provide composition frameworks enabling the systematic design of logic gates performing Boolean or history-dependent logic within living cells.

Many applications of synthetic biology like multiplexed signal processing for diagnostics require some form of engineered biological computation. In order to “program” living cells, researchers inspired from electronics to build biological logic gates, devices responding to various combinations of inputs according to a specific logic function or “program”. We are taking advantage of division of labor at the level of a multicellular consortia to design robust frameworks for the systematic implementation of logic gates integrating an arbitrary number of inputs. These scalable and composable designs will support research and engineering applications requiring complex programs to be executed by living cells.

Collaborations: M. Leclère and F. Uliana (ULRMA Montpellier)
Platforms and core facilities

The Integrated Platform of Biophysics and Structural Biology (PIBBS) acts as a research resource to the local, national and international scientific community, providing scientific expertise and access to state-of-the-art equipment made available at the CBS. The uniqueness of the platform is to offer a real multi-disciplinary and integrated approach for structure-function studies of biomolecules thanks to the combination of numerous on-site technologies in Structural Biology and Biophysics. While access to our instrumentation is open to outside users for short term experiments, platform projects can be studied over extended periods with the strong input of CBS researchers and engineers.

1 - Liquid state NMR
Avance III Bruker 700, 800 MHz equipped with cryo-probes and autosampler, 600 MHz with high pressure device

2 - X-ray Crystallography
Automated crystallization and visualization, X-ray diffractometer equipped for in situ data collection

3 - Electron Microscopy
FEG200-JEOL equipped for cryo-electron microscopy and tomography

4 - Atomic Force Microscopy
High-speed AFM, fluorescence- and super resolution- coupled AFM setups

5 - Fluorescence Microscopy
Home-built set-ups equipped for super-resolution PALM/STORM, PIE-FCCS, FLIM, SPT and smFRET

6 - Bio-informatics
Online tools for protein modeling and ligand screening

7 - Biophysical characterization of biomolecules
SEC-MALS, UV-CD, ITC, DSC, DLS

The PIBBS platform is supported by the GIS IBISA and belongs to 2 national infrastructures (FRISBI and FBI). It is organized in 7 poles of competence offering classical and advanced research equipment with highest quality standard:
Teaching, training and sharing scientific expertise are some of the core missions of the CBS. It is actively involved in the teaching and training of students at all levels, from elementary schools to visiting senior scientists. As a laboratory affiliated to Montpellier University (UM), the CBS hosts two Professors and one Lecturer that are responsible of undergraduate and graduate studies in the field of Structural Biology and Biophysics.

CBS members belong to many national and international networks, and regularly participate to the organization of summer schools, technological workshops or scientific meetings as well as events contributing to the diffusion of scientific knowledge to a large public.

Masters and PhD program
The CBS participates to several Masters’ degrees delivered by Montpellier University and the Faculty of Pharmacy:
- Master in Bio-Health (Biophysics, Structures and Systems)
- Master in Drug Sciences (Structural Biology and Rational Design of Bioactive Molecules)
- Master PIV (Physics and Engineering of Living Systems)
- Master EPHE (Ecole Pratique des Hautes Etudes)

PhD students are recruited through the CBS2 Doctoral School of Biology and Health of Montpellier University. Three-years PhD fellowships are financed by Montpellier University; other local, national or European Institutions or industrial contracts. Applicants are encouraged to check the website of the CBS2 doctoral school: www.adum.fr/as/ed/cbs2

The CBS provides an exceptional working environment, offering state-of-the-art infrastructures and equipment for developing interdisciplinary projects built on highly interactive research.

In recent years, the CBS was able to attract and support promising young scientists, contributing to the recognition of the CBS as a research center of excellence with increasing success in National and European funding applications. Gathering researchers of 14 different nationalities, weekly seminars and lab meeting in English, as well as regularly organized social events, also contribute to the international, dynamic and friendly atmosphere found at the CBS.

Post-doc’s and engineers
Young scientists willing to strengthen their research and technological skills benefit from the wide range of scientific expertise and equipment available at the CBS. Post doctoral fellows as well as contractual engineers are usually recruited for 2 to 4 years and financed by grants attributed to CBS teams and advertised on the CBS website: www.cbs.cnrs.fr

Networks
- iPoLS (International Physics of Living Systems)
- SPM2.0-ITN (Innovative Training Network funded by EU)
- ReNaFoBIS (National Network of Integrative Structural Biology Training)
- ReMiSoL (National Near-Field Microscopy Network)
- IGEM (International Genetically Engineered Machine Competition)
- Labex EpigenMed

Workshops and summer schools:
- EMBO workshop
- EBSA Membrane Biophysics Workshop
- AFMBioMed Summer school
- Biocampus UMS workshop

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Living, studying in Montpellier

Montpellier is in the top five academic centres in France, with 75,000 students, two universities, numerous engineering, art, and business schools, and over 250 research structures. In 2017, it was ranked the 12th most innovative European University and one of the biggest high-tech start-up incubators in France. Montpellier hosts the oldest operational Faculty of Medicine in the Western world, and is still a leading place for higher education and research in life sciences. Surrounding the CBS, a high density of academic and research institutions in medicine, biology, agronomy, chemistry, and computational science form a highly dynamic scientific community favoring intense collaborative networks and lively social events.

The CBS is located in Montpellier, a sunny town on the Mediterranean coast of France. A pleasant climate and cozy atmosphere make Montpellier an especially attractive destination enjoyed by tourists from around the world. A splendid seaside and popular hiking and climbing spots are within a 30 min drive. From Montpellier, it takes only 3 ½ h to reach Paris and 3 h to Barcelona by high-speed trains. An international airport is also easily accessible by public transportation from the city centre.

Montpellier stands in the tradition of the great European medieval cities. The old town, dating back to the 13th century, is linked to modern districts designed by some of the greatest contemporary architects. The surroundings offer many places of natural or historical interest, including six UNESCO World Heritage Sites. It is in the heart of the world’s best wine growing region, providing a gateway to the natural reserve of the Camargue and the Cévennes hills. Montpellier is also an internationally renowned cultural capital with two magnificent operas and a national orchestra, museums and art galleries, and world famous music, dance, film, and theater festivals organized all year round.

Montpellier is the historical Centre of the Americas; INSERM | 2 Institut de Génétique Humaine (IGH); Institut de Génomique Fonctionnelle (IGF) | 3 Centre Hospitalier Universitaire; Faculté de Médecine | 4 Laboratoire d’Informatique, de Robotique et de Microélectronique (LIRMM) | 5 Campus CNRS; Institut de Génétique Moléculaire (IGMM); Centre de Recherche en Biologie cellulaire de Montpellier (CRBM) | 6 Campus Agropolis; Institut de Recherche et Développement (IRD); CIRAD | 7 Université des Sciences | 8 Université des Lettres | 9 École Nationale Supérieure de Chimie de Montpellier (ENSCHM) | 10 Faculté de Pharmacie | 11 Campus INRA-SupAgro | 12 Historical Centre
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Index

A
Abkarian, Manouk 25
Allemand, Frédéric 8
Atomic Force Microscopy (AFM) 22, 28

B
Barducci, Alessandro 16
Barthe, Philippe 6
Bellot, Gaëtan 20
Bénistant, Christine 20
Bernado, Pau 8
Bioinformatics 14, 28
Bonnet, Jérôme 26
Bourguet, William 12
Boutin, Marion 34
Bron, Patrick 10

C
Cancer 12, 14, 18, 22
Cattoni, Diego 18
Chromosome 18
Clerté, Caroline 20
Cohen Gonsaud, Martin 26
Costa, Luca 20

D
Debain, Didier 34
Declerck, Nathalie 20
Delfosse, Vanessa 12
Déméné, Hélène 6
Didier, Philippe 18
DNA origami 10, 20
Dosset, Patrice 20
Doucet, Christine 20
Drug design 14, 28

E
Electron Microscopy (EM) 10, 28
Enzymology 14

F
Fiche, Jean-Bernard 18
Fluorescence microscopy 18, 20, 22, 28
Fluorescence spectroscopy 20, 28
Fournet, Aurélie 8

G
G-protein coupled receptor (GPCR) 6, 9, 23
Gélin, Muriel 14
Germain, Pierre 12
Godefroy, Cédric 20
Gracy, Jérôme 14
Guichou, Jean-François 14

H
High-pressure 6, 21, 8, 28
Hoh, Francois 10
Houbron, Christophe 18

I
Infectious diseases 7, 10, 15, 22
Intrinsically Disordered Proteins (IDP) 8

L
Lai Kee Him, Joséphine 10
Legall, Antoine 18
Le Maire, Albane 12
Lepage, Florence 34
Lipid 13, 22
Lionne, Corinne 14

M
Margeat, Emmanuel 20
Membrane 13, 20, 22, 24, 25
Microfluidics 19, 25
Milhiet, Pierre-Emmanuel 20
Molecular modeling 9, 14, 16, 28
Molecular motors 19, 24
Montet de Guillel, Karine 6
Moreau, Violaine 14

N
Nollmann, Marcelo 18
Nuclear Magnetic Resonance (NMR) 6, 8, 27
Nuclear receptor 9, 12, 16
Nucleus 23

P
Padilla, André 6
Pedaci, Francesco 24
Pons, Jean-Luc 14

R
Roumestand, Christian 6
Rheology 24, 25

S
Sibille, Nathalie 8
Single molecule 10, 18, 20, 22, 24, 28
Small Angle X-ray Scattering (SAXS) 8
Super-resolution 18, 22, 28
Synthetic biology 26

T
Transcriptional regulation 9, 12, 20
Trapani, Stefano 10
Tweezers (magnetic, optical) 18, 20, 24, 25

X
X-ray crystallography 10, 12, 14, 27, 28

Y
Yang, Yinshan 6
The CBS is easily accessible by Tramway (Line 1) from the city center and the main train station (about 20 min).