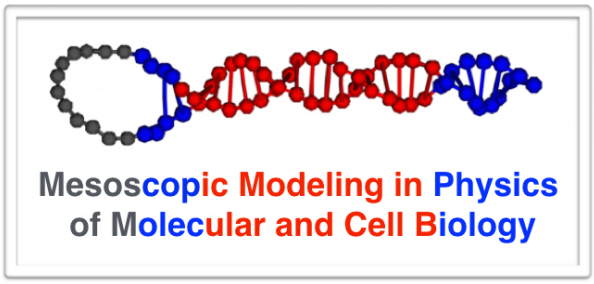
Mesoscopic Modeling in Physics of Molecular and Cell Biology



October 10, 2016 - October 13, 2016
Toulouse, France (CECAM-FR-GSO)
CNRS-CEMES campus

Nicolas DESTAINVILLE
Université Toulouse III-Paul Sabatier, France

Manoel MANGHI
Université Toulouse III-Paul Sabatier, France

John PALMERI
CNRS & Université de Montpellier, France

Roland R. NETZ
Free University of Berlin, Germany

Aloïs WURGER
Université de Bordeaux, France

1 Description

With the involvement of an increasing number of physicists in the field of mesocsopic modeling of molecular and cellular biological processes, huge progress has been accomplished in the two past decades.
However many questions remain unsolved and the spectacular development of experimental techniques (e.g. as microscopy at super-resolution and single molecule experiments) promises that the number of open questions will keep growing in the future.
This workshop intends to gather theoretical physicists specialized in statistical physics and soft matter, and working on different subjects related to molecular and cell biology, but using very similar paradigms and tools. They belong to:

- **coarse-grained models** (where a small group of atoms is modeled as one particle)
- **effective mesoscopic models** (where elementary particles are as large as molecules or subparts of macromolecules)
- **analytical approaches** using mesoscopic models from the **statistical physics**, eventually coupled to hydrodynamics, elasticity, or electrostatics.

The adequate numerical techniques are Monte Carlo simulations, Brownian dynamics with or without hydrodynamic interactions, metadynamics, lattice-Boltzmann methods or dissipative particle dynamics.

Standard analytical tools are commonly used in this field, such as Markov chains, Langevin and Smoluchowski equations, elasticity theory, field-theoretic approaches, hydrodynamics, charged fluids, etc.

One important goal of this workshop is to focus on the application of these various techniques to the physical mechanisms, depending on the time or the length scales under study and the biological issue.

2 Program

Day 1 - Monday October 10, 2016

Active living matter

- 9:00 to 9:30 - Welcome
- 9:30 to 10:45 - Contributed talks
- 10:45 to 11:00 - Coffee Break
- 11:00 to 13:00 - Contributed talks
- 13:00 to 14:30 - Lunch

Genome physics

- 14:30 to 16:15 - Contributed talks
- 16:15 to 16:30 - Coffee Break
- 16:30 to 17:00 - Contributed talks & **Poster session**

Day 2 - Tuesday October 11, 2016

Nucleic acids

- 9:00 to 10:45 - Contributed talks
- 10:45 to 11:00 - Coffee Break
- 11:00 to 13:00 - Contributed talks
- 13:00 to 14:30 - Lunch

Viruses, cells and beyond

- 14:30 to 16:15 - Contributed talks
- 16:15 to 16:30 - Coffee Break
- 16:30 to 18:00 - Contributed talks

Day 3 - Wednesday October 12, 2016

Bio-molecules, bio-polymers, etc.

- 9:00 to 10:45 - Contributed talks
- 10:45 to 11:00 - Coffee Break
- 11:00 to 13:00 - Contributed talks & **Poster session**
- 13:00 to 14:00 - Lunch

Dynamics in the cell

- 14:30 to 16:15 - Contributed talks
- 16:15 to 16:30 - Coffee Break

- 16:30 to 18:30 - Contributed talks

Day 4 - Thursday October 13, 2016

Bio-molecules, bio-polymers, etc.

- 9:00 to 10:15 - Contributed talks
- 10:15 to 10:30 - Coffee Break
- 10:30 to 12:00 - Contributed talks
- 12:00 to 13:00 - **Round Table Discussion**: Future Directions
- 13:00 to 14:00 - Lunch

3 Participant List

Barbi, Maria - LPTMC, Université Pierre et Marie Curie, Paris, France
Bitbol, Anne-Florence - Laboratoire Jean Perrin, Université Pierre et Marie Curie, France
Broedersz, Chase - Ludwig-Maximilians-Universität München, Germany
Carlon, Enrico - Theoretical Physics, KU Leuven, Belgium
Carrivain, Pascal – ENS, Lyon, France
Castelnovo, Martin - Laboratoire de Physique ENS Lyon, France
Cleri, Fabrizio - University of Lille, France
Cocco, Simona - Laboratoire de Physique Statistique, Ecole Normale Supérieure, France
Destainville, Nicolas - Université Toulouse III-Paul Sabatier, France
Dlugosz, Maciej - University of Warsaw, Centre of New Technologies, Poland
Doye, Jonathan - University of Oxford, United Kingdom
Dršata, Tomáš - Institute of Organic Chemistry and Biochemistry AS CR v.v.i., Prague, Czech Republic
Elezgaray, Juan - CBMN, UMR 5248, CNRS, France
Florescu, Ana-Maria - SISSA, Italy
Fournier, Jean-Baptiste - Université de Paris 7, France
Gompper, Gerhard - Research Center Jülich, Germany
Guérin, Thomas - LOMA, Bordeaux, France
Holcman, David - ENS, Paris, France
Ipsen, John H. - The University of Southern Denmark, Denmark
Jost, Daniel - CNRS, TIMC-IMAG, France
Joyeux, Marc - Université Joseph Fourier, Grenoble, France
Kroy, Klaus - Institut für Theoretische Physik, Universität Leipzig, Germany
Kulic, Igor - University Strasbourg, France
Lahiri, Ansuman - University of Calcutta, India
Lankas, Filip - Institute of Organic Chemistry and Biochemistry, Czech Republic
Lepage, Thibaut - TIMC-IMAG, CNRS, France
Lequieu, Joshua - University of Chicago, USA
Lesne, Annick - CNRS, France
Liverpool, Tanniemola - Unversity of Bristol, United Kingdom
Lorman, Vladimir - L2C Montpellier, France
Manghi, Manoel - Université Toulouse III-Paul Sabatier, France
Netz, Roland - Free University of Berlin, Germany
Müller, Martin Michael - Université de Lorraine, France
Noguchi, Hiroshi - University of Tokyo, Japan, Japan
Palmeri, John - CNRS & Université de Montpellier, France
Parmeggiani, Andrea - Université de Montpellier, France
Pezeshkian, Weria - MEMPHYS-Center for Biomembrane Physics, Denmark
Risler, Thomas - Laboratoire Physico-Chimie Curie, Paris, France
Schiessel, Helmut - Instituut-Lorentz for Theoretical Physics, Leiden, The Netherlands
Sens, Pierre - ESPCI, Paris, France,
Sicard, Francois - University College London, United Kingdom
Thalmann, Fabrice - Institut Charles Sadron CNRS & UniStra, France
Vaillant, Cedric - Laboratoire de Physique, ENS Lyon, France
Voituriez, Raphaël - LPTMC, Paris, France
Walter, Jean-Charles - Laboratoire Charles Coulomb, Montpellier, France
Walther, Jürgen - IRB Barcelona, Spain
Würger, Aloïs - Université de Bordeaux, France
Zocchi, Giovanni - UCLA Dept. of Physics and Astronomy, USA

4 Abstracts (talks and posters)

Barbi, Maria – *Modeling superresolution imaging of epigenetic domains in Drosophila*

Eukaryotic chromatin structure at genomic lengths between 10 kb and 1 Mb is still poorly known. Yet, the functional role of these length scales is increasingly shown to be crucial, inasmuch as they parallel the size of Topologically Associating Domains (TADs) or equivalently (in Drosophila) of epigenetic domains. The recent observations by the group of Xiaowei Zhuang at Harvard University (Boettiger et al, *Nature* 2016) give access to the structural characteristics of epigenetic domains with unprecedented resolution. In particular they provide histograms of the radius of gyration of these domains. The scaling of radius of gyration median values with the domain length revealed three characteristic regimes according to the epigenetic type of the domain: active, inactive, repressed. However, these scaling laws have no known counterparts in polymer physics.

We re-analyzed the whole set of histograms in the framework of finite size scaling analysis of the coil globule transition of block copolymers, and proved that the three exponents found by Boettiger et al can be given a common interpretation as crossover exponents of the coil-globule transition of macromolecules. Our results strongly suggest that epigenetic domains all function around their coil-globule transition. Moreover, our analysis also gives access to new estimations of the respective Kuhn lengths (in bp), linear mass densities (in bp/nm) and interaction energies of active, inactive and repressed chromatin fibers.

Bitbol, Anne-Florence – *Inferring interaction partners from protein sequences*

Specific protein-protein interactions play crucial roles in the stability of multi-protein complexes and in signal transduction. Thus, mapping these interactions is key to a systems-level understanding of cells. However, systematic experimental identification of protein interaction partners is still challenging, while a large and rapidly growing amount of sequence data is now available. Is it possible to identify which proteins interact just from their sequences? We propose an approach based on sequence co-variation, building on methods used with success to predict the three-dimensional structures of proteins from sequences alone. Our method identifies specific interaction partners with high accuracy among the members of two ubiquitous prokaryotic protein families, and paves the way to identifying novel protein-protein interactions directly from sequence data.

Broedersz, Chase – *Active stresses and mechanosensation in cells and tissue*

Carlon, Enrico – *The effect of twist-bend coupling on the torsional properties of double-stranded DNA*

Single-molecule magnetic tweezers experiments performed in the past few years report a clear deviation of the effective torsional stiffness of double stranded DNA from the predictions of the twistable worm-like chain model. Here we show that this discrepancy can be resolved if a coupling term between bending and twisting is introduced. Although the existence of such an interaction was predicted more than two decades ago (Marko and Siggia, *Macromol*. 27, 981 (1994)), its effect on the static and dynamical properties of DNA has been largely unexplored. Our analysis yields a twist-bend coupling constant of G=40+/-10 nm. We show that the introduction of twist-bend coupling requires a retuning of the other elastic parameters of DNA, in particular for the intrinsic bending stiffness.

Castelnovo, Martin – *Viral self-assembly and mechanical stress relaxation*

A wide range of capsid morphologies is observed in viral kingdom. Some of them are very regular, with icosahedral symmetries producing rather compact viruses, while others seem irregular and are associated to elongated shapes. In this talk, we will show that the rationale for these observed behaviors can be deduced by analyzing the viral assembly pathway at the light of the elasticity of thin shells. This pathway is shown to follow qualitatively a rule of mechanical stress relaxation. More precisely, it is the strong coupling between pentamer « defects » and the spontaneous curvature of the shell that determines the global morphology of the viral capsid.

Cocco, Simona – *Competition processes facilitate the expulsion of oligonucleotides bounded to an open hairpin loop and the dissociation of proteins from DNA*

I will introduce a stochastic step-by-step competition model to explain rapid dissociation of an oligonucleotide bound on an open DNA hairpin under tension, facilitated by the closure of the hairpin fork. Such rapid dissociation has been experimentally indicated by single-molecule experiments done in V. Croquette Lab (LPS-ENS). Similarly I will introduce multi-units replacement models in which stochastic competition between a multi-unit invader protein and a protein bound to DNA facilitate the dissociation of the latter. These models allow one to explain recent results on concentration dependent dissociation rates of proteins bound on DNA, which are much larger than what expected by spontaneous unbinding.

Doye, Jonathan – *Coarse-grained modelling for DNA biophysics using oxDNA*

The oxDNA model is a coarse-grained model at the nucleotide level that has been designed to reproduce the structural, mechanical and thermodynamic properties of single- and double-stranded DNA. Coupled with a GPU dynamics code it is able to simulate systems with tens of thousands of nucleotides. We have extensively applied the oxDNA model to study biophysical properties of DNA. We have studied the kinetics of basic processes such as hybridization, hairpin formation, and toehold-mediated strand exchange. We have also examined the response of DNA to tensile, twist and bending stress. For example, we were able to provide new insights into the coupling of denaturation and writhing for long, negatively supercoiled DNA under tension. We are also able to compute accurate FRET values for dyes attached to DNA allowing us to help interpret experiments on the substrates of DNA-processing machines, such as polymerases. A brief overview of applications to DNA nanotechnology will also be given.

Dršata, Tomáš (poster) – *Using molecular dynamics simulations to model DNA allostery*

It is becoming increasingly appreciated that DNA can serve as anallosteric mediator. Binding of a small ligand or protein constrains DNA locally, which causes change in the DNA overall structure and flexibility in a way that affects binding of a subsequent ligand. The underlying mechanism of the effect remains poorly understood. In this work, we propose a general model of DNA allostery. We describe DNA in a coarse-grained manner by a set of internal coordinates defining relative displacement and orientation of the individual bases as well as the widths of the major and minor grooves. The binding of a ligand is mimicked by constraining a subset of these coordinates. Quadratic deformation energy is assumed, yielding analytical expressions to describe the change in DNA structure and stiffness and quantify the binding affinity of the second ligand. Model parameters are inferred from large-scale unrestrained, atomic resolution molecular dynamics simulations of naked DNA. The model is first applied to study minor groove binding of diamidines and pyrole-imidazole polyamides [Drsata, T. et al., *J. Phys. Chem. Lett.*, 5, 3831-3835, 2014]. The predicted DNA bending is in quantitative agreement with experiment and suggests that diamidine binding to the alternating TA sequence brings the DNA closer to the A-tract conformation, with potentially important functional consequences. We further show that the model is able to reproduce experimentally observed allosteric coupling between two proteins bound to DNA [Drsata, T. et al., *Biophys. J.*, 110, 874-876, 2016]. The predicted cooperativity is in nearly quantitative agreement with experiment data.

Elezgaray, Juan – *Modelling the folding of DNA origami*

DNA based nanostructures built on a long single stranded DNA scaffold, known as DNA origamis, are nowadays the basis of many applications. These applications range from the control of single- molecule chemical reaction networks to the organization at the nanometer scale of various molecules including proteins and carbon nanotubes. However, many basic questions concerning the mechanisms of formation of the origamis have not been addressed so far. For instance, the robustness of different designs against factors, such as the internal topology, or the influence of the staple pat- tern, is handled empirically. We have built a model for the folding and melting processes of DNA origamis that is able to reproduce accurately several thermodynamic quantities measurable from UV absorption experiments. The model can also be used to design a new distribution of crossovers that increases the robustness of the DNA template. The model provides predictions among which a few of them have been already successfully verified. Therefore, in spite of its complexity we propose an algorithm that gives the capability to design and fabricate templates with dedicated properties, a necessary step for technological development.

Florescu, Ana-Maria – *Large-scale chromosome folding is stable against local changes in chromatin structure*

Characterizing the link between small-scale chromatin structure and large-scale chromosome folding during interphase is a prerequisite for understanding transcription. Yet, this link remains poorly investigated. Here, we introduce a simple biophysical model where interphase chromosomes are described in terms of the folding of chromatin sequences composed of alternating blocks of fibers with different thicknesses and flexibilities, and we use it to study the influence of sequence disorder on chromosome behavior in space and time. By employing extensive computer simulations, we thus demonstrate that chromosomes undergo noticeable conformational changes only on length-scales smaller than 105 base-pairs and time-scales shorter than a few seconds, and we suggest there might exist effective upper bounds to the detection of chromosome reorganization in eukaryotes. We prove the relevance of our framework by modeling recent experimental FISH data on murine chromosomes.

Fournier, Jean-Baptiste – *Dynamics of the interactions between active membrane inclusions*

We investigate the dynamical response of a fluid bilayer membrane to the sudden conformation change of active inclusions. Our study takes into account the full dynamics of the membrane, which is controlled by the dissipation in the bulk solvent, in the monolayers and at the inter-monolayer surface. The mutual force between two inclusions triggered simultaneously is shown to exhibit a transient maximum larger than the equilibrium force. Even in the presence of tension, this dynamical interaction appears as long-range over distances much larger than the correlation length. We derive the scaling laws describing these phenomena analytically, and we stress the importance of the damping due to inter-monolayer friction.

Gompper, Gerhard – *Active and adaptive red blood cells: from nanoparticle uptake to malaria parasite invasion*

Invasion of the human red blood cell (RBC) by the Plasmodium parasite begins the blood stages of infection, responsible for all symptoms of the malaria disease. Because of its centrality to the disease, it is essential to fully understand how the micron-sized parasite enters the RBC, an otherwise robust yet flexible cell that can undergo radical shape changes, without compromising its integrity. To date, models of invasion have centered on the motile parasite forcing its way in. This, however, ignores an increasing appreciation for RBC mechanics and dynamism. Therefore, it is necessary to combine detailed knowledge from biology of the proteins and cellular machinery involved, tools for modeling and simulation from soft-matter physics, and novel biophysical experimental approaches. The modeling and simulation of these processes relies on a description of RBC membrane mechanics and fluctuations on the basis of triangulated surfaces, and a particle-based mesoscale hydrodynamics approach for the fluid.

The talk will focus on (i) the central role played by passive wrapping of nanoparticles by the cell membrane in the uptake of nanoparticles into red blood cells; (ii) the exploitation of the adaptability of the red blood cell membrane by the malaria parasite for invasion; and (iii) the role of activity in the RBC itself. These key elements for the interaction of the RBC with the parasite give the RBC an important role as a target for therapeutics.

Guérin, Thomas – *Mean first-passage times of non-Markovian random walkers in confinement*

The mean first-passage time, defined as the time a random walker takes on average to reach a target point, is an important quantity to characterize the efficiency of processes as varied as diffusion-limited reactions, target search processes or the spread of diseases. Most methods of determining first passage times in confined domains have been limited to Markovian (memoryless) processes. However, as soon as the random walker interacts with its environment, memory effects cannot be neglected.

Examples of non-Markovian dynamics include the motion of a tracer particle attached to a polymeric chain or diffusing in complex fluids such as viscoelastic solutions, nematics or crowded narrow channels.
Here we introduce an analytical approach to calculate the mean first-passage time of a Gaussian non-Markovian random walker to a target in confinement. Our theory provides the mean first passage time as a functional of the temporal Mean Square Displacement (MSD) curve that can be measured in experiments without target.

The non-Markovian features of the dynamics are encompassed by determining the statistical properties of the fictitious trajectory that the random walker would follow after the first-passage event takes place, which are shown to govern the first-passage kinetics. Our theoretical predictions are confirmed by numerical simulations for several examples of non-Markovian processes, including long time correlated ones, in one and higher spatial dimensions [T. Guérin, et al., *Nature*, 534,356–359 (2016)].

Holcman, David – *Analysis of superresolution SPTs for recovering diffusion processes in cellular microdomains*

Biophysical parameters can be extracted from the statistical analysis of large amount of single particle trajectories (SPTs) originating from superresolution microscopy. Features are diffusion tensors or potential wells, predicted more than 10 years ago. The analysis is based on the Langevin equation, where empirical estimators are constructed from the stochastic processes to extract drift and diffusion tensor at few nanometers precision. We summarize here recent progress in analytical and statistical methods, to construct estimators, to de-convolve the data and to estimate first passage and narrow escape times from PDEs and hybrid simulations in empirical domains. The analysis reveals the heterogeneous organization of various microdomains such as GAG HIV virus assembly, endoplasmic reticulum, synaptic terminals of neuronal cells.

Ipsen, John H. – *Membrane shape and in-plane orientational order*

While the cooperativity in the compositional degrees of freedoms of lipid membranes plays a central role in the discussion of biomembrane function, the in-plane orientational degrees of freedoms are mostly ignored. However, many membrane inclusions display elongated or other approximate symmetric shapes with accompanying anisotropic mutual interactions and have the capacity to lateral ordering of the membrane. Furthermore, they may have a local curvature imprint on the lipid membrane, which give them formidable membrane shape modulation capacity at mesoscopic and macroscopic length scales. The characteristics of such membranes can be captured by simple phenomenological continuum models, where just a few molecular characteristics are considered and only the coarse features of the membrane are taken into account. Nevertheless, the complexity of the statistical mechanics of membranes makes the application of standard tools of theoretical analysis very limited. We explore the statistical mechanics of such membranes by Monte Carlo simulation of triangulated random surfaces with build-in elements of discrete differential geometry. The interplay between membrane shape, in-plane order and disclinations is discussed for nematic and p-atic membranes.

Jost, Daniel – *Epigenomics in 4D: modeling the dynamic coupling between epigenome and chromatin organization*

Cellular differentiation occurs during the development of multicellular organisms and leads to the formation of many different tissues where gene expression is modulated without modification of the genetic information. These modulations are in part encoded by chromatin-associated proteins or biochemical tags that are set down at the chromatin level directly on DNA or on histone tails. These markers are directly or indirectly involved in the local organization and structure of the chromatin fiber, and therefore may modulate the accessibility of DNA to transcription factors or enzymatic complexes, playing a fundamental role in the transcriptional regulation of gene expression. Statistical analysis of the repartition of this epigenomic information along the chromosomes has shown that genomes of higher eukaryotes are linearly partitioned into domains of functionally distinct chromatin states. In particular, experimental evidence has shown that the pattern of chromatin markers along chromosomes is strongly correlated with the 3D chromatin organization inside the nucleus. This suggests a coupling between epigenomic information and large-scale chromatin structure that could statistically quantified. Recently, using polymer physics and numerical simulations, we showed that attractive interactions between loci of the same chromatin state might be the driving forces of the folding of chromatin inside the nucleus. In this study, we assumed that the epigenomic information pre-exists to the 3D organization. However, increasing number of experimental results suggests that chromatin marks are themselves highly dynamic during cell cycle or developmental stages and that 3D organization of chromatin might play a key role in the stabilization and function of chromatin markers. We will describe our efforts to better understand the dynamical crosstalk between the epigenome and the 3D organization. In particular, we show that epigenomic-driven contacts and the formation of interacting compartments coupled to a reader-writer mechanism of epigenetic maintenance lead to a better and more robust control of epigenome, suggesting that 3D organization of chromosome plays a functional role at the epigenetic regulation level.

Joyeux, Marc – *In vivo compaction dynamics of bacterial DNA: A fingerprint of DNA/RNA demixing ?*

The volume occupied by unconstrained bacterial DNA in physiological saline solutions exceeds 1000 times the volume of the cell. Still, it is confined to a well-defined region of the cell called the nucleoid, which occupies only a fraction of the cell volume. This is puzzling, because bacterial DNA is not delimited by a membrane, in sharp contrast with the nucleus of eukaryotic cells. There is still no general agreement on the mechanism leading to the compaction of the DNA and the formation of the nucleoid. However, advances in in vivo sub-wavelength resolution microscopy techniques have recently allowed the observation of the nucleoid at an unprecedented level of detail. In particular, these observations show that the compaction of the nucleoid is not static but is instead a highly dynamic feature, which depends on several factors, like the richness of the nutrient, the cell cycle stage, temperature, the action of an osmotic shock or antibiotics, etc. After a short description of the electrolyte content of the cytosol and a brief overview of the different mechanisms that may lead to the formation of the nucleoid, this talk will review some of the most fascinating recent results of in vivo sub-wavelength resolution microscopy. It will furthermore be argued that these observations provide converging indications in favor of a model that describes the cytosol as an aqueous electrolyte solution containing several macromolecular species, where demixing and segregative phase separation occur between DNA and RNA (essentially rRNA and mRNA involved in translation complexes, but also the large amounts of rRNA synthesized at the rrn operons of cells growing in rich media). It will also be pointed out that crowding may play a crucial role through its synergy with electrostatic forces. By constraining macromolecules to remain at short distances from one another and feel electrostatic interactions in spite of the strong screening exerted by electrolyte species, crowding favors stronger DNA/RNA demixing and nucleoid compaction.

Kroy, Klaus – *Microstructure of sheared entangled solutions of semiflexible polymers*

We study the influence of shear on the microstructure and rheology of solutions of entangled semiflexible polymers theoretically and by numerical simulations and experiments with filamentous actin. Based on the tube model of semiflexible polymers, we predict large finite shear deformations to strongly affect the average tube width and curvature, thereby exciting considerable restoring stresses.

In contrast, the associated shear alignment is moderate, with little impact on the average tube parameters, and thus expected to be long-lived and detectable after cessation of shear. Similarly, topologically preserved hairpin configurations are predicted to leave a long-lived fingerprint in the shape of the distributions of tube widths and curvatures. Our numerical and experimental data support the theory.

Kulić, Igor – *Confotronic Machines*

Many biological structures including viral capsids, transmembrane proteins and filaments (DNA, F-actin, bacterial flagella and microtubules) are well known to undergo conformational transitions. The field of confotronics deals with the many-body dynamics of a large number of soft switchable monomer units constituting and animating such complex structures. In this talk I will outline how Nature and our man-made technology utilize confotronic motifs to design highly versatile and functional soft machines from the nano- up to the macro- scale.

Lahiri, Ansuman (poster) – *Coarse-grained simulation of supercoiled DNA minicircles: testing the SIRAH force field*

DNA minicircles have been studied as model systems for DNA loops that are thought to be essential for gene regulation. Simulations provide insight about the physical interactions at play in determining their structural and dynamical characteristics. Coarse-grained models such as SIRAH [Dans D. P. et al. (2010) *J. Chem. Theory Comput.* 6:1711–1725] strive to retain near atomic resolution along with a significant speed-up in sampling. We intend to present data on conformational ensembles of supercoiled DNA minicircles generated using the SIRAH force field and compare them with experimental observations and other atomic resolution simulations [Irobalieva R.N.et al. (2015) *Nature Comm.* 6:8440].

Lankas, Filip – *DNA and RNA molecules as linear elastic systems*

Mechanical properties of DNA play an important role in its recognition by proteins, nucleosome positioning, or three-dimensional organization of the genome. RNA mechanics is decisive for the functioning of the

ribosome and other molecular machines or in RNA interference. Besides that, both DNA and RNA serve as building blocks in artificial nano-devices. In all these situations, nucleic acids should be understood as multiscale objects, with relevant length scales spanning from atomic resolution up to continuum flexible chains. In our approach, we mainly describe DNA or RNA molecules within the framework of linear elasticity, where the deformation energy is a general quadratic function of suitably chosen internal coordinates. This allows to infer model parameters (the minimum energy shape and the stiffness) from unrestrained thermodynamic fluctuations of the coordinates. These, in turn, are generated in large-scale, atomic resolution molecular dynamics simulations of the systems in question. The approach provides nearly quantitative predictions in problems such as peculiar mechanical features of DNA A-tracts [T. Drsata, al. (2014), *Nucleic Acids Res.* 42, 7383-7394], coupling between twisting and stretching of DNA and RNA helices [K. Liebl, et al. (2015), *Nucleic Acids Res.* 43, 10143-10156], or allosteric effects in DNA [T. Drsata, et al. (2014), *J. Phys. Chem. Lett.* 5, 3831-3835; T. Drsata, et al. *Biophys. J*. 110, 874-876].

Lepage, Thibaut – *A polymer model of supercoiled DNA including multiple structural forms of the molecule*

Lequieu, Joshua – *A molecular view of nucleosome energies and dynamics*

The structure and compaction of eukaryotic genomes is one of the most fundamental, yet unsolved, processes in modern biology. The smallest unit of this compaction is the nucleosome, a protein-DNA complex containing ~150 base-pairs of DNA. In this talk, we present recent progress elucidating the subtle interactions within the nucleosome using detailed coarse-grained models of DNA and proteins. Our model is shown to be in excellent agreement with available experimental measurements and can accurately predict the free energies of nucleosome formation. By interrogating our model, we demonstrate that nucleosome stability is dramatically modulated by subtle factors, such as ionic environment and post-translational modifications. Lastly, we perform a detailed analysis of the dynamics of nucleosome motion, and show that this motion is strongly dependent on the underlying DNA sequence within the nucleosome. Notably, we show that different DNA sequences reposition within the nucleosome by dramatically different mechanisms, depending on their affinity for the protein surface.

Lesne, Annick – *A plausible role of DNA torsional constraints in transcription: RNA-polymerase II convoys*

A recently developed single-molecule in-vivo imaging technique evidenced the synchronization of RNA-polymerases II motion during the transcription of some highly active genes, in the form of “RNAP convoys”. On the other hand, single-molecule measurements have shown that DNA supercoiling controls RNA-polymerase velocity, while being itself modified by polymerase activity. Physical modeling allows the quantitative description of how DNA supercoiling and torsional constraints mediate a mechanical coupling between adjacent polymerases. On this basis, a mechanism is proposed that may explain the existence and functioning of RNAP convoys [T. Tantale et al., *Nature Commun*. 7:12248 (2016)].

Liverpool, Tanniemola – *Mesoscopic models of synthetic biological systems*

Synthetic biology involves the design and construction of new biological parts, devices, and systems, as well as the re-design of existing, biological systems for useful purposes. Predictive mathematical models form an intrinsic part of the design and testing of synthetic biological systems. To access experimental timescales and (collective) behaviour of these systems at the 100nm - micron scale, atomistic models are not feasible requiring the use of mesoscale models widely used in soft matter physics. I will describe and summarise recent theoretical work characterising the behaviour of two examples of synthetic biological systems, (i) active nematic liquid crystalline films of mixtures of protein filaments and molecular motors and (ii) the dynamics of self-assembly of nano and micro-structures built from synthetic coil-coil proteins.

Lorman, Vladimir – *Physical modeling of viral capsid structure and self-assembly process*

Viruses represent self-assembling nanoscale objects, intermediate between living and nonliving matter. The viral genome is vulnerable outside of the host cell. The protein shell (capsid) protects the genetic material and assists its transmission to a host cell. In the present work we propose the physical principles of structural organization in these spherical nano-assemblies with the icosahedral symmetry. We study the unconventional positional order of protein subunits in the shell, thermodynamics and physical mechanisms

of the self-assembly, shape and mechanical stability of the shell. The approach modifies the paradigmatic Caspar and Klug (CK) model of icosahedral viral capsids and demonstrates the common origin of both the "anomalous" and conventional capsid structures. The theory associates viral capsid formation with the unconventional crystallization process and describes the capsid self-assembly using a generalization of the Landau theory of crystallization. It is based on the successive application of methods of the theory of representations of continuous and discrete groups and theory of bifurcations of invariant functionals. We develop an explicit method which simulates the protein density distributions in viral capsids in the vicinity of the self-assembly transition and compare the predictions of the theory with the available cryo-electronic microscopy and AFM data. We show the relation between the protein density distributions obtained and the infectivity properties for several human viruses. The protein density variation during the pH-driven capsid reconstruction during the maturation process is also discussed. To illustrate the notions of the theory and the results obtained we focus on viruses of the Flavivirus family, Papillomavirus family and double-shelled capsids of Reoviruses.

Manghi, Manoel – *Interplay between base-pairing and chain dynamics in DNA*

We review the various theoretical developments on the physics of DNA base-pairing dynamics, which brought quantitative insights into the biophysics experimental works. We discuss the dynamics at the base-pair scale and its pivotal coupling with the polymer one, with a length running from a few nucleotides to tens of kilo-bases. This includes opening and closure of short hairpins and oligomers as well as zipping and unwinding of long macromolecules. We will focus on thermally assisted denaturation bubble nucleation and closure where both base-pairing and chain degrees of freedom have similar timescales which appeal to far-from-equilibrium statistical mechanics.

Müller, Martin Michael – *To pinch or not to pinch-a short story about turtles and cells*

We consider two elastic systems for which shape control is of eminent importance. In the first example the axial compression of a thin sheet wrapped around a rigid cylindrical substrate will be discussed [M. M. Müller and N. Stoop, *Int. J. Non-Linear Mech*. 75, 115 (2015)]. In contrast to the wrinkling-to-fold transitions exhibited in similar systems, we find that the sheet always buckles into a single symmetric fold, while periodic solutions are unstable. Upon further compression, the solution breaks symmetry and stabilizes into a recumbent fold. This simple system is of potential relevance for situations as diverse as intestinal inversion or even the neck of hidden-necked turtles.

In the second example we will see how bio-filaments can twist fluid lipid membranes in the cell [J. Fierling et al, *Soft Matter* 12, 5747 (2016).]. In the limit of small deformations, a general expression for the energy and the deformation field of the membrane is derived and specialized to different important cases including closed and helical bio-filaments. In particular, we analyze interface-mediated interactions and membrane wrapping when the filaments apply a local torque distribution on a tubular membrane.

Noguchi, Hiroshi – *Membrane shape transformation induced by banana-shaped proteins and nuclear pore complexes*

In living cells, morphology of bio-membranes is regulated by various proteins such as BAR superfamily proteins that have a banana-shaped binding domain. We will present how anisotropic spontaneous curvatures of banana-shaped protein rod induce effective interaction between the proteins and change membrane shapes by using implicit-solvent meshless membrane simulations. We also present a construction of a nuclear envelope shape by high-genus vesicles under pore-size constraint using dynamically triangulated membrane simulations.

Parmeggiani, Andrea – *Regulating matter concentration in the cytoplasm: a modeling view from exclusion processes*

One of the major abilities of biological cells is the control of matter gradients to dynamically organize the cytoplasm for biological functions. I will present here a class of non-equilibrium lattice gas models called Exclusion Processes that can be used to describe how matter concentration gradients arise in cells and how biophysical parameters control a rich and frequently counter-intuitive phenomenology. This theoretical analysis can inspire direct measurements in-vitro and in-vivo conditions.

Pezeshkian, Weria (poster) – *Membrane invagination induced by shiga toxin B-subunit: membrane curvature, protein clustering and tube Formation.*

Risler, Thomas – *Instabilities and fluctuations in epithelial tissues*

In multilayered epithelia, the basal side of the tissue often presents undulations, typically more pronounced in tumorigenic tissues. We propose that part of these undulations originate from a mechanical instability due to a differential cell flow in the epithelium [M. Basan, J.-F. Joanny, J. Prost, and T. Risler, *Phys. Rev. Lett.* 106, 158101 (2011)]. Two different instability wavelengths can exist when the diffusion of metabolites is considered, via a mechanism reminiscent of the Mullins-Sekerka instability in diffusion-limited aggregation [T. Risler and M. Basan, *New J. Phys.* 15, 065011 (2013)]. Such undulations may also be present at steady state if cell-renewal and force-generation processes are stochastic. We characterize the surface fluctuations of a thick cellular tissue lying on a rigid substrate and show that its fluctuation spectrum can be mapped onto classical spectra in appropriate asymptotic regimes, such as those of incompressible fluids, compressible elastomers, and permeable membranes [T. Risler, A. Peilloux, and J. Prost, *Phys. Rev. Lett.* 115, 258104 (2015)]. For a living tissue, detailed balance is broken, but a generalized fluctuation- response relation is recovered in terms of appropriate observables.

Schiessel, Helmut – *The mechanical genome*

In this talk I will show that DNA molecules contain another layer of information on top of the classical genetic information. This different type of information is of mechanical nature and guides the folding of the DNA molecule inside cells. With the help of a new Monte Carlo technique, the Mutation Monte Carlo method, my group demonstrated recently that the two layers of information can be multiplexed (as one can have two phone conversations on the same wire) [B. Eslami-Mossalam, R. D. Schram, M. Tompitak, J. van Noort, H. Schiessel, *PLoS ONE 11*, e0156905 (2016)]. For instance, we can guide on top of genes with single base-pair precision the packaging of DNA into nucleosomes. Finally, by showing that the complexity of an organism is correlated to the mechanics of its genome, I provide concrete evidence for the evolution of "mechanical genomes" across the tree of life.

Sens, Pierre – *Stick-slip model of the lamellipodium*

Crawling cell motility is powered by actin polymerization and acto-myosin contraction. When moving over a flat and rigid substrate, cells usually develop thin and broad protrusions at their front, called lamellipodia, where actin polymerisation generates a protrusive force pushing the front edge of the cell forward. The lamellipodium displays interesting dynamics, including normal and lateral waves, possibly relevant to cell polarisation and the initiation of motion. I will discuss a stochastic model of mechano-sensitive cell adhesion, and discuss its relevance for symmetry breaking, cell polarisation, and motility.

Sicard, Francois – TBA

Thalmann, Fabrice – *A coarse-grained model for peroxidized POPC molecules and a few case studies.*

We present a coarse-grained model for molecular dynamics of peroxidized POPC and DOPC phospholipid molecules. After providing a justification for our model, we investigate some suggested trends for the lateral peroxide group distribution and the miscibility properties of the original vs peroxidized lipid species [Guo et al, *Soft Matter*, 12, 263 (2016)].

Voituriez, Raphaël – *First-passage statistics and search strategies*

How long does it take a "searcher" to reach a "target" for the first time? This first-passage time is a key quantity for evaluating the kinetics of various processes, and in particular chemical reactions involving "small" numbers of particles such as gene transcription, or at larger scales the time needed for animals to find food resources.

I will present recent results that enable the evaluation of the distribution of first-passage time for a wide range of random search processes evolving in a confined domain. This approach reveals a general dependence of the first-passage time distribution on the geometry of the problem, which can become a

key parameter that controls the kinetics of the search process. I will show how these results apply to transport in disordered and fractal media, and show how they can be generalized to other observables, such as cover times.

Walter, Jean-Charles – *Physical modeling of active bacterial DNA segregation*

Genome processing relies on the intracellular localization and dynamic assembly of higher-order nucleoprotein complexes. In bacteria, the mechanism of assembly for the most widespread partition systems, ParABS, responsible for active DNA segregation remains elusive. We have combined super-resolution, genome-wide, biochemical and modeling approaches to investigate quantitatively the formation of the nucleoprotein complex organized around the centromere-like sequences, parS. We found that the active confinement of nearly all ParB proteins around parS, observed at the single molecule resolution, relies on a network of synergistic interactions involving protein-protein and protein-DNA interactions. Our physico-mathematical modeling of ParB binding pattern revealed that ParB binds stochastically in the vicinity of parS over long distances. Based on our findings, and consistent with previous data, we propose a new model that relies on a nucleation and looping mechanism leading to the formation of a dynamic lattice for the partition complex assembly. We thus provide new bases to model the DNA segregation process. Our original assembly model may also apply to many unrelated proteins that self-assemble in superstructures through nucleation centers. [A. Sanchez, D.I. Cattoni, J.-C. Walter, J. Rech, A. Parmeggiani, M. Nollmann & J-Y. Bouet, *Cell Systems* 1 163-173 (2015)].

Zocchi, Giovanni – *Nano-rheology of enzymes*

Enzymes couple a chemical process to conformational motion. While end states are often known structurally, a dynamic description of conformational motion is almost entirely lacking. However, it is in the dynamics that some universality may emerge.

We have developed a nano-rheology method where the ensemble averaged deformation of an enzyme subjected to an oscillatory stress is measured with sub-Angstrom resolution – an improvement of a factor 100 over previous mechanical measurements, giving access to the rheology of the folded state. Measurements on the enzyme Guanylate Kinase reveal a viscoelastic transition in the dynamics. We propose that ligand induced conformational changes generally operate in this viscoelastic regime: the enzyme “flows” from one solid-like conformation to another. It appears that the molecules we are made of behave dynamically like “silly putty”!