M2 internship + PhD project

A Polymer physics based approach to chromosome dynamics

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The highly organized DNA-protein assembly that fills the cell nucleus, called **chromatin,** is a plastic DNA-protein assembly organized in multi-scale compartments. "Chromosome Conformation Capture" technology [Lieberman-Aiden 2009] has revealed one of these levels of organization called **Topologically Associated Domains (TAD)**, at the 100 nanometer / 1 M base pairs scale. Interestingly, in the *Drosophila* fly, TADs are also both chemically characterized by the presence of specific **epigenetic marks,** and correspond to specific **transcriptional activity** states. We have recently shown by combining numerical and theoretical work [Lesage 2019] and based on super-resolution (STORM) imaging data [Boettiger 2016] that **the folding state of TADs is in the vicinity of the critical point of the coil-globule phase transition (Figure 1)**.

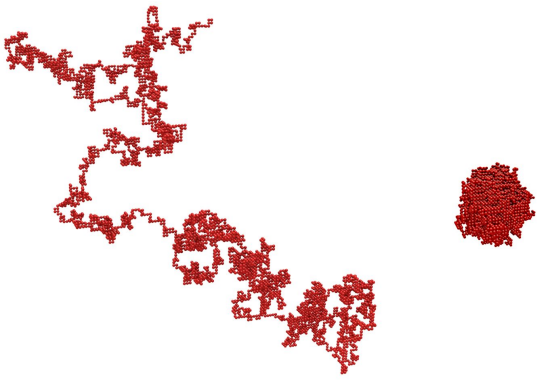

Figure 1: A polymer in coil (left) and globule (right) configurations.

The next crucial step will be to describe the **interplay between the universal phase transition observed in chromatin domains and the dynamics of DNA loci**. To this aim, we have to connect dynamical properties as loci diffusion, inter-loci distance fluctuations or inter-loci contact frequencies with the underlying folding state of chromatin.

What are the movements compatible with a given arrangement, what is the dynamic signature of a structural modification, what are the dynamical consequences of biological activities such as transcription? To aim of the **internship work** will be to **characterize these dynamical properties based on theoretical models** (e.g. Rouse dynamics) and **numerical simulations** of self-interacting polymers as a function of their different folding states. This problem has not yet been addressed. A related question is that of **ergodicity**, i.e. the equivalence between population average and time average, in such critical conditions. The answer will depend on whether a single polymer is quenched in metastable folded states or, conversely, scans the whole set of folding patterns when close to transition, with strong implications for the biological activity.

Once the dynamics is well characterized from the polymer physics point of view, the **PhD project** will focus on the **study of similar features in the *Drosophila* fly genome**. We have connections with **several experimental groups** that are actively working on the characterization of DNA loci dynamics. Multiple dynamical, low-frequency, yet specific interactions have indeed been observed in *Drosophila* TADs [Cattoni 2017]. *In vivo* tracking of chromosome fluctuations also allows to quantify loci diffusion [Socol 2017], pointing towards the existence of transient contacts between loci [Socol 2017]. **In the framework of the ANR project funding this PhD, we will collaborate with the Thomas Gregor's team** (Institut Pasteur), which combined genome editing

and multi-color live imaging to **simultaneously visualize specific inter-loci distances and transcription activity at the single-cell level** in *Drosophila* embryos [Chen 2018]. Diffusion, encounters, and association time-scales can thus be directly related to the functionally relevant impact of transcription.

Because of the strong connection with experiments, **data analysis will represent an important part** of the PhD work, as well as the collaboration with the experimental team in the design of specific experiments. The PhD will benefit of the collaboration with the **Vincent Dahirel's team at PHENIX** (Physicochimie des Electrolytes et Nanosystèmes interfaciaux, Sorbonne Université) leader in numerical modeling of both transport and electrostatics features in biological systems and involved in the ANR project with a 2-year post-doctoral fellowship. **The PhD will also have the possibility to spend a period in Thomas Gregor's laboratory in Princeton to learn and participate in the experimental work**.

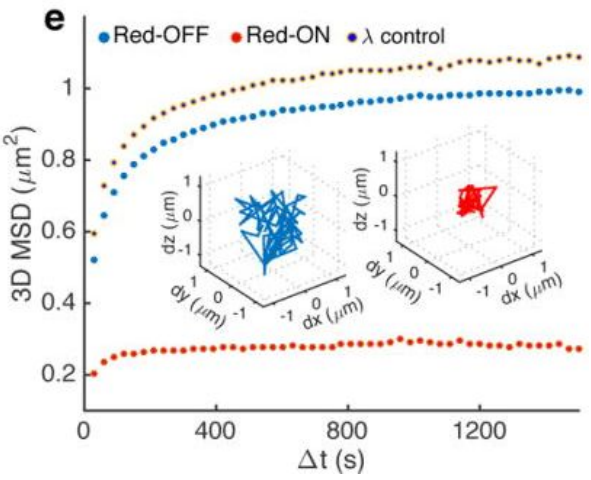

Figure 2: Population-averaged mean-squared displacement (MSD) for transcriptionally active (blue) and inactive (red)domains. Inset: two representative trajectories (same color code).

Host team

The **Multiscale Modeling of Living Matter (M3V) team, in the LPTMC (Laboratoire de Physique Théorique de la Matière Condensée)** lab of **Sorbonne Université**. The work of this team involves both statistical physics and mechanics applied to biological systems, and the team has developed a particular expertise in **modeling of polymers**. They developed numerical and theoretical modeling tools to study the organization of chromosomes in its functional and dynamic aspects, always in close collaboration with experimental biology groups. The LPTMC team is also coordinating a research group at the CNRS on Architecture and Nuclear Dynamics (**GdR ADN**), bringing together more than 80 French research teams in biology, physics and bioinformatics, both experimental and theoretical.

References related to the project

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