Laboratoire Physico-Chimie Curie

Institut Curie, 11 Rue Pierre et Marie Curie-75005 PARIS

TITRE DU STAGE :

Out-of-equilibrium statistical mechanics of a polymer undergoing loop extrusion

DIRECTEURS de Stage : Vittore Scolari (vittore.scolari@curie.fr) & Antoine Coulon

Ce stage peut être poursuivi en thèse : à discuter.

SUJET du stage :

The secrets of life are encoded in DNA, as a sequence of 4 letters (the sugars A, T, C and G) that contains essential information required for our cells to thrive. Nevertheless, having access to those sequences, collected by the community and stored in the genetic databases, is not enough to understand their meaning. Different cells of the same organism, such as a stomach and a brain cell, share the same genetic code, but look different and perform a totally different duty. This leads us to an extra layer of more volatile information, that is not encoded in the sequence but rather is written on top of that, which is called epigenetics, and consists of a large quantity of molecules and biochemical processes associated to DNA in chromatin, making up the chromosomes. Those molecules are always associated to the physical position of DNA in the 3D space, and often have an important effect on the way the chromosomes fold inside the nucleus. Our overarching objective is to understand the connections between the function of the molecular elements which constitute epigenetics and the spatial organization and dynamics of chromosomes.

Specifically to this project, we are interested in genomic elements called ‘enhancers’: because these elements can switch the transcriptional activity of genes located hundreds of kilobases away from their position in the sequence. How enhancers and genes communicate in space and time is a great mystery and is a major subject of current research. The current paradigm of understanding, is based on “loop extrusion”, as it has been hypothesized that this governs the local conformation of mammalian chromosomes (Fudenberg *et al.*, 2017). It posits that molecular motors create and grow local DNA loops (typically < 1 Mb) until it encounters a roadblock. This model can account for many experimental observations, creating local conformational structures likely to influence the communication between genes and enhancers (Valton and Dekker, 2016).

The goal of this internship is (i) to develop an analytical theory for the dynamics of polymers undergoing loop extrusion, using the tools of out-of-equilibrium statistical mechanics, and (ii) to be able to identify "loop extrusion" in experimental data obtained in our lab and others. To study local genome conformation and enhancer-gene communication in the lab, we measure the 3D trajectories of genomic elements and the activity and position of individuals genes that share the same enhancer(s). The problem arises by the fact that the position of such objects, at mesoscopic scales, is dominated by chaos. And chaos can be the result of purely Brownian diffusion (the Rouse model of free polymers), as well as the outcome of averaging over space

and time (Egolf, 2000). In order to highlight the effect of activity above the background of equilibrium chromatin, the intern will develop the following:

1. Null model theory: parametrization of the Rouse model using a statistical micro-ensemble, analytical calculation of the probability fluxes as a function of time.
2. Adaptation of available numerical simulations of loop extrusion, to test the predictions obtained in point 1, in presence and absence of loop extrusion. Quantification of the effects of polymer relaxation
3. Comparison of the theory to data from our lab and from the literature (e.g. Bintu et al. 2018): contact probability maps of chromosomes (Hi-C), distance distributions and conformation ensembles (Oligopaint DNA FISH), gene activity (RNA FISH), 3D trajectories of genomic loci.
4. explore the effect of different hypotheses in the extrusion model (Ganji *et al.*, 2018; Vian *et al.*, 2018)

Candidates should have substantial programming skills (Python preferred), knowledge in statistical physics, and a genuine interest in approaches combining theory and experiments for solving questions at the physics-biology interface.

More information on the lab: www.coulonlab.org

Related literature:

Bintu, B. et al. (2018). Super-resolution chromatin tracing reveals domains and cooperative interactions in single cells. *Science*, **362**(6413), eaau1783–10.

Egolf,D.A. (2000) Equilibrium Regained: From Nonequilibrium Chaos to Statistical Mechanics. *Science*, **287**, 101–104.

Fudenberg,G. *et al.* (2017) Emerging Evidence of Chromosome Folding by Loop Extrusion. *Cold Spring Harb Symp Quant Biol*, **82**, 45–55.

Ganji,M. *et al.* (2018) Real-time imaging of DNA loop extrusion by condensin. *Science*, **360**, 102–105.

Valton,A.-L. and Dekker,J. (2016) TAD disruption as oncogenic driver. *Current Opinion in Genetics & Development*, **36**, 34–40.

Vian,L. *et al.* (2018) The Energetics and Physiological Impact of Cohesin Extrusion. *Cell*, **173**, 1165-1178.e20.