M2 internship – Coulon lab, Institut Curie, Paris – http://coulonlab.org/

Modeling the conformational and transcriptional dynamics of a genomic locus undergoing loop extrusion

Cells in our body contain several meters of DNA, organized in a small nucleus of a few microns in diameter. At many levels, the spatial conformation of the genome in the nucleus and its dynamics over time are linked to its functions. In particular, many genes are regulated by genomic elements called 'enhancers', which can be located hundreds of kilobases –or more– from the gene(s) they regulate. How enhancers and genes communicate in space and time is not understood and is a major subject of current research. Our approach in the lab to understand structure-dynamics-function relationships in genome organization is to combine single-molecule microscopy (to visualize particular genes, RNAs and/or proteins) with biophysical modeling approaches (polymer dynamics, diffusion models, stochastic processes…). To study enhancer-gene communication specifically, we measure the activity and position of pairs of individuals genes that share the same enhancer(s) as to observe spatio-temporal patterns and signatures in their activities revealing the underlying molecular and biophysical mechanisms.

The goal of this internship is to simulate the conformational dynamics of a genomic locus, based on a mechanism called "loop extrusion", and to predict how it results in correlated patterns of activity between genes. The "loop extrusion" model has recently been hypothesized to govern the local conformation of mammalian chromosomes [Fudenberg et al. 2017]. It posits that molecular motors create and grow local DNA loops (typically up to < 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 genomic elements called enhancers [Valton et al. 2016]. If this mechanism is indeed at work, we can expect nearby genes in the genome to show characteristic patterns of temporal correlations in their transcriptional activity and relative position – which we can measure experimentally in our lab using live-cell and fixed-cell single-molecule imaging techniques to visualize nascent RNAs [Coulon et al. 2014, 2016]. The internship will consist in predicting such patterns and show how they may reveal the underlying principle of gene regulation.

Practically, the student will expand an existing implementation in Python that simulates loop extrusion with an implicit polymer representation. We will take a first-principle approach by starting with the simplest version of the model and considering an 'idealized' locus (e.g. with 2 genes, a single enhancer… etc), before refining it further. Depending on the duration of the internship, the student will:

- predict transcriptional signatures expected in live-cell data (MS2/PP7) and fixed-cell data (RNA FISH)
- compare simulations to data from the literature (i.e. Hi-C maps, distance distributions from DNA FISH)
- explore the effect of different hypotheses in the extrusion model [Ganji et al. 2018; Vian et al. 2018]
- relate the predicted patterns to hypotheses/parameters using reduced mathematical/physical models
- refine the implicit representation of the polymer to account for out-of-equilibrium dynamics

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

For application, please contact: Antoine Coulon at recruitment@coulonlab.org

Related literature:

Fudenberg, G., Abdennur, N., Imakaev, M., Goloborodko, A., & Mirny, L. A. (2017). Emerging Evidence of Chromosome Folding by Loop Extrusion. Cold Spring Harbor Symposia on Quantitative Biology, 82, 45–55. http://doi.org/10.1101/sqb.2017.82.034710

Valton, A.-L., & Dekker, J. (2016). TAD disruption as oncogenic driver. Current Opinion in Genetics & Development, 36, 34–40. http://doi.org/10.1016/j.gde.2016.03.008

Coulon, A., Ferguson, M. L., de Turris, V., Palangat, M., Chow, C. C., & Larson, D. R. (2014). Kinetic competition during the transcription cycle results in stochastic RNA processing. eLife, 3, e1002215. http://doi.org/10.7554/eLife.03939

Coulon, A., & Larson, D. R. (2016). Fluctuation Analysis: Dissecting Transcriptional Kinetics with Signal Theory. Methods in Enzymology, 572, 159–191. http://doi.org/10.1016/bs.mie.2016.03.017

Ganji, M., Shaltiel, I. A., Bisht, S., Kim, E., Kalichava, A., Haering, C. H., & Dekker, C. (2018). Real-time imaging of DNA loop extrusion by condensin. Science, 360(6384), 102–105. http://doi.org/10.1126/science.aar7831

Vian, L., Pekowska, A., Rao, S. S. P., Kieffer-Kwon, K.-R., Jung, S., Baranello, L., et al. (2018). The Energetics and Physiological Impact of Cohesin Extrusion. Cell, 173(5), 1165–1170.e20. http://doi.org/10.1016/j.cell.2018.03.072

Bintu, B., Mateo, L. J., Su, J.-H., Sinnott-Armstrong, N. A., Parker, M., Kinrot, S., et al. (2018). Super-resolution chromatin tracing reveals domains and cooperative interactions in single cells. Science, 362(6413), eaau1783–10. http://doi.org/10.1126/science.aau1783