THEORY OF GENOME ORGANIZATION BY PHASE-SEPARATION

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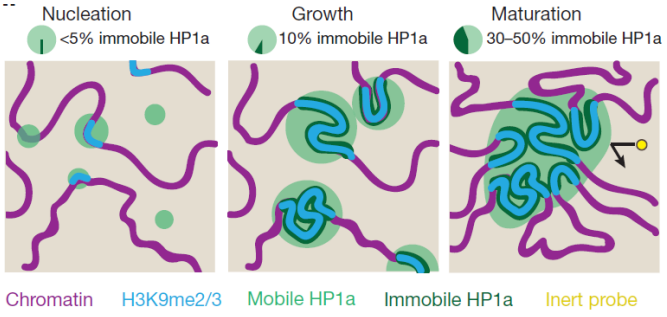
Profil recherché: Physique statistique, physique des polymères, séparation de phases, simulations numériques

Financement envisagé : Bourse doctorale

Résumé :

General Context: Inside the cellular nucleus, DNA is tightly packed into a polymer-like structure called chromatin. The nuclear organisation of chromatin is non-random and is characterized by a phase separation of transcriptionally active and silenced parts of the genome that associate into separate membrane-less compartments. There are now growing evidences that such micro-phase separation plays a crucial role in the regulation of genome activity. Active and silent nuclear sub-compartments may function to concentrate target genomic loci and the proper regulators (activators/repressors) to increase their bio-chemical activities. However, despite their importance, the mechanism of formation of such compartments, their physical nature and how they achieve their functions remains largely elusive due to a lack of quantitative modelling as well as controlled experiments. Recent studies have shown that liquid-liquid phase separation driven by multivalent macromolecular interactions between architectural/scaffolding proteins might be an important organizing principle for such sub-compartment formation. These proteins are primarily recruited at specific genomic sites, forming first small chromatin-proteins agregates that would eventually grow and coalesce to form larger compartment (See Fig).



Objectives: In this project, we propose to develop molecular models and numerical simulations to better understand the mechanisms behind the *de novo* formation, growth and maturation of these chromatin sub-compartments. Recently we introduced a coarse-grained co-polymer model with an effective immiscibility between active vs inactive monomers; this immiscibility was introduced as an effective parameter to account for the multimerizing ability of scaffolding proteins; (eg HP1, Fig). We showed that such model very well account for the micro-phase separation at large scales (1,2) and that such micro-phase separation is required to maintain the local active/inactive state of monomers (3).

Here, we propose to refine and extend these preliminary studies in order to be more quantitative. We propose two approaches for two different internships: (I) Further investigate microphase separation with effective copolymer models: based on our previous works, the student will have to introduce more realistic models, with input parameter derived from/constrained by experimental datas. (II) The "strings and binder" copolymer model where now, in addition to the polymeric chain, we will explicitly describe the self-associating phase of architectural proteins. The student will have to investigate the thermodynamical properties of such system at the mesoscopic scale, ie the physics small phase "droplets".

Expected results: For approaches (I) and (II), the characterization of the phase diagram of the system will help us to understand the importance of each ingredient of the model into the chromatin organization. Quantitative comparisons with experimental data (from our collaborators G. ,Cavalli (IGH, Montpellier) and Yad Ghavi-Helm (GFL, ENS Lyon)) will be performed to test the prediction power of the model. We expect these project to give new insights into the mechanisms controlling the 3D functional organisation of the genome.

References: (1) Jost et al, Nucleic Acids Res 42: 9541 (2014).(2) Olarte-Plata et al, Phys Biol 13: 026001 (2016). (3) Jost et al. Nucleic Acids Res 46: 2252 (2018).