PhD Position

PHYSICS OF CHROMATIN CONDENSATION

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N° and title of the relevant Doctoral School: ED PHAST (Lyon)
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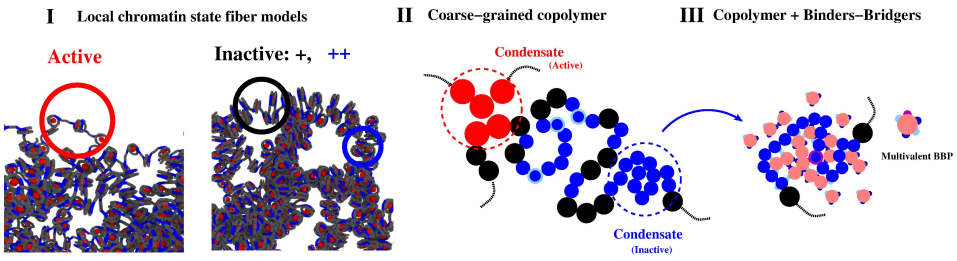
Profile sought: Statistical physics, polymer physics, phase separation, numerical simulations

General Context: Genomes of eukaryotes are packaged in a condensed nucleo-proteic complex called chromatin, whose primary unit, the nucleosome, is composed of about 147 DNA base pairs wrapped around a core of histone proteins. The chain made by the succession of nucleosomes and free DNA (linker DNA) (~1 nucl/200bp) is called the nucleosomal array or chromatin fiber (Fig I). Further levels of genome condensation occurs through higher-order assembly of the nucleosomal array that is controlled in part by nucleosome-nucleosome interaction and chromatin-binding self-associating proteins (Binder-Bridgers Proteins, "BBPs", Fig. III). By modulating accessibility of underlying DNA to the nuclear environment, chromatin plays an essential role in the regulation of genome activity such as gene transcription, replication, repair and insertion of transposable elements. Locally it has been shown that chromatin can indeed adopt different structural states that are more or less permissive to DNA accessibility constituting different functional states: schematically, we can distinguish the euchromatin states (open/accessible, active (red in Fig. I,II)) from heterochromatin states (compact/less accessible, inactive (black & blue in Fig. I,II)). Interestingly, these states can assemble reversibly along extended genomic domains that condensate and phase-separate in 3D to form segregated functional compartments (Fig. II). But despite its importance, the mecanisms that regulate the local structure and assembly of nucleosomal array and its higher-order 3D folding remain unclear due to the lack of quantitative modeling. 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 some chromatin-binding proteins (BBPs) (Fig. III). 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.



Objective: In this project we will focus on the theoretical investigation of higher-order folding of the chromatin fiber: how chromatin fiber 3D organisation depend on the local nucleosome dynamics (fully vs partial wrapping of the nucleosomal DNA), on the nucleosome distribution along the genome (periodic vs random), on nucleosome-nucleosome interaction (strength, shape, valency ?). Expected results **(1)** Using computational tools (MD & MC) already developed in the group (4) (Fig. I) the student will derive phase diagrams vs control parameters of local chromatin fiber, where phases will be, in particular, characterized by probing the accessibility level of typical DNA binding proteins to their DNA target sites. **(2)** Starting from this "fine-grained" chromatin fiber model the student will have: (i) to build a coarse-grained bead-spring copolymer model of chromatin fiber at few (5-10) nucleosome resolution (Fig. II) and (ii) to develop the "copolymer & BBPs" model (Fig. III) where now, in addition to the chromatin fiber copolymer model, he will explicitly describe the self-associating phase of BBPs. The student will have to investigate the thermodynamical properties of such system at the mesoscopic scale, ie the physics of small phase "droplets". He will specifically adress the role of multivalency using the Wertheim theory (5).
This PhD thesis is part of the ANR project "LivChrom" and will be carried out in close collaboration with the experimentalists of G. Cavalli's group at the IGH Montpellier.

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) (4) Socol et al., Nucleic Acids Res 47, 6195 (2019) (5) Russo et al. J. Chem. Phys 131: 014504 (2009) .