PROPOSITION DE STAGE ET THÈSE:

THE PHYSICS OF CHROMATIN CONDENSATION (AT MESOSCOPIC SCALES)

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

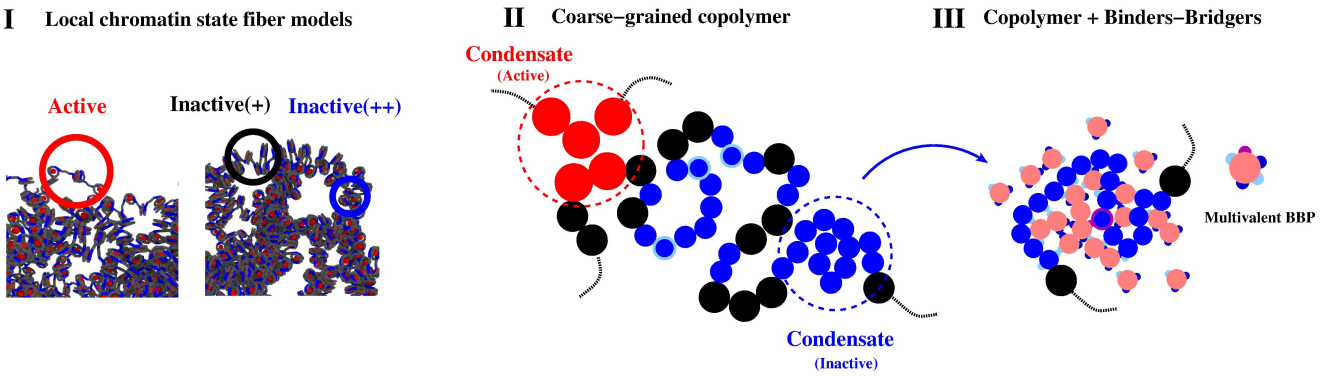

Fig.

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. 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 proteins (Binder-Bridgers Proteins, 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.

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 (periodic vs random), on nucleosome-nucleosome interaction (strength, shape, valency ?). Expected results (1) Internship: Using computational tools (MD & MC) already developed in the group (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) PhD Thesis: The student will improve the model and computational approach by accounting for chromatin binding and self-associating proteins (Fig. III); he will also build coarse-grained bead-spring models of chromatin fiber at few (5-10) nucleosome resolution (Fig. II). The internship and the PhD thesis are 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.