Modelling the Chromosome structural transition in Mitosis using Density Function Theory

During cell division (mitosis) the architecture of the cell dramatically changes (see figure A). Chromosomes are condensed and caught by the microtubules to form the mitotic spindle (in the centre on figure A). The remarkable feature about this conformational change is that the subunits (proteins) which interact to form these architectures are the same. The only thing that change is the way they interact with each other. This change in stereo-specific interactions is mediated by chemical modification that take place at the surface of proteins. The aim of this internship is to model this change at the level of the chromosome.

In chromosomes, DNA is compacted by proteic spools termed nucleosomes, which are regularly spaced along the genome forming the nucleosomal filament (see figure B). Nucleosomes are attracted to each other and can form various structures ranging from fibres (see figure C) to plates (see figure D) depending on the way these attractions are tuned. Based on these experimental facts, we propose a model to account for the compaction of chromosomes during mitosis. In this model, the number of nearest neighbours of nucleosomes can change from 2 to 6. This change is mediated by the modifications of specific residues in nucleosomes. This change results in a transition of the chromosome structure from a one dimensional polymeric fibre during cell interphase to a tree dimensional liquid crystal during mitosis.

In order to tackle this problem in practice, we propose to use a density functional formalism tailored to handle the complexity of the problem. Starting from a simple form of a free-energy functional, we introduce in it the effective interaction between two nucleosomes, modelled as Gay-Berne cylinders. This functional is then minimised with respect to different guesses of the form of the nucleosomal filament (fibre-like or 3D liquid crystal-like) with appropriate parameters ruling the switch from one form to the other. The existence of an absolute minimum for the free-energy permits one to locate the allowed form of the filament under specific interacting conditions. The full calculations could be the subject of a subsequent doctorate study, with expected collaborations with experimental groups. At the level of the internship, however; it will be sufficient to locate the stability conditions of the various fibre shapes. A good knowledge of the physics of liquids is a necessary prerequisite.