PROPOSITION DE STAGE & THESE

Stochastic Modeling of Epigenome regulation

Laboratoire: Laboratoire de Physique de l'ENS Lyon & Laboratoire TIMC-IMAG (Grenoble)

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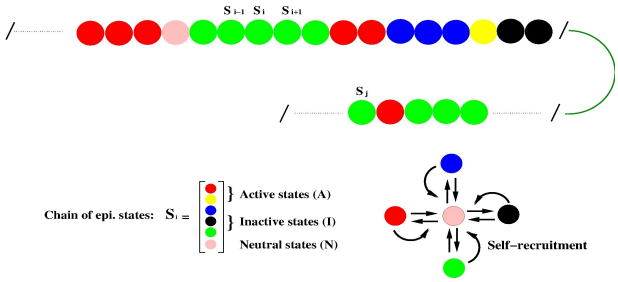
Profil recherché: Statistical Physics, Numerical simulations**,** Computational biology

Durée : (Internship) between 4 and 6 months.

Financement: (PhD thesis) Ecole Doctorale de Physique (ED-Phast)
Lieu : ENS de Lyon (CBP) ou Grenoble (TIMC-Imag)



Context:
The ability of organisms to precisely regulate gene expression is central to their development. Proper temporal and spatial expressions of genes in higher eukaryotes require activation of transcription during the appropriate developmental stages. In response to environmental and developmental cues, cells can adopt different gene expression patterns to differentiate into a variety of cell types; once established, this pattern is frequently maintained over several cell divisions despite the fact that the initiating signal is no longer present. This ability of translating transient external stimuli into diverse and stable phenotypes without alteration of the genomic sequence is at the heart of ``epigenetic'' regulation of gene expression. Transcription in eukaryotes is regulated by factors that associate with the genome at specific loci including proximal promoters, enhancers and repressors. The packaging of eukaryotic DNA into chromatin contribute to this regulation via the modulation of the accessibility and specificity of regulators to their DNA target sites. The local chromatin state is characterized by various features like the nucleosome positioning, the covalent modifications of DNA and histones tails and the binding of architectural proteins. This pattern of chromatin state along the genome, the so-called "epigenome", is itself regulated by the combined action of different specialized regulators like chromatin remodellers, modifying enzymes or histone chaperones. The epigenome is organized into domains of eu-chromatin and hetero-chromatin states that correspond to active and inactive transcription states respectively. Misregulation of these domains is a clear hallmark of many diseases such as cancer. Despite its importance, the mechanisms behind the establishment and maintenance (heritability) of the epigenome and the mechanisms by which it fulfills its function (activation/repression) remain largely to be elucidated.

Objectives:
Current models of epigenome assembly mainly consider a “spin-like” chain models where chromatin can adopt several ``internal'' epigenomic states (for example Active/Represssive/Unmarked) (1,2,3) (see Fig.). The stochastic dynamics of epigenomic state is assumed to be driven by the interplay between “noisy” conversion (leaky enzymatic activity, nucleosome turn-over, replication) and “recruited” conversion (self-recruitment by “reader/writer” enzymes or by DNA-binding proteins at a specific genomic locus). Dynamical properties are then computed via stochastic simulations to extract phase and bifurcation diagrams as a function of the model parameters (reaction rates, cell cycle length, etc...).(2,3). The general objective of the internship and thesis will be to implement and refine such models in order to make quantitative predictions of the epigenome regulation or deregulation as observed in various concrete biological systems, ranging from the heterochromatin inheritance in the yeast *S. pombe* to the DNA methylation deregulation in cancer cells. The internship will focus on the yeast system where recent experiments have confirmed and enlighten new principles for heterochromatin maintenance (4). Then PhD thesis will be dedicated to the modelling of DNA methylome deregulation in lung cancer.

References: 1. I. Dodd et al., Cell 129: 813-822 (2007) 2. D. Jost, Phys. Rev. E 89:010701 (2014) 3. M. Zerihun, C. Vaillant and D. Jost, Phys. Biol 12:026007 (2015) 4. Ragunathan et al., Science 348 (2015);N.C. Pauline et al., Science 348:132-135.