Réunion annuelle du GDR ADN&G et 4ème Rencontre scientifique des Grands Causses

lundi 27 septembre 2021 - mercredi 29 septembre 2021

Recueil des résumés

Contents

4

SPT Gaussian mixture classification to define the state of the NURD complex

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We will present our recent analysis of SPT classification and we will apply it to the NURd complex. Work in Coll with the group of E. Laue, Cambridge, UK.

5

Bacterial amyloids: a new way of nucleic acids structuring

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Hfq is a bacterial pleiotropic regulator that mediates several aspects of nucleic acids metabolism. The protein notably influences translation and turnover of RNAs. Although most previous contributions concentrated on Hfq's interaction with RNA, its association to DNA has also been observed for years. Nevertheless, although Hfq presence in the nucleoid has been reported, its precise function is still unclear. Recently, we showed that Hfq belongs to the bridging family of Nucleoid Associated Proteins (NAPs). Its bridging mechanism relies on the formation of an amyloid-like structure, mediated by the C-terminal region of the protein. Various experimental methodologies, including cellular and molecular microscopy, neutron scattering and synchrotron radiation circular dichroism, provide evidence regarding Hfq's role in DNA structuring. Results will be discussed in relation with the function of the protein in fundamental cellular processes.

6

Assessing the polymer coil-globule state from the very first spectral modes

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The determination of the coil-globule transition of a polymer is generally based on the reconstruction of scaling laws, implying the need for samples from a rather wide range of different polymer lengths N. The spectral point of view developed in this work allows for a very parsimonious description of all the aspects of the finite-size coil-globule transition on the basis of the first two Rouse (cosine) modes only, shedding new light on polymer theory. Capturing the relevant configuration path features, the proposed approach enables to determine the state of a polymer without the need of any information about the polymer length or interaction strength. Importantly, we propose an experimental implementation of our analysis that can be easily performed with modern fluorescent imaging techniques, and would allow differentiation of coil or globule conformations by simply recording the positions of three discernible loci on the polymer.

7

Curved DNA hexagonal arrays in vitro & in vivo

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DNA is a negatively charged semi-flexible polymer, which forms extended coils in water, due to the electrostatic repulsions between its negatively charged segments and its bending rigidity. However, in vivo, it is tightly packed and curved. The most extreme confinements are achieved through hexagonal arrays found in vivo in some viral capsids or spermatozoa. Curved and dense arrays also spontaneously form in vitro upon DNA condensation: in the presence of multivalent cation, basic proteins or crowding agents, long DNA molecules collapse in the form of compact toroidal globules. We use cryo electron microscopy to analyse the structure of curved DNA curved hexagonal arrays in DNA toroids and in bacteriophage capsids. In both cases, curved DNA hexagonal arrays are complex liquid crystalline objects are where topological constraints imply the presence of defects. Beyond the simple cross over due to the continuity of the chain, the reversal of the folding direction and the competition between twist induced by DNA helicity and the parallelism of the hexagonal order results in polymorphic geometries. The analysis of DNA local order with groove correlations sheds light on the interaction between highly curved helices at high density and reveals curvature-dependent inter-helix interactions.

8

Bottom-up engineering of extra artificial chromosomes reveal principles of genome folding

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Cohesin-dependent chromatin loops bring together distal regulatory elements and gene promoters in mammals and compact metaphase chromosome during budding yeast mitosis. Loop extrusion is a ubiquitous model that stipulates that SMC rings organize genomes by gradually enlarging small DNA loops into larger structures. Transcription and specific DNA-binding proteins were shown

to be involved, but current investigations are hindered by the complex nature of chromosomes that display an intertwined, multi-scale network of structures resulting from metabolic processes, protein binding, supercoiling, loops, cohesion and compaction. We developed a bottom-up approach to investigate chromosome folding using an artificial, non-coding Mb long chromosome implanted into the yeast genome. HiC experiments show that a DNA with a low GC content (20%) can compact in mitosis in the absence of positioned loops and stripes. These features appear on a chromosome that contains a 40% GC content and correlate with an enrichment at specific sites of cohesin and polymerase II, respectively. Introduction of inducible transcription units create DNA stripes that do not depend on cohesin binding nor contribute to cohesin dependent DNA loop borders.

9

Creation of a Poly-Nucleotide Reference Dataset for Circular Dichroism

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Circular dichroism is a sensitive absorption spectroscopy probing the chirality of macromolecules such as proteins, nucleic acids and sugars. Widely used by molecular biologists and biophysics in industrial and academic research, it is a proven technique for protein -folding, -thermal stability, -dynamics as well as protein-protein interactions.
In the past 16 years protein CD/SRCD spectra and associated bioinformatics and experimental meta-data have been gathered, deposited and archived in a publicly accessible database the PCDDB (BBK, UK).
For poly-nucleotides the spectral CD band is larger and more variable than for proteins.
Currently, no systematic open-access deposition site exists. Reasons for this include physically the difference of the electronic transitions excitable in the polarized ultraviolet light as well as the structural sensitivity of nucleotides to their environment (pH, salinity, temperature). Indeed, the attribution of electronic transitions within the nucleotides, pairing nucleotides to their corresponding absorption maxima and minima is far more complex compared to the well understood n-pi*and pi-pi* transitions of the peptide bond.
Based on the success of the PCDDB databank we are aiming at establishing a database for poly-nucleotide CD spectra. All entries will undergo validation and curation procedures to ensure completeness, redundancy and quality of the data included. An open-access web interface shall enable users to browse and query samples, meta-data including other biophysical assays. Ultimately spectra in graphical display and tabulation format shall be made accessible to experimentalists as well as theoreticians.
Here we will present the first steps and suggestions of how to accumulate and standardize CD spectra of nucleotides, their archiving and classification following the folding patterns of DNA and RNA macro-molecules.

10

Evolution drives interdependency in symbiosis

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Symbiosis evolution is often viewed as a progress, with emergence of new adaptive properties. However, symbiosis also enhances the interdependence between partners. I describe several such interdependences, and emphasize that they arise without emergence of new property. Generally, when two partners permanently interact, a mutation in one partner can be complemented by the other. Independency is then lost without any positive selection, in a neutral evolution. The accumulation of such steps makes the reversion to independency unlikely, and drives interdependency in symbiosis.

11

Nucleosome positioning by nucleosome inhibitory energy barriers is mediated by Alu element transposition

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Transposition potentially disrupts genomic sequence but also modifies the template for chromatin formation. If the consequences of the former have been extensively studied, the interplay between transposable elements (TEs) and chromatin structure has not been fully explored. We compared the respective localization of (i) Alu elements, a very successful primate specific TE that covers about 10% of the human genome with more than one million copies, and (ii) the ~1.9 million nucleosome inhibitory energy barriers (NIEBs) previously described along the human genome using a sequence-based elastic model of DNA bending. NIEBs are short sequences (mean 153 bp) that inhibit the nucleosome formation, with two nucleosomes well positioned at each of their borders.

Alu size and sequence allow them to wrap exactly two histone cores side by side. We found that as much as 70% of Alu are inserted at NIEB borders, in phase with the well positioned nucleosomes. This suggests an association between NIEB chromatin and Alu localisation with a powerful purifying selection of the "out-of-phase" insertions and/or a transposition mechanism favouring "in-phase" insertions. Our analysis of intraspecific insertion polymorphisms in human is in favour of the purifyingselection model. Therefore, the compatibility with the chromatin structure seems to be a key factor for Alu fixation. Moreover, our results indicate that Alu insertions likely generate NIEBs, suggesting a possible role for these TEs in the evolution of NIEBs and in turn chromatin structure at a genome scale. The evolutionary interplay of TEs and chromatin could explain the strong transposition success of Alu in human, but also of other chromatin-compatible TE families in primates and other species.

12

multiplexed imaging in Drosophila embryos reveals celltype independent chromatin organization

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DNA is organized at multiple length scales, from nucleosomes to chromosome territories. However, it is at intermediate levels of organizations that tissue-specific transcriptional regulation takes place. We will investigate this regulation during the early stages of differentiation in Drosophila embryonic development. For this, we have developed new imaging methods that rely on the use of microfluidics to perform sequential and combinatorial acquisition of tens of different species in single cells. These techniques revealed the existence of activating or repressing enhancer hubs that provide a scaffolding for the regulation of transcription during early embryogenesis.

13

Architecture du génome chez le ver à soie Bombyx mori, un modèle holocentrique

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En plus de leur rôle essentiel dans la ségrégation des chromosomes, les centromères ont un impact important sur l'organisation linéaire et spatiale des génomes. En particulier, les expérience de Hi-C chez de nombreux organismes modèles montrent que le regroupement des centromères est la caractéristique la plus frappante des contacts inter-chromosomiques et qu'ils forment un sous-compartiment spécifique à l'intérieur du noyau. De plus, les centromères forment une barrière à l'intérieur de chaque chromosome et réduisent ou même empêchent certains types de contacts entre les deux bras chromosomiques adjacents. Par conséquent, dans la plupart des expériences de capture de la conformation des chromosomes, ce sont les bras de chromosomes qui constituent les unités de base, et non les chromosomes entiers.
Dans ce tableau, peu de données ont été rapportés sur l'architecture des génomes d'espèces qui ont des centromères multiples et tout le long de chaque chromosome qui sont appelés holocentriques. Nous essayons de combler cette lacune en étudiant le ver à soie *Bombyx mori*, un insecte (lépidoptère) représentatif de cette catégorie et disposant d'un assemblage du génome de bonne qualité pour pouvoir effectuer des analyses NGS.
En commençant par une analyse génomique de base en combinaison avec des expériences ChIP-seq et Hi-C, nous montrons que le génome de Bombyx partage certaines caractéristiques avec l'autre représentant connu du mode de vie holocentrique : *Caenorhabditis elegans*. En outre, l'étude des cartes Hi-C d'embryons tardifs (post-diapauses) de *B. mori* nous a permis de décrire des caractéristiques architecturales courantes, telles que des compartiments A et B, des TAD et des boucles, mais également des régions présentant un profile de contact particulier et non décrit précédemment. Ces régions présentent des interactions à courte distance, formant une structure de type TAD assez forte, mais très peu ou pas d'interactions à plus longue distance, avec d'autres régions génomiques ou entre elles. Dans l'ensemble, l'intégration des diverses données génomiques qui sont maintenant entre nos mains nous conduira à une meilleure caractérisation et compréhension de l'architecture du génome de *B. mori*.

14

How heterogeneous organization of interphase chromosome leads to local anomalous diffusions

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Interphase chromosomes hierarchically organized into topologically-associated domains (TADs) at few kilo-basepair scales and compartments at mega-basepair scales. Recent studies suggest that the structural properties of chromosomes may alter local chromosome dynamics. Using heteropolymer model and Monte-Carlo simulations, we provide a comprehensive study of chromosome dynamics. We show that local heterogeneous dynamics emerge from TADs and compartments. Our analysis reveals that strong intra-TAD encounters lead to three-dimensional (3D) condense regions and eventually coherent motions and anomalous diffusions. We show that our model is able to qualitatively predict the heterogenous dynamics of chromosome loci inside the nucleus as well as the local anomalous diffusions, reported by live tracking single-locus experiments.

15

THE PLANT NUCLEAR PERIPHERY AS A FUNCTIONAL COMPARTMENT IN NUCLEAR ORGANIZATION.

Auteur: Christophe Tatout[1]

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Our long-standing objective is to investigate the impact of chromatin organization on the dynamic transcriptional regulation occurring during plant development or in response to environmental stimuli. To this aim, our group is using the model species Arabidopsis thaliana to study chromatin organization (i) at the level of the chromatin fiber by analyzing histone variants and high mobility group proteins and (ii) the interaction of chromatin with components of the nuclear periphery, a more spatial (3D) aspect of chromatin organization.
I will review our work on the impact of the nuclear periphery in transcriptional control. In particular, I will describe our recent findings about components of the nuclear envelope and nucleoskeleton that support the nuclear periphery as a functional compartment in nuclear organization and regulation of gene expression (1). Our investigations strongly benefited from our recent developments in 3D bio-imaging allowing the fine and automated description of nuclear morphology and chromatin organization (2). This work was performed in the frame of the INDEPTH COST Action (CA16212) (3).

1. S. Mermet et al., “Evolutionary conserved protein motifs drive attachment of the plant nucleoskeleton at nuclear pores” (2021), p. 2021.03.20.435662.
2. T. Dubos et al., Nucleus. 11, 315–329 (2020).
3. G. Parry, V. Probst Aline, C. Baroux, C. Tatout, Journal of cell science. 131 (2018).

16

What S.cerevisiae whispers about genome organization in human

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The genome of higher Eukaryotes, and in particular of humans, is organized in 2 compartments in the space of the nucleus, the euchromatin which is favorable to gene expression, and the heterochromatin which is unfavorable, also called A and B compartments.
I often hear that the organization of the genome in nuclear space is very different in the yeast S.cerevisiae from nuclear organization of the genome in a human cell, and this is indeed the case for most differentiated human cell types. This is true, but there are also fundamental aspects that are conserved such as the existence of a "heterochromatin system", dependent on the HP1a protein in humans and the SIRc complex in yeast. Thus, the SIRc complex is found at the level of constitutive heterochromatin sequences, which are constituted in yeast by telomeres, and at the level of two loci, the HM "mating-type cassettes" - and we will consider that these sequences represent the B compartment in yeast. While B compartment, driven by the HP1a dependent heterochromatin system covers 50% of the human genome, i.e. 1.5Gb for a haploid genome, B compartment in yeast covers 0.25% of the genome, i.e. 30kb, which makes it a prime model system to study precisely "how heterochromatin works".
Indeed, yeast has been instrumental in understanding some basic rules of Eukaryotic genome organization (1, 2), as I will illustrate by presenting the concept of "heterochromatin ambiance".

1. Fourel G, Lebrun E, Gilson E. 2002. Protosilencers as building blocks for heterochromatin. Bioessays 24:828-35.

2. Fourel G, Magdinier F, Gilson E. 2004. Insulator dynamics and the setting of chromatin domains. Bioessays 26:523-32.

17

What is the role of phase separation in chromatin organization?

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Chromatin is partitioned into subcompartments that differ from each other with respect to their compaction, molecular composition and biological function. One example are the micron-sized spherical heterochromatin foci that are present in several differentiated cell types. It has recently been proposed that phase separation is the driver of this type of chromatin organization. I will briefly introduce the different flavors of phase separation that might be at play, along with the strategies to detect them. I will then compare the different models to our recent experiments on DNA-based condensates in the test tube and on heterochromatin foci in living cells, and to our in silico analysis of cellular stoichiometries.

see also the two companion posters:

Cheryn ALI : What the composition of condensates teaches us about phase separation

Dominika LEWANDOWSKA : Visualizing heterochromatin formation on the single-molecule level

18

What the composition of condensates teaches us about phase separation

Auteur: Cheryn ALI[None]

19

Visualizing heterochromatin formation on the single-molecule level

Auteur: Dominika LEWANDOWSKA[None]

20

Rôle des insulateurs dans l'organisation 3D de la chromatine chez la drosophile

Auteur: Olivier MESSINA[None]