Huitième réunion annuelle du GdR Architecture et Dynamique Nucléaires (ADN)

Rapport sur les contributions

https://indico.in2p3.fr/e/18794

ID de Contribution: **27** Type: **Non spécifié**

Modeling heterochromatin reorganization during senescence

I will present our last results regarding the reorganization of heterochromatin during oncogene-induced senescence. Using polymer physics models in addition to microscopy and Hi-C data from the Cavalli's lab, we show that the formation of heterochromatic foci during senescence may be interpreted as a general screening of of HP1-mediated interactions.

Auteurs principaux: Dr JOST, Daniel; CAVALLI, Giacomo (CNRS); Dr VAILLANT, cedric; Dr SATI, Satish (IGH)

Orateur: Dr JOST, Daniel

ID de Contribution: **28** Type: **Non spécifié**

Viral transactivators shape the nucleus of human B-cells for oncogenesis

Recently we discovered a novel mechanism explaining how B-cell lymphomas might be induced in HIV-infected persons. HIV-positive subjects have an increased risk to develop specific lymphoma subtypes including Burkitt lymphoma (BL). We found that the viral transactivator of transcription (Tat) protein, which is released by infected cells into the blood stream, could remodel the B-cell nucleus bringing together the potential translocation partners, the *MYC* loci at the chromosome 8 and the *IGH* loci at the chromosome 14, thus increasing the probability of the t(8;14) translocation characteristic of BL. Tat induces the mobility of the *MYC* locus in the nucleus via induction of a double strand break in the vicinity of the *MYC* gene and its further repair by NHEJ (Germini et al., 2017, Sall et al., 2019). We shall discuss this and other mechanisms by which HIV-1 Tat and its functional homologue Zta of the Epstein-Barr virus can induce oncogenesis.

Auteurs principaux: Dr GERMINI, Diego (CNRS UMR8126); Dr SALL, Fatimata Bintou (CNRS UMR8126); Dr LIPINSKI, Marc (CNRS UMR8126); Dr VASSETZKY, Yegor (CNRS UMR8126)

Orateur: Dr VASSETZKY, Yegor (CNRS UMR8126)

ID de Contribution: **29** Type: **Non spécifié**

Nuclear Beta-Actin and Nuclear Myosin I are required for rDNA/RNAP1 repositioning within the nucleolus after rDNA repair.

During DNA Repair, ribosomal DNA and RNA polymerase I (rDNA/RNAP1) are reorganised within the nucleolus and undergo relatively long-distance movements that are normally not observed except when cells are in mitosis.

UV lesions trigger the DNA repair reaction, blocking RNAP1 transcription and displacing the rDNA/RNAP1 complex at the periphery of the nucleolus. Because most repair proteins are present outside the nucleolus, this movement is believed to be important for the repair reaction to take place properly. Only when the repair reaction is fully completed, the rDNA/RNAP1 complex returns within the nucleolus.

The proteins and the molecular mechanism governing this movement remain unknown.

Here we show that Nuclear Myosin I (NMI) and Nuclear Beta Actin (ACTβ) are essential for the proper re-entry of the rDNA/RNAP1 within the nucleolus, after completion of the DNA Repair reaction.

We found that, in NMI and ACTβ depleted cells, the rDNA/RNAP1 complex can be displaced at the periphery of the nucleolus after DNA damage induction but cannot re-enter within the nucleolus after completion of the DNA Repair reaction. In these cells, repair is proficient and rDNA transcription normally restarts after the lesions-induced blockage. Both proteins act concertedly in this process. NMI binds the rDNA that is displaced at the periphery of the nucleolus during repair reactions while ACTβ brings the rDNA back within the nucleolus after DNA repair completion.

Our results reveal a previously unidentified function for NMI and ACTβ within the nucleolus and disclose how these two proteins work in coordination to re-establish the proper rDNA position after DNA repair.

Auteurs principaux: GIGLIA-MARI, Ambra (CNRS); CERUTTI, Elena; DANIEL , Laurianne; DONNIO, Lise-Marie; MARI, Pierre-Olivier

Orateur: GIGLIA-MARI, Ambra (CNRS)

ID de Contribution: **30** Type: **Non spécifié**

Boost-HiC: computational enhancement of long-range contacts in chromosomal contact maps

Abstract
Motivation

Genome-wide chromosomal contact maps are widely used to uncover the 3D organization of genomes. They rely on collecting millions of contacting pairs of genomic loci. Contacts at short range are usually well measured in experiments, while there is a lot of missing information about long-range contacts.
Results

We propose to use the sparse information contained in raw contact maps to infer high-confidence contact counts between all pairs of loci. Our algorithmic procedure, Boost-HiC, enables the detection of Hi-C patterns such as chromosomal compartments at a resolution that would be otherwise only attainable by sequencing a hundred times deeper the experimental Hi-C library. Boost-HiC can also be used to compare contact maps at an improved resolution.
Availability and implementation

Boost-HiC is available at https://github.com/LeopoldC/Boost-HiC.

Auteurs principaux: M. CARRON, Léopold (LPTMC); Dr MORLOT, Jean-Baptiste; MATTHYS, Vincent; LESNE, Annick (CNRS); MOZZICONACCI, Julien

Orateur: M. CARRON, Léopold (LPTMC)

ID de Contribution: **31** Type: **Non spécifié**

Séparation de phase de protéines liées à l'ADN

Le confinement des espèces chimiques à l'intérieur du cytoplasme est capital pour l'organisation spatio-temporelle de l'activité cellulaire. Les cellules compartementalisent en effet l'espace cytoplasmique en utilisant soit des vésicules membranaires soit des organelles sans membranes. Pour ces dernières, les cellules peuvent utiliser la séparation de phase pour créer des régions localisées à haute densité dans lesquelles des réactions spécifiques se produisent. Ces séparations de phase biologiques nécessitent souvent des échafaudages moléculaires tels que l'ADN ou l'ARN pour lier les espèces chimiques. Nous proposons un cadre théorique général tridimensionnel pour des particules en interactions et liées à un polymère. Nous en dérivons un modèle effectif unidimensionnel de gaz sur réseau avec des interactions à courte et longue portée, ces dernières émergeant des fluctuations du polymère. Nous apportons la preuve que les séparations de phase 1D, au sens thermodynamique, peuvent exister au sein de tels systèmes et nous traçons le diagramme de phase occupation moyenne et température en utilisant une méthode variationnelle testée sur un cas exact. En illustration, nous appliquons ce modèle au cas biologique pertinent du système ParAB*S*, un important système de partition de l'ADN bactérien, pour étudier la formation des complexes ParB*S* sur l'ADN.

Auteur principal: DAVID, Gabriel (Laboratoire Charles Coulomb, Université de Montpellier)

Co-auteurs: Dr WALTER, Jean-Charles; Dr BROEDERSZ, Chase (Arnold Sommerfeld Center for Theoretical Physics and Center for Nanoscience, Ludwig-Maximilian-Universität); Dr DORIGNAC, Jérôme (Laboratoire Charles Coulomb, Université de Montpellier); Dr GENIET, Frédéric (Laboratoire Charles Coulomb, Université de Montpellier); Prof. PARMEGGIANI, Andrea (Laboratoire Charles Coulomb, Université de Montpellier); WALLISER, Nils-Ole ({UAI}0342321N); Dr PALMERI, John (Laboratoire de Montpellier, CNRS)

Orateur: DAVID, Gabriel (Laboratoire Charles Coulomb, Université de Montpellier)

ID de Contribution: **32** Type: **Non spécifié**

Chromosome structuring versus genome organisation in bacteria

I will present results about the relationship between the hierarchical structuring of bacterial chromosomes observed in HiC experiments and the 1D functional partitioning of genomes obtained from comparative genomics.

Auteur principal: M. JUNIER, Ivan (TIMC-IMAG, Grenoble)

Orateur: M. JUNIER, Ivan (TIMC-IMAG, Grenoble)

ID de Contribution: **33** Type: **Non spécifié**

From open large image datasets to scientific insights in developmental biology

Embryogenesis is the process by which a single fertilized cell is turned into a multi-cellular organism. It is a process involving coordinated dynamics at multiple scales, from single molecules, to cells, to tissues, to organs. Dynamical processes in biology are studied using an ever-increasing number of microscopy techniques, each of which brings out unique features of the system. To learn from these partial measurements we need to integrate heterogeneous data, develop pattern recognition algorithms and invent predictive theories. The techniques that we are using stem from the fields of multi-dimensional statistics, machine learning, image processing, complex systems and data visualization. We will illustrate our approaches with specific examples using datasets from studies of development in the sea urchin, drosophila, and mouse embryos and show how we can take advantage of the Open Science movement to foster interdisciplinary collaborations.

Auteur principal: VILLOUTREIX, Paul (Turing Center for Living Systems - LIS)

Orateur: VILLOUTREIX, Paul (Turing Center for Living Systems - LIS)

ID de Contribution: **34** Type: **Non spécifié**

Emergence of the spatio-temporal replication program: from 1D signals to 3D chromatin structures

In the last few years, several models of the spatio-temporal replication program in eukaryotic cells were proposed in the literature. We proposed a simpler model with natural hypothesis that reproduces the frequency of new replication origin firing per length of unreplicated DNA along the S-phase, I(t), a fundamental quantity which present a universal bell shape in eukaryotes. Our model also predicts that the maximum value of I(t) is the product of the replication propagation speed with the squared density of origins. We verified this prediction in budding yeast, fission yeast, fly, frog and human cells which have very contrasted genome sizes and replication time (20 min to 8 hours).

In higher eukaryotes, the positioning of potential origins, their numbers and width are still under debate. This model with only one free parameter is a solid basis to study how observables such as Mean Replication Timing (MRT) profiles and Okasaky Seq (OK-Seq) profiles can emerge from spatial inhomogeneous distribution of potential origin. This distribution can be drawn from experimental signals that predict origin positioning (ORC2, SNS, Bubble Seq) or signals that are not related to the replication pathway (e.g. DNase I sensitivity) but that has been show to be good descriptors for origins positioning. We will present to which accuracy low and high resolution profiles (MRT ~100kb, OK-seq ~5kb) can be reproduced starting from these signals. We will also study the coherency between MRT and OK-Seq in the framework of this model by finding if a single optimized distribution of potential origin can reproduced both observables.

Potential origins of replication have been shown to bind on DNA in a sequence independent manner, and we will show in human how 3D spatial chromatin structures compatibles with Hi-C experiment can give rise by excluded volume to accessibility profile such as DNase I sensitivity, and naturally explain the observed MRT experiments.

Auteurs principaux: ARBONA, Jean-michel (ENS-Lyon); M. GOLDAR, Arach (Ibitec-S, CEA, Gif-sur-Yvette, France.); HYRIEN, Olivier (IBENS); ARNEODO, Alain (Université de Bordeaux); AUDIT, Benjamin (Laboratoire de Physique de l'ENS de Lyon - UMR 5672 CNRS / ENS de Lyon)

Orateur: ARBONA, Jean-michel (ENS-Lyon)

ID de Contribution: **35** Type: **Non spécifié**

Probing genome organization with intra-nuclear mechanical micro-manipulation

Over the past decades, our understanding of the physical organization of the genome has improved tremendously. Developments in imaging and chromatin conformation capture have uncovered how eukaryotic chromosomes are structured at different scales (territories, compartments, TADs, loops) and how each level of organization relates to genome functions. A lot of effort is currently put on observing this organization in 4D and building physical models and concepts from observations. However, perturbation approaches to validate these concepts are often rather indirect. The lack of tools to directly exert and measure forces on nuclear and genomic structures in vivo fundamentally limits our understanding of their physical nature.

To address this gap, we are developing a novel tool to actively manipulate individual genomic loci using magnetic forces in the nucleus of living cells. It consists in targeting iron-containing nanoparticles to a genomic locus of interest and applying a controlled magnetic field. Through this approach, we are able for the first time to physically move an individual genomic locus through the nuclear space. The ability to mechanically manipulate genomic structures and observe their response in real time as they unfold offers a unique opportunity to probe their material properties at various spatial, temporal and force scales.

We will present the very first data obtained through this approach, already revealing non-trivial physical properties of chromatin, such as strongly heterogenous viscoelastic properties –reflective of different nuclear structures –and partial reversibility –as one would expect for reactive living matter. This technique opens obvious roads to probe how the physical properties of the genome at various scales relate to key genome functions, including transcription, DNA damage/repair, replication, chromosome segregation and genome integrity.

Auteurs principaux: KEIZER, Veer (Institut Curie); KOLAR-ZNIKA, Lorena (Institut Curie); BAROUX, Remi (Institut Curie); AIZEL, Koceila (Institut Curie); HOFFMANN, Sebastian (Institut Curie); FACHINETTI, Daniele (Institut Curie); DAHAN, Maxime (Institut Curie); COULON, Antoine (Institut Curie)

Orateur: COULON, Antoine (Institut Curie)

ID de Contribution: **36** Type: **Non spécifié**

Global and ancestral regulation of bacterial transcription by DNA supercoiling

DNA supercoiling acts as a global and ancestral transcriptional regulator in bacteria, that plays an important role in adapting their expression program to environmental changes, but for which no quantitative or even qualitative regulatory model is available. I will present two quantitative thermodynamic models of (1) promoter binding by the RNA Polymerase and (2) promoter opening during transcription initiation, which show how bacterial cells can globally and selectively activate subsets of their promoters by adjusting their topological level, depending on the promoter structures. This regulation mode is based on the basal interaction betweel RNA Polymerase and the promoter elements, independently of any additional transcriptional regulator, and is therefore relevant to all bacterial species. To demonstrate this ancestral role, I will show that our models are predictive of the global transcriptional response to antibiotics-induced DNA relaxation in a wide range of evolutionarily distant organisms, as well as the modifications in gene expression observed in a long-time evolution experiment with *Escherichia coli*.

Auteur principal: MEYER, Sam (MAP, INSA Lyon)

Orateur: MEYER, Sam (MAP, INSA Lyon)

ID de Contribution: **37** Type: **Non spécifié**

Molecular dynamics insights for DNA lesions in oligonucleotides and nucleosomal DNA

The identification of complex oxidatively-generated DNA lesions involving not only a single-nucleobase but two proximal nucleotides has recieved much attention over the last years since such lesions are formed with a very low occurrence (typically a few lesions per 10^9 nucleotides) but turn out to be highly mutagenic. The structural elucidation of such complex lesions is extremely challenging.

We rely on classical all-atom MD simulations to probe the structures of oligonucleotides featuring a given lesion (abasic sites or intrastrand cross-links). We can monitor the B-helix distortion and the outcome of the initial Watson-Crick pairing: whereas NMR or X-ray structures are not available, our simulation provide a rationale for sequence-dependent repair efficiencies. Another application of all-atom molecular dynamics aspect is the exploration of DNA-photosensitizers interactions.

I will also present our recent efforts towards all-atom simulations of nucleosomal harbouring DNA lesions.

Auteur principal: DUMONT, Elise (LCH, UMR 5182, ENS de Lyon)

Co-auteur: Dr BIGNON, Emmanuelle (ISA Univ Lyon 1)

Orateur: DUMONT, Elise (LCH, UMR 5182, ENS de Lyon)

ID de Contribution: **39** Type: **Non spécifié**

Studying the effects of single mutations on nucleosome positioning with deep neural network.

The MNase protocol makes it possible to experimentally study the positioning of the nucleosomes along the genome. Studying the effects of point mutations on this positioning can help us to understand how the DNA sequence encodes nucleosomes positions.
We propose to use deep neural networks to provide a tool to study the effect of single mutations at a genome wide scale . We trained a deep neural network to predict the nucleosome landscape in S.cerevisiae from the underlying DNA sequence. Being able to faithfully reproduce experimental results the neural network acts like the S.cerevisiae nucleosome positioning machinery. With this tool in hand, we can test the effect of the mutation of every single nucleotide in the genome. This allows us to detect nucleotides and sequence motives that are the most important for nucleosomes positioning.

Auteurs principaux: ROUTHIER, Etienne (LPTMC Sorbonne Université); MOZZICONACCI, Julien

Orateur: ROUTHIER, Etienne (LPTMC Sorbonne Université)

ID de Contribution: **40** Type: **Non spécifié**

Highly rearranged chromosomes reveal uncoupling between genome topology and gene expression

Chromatin topology is intricately linked to gene expression, yet its functional requirement remains unclear. We comprehensively assessed the interplay between genome topology and gene expression using highly rearranged chromosomes (balancers) spanning ~75% of the Drosophila genome. Using transheterozyte (balancer/wild-type) embryos, we measured allele-specific changes in genome topology and gene expression in cis, whilst minimizing trans effects. Through genome sequencing, we resolved eight large nested inversions, smaller inversions, duplications, and thousands of deletions. These extensive rearrangements caused many changes to chromatin topology at the level of long-range loops, TADs and promoter interactions, yet these are not predictive of changes in expression. Gene expression is generally not altered around inversion breakpoints, indicating that mis-appropriate enhancer-promoter activation is a rare event. Similarly, shuffling or fusing TADs, changing intra-TAD connections and disrupting long-range inter-TAD loops, does not alter expression for the majority of genes. Our results suggest that properties in addition to genome topology ensure productive enhancer-promoter interactions.

Auteurs principaux: GHAVI-HELM, Yad (CNRS); ALEKSANDER JANKOWSKI, SASCHA MEIERS, REBECCA VIALES, JAN KORBEL AND EILEEN FURLONG

Orateur: GHAVI-HELM, Yad (CNRS)

ID de Contribution: **42** Type: **Non spécifié**

CTCF binding controls the expression of imprinted Dlk1-Dio3 and Igf2-H19 loci by structuring allele-specific sub-domains

Mammalian genome are organized into structural units known as Topological Associating Domains (TADs), with CTCF protein being enriched at their borders. Mammalian genomic imprinting provides a unique paradigm to explore intra-cellular differences in chromatin 3D-structuration.
In this presentation, I will focus on the two conserved paternally-imprinted domains in mammals, the Igf2-H19 and Dlk1-Dio3 domains. Both contain allele-specific CTCF binding sites at or near differentially methylated regions (DMRs) essential for correct imprinting.
Although Igf2-H19 and Dlk1-Dio3 domains are embedded into TADs with similar borders on the two parental chromosomes, the internal sub-TAD organization is pronouncedly different between the parental chromosomes. On both loci, the allele-specific binding of CTCF can hijack existing sub-TAD organization to constrain regulatory elements. Importantly, on the Dlk1-Dio3 locus, the formation of allelic distinct 3D-organization is functionally important to prevent the activation of the paternally-expressed Dlk1 gene from the maternal chromosome. Our results thus highlight the importance of allele-specific 3D-orgnization to ensure correct mono-allelic expression at paternally imprinted domains.

Auteur principal: MOINDROT, Benoît (I2BC / Université Paris-Sud)

Orateur: MOINDROT, Benoît (I2BC / Université Paris-Sud)