ÉCOLE NORMALE SUPÉRIEURE DE LYON

Master 1&2 Internship offer

Date of the offer: January-June 2025

Internship supervisor and Host laboratory:

Lab: Genome Mechanics

Team leader: Aurèle Piazza, CR CNRS

Contact e-mail: aurele.piazza@ens-lyon.fr

Address of the internship: ENS de Lyon, LBMC, 46, allée d'Italie 69007 Lyon

Team Website : http://www.ens-lyon.fr/LBMC/equipes/mecanique-du-genome/

Languages spoken in the lab: French and English

Previous ENS student: Vinciane Piveteau (now doing her PhD in the lab)

A mechanical basis for homolog pairing in meiosis

Keywords: Meiosis, DNA repair, Homologous recombination, 3D genome

Project description:

Meiosis is the specialized cell division at the basis of sexual reproduction. It involves the formation of hundreds of DNA double-strand breaks whose repair by homologous recombination drives recognition, pairing, and physical attachment via **crossover** (CO) of the parental homologs for their proper segregation at the first meiotic division. Three outstanding phenomena underlie this recombination-driven pairing process (see **Figure 1**):

Homolog bias: how does the repair occurs preferentially on the homologous chromosome rather than the nearby sister chromatid, such as in mitosis?

Obligatory CO: how at least one, and rarely more than one CO is formed per pair of homolog?

CO interference: how does the local CO designation decision can inhibit formation of subsequent COs at a distance of several dozens to hundreds of kilobases?

The mechanism(s) underlying these three phenomena remains unknown decades after their identification. We know it involves chromosome structure, organized as arrays of chromatin loops anchored on a semi-rigid protein axis, but how this cytological-scale organization mediates or provides input for the molecular-scale recombination process remains unknown.

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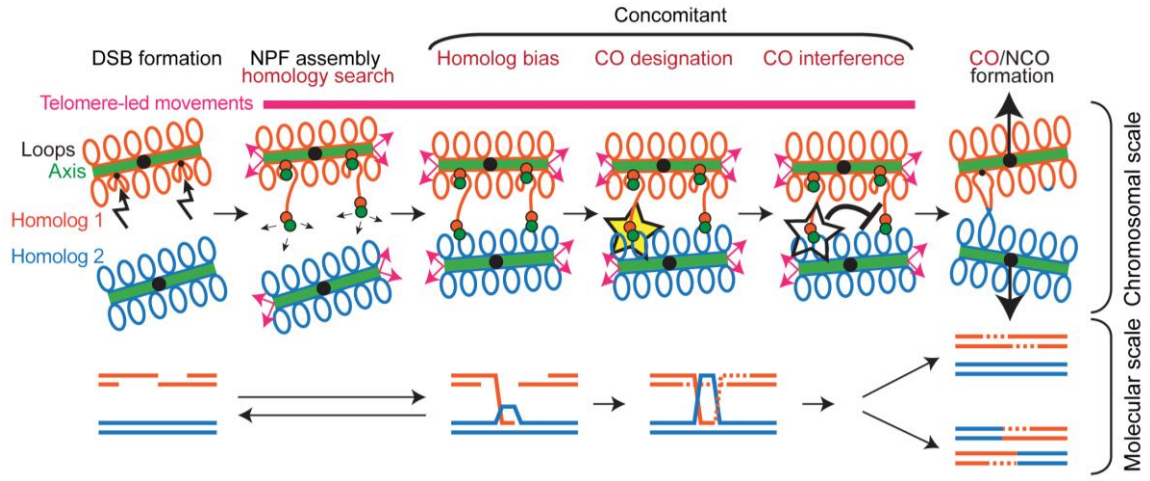

Figure 1: Overview of the molecular and chromosomal events of meiosis.

The student will be in a unique, and immediately productive position to tackle these great questions of the field, as all the upfront work to develop techniques and build ambitious experimental systems has been completed: novel physical assays to track early recombination intermediates have recently been developed by the team leader (refs. 1, 2, 3 and 5), and the assembly of two redesigned chromosomal region of 150-kb (SynIV) dedicated to the study of meiosis with these assays and Hi-C has been completed (first version in ref. 4). The approach will consist in simultaneously tracking (i) the genome-wide structuration of chromatin, (ii) the pairing of homologs, and (iii) the progression of the HR reaction at the level of 22 recombination hotspots in the redesigned region during synchronous meiosis in *S. cerevisiae* for which the chromosome structure and dynamics have been altered (**Figure 2**).

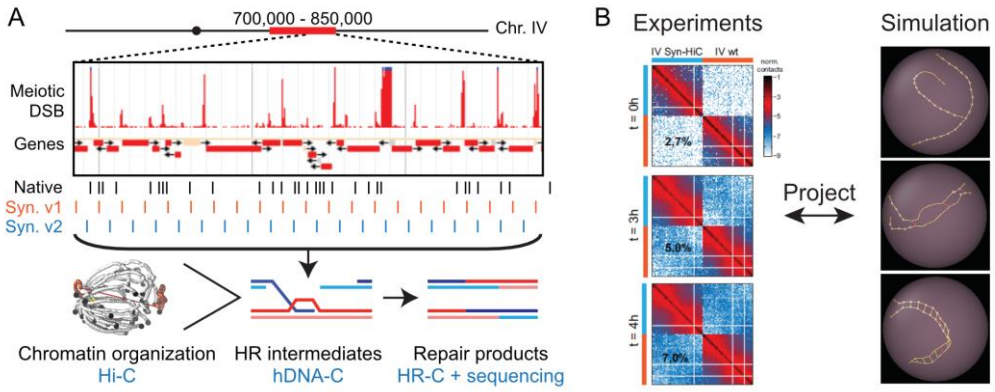

Figure 2: Experimental system to study the chromosomal and molecular events of meiosis. (A) *Redesigned region on chr. IV containing 22 meiotic hotspots.* ***(B)*** *Detection of individual homolog's structure and pairing in meiosis, obtained with the first version of the system (ref. 4). (**C**) Polymer model of meiotic chromosomes developed by a biophysicist in the lab. The project will allow comparing data and simulation to extract physical parameters dictating homologs' pairing.*

Supervision: The student will be supervised by Vinciane Piveteau (PhD ENS, 2rd year) and Aurèle Piazza. The work will be tightly coupled with the output of polymer models developed by Nicolas Mendiboure (PhD CNRS, 2rd year)

Techniques the candidate will learn: HiC experiment + data analysis, capture-C, physical assays for high-throughput DNA joint molecules quantification, synthetic biology approaches in yeast.

Research fields the candidate will gain expertise in: DNA repair, spatial genome organization, meiosis

Lab publications related to the subject:

1. Dumont A, Mendiboure N, Savocco J, Anani L, Moreau P, Thierry A, Modolo L, Jost D, Piazza A (2023) **Mechanism of homology search expansion during recombinational DNA break repair**, **bioRxiv** (Mol. Cell, in revision)
2. Reitz D, Djeghmoum Y, Watson AR, Rajput P, Argueso JL, Heyer WD, Piazza A, (2023) **Delineation of two multi-invasion-induced rearrangement pathways that differently affect genome stability**, **Genes and Development** doi: 10.1101/gad.350618.123.
3. Piazza, A, Shah, SS, Wright, WD, Gore, SK, Koszul, R, and Heyer, W (2019). **Dynamic processing of displacement loops during recombinational DNA repair** **Molecular cell**, 73(6):1255–1266.
4. Muller, H, Scolari, VF, Agier, N, Piazza, A, Thierry, A, Mercy, G, Descorps-Declere, S, Lazar-Stefanita, L, Espéli, O, Llorente, B, and others (2018). **Characterizing meiotic chromosomes' structure and pairing using a designer sequence optimized for Hi-C** **Molecular systems biology**, 14(7).
5. Piazza, A, Wright, WD, and Heyer, W (2017). **Multi-invasions are recombination byproducts that induce chromosomal rearrangements** **Cell**, 170(4):760–773.