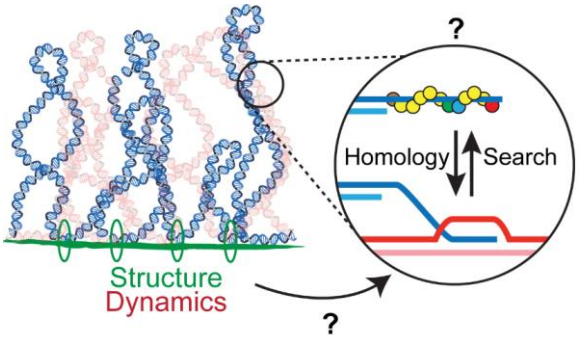
ÉCOLE NORMALE SUPÉRIEURE DE LYON

Master 1 or 2 internship offer (3-6 months)



Simulating meiotic chromosomes structure and dynamics: a role for mechano-sensing in meiotic recombination?

Internship supervisor and Host laboratory:

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Keywords:

Spatial genome organization, Polymer modeling, DNA repair, Meiosis

Project description:

Meiosis is the specialized cell division at the basis of sexual reproduction. It involves the formation of hundreds of DNA double-strand break (DSBs) in the genome, whose repair by homologous recombination (HR) drives recognition, pairing, and physical attachment via crossover (CO) of the parental homologs for their proper segregation at the first meiotic division. The repair partner choice (*i.e.* homologous chromosome rather than the sister chromatid) and decision to resolve the repair intermediate as a crossover are subjected to meiosis-specific regulations whose nature remain enigmatic (see **Figure 1**). 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 DSB repair process remains unknown. We suspect it involves the dynamic telomere-led chromosome movements for which no clear role has been identified. These movements, transduced through the chromosome axis, are expected to exert mechanical challenges at inter-chromosomal contact points mediated by HR proteins. This mechanical challenge may thus signal the nature of the template (homolog vs. sister) and directs the faith of the repair towards crossover designation**.** Our lab aims at addressing this possibility, and crack these long-lasting conundrums if the meiosis and recombination fields.

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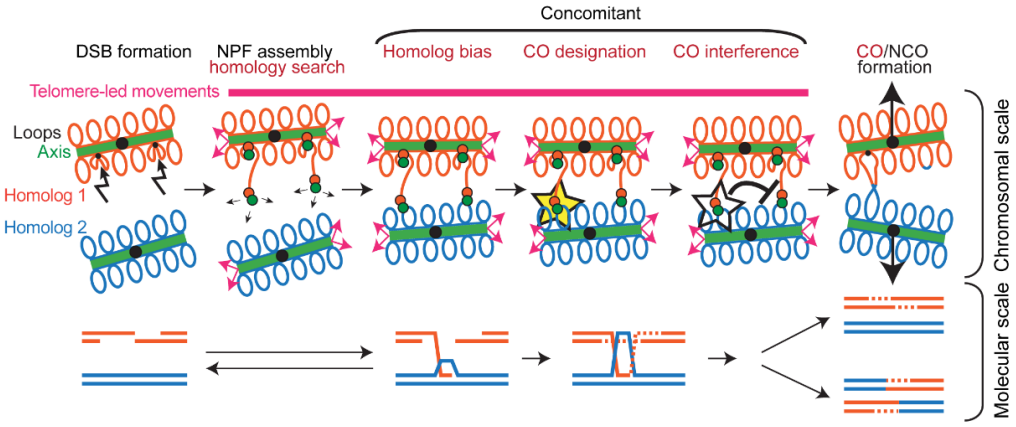

***Figure 1**: Overview of the molecular and chromosomal events of meiosis.*

The goal of the student's internship will be to build upon a rudimentary polymer model of meiotic chromosomes developed in the laboratory. She/He will then use this model to explore a range of parameters (chromosome length, rigidity, movement bursts and speed, etc) on first passage time and forces exerted between chromosomes. These results will in turn lead to predictions that will be tested experimentally by yeast geneticists in the laboratory thanks to an ambitious experimental system we recently developed in *S. cerevisiae*: a redesigned chromosomal region of 150-kb (SynIV) dedicated to the study of meiosis by Hi-C at high resolution (first version see Muller et al., MSB 2018). The student will have first-hand access to these data, to determine the influence of chromatin structure on chromosome pairing, homolog bias, CO designation and interference.

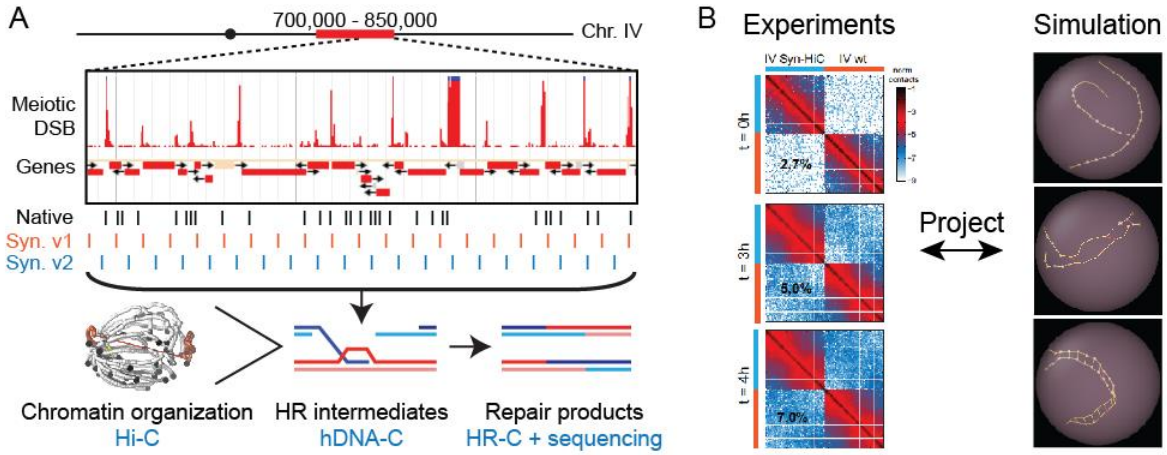

***Figure 2: Project**. **A**) Experimental system to study the chromosomal and molecular events of meiosis over a redesigned region of 150 kb on budding yeast chromosome IV. Restriction sites have been evenly repositioned over the SynIV regions to enable discriminating the two parental homologs at high resolution. See Muller et al. for more details. **B**) The project aims at confronting experimental data and simulation outputs.*

Supervision: The student will be supervised by myself, Nicolas Mendiboure (bioinformatician) and Jean-Michel Arbona (biophysicist in the Jost team).

Methodologies: Polymer modelling and Hi-C analysis.

Mission:

- Development of a polymer model of yeast chromosomes during meiosis
- Analysis of Hi-C contact data.

Candidate profile:

- Expertise in UNIX, Python and/or R languages.
- Knowledge in polymer physics/modelling.
- Experience with high-throughput sequencing data.
- Notions in basic molecular genetics (DNA replication, repair, chromosome organization…)
- Good organization and presentation skills, autonomy, curiosity, enthusiasm towards science.

Internship gratification will be allocated.

Lab publications related to the research project (available here):

Piazza, A*, Bordelet H, Dumont A, Thierry A, Savocco J, Girard F, Koszul R* "*Cohesin regulates homology search during recombinational DNA repair*" **Nature Cell Biology 2021** Nov;23(11):1176-1186. *co-corresponding

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**, **2019** 73(6):1255–1266.

Muller H*, Scolari V*, Agier N, Piazza A, Lazar-Stefanita L, Mercy G, Descorps-Declere S, Espeli O, Llorente B, Fischer G, Mozziconacci J, Koszul R, "*Characterizing meiotic chromosomes structure and pairing using optimized Hi-C designer chromosome*", **Molecular Systems Biology, 2018** Jul 16;14, e8293.

Piazza, A, Wright, WD, and Heyer, W. "*Multi-invasions are recombination byproducts that induce chromosomal rearrangements*" **Cell**, **2017** 170(4):760–773.