« INTERNSHIP AND THESIS PROPOSAL »

Laboratory: *Quantitative Genetics and Evolution*
Address: Chemin du Moulon, Gif-sur-Yvette, 91190
Lab head: Olivier MARTIN
Research team: Recombination of Alleles in Meiosis: Determinism, Applications, Modeling
Team head: Olivier MARTIN
Internship head: Olivier MARTIN
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Doctoral School of the host: Structure and Dynamics of Living Systems (ED 577)
Preferred background: Solid training in statistical physics and computation, interest in interdisciplinary applications
**Possibility of continuing with a thesis:** Yes
If yes, fundings considered: Funding from Labex, IDEX or private sector

Title of the internship: *Messaging between crossovers in meiosis:*
model construction and inference algorithms to solve a century-old challenge

Summary: Meiosis is at the heart of the dynamics that drive evolution and adapation of all sexual organisms. Indeed, at each generation of sexual reproduction, meiotic crossovers shuffle the parental genomes, leading to new allelic combinations genome-wide. Furthermore this shuffling is key to all breeding programs which seek to produce « improved » varieties of plants or animals, justifying why there is currently much interest in understanding what limits the number of crossovers during meiosis (McDonald et al.). Two features of meiotic crossovers are particularly striking: (i) for each meiosis, almost all species have between 1 and 3 crossovers per pair of homologous chromosomes, even though the length of the chromosomes vary by 4 orders of magnitude across different species; (ii) there is a messaging system along chromosomes which leads to a mutual inhibition between crossovers, a phenomenon coined « crossover interference ». Crossover interference was first discovered in 1915 but the nature of the associated messages remains a mystery to this day. Such messages are able to propagate out to the ends of the considered chromosomes and most plausibly are the causal limitation to the number of crossovers. We now know that the interference signal can be hampered in various ways. Some of these perturbations lead to a large *increase* in the number of crossovers as we have recently shown (Pélé et al. 2017), opening very promising perspectives both for evolutionary biology and for applied breeding, explaining why even the private sector is keeping an eye on these developments.

To date, only naïve models have been proposed for modeling interference (Kleckner et al. 2004 and Kim and Mortimer 1990): one assumes a mechanical (stress-based) messaging and the other assumes a chemical messaging system:

Mechanical messaging (Kleckner et al.)   *Chemical messaging (Kim and Mortimer)*
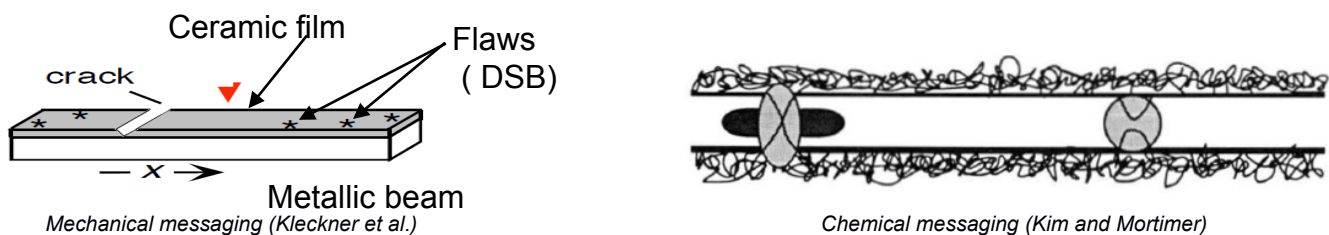
These models are inadequate because (1) they do not provide a way to have a heterogeneous density of crossovers and (2) the interference signal propagates identically through the different chromosomal regions, be-they euchromatin or heterochromatin (the two characteristic compaction levels of DNA).

The goal of the present research project is to overcome the bad aspects of the two models above by working instead with a framework based on so called « Stationary Renewal Processes ». Mathematically, the challenge is to extend that rather elegant framework to allow heterogeneous environments. This extension can be done using the tools of statistical physics and leads to a new and improved model in which both the density of crossovers (particles on a segment) and their interference (mutual inhibition law) are heterogeneous in space. To study this more complex model, we will work with its partition function Z. The computation of Z relies on extensions of the transfer matrix and on efficient algorithms for dealing with the long range interactions between the crossovers. Given these tools, it is then possible to generate an inference algorithm that can take experimental data and infer the way the interference signal propagates along chromosomes. Although the planned inference approach is based on alternating between maximum likelihood and root finding, the intern may provide other ways for extracting the most information from the experimental data sets while taking into account computational complexity. Once the methodological tools are finalized, the intern will apply them to analyse a state of the art data set of crossovers we have previously published. This proposed work should then provide the first quantitative evidence that interference is heterogeneously propaged along chromosomes. In particular we anticipate that the methods will show that there are differential propagation laws for interference near telomeres and within the heterochromatic pericentromeric regions typical of many crop genomes.

Références
- McDonald et al., (2016). Sex speeds adaptation by altering the dynamics of molecular evolution. Nature 531:233.
- Pélé et al., (2017). Amplifying recombination genome-wide and reshaping crossover landscapes in Brassicas, PLOS Genetics, 13(5): e1006794. See also the press coverage of that work:
        http://presse.inra.fr/Communiques-de-presse/Coup-de-booster-pour-la-recombinaison-meiotique
- Kleckner et al., (2004). A mechanical basis for chromosome function. PNAS 101 (34) 12592.
- King and Mortimer, (1990). A polymerization model of chiasma interference and corresponding computer simulation. Genetics 126 (4) 1127.