Dissecting the kinetics of long-distance enhancer-promoter interactions

Keywords: quantitative biology; live imaging; transcription; stem cells; embyros

Presentation of the laboratory and its research topics:
The Unit for the Physics of Biological Function at Institut Pasteur studies the basic physical principles that govern the existence of multicellular life. A core focus of the lab is to understand biological development–the complex process through which an organism grows from a single cell into a differentiated, multicellular organism–from a physics perspective. As such, we formulate and experimentally validate quantitative models that describe how individual cells interact and organize in order to generate complex life forms.
Our main interests lie in:

- multicellular pattern formation
- transcriptional regulation in the context of development
- molecular limits to biochemical sensing
- emergence of collective behaviors in multicellular systems.

Description of the project:
The dynamic organization of the genome in time and space plays a crucial role in the functional specification of a cell. In particular the interplay between multiple distant enhancers and their target gene promoters has critical mechanistic consequences on gene activity patterns during cell differentiation and development.

The goal of the current project is to shine light (literally!) on these processes and to visualize for the first time in living cells the interaction between an enhancer and its target promoter and how that interaction influences transcription kinetics. The PhD candidate will learn and develop microscopy and imaging modalities that allow us to reach this goal and will subsequently probe the functional consequences of different enhancer-promoter kinetics.

The core technical hurdles of this project have recently been pioneered by my laboratory: quantitative imaging of transcriptional activity, super-resolution imaging of multiple individual DNA foci, simultaneous imaging of 4 multi-colored foci, and all in real time in living embryos (see references below). The first task of the current project is to put these techniques together to visualize how actual enhancer-promoter looping results in productive transcription activity.

References:

- Chen *et al*. (2016). *Direct visualization of transcriptional activation by physical enhancer-promoter proximity.* bioRxiv 099523; doi: https://doi.org/10.1101/099523
- Gregor T, Garcia HG, Little SC (2014). *The embryo as a laboratory: quantifying transcription in Drosophila.* Trends in Genetics 30 (8): 364–375.
- Garcia HG, Tikhonov M, Lin A, Gregor T (2013). *Quantitative imaging of transcription in living Drosophila embryos links polymerase activity to patterning*. Current Biology 23 (21): 2140–2145.

Expected profile of the candidate:
The ideal candidate has a strong interest for collaborative and interdisciplinary research and to bridge quantitative and live sciences. A background in mathematics, computer science and/or the physical sciences is a plus. Prior training in biology is not necessary but encouraged.

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