**PhD PROPOSAL FOR THE**

**PASTEUR - PARIS UNIVERSITY INTERNATIONAL DOCTORAL PROGRAM**

Time for applicants to contact host laboratories: September 13 – November 2, 2017

Deadline for full application: November 13, 2017

Interviews: January 30, February 2, 2018

Start of the Ph.D.: October 1, 2018

**Title of the PhD project:** Super-resolution imaging and computational modeling of dynamic chromosome architecture

**Keywords:** Chromatin, polymers, simulations, super-resolution microscopy, nuclear architecture, DNA damage, gene expression

**Department:** Cell biology and infections

**Name of the lab:** Imaging and Modeling Unit

**Head of the lab:** Christophe Zimmer

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<https://research.pasteur.fr/en/team/imaging-and-modeling/>

***Doctoral school affiliation and University*:** Complexité du Vivant, Frontiers in Life Sciences

**Presentation of the laboratory and its research topics:**

The Imaging and Modeling Unit is an interdisciplinary team comprising experts in physics, optics, computer science, cell biology and microbiology. Our lab builds quantitative descriptions and models of chromosome architecture, and develops high-resolution and high throughput imaging approaches. Achievements of the lab include: (i) development of a computational imaging method to map nuclear gene territories in yeast, (ii) identification of determinants of chromosome positions, (iii) predictive modeling of dynamic chromosome organization, (iv) establishment of a non-invasive super-resolution imaging method, (v) development of a software to count individual mRNA in single cells, (vi) co-development of a new genome assembly method, (vii) characterization of mechanical chromatin properties in yeast, and (viii) investigation of how chromatin is altered during DNA damage. Current work focuses on the dynamic 3D architecture of chromosomes and its implications for cellular function, and on developing improved single molecule super-resolution imaging methods.

Description of the project:

The 3D architecture of chromosomes and its dynamics impacts all fundamental functions of the genome, from the regulation of gene expression to the preservation of genome integrity, but is not characterized and understood in detail (Cavalli & Misteli, 2013). Although genome-wide chromosome conformation capture provides very rich data about population-averaged nuclear architecture features, it cannot provide direct views of chromosome structure in single cells and is restricted to fixed cells. Our laboratory develops experimental and computational imaging and modeling approaches to study the biophysical principles that underlay chromosome organization and some of its functional implications. Over the years, we have developed imaging based techniques to describe chromatin locus territories in yeast, and polymer simulations to predict chromosome configurations and movements in silico (Berger *et al*, 2008; Thérizols *et al*, 2010; Wong *et al*, 2012; Arbona *et al*, 2017). We also develop super-resolution microscopy methods based on single molecule localization that achieve ~20-30 nm lateral resolution (Henriques *et al*, 2010; Lelek *et al*, 2012) and that we have recently extended to 3D imaging of entire cells, to high throughput imaging of hundreds of cells, and to live cell imaging (Ouyang *et al*, 2017).

The proposed project aims to leverage our super-resolution imaging techniques in combination with several fluorescent labeling approaches to image chromosomes at high resolution, with sufficient detail to allow computational tracing the chromosomal fiber in 3D throughout the nucleus, and to study how chromosomes change their folding properties and dynamics upon transcriptional activation or induced DNA double strand breaks. This project will build on recent experimental and computational work from our lab (in collaboration with E. Fabre) about the average properties of chromatin in yeast and how chromatin fiber properties are modified by DNA damage (Arbona et al. 2017, Herbert et al. 2017). It will also benefit from an ongoing (unpublished) study of chromatin fiber structure in human cells and on our experience with expansion microscopy, a powerful new super-resolution imaging technique based on inflation of the sample. The project will consist first in visualizing single chromosomes in isolation (but in situ), then all chromosomes together, at 3D resolutions well below 50 nm. For this purpose, we will make use of complementary sequence-specific and unspecific fluorescent labeling techniques currently employed in the lab. This will allow direct comparison with our polymer simulations and enable iterative improvements of the computational model. We will then test experimentally induced alterations of nuclear architecture, by induction of DNA damage and gene expression. Furthermore, we will aim to extend the imaging approach to live cells. If successful, this project could provide the first direct high resolution views of chromosome architecture and dynamics in single cells and will shed new light on how this architecture affects or is affected by gene expression and DNA damage.

References

Arbona J-M, Herbert S, Fabre E & Zimmer C (2017) Inferring the physical properties of yeast chromatin through Bayesian analysis of whole nucleus simulations. *Genome Biol.* **18:** 81 Available at: http://genomebiology.biomedcentral.com/articles/10.1186/s13059-017-1199-x [Accessed May 3, 2017]

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Cavalli G & Misteli T (2013) Functional implications of genome topology. *Nat. Struct. Mol. Biol.* **20:** 290–299 Available at: http://dx.doi.org/10.1038/nsmb.2474 [Accessed March 5, 2013]

Henriques R, Lelek M, Fornasiero EF, Valtorta F, Zimmer C & Mhlanga MM (2010) QuickPALM: 3D real-time photoactivation nanoscopy image processing in ImageJ. *Nat. Methods* **7:** 339–340

Lelek M, Di Nunzio F, Henriques R, Charneau P, Arhel N & Zimmer C (2012) Superresolution imaging of HIV in infected cells with FlAsH-PALM. *Proc. Natl. Acad. Sci. U. S. A.* **109:**

Ouyang W, Aristov A, Lelek M, Hao X & Zimmer C (2017) ANNA-PALM : Accelerating localization microscopy with deep learning. *submitted*

Thérizols P, Duong T, Dujon B, Zimmer C & Fabre E (2010) Chromosome arm length and nuclear constraints determine the dynamic relationship of yeast subtelomeres. *Proc. Natl. Acad. Sci.* **107:** 2025

Wong H, Marie-Nelly H, Herbert S, Carrivain P, Blanc H, Koszul R, Fabre E & Zimmer C (2012) A Predictive Computational Model of the Dynamic 3D Interphase Yeast Nucleus. *Curr. Biol.* **22:** 1881–90 Available at: http://www.ncbi.nlm.nih.gov/pubmed/22940469 [Accessed October 29, 2012]

Expected profile of the candidate (optional):

We are open to candidates from various backgrounds, including but not limited to cell and molecular biology, physics, and computer science. We expect high dedication, autonomy and ability to work in a strongly interdisciplinary environment.

Contact:

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