2016-08

IC-**3i** International PhD Program

PhD thesis project

2017 Call for application

Spatio-temporal coordination between co-regulated genes observed by single-molecule imaging of transcription in 4D

General information

Call	2017
Reference	2016-08-COULON
Keyword(s)	genome organization, transcriptional regulation, nuclear dynamics, single-molecule microscopy, computational modeling

Director(s) and team

Thesis director(s)	Antoine Coulon
Research team	Genome Functions in Space and Time
Research department	UMR3664 – Nuclear Dynamics & UMR 168 - Physical Chemistry

Description of the PhD thesis project

The eukaryotic genome is highly organized in both space and sequence. Preferred positions in the nucleus are observed from whole chromosomes to single loci, in close link with gene expression. Yet this complex organization and its functional roles for transcriptional coordination are poorly understood, mainly due to a lack of appropriate tools. Indeed, most experimental techniques used in this field give an incomplete picture – fixed-cell microscopy (FISH), population-levels assays (Hi-C)... A true understanding of these processes in 4D is still missing.

Our lab combines cutting-edge microscopy and computational approaches to study the two-way relationship between the dynamic organization of the genome in the nuclear space and the coordinated regulation of its expression. This approach relies on our 3 areas of expertise: (i) single-molecule microscopy techniques for real-time imaging of transcription in 4D (MS2/PP7 RNA imaging), (ii) signal-theory data analysis tools to interpret spatio-temporal data and (iii) physical/mathematical modeling of stochastic nuclear processes.

How does genome folding shape the concerted regulation of genes? How does the sharing of a pool of factors/enzymes between genes contribute to their co-regulation? How do enhancers interact with individual genes in a single nucleus and coordinate transcription domain-wide? To address these timely questions, the student will visualize and interpret the transcriptional coordination between pairs of individual genes. Depending on the student's background (biology, physics, comp. sci.), the project can focus towards either a genome-level picture with high-throughput imaging, or an in-depth understanding of specific loci in breast cancer cells (endogenous labeling by CRISPR/Cas9). Visualizing genes and modeling their spatio-temporal coupling, the student will investigate how nuclear compartmentalization, resource limitation and/or enhancer-gene communication underlies coordinated gene regulation.

International, interdisciplinary & intersectoral aspects of the project

This interdisciplinary project is based on a unique combination of state-of the-art microscopy, data analysis and modeling approaches. Our lab develops tools for high-throughput live-cell single-molecule microscopy, which will get the student privileged contacts with hardware companies (eg. testing of equipment before commercial release). Skills in automated microscopy and image analysis are also in high demand from pharmaceutical companies. This will place the student at a prime place on the industry job market. The student will benefit from our lab's network of world-class collaborators. Depending on the project's needs and the student's background, she/he may be sent to labs abroad, in institutions including the NIH (Washington DC area), the NKI (Amsterdam) or the MIT (Cambridge).

Recent publications

1. **Coulon A***, Ferguson ML*, de Turris V, Palangat M, Chow CC & Larson DR.
Kinetic competition during the transcription cycle results in stochastic RNA processing.
Elife. 2014 Oct 1;3. doi: 10.7554/eLife.03939.

2. Lenstra T, **Coulon A**, Chow CC & Larson DR.
Single-molecule imaging reveals a switch between spurious and functional ncRNA transcription.
Mol Cell. 2015 Nov 19;60(4):597-610. doi: 10.1016/j.molcel.2015.09.028.

3. **Coulon A**, Chow CC, Singer RH & Larson DR.
Eukaryotic transcriptional dynamics: from single molecules to cell populations.
Nat Rev Genet. 2013 Aug;14(8):572-84. doi: 10.1038/nrg3484.

4. **Coulon A** & Larson DR.
Fluctuation Analysis: Dissecting Transcriptional Kinetics with Signal Theory.
Methods Enzymol. 2016;572:159-91. doi: 10.1016/bs.mie.2016.03.017..

5. Stavreva DA*, **Coulon A***, Sung MH, John S, Baek S, Stixova L, Tesikova M, Hakim O, Miranda T, Hawkins M, Stamatoyannopoulos JA, Chow CC & Hager GL.
Dynamics of chromatin accessibility and long-range interactions in response to glucocorticoid pulsing.
Genome Res. 2015 Jun;25(6):845-57. doi: 10.1101/gr.184168.114.

Expected profile of the candidate

We are looking for highly talented students with a strong motivation for interdisciplinary research and a high capacity for independent and creative thinking. We will consider candidates from various backgrounds, with a preference for those combining experience in cell/molecular biology with one or more of the following fields: live-cell microscopy, theoretical biophysics (e.g. soft-matter, polymer), computer science and applied mathematics (stochastic modeling/simulation). The selected candidate, regardless of her/his main background, will be trained in every aspect of the project.