EuReCa International PhD Program

PhD thesis project

2023 Call for application

Polymer modeling of local chromosome dynamics upon gene induction

General information

Call	2023
Reference	2023-03-COULON_SCOLARI
Keyword(s)	nuclear organization, chromosome conformation, soft-matter, modelling, data analysis

Director(s) and team

Thesis director(s)	Antoine Coulon & Vittore Scolari
Research team	Genome Functions in Space and Time
Research departments	UMR3664 – Nuclear Dynamics / UMR168 - Physical Chemistry Curie

Description of the PhD thesis project

All genomic processes involving energy-dependent molecular machines potentially keep chromosomes away from equilibrated conformations. Using polymer simulations and analytical models based on first principles, this PhD project aims to understand the role of non-equilibrium dynamics in chromosome conformation and its implications for gene regulation.
First, the student will develop new models to understand the process of loop-extrusion by cohesin –a molecular motor involved in local chromatin folding– with the objective to separate explicitly the energy-dependent process from the passive/thermal fluctuations and to make testable predictions on patterns of genome folding and gene induction kinetics.
Second, the student will incorporate an additional layer of constraints on chromosome conformation by modelling the formation of phases of the ERα transcription factor upon exposure of mammary cells to the hormone estrogen.
Predictions made by the student will be tested against experimental data –both public data and data produced in the host lab– in order to detect and characterize biological processes keeping chromosomes out of equilibrium. Although mainly a theory/computational PhD project, the student will have the opportunity to produce some simple experimental data to test her/his theory.

Objectives
Using theory and simulations, this PhD project aim to understand the role of non-equilibrium dynamics — namely of loop extrusion and ERα mediated polymer collapse— in organizing the genome in space and in regulating gene expression.

The specific objectives are:

Part 1: Loop extrusion and conformational memory of chromosomes

i. Model non-equilibrium loop extrusion by combining analytical polymer theory results with lattice-based simulations of cohesin dynamics
ii. Predict Hi-C contact maps and 3D oligopaint/FISH data from CTCF binding sites and ChIP-seq data
iii. Predict gene induction kinetics from local architecture of genomic elements. Test and compare mechanistic models.
iv. Make a user-friendly implementation of 'ii.' as a tool for the community.

Part 2: Local chromosome dynamics during ERα-mediated gene induction

i. Develop analytical theory for monomer-monomer first-passage encounter from non-equilibrated polymer
ii. Implement event-based simulation of reversible polymer collapse in the context of loop extrusion and ERα foci formation
iii. Make predictions on (a.) ERα dynamics and chromosome mobility, and (b.) on gene co-regulation upon estrogen stimulation.
iv. Generate data on ERα dynamics or chromosome mobility using the techniques already in place in the lab (experimental)
v. Extend analytical approach to include force generation by ERα/FOXA1 condensates.

International, interdisciplinary & intersectoral aspects of the project

International

Objective 2.i will be done in collaboration with Marco Cosentino Lagomarsino, who is a Professor in Theoretical Physics at the University of Milan and group leader in Biophysics at the IFOM in Milan, Italy. His expertise is modeling of complex biological phenomena using the tools of statistical mechanics. The intersectoral experience (see below) in 'Eagle Genomics' in Cambridge, UK will also be an international experience. Having international experience will be highly beneficial to broaden the scientific horizon and network of the student.

Intersectoral

Bioinformatics and Data Science industries are keenly interested in novel computational approaches. Objective 1.iv will be the occasion for the student to develop, within a company, a user-friendly software, but more broadly to realize the need of the industry for new statistical approaches, and to experience working in a non-academic environment. Bogdan Mirauta, who will supervise the student during her/his 2-month secondment, is a scientist in Eagle Genomics, a leading company producing user-friendly software for biological data analysis.

Interdisciplinary

This PhD aims to use the tools of Theoretical Polymer Physics to understand a Biological phenomenon that is currently investigated and has been observed experimentally in the host lab. A great way to use theories is to make quantitative predictions and then design new experiments to verify them. Being embedded in an experimental lab the student will be able to propose experiments and have them tested experimentally. In addition, objective 2.iv will be a small and simple experimental project for the student, giving her/him a first-hand experience with data production, which is key to understand the challenges and the reality of experimental work. The planned experiment will involve the use of an experimental system already

established in the lab –the same system has already been successfully exploited by another theory student in the lab.

Recent publications

1. Scolari, V. F. & Cosentino Lagomarsino, M. Combined collapse by bridging and self-adhesion in a prototypical polymer model inspired by the bacterial nucleoid. *Soft Matter* **11**, 1677–1687 (2015).
2. Scolari, V. F., Mercy, G., Koszul, R., Lesne, A. & Mozziconacci, J. Kinetic Signature of Cooperativity in the Irreversible Collapse of a Polymer. *Phys. Rev. Lett.* **121**, 057801 (2018).
3. Keizer, V. *et al.* Live-cell micromanipulation of a genomic locus reveals interphase chromatin mechanics. *Science* 377, (2022).
4. Nora, E. P. *et al.* Molecular basis of CTCF binding polarity in genome folding. *Nat Commun* **11**, 5612 (2020).
5. Scolari, V. F., Sclavi, B. & Cosentino Lagomarsino, M. The nucleoid as a smart polymer. *Front Microbiol* **6**, (2015).

Expected profile of the candidate

Applicants should know the basics of statistical mechanics. Background in physics is strongly recommended. The project highly relies on the Python programming language and the NumPy libraries, for which the applicant should have basic experience.