Funded PhD project

Modeling the information transfer between metabolism and epigenetics

Graduate School: EDISCE (Engineering for Health, Cognition and Environment, University Grenoble-Alpes)
Location*:* TIMC-IMAG lab (University Grenoble-Alpes, CNRS, Grenoble INP)
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Profile and skills required:
Master 2 level (university, engineer school or equivalent) with a major either in mathematics, physics, computer science, systems or computational biology.
Advanced skills in mathematical/physical modeling and in scientific programming.
Strong interest in biological and medical applications.
Capacity to work in team in an interdisciplinary context.

Keywords: mathematical/physical modeling, stochastic systems, numerical simulations, systems biology

Project:
A recent paradigm shift defines metabolism not only as a series of mass and energy conversions, but also as a signaling mechanism. "Information carrying" metabolites seem to play a central role in modulating epigenetics, the so-called reprogramming of genetic information by chemical modifications of DNA and histones, finally leading to altered gene expression. Since metabolism is strongly influenced by environmental conditions and life-styles, this new concept of metabolo-epigenetics has important and far-reaching consequences for human health, and is a fast-growing research area.

In this project, we propose to formalize such concept by using mathematical and physical modeling in close interactions with experimental biologists. While many efforts have been devoted to model metabolism and epigenetics separately, very few theoretical approaches have addressed the information transfer between these two important classes of cellular processes. Combining dynamical systems, stochastic modeling and information theory, the PhD candidate will develop quantitative, mechanistic frameworks to investigate the role of metabolism in controlling gene expression via epigenetic regulation. Advanced numerical simulations will be performed to analyze the complexity of such approaches. Building on generic models accounting for key mechanisms, the student will develop novel, universal concepts on the information transfer between the metabolite/energy supply chains and gene expression via epigenetic regulation. Of particular interest, will be to understand the impact of limited metabolic resources on the maintenance of a robust epigenetic information and memory. Then, the candidate will contextualize these frameworks to specific biological examples like the role of acetyl-coA metabolites in controlling gene activation via the acetylation of histone tails. This will be done in close interaction with experimental biologists (Saadi Khochbin, Institute of Advanced Biosciences; Uwe Schlattner, Laboratory of Fundamental and Applied Bioenergetics; Univ. Grenoble-Alpes) and will

require to manipulate large-scale 'omics' data. We expect this project to formalize new theoretical notions and biological hypothesis that will be tested experimentally, improving our current understanding of the metabolo-epigenetic coupling.

Scientific environment:
This PhD project will be part of an international, interdisciplinary consortium called SyMER (A Systems approach to new paradigms in Metabolic and Epigenetic Regulation) grouping biologists, mathematicians, physicists, physicians, data scientists and sociologists around the question of the coupling between metabolism and epigenetics within a systems biology approach.
Moreover, the PhD candidate will benefit from the excellent scientific environment of the TIMC-IMAG laboratory which gathers scientists and clinicians towards the use of computer science and applied mathematics for understanding and controlling normal and pathological processes in biology and healthcare. He/She will have access to local and regional computing clusters to perform his/her research.

Supervision:
The PhD candidate will be supervised by Eric Fanchon, Daniel Jost and Angelique Stéphanou, all CNRS Research Associates at TIMC-IMAG laboratory and expert in mathematical and physical modeling of biological systems. Regular meetings with the supervisors will be organized to discuss the current achievements and to define the next scientific objectives. An annual meeting with experts in the domain will be organized to evaluate the global orientations of the project.

Bibliography:
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S. Berry, C. Dean & M. Howard (2017) Slow Chromatin Dynamics Allow Polycomb Target Genes to Filter Fluctuations in Transcription Factor Activity, Cell Systems, 4, 1-13.
D. Jost (2014) Bifurcation in epigenetics: implication to development, proliferation and diseases, Phys. Rev. E, 89, 010701.
M. Zerihun, C. Vaillant & D. Jost (2015) Effect of replication on epigenetic memory and consequences on gene transcription, Phys. Biol., 12, 026007.
E. Pourcelot, …, E. Fanchon, J.-M. Moulis, P. Mossuz (2015) Iron for proliferation of cell lines and hematopoietic progenitors: Nailing down the intracellular functional iron concentration, Biochim. Biophys. Acta, 1853, 1596-1605.