MASTER 2 RESEARCH INTERNSHIP

Reconstructing developmental energy landscapes of early embryos from mechanical and genetic maps

Laboratory: Collège de France
Center for Interdisciplinary Research in Biology (CIRB)
11, place Marcelin Berthelot, 75005 Paris

Supervision: Dr. Hervé Turlier herve.turlier@college-de-france.fr

Team: *Multiscale Physics of Morphogenesis* www.turlierlab.com

PhD thesis after internship: YES, recommended **Benefits:** ~500€/month

Expected profile: The candidate should be trained in **applied mathematics,** or **(bio)informatics** or **physics**, and demonstrate **excellent programming skills** (Python and C++), should have some prior knowledge of dynamical systems and a strong interest for statistical learning methods and optimisation (machine-learning, inverse problems).

Project: This master internship will address the generic question of mechanochemical interplay in developmental biology, combining statistical data analysis methods and forward biophysical modeling approaches. The goal will be to infer developmental landscapes defining embryonic cell trajectories from a fate and mechanical perspective.

Biological systems, such as early embryos or tissues, develop by a combination of mechanical events (divisions, growth, rearrangements, etc..) [**1-3**] and biochemical events (gene expression, genetic and signalling circuits, cell-cell communication etc…). For almost a century, a dominant hypothesis in developmental biology has rested on Waddington's notion of an 'epigenetic landscape' [**4**]. According to this traditional metaphor, cells navigate through an energy-like landscape featuring valleys divided by kinetic ridges, acting as barriers to the spontaneous transformation of one cell type into another (**Fig.1**). Certain developmental processes are 'canalized,' with cells adhering to routes along the bottoms of deep troughs, while other developmental processes are influenced by shallower landscapes, providing more chances for cells to move unrestrictedly. Rapid progress in gene sequencing methods have allowed researchers to create cell-resolved spatiotemporal maps of gene expression in developing embryos [**5-6**]. This allowed recently the reconstruction of 'Waddington-like energy landscapes', from which cell dynamics may be directly derived [**7-8**]. However, this approach does not account yet for spatial, geometric and mechanical information of individual cells. In parallel, our team recently developed methods to create cell-resolved atlases of cell shape and mechanics of early embryos and tissues in 3D [**9-11**]. The combination of mechanical and genetic atlases of developing embryos has the strong potential for inferring unknown feedbacks between gene expression, cell-cell signalling and cell mechanics, and to reconstruct 'Waddington-like landscapes' predicting single cell trajectories and encompassing self-organisation principles underlying embryo or tissue development.

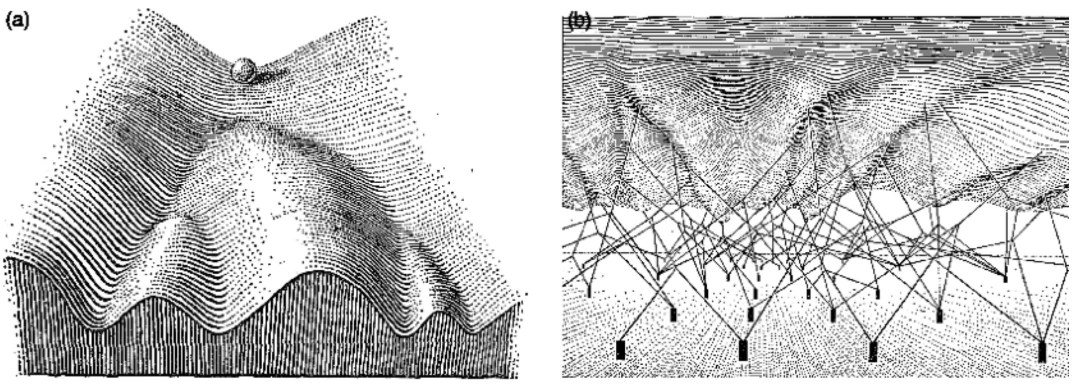

Figure 1: **a**) Waddington's representation of the epigenetic landscape with a cell about to take a trajectory. **b**) Vision behind an epigenetic landscape where genes control the depths of valleys.

This internship will aim at defining a suitable theoretical framework and adapted computational approaches to bridge the gap between gene expression and mechanics in a multicellular context. The generation of synthetic data through realistic 3D simulations will be key to the development and validation of inference methods. The continuation of this project over a PhD thesis is expected to lead to the development of novel theoretical concepts and original methods to infer systems-level developmental landscapes underlying collective cell dynamics. The work will benefit from strong and established collaborations with experimental biology teams working on several embryo species (ascidian, mouse…).

Working environment: We are committed to establishing a welcoming place for all and fostering inclusion and diversity. The student will be welcomed in renovated premises at Collège de France, into the interdisciplinary team "Multiscale physics of morphogenesis" led by Dr. Hervé Turlier and composed of ~10 researchers. She/he will be able to attend public lessons at Collège de France in biophysics and developmental biology, and will be provided access to a powerful laptop and to a high performance computing cluster fully dedicated to the team (12 GPUs, 396CPUs).

[**1**] Maître, Turlier et al. ***Nature*** 2016

[**2**] Dumortier et al. ***Science*** 2019

[**3**] Firmin et al. ***Nature*** 2023 (in press)

[**4**] Waddington, The Strategy of the genes 1957.

[**5**] Sladitschek et al. ***Cell*** 2020

[**6**] Kumar et al. ***Nat Gen*** 2023

[**7**] Saez et al. ***Cell Systems*** 2022

[**8**] Saez, Briscoe & Rand, ***Interface Focus*** 2022

[**9**] Ichbiah et al. ***Nature Methods*** 2023

[**10**] Ichbiah, Delbary & Turlier ***arXiv*** 2023

[**11**] Yamamoto et al. ***bioRxiv*** 2023