Mechanistic modeling and statistical inference of Notch-driven cell fate decisions in an adult stem cell population

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Project description:

Scientific context

Most adult tissues renew continuously thanks to a finely regulated stem cell population that balances quiescence, division and differentiation. In the adult zebrafish pallium (part of the brain), this stem cell population has been characterized in depth: it forms a two-dimensional pseudo-epithelium with cell division and delamination but without cell migration and remains dynamically stable for more than a year and each cell can be assigned to molecularly identifiable, lineage-related subpopulations [1]. Important fate decisions are regulated by the Notch signaling pathway. The lab has recently shown a new layer of complexity emerging from that relatively simple cell signaling pathway where two ligands acting on the same receptor have different outcomes; DeltaA drives quiescence via lateral inhibition while Jagged1b maintains stemness through lateral induction [2]. Which gene network does Notch actually act on to trigger a fate transition? How does the exchange of ligands between immediate neighbors keep the population at equilibrium, and how does it restore the equilibrium after a local perturbation? These questions remain open.
Multiplexed smFISH combined with immunohistochemistry now gives, for every cell of a large field of view, the counts of a panel of about ten Notch pathway transcripts, cell-state markers, and the full geometry of the cell and of its contacts with its neighbors [3]. Preliminary work between N. Dray and E. Ventre has shown that such data are well reproduced by a mechanistic model of stochastic gene expression at equilibrium [4], which opens the way to inferring the Notch network by reverse engineering, as an intracellular circuit coupled to intercellular communication.

Objective of the internship

A static, quasi-stationary dataset only constrains inference weakly: causal interactions become identifiable once the system is pushed out of equilibrium. A time series of smFISH datasets acquired after pharmacological perturbation of Notch will be available and already segmented at the beginning of the internship.

The aim is to build an inference method that exploits these dynamic, spatially resolved data. The starting point is an optimal-transport-based trajectory inference framework recently developed for time series of transcriptomic snapshots, which relies on the same mechanistic model of gene expression [5]. The work will consist in extending it in two directions, whose relative weight can be adjusted to the intern's taste:

- **Spatial coupling.** The ligands expressed by the neighbors of a cell act as inputs to its regulatory network, but ligands are limited and neighboring cells compete for the same receptors. Collective optimal transport formulations of cell–cell communication [6] offer a natural way to estimate an effective ligand–receptor interaction map directly from the data, and a big challenge is to confront it with explicit biological hypotheses: competition between DeltaA and Jagged1b, distinct cis and trans effects, or a dependence of signaling strength on the shared contact area.
- **Dynamics under perturbation.** Going beyond the stationary assumptions by aligning successive snapshots, so as to quantify how the inferred network is modified by the perturbation, in other words, which interactions are required to explain both the loss and the recovery of the equilibrium state.

These analysis should ultimately feed a tissue-scale model developed in parallel within the consortium.

Nature of the project

This is first and foremost a modeling and statistical inference project. The point is not to run generic machine learning on a large dataset, but rather the opposite: to write a parsimonious mechanistic model of a small and already well-understood system, about ten genes, a few cell states, known ligand–receptor pairs, and to develop the inference tools that make it identifiable from a limited number of carefully acquired images. Biological prior knowledge is used throughout as a constraint on the model, not as something to be rediscovered from data. Joint analysis of expression, lineage and spatial position is central here. The intern will work in direct contact with the experimentalists producing the data, and the methodological developments are intended to be published as such. This project is part of an ANR funded project.

Candidate profile

- M2 or final year of an engineering school, in applied mathematics, statistics or physics
- Taste for probabilistic modeling; prior exposure to stochastic processes, statistical inference or optimal transport is welcome but is not a prerequisite
- Comfortable programming in Python
- Real curiosity about biological questions and about working alongside experimentalists

Practical details

- Duration 4 to 6 months, starting date flexible; internship allowance according to the host institution
- Preferentially hosted in Marseille but can be hosted in Paris (Institut Pasteur), with regular exchanges with Elias, Solène in Marseille and Nicolas in Paris.
- The internship is part of a longer-term interdisciplinary effort combining spatial statistics, mechanistic modeling and quantitative imaging, and may open onto a PhD (in Marseille)

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References

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