

Title : *Learning of stochastic mixed-effects models of gene expression dynamics in microbial cells*

Project type : Research project (possible continuation into a Ph.D)

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Workplace : Inria Grenoble-Rhône-Alpes, Montbonnot

Context, objectives, competences required :

Modern experimental technologies allow one to monitor the response of microbial organisms to environmental stimuli at the level of individual cells. Observation of single-cell dynamics reveals the variability of this response across different cells, as well as the stochasticity of the dynamics in terms of fluctuations over time within the same cell. Quantitative understanding of this variability is key to investigate the origins of randomness in gene expression, as well as its functional role for the survival and proliferation of microbial populations in changing environments. Development of methods for the reconstruction of quantitative models of single-cell response is thus an active research field.

This proposal concerns the implementation of a new method for learning Mixed-Effects models of gene expression dynamics from single-cell data. Contrary to existing approaches, where standard ME modelling is used to describe variability across cells in terms of parameter variability of a deterministic response, we will capture random fluctuation of any given cell response in terms of stochastic dynamics. Starting from existing inference algorithms for standard ME models, the internship will address the integration of a novel step accounting for these stochastic dynamics in a computationally effective manner. In more detail, the project will consist of the following steps:

- Familiarization with existing algorithms/software (Monolix) for the inference of ME models
- Extension of the code with functions accounting for the stochastic dynamics
- Testing of the resulting algorithm on simulated data (and real data, if time allows)

The intership will be carried out at INRIA Grenoble - Rhône-Alpes under the supervision of Eugenio Cinquemani (IBIS, INRIA Grenoble - Rhône-Alpes; <https://team.inria.fr/ibis/eugenio-cinquemani/>), in collaboration with Jakob Ruess (INBIO, INRIA Saclay - Île-de-France and Institut Pasteur Paris; <https://research.pasteur.fr/fr/member/jakob-ruess/>) and Marc Lavielle (XPOP, INRIA Saclay - Île-de-France and CMAP, Ecole Polytechnique; <http://www.cmap.polytechnique.fr/~lavielle/>).

Interested candidates are expected to be familiar with Matlab programming, have a reasonable understanding of dynamical systems/probability theory/stochastic processes, and be interested in biological applications. Successful candidates will be working in collaboration in a stimulating international context. Standard internship remuneration will be provided.

Relevant tracks : MSCI and DS (FDS and LSDS)

Short bibliography :

- A. Llamosi, A.M. Gonzalez-Vargas, C. Versari, E. Cinquemani, G. Ferrari-Trecate, P. Hersen, G. Batt, “What population reveals about individual cell identity: Single-cell parameter estimation of models of gene expression in yeast”. PLoS Comput Bio (2016) 12(2):e1004706
- S.B. Mortensen *et al.*, “A matlab framework for estimation of NLME models using stochastic differential equations”, J Pharmacokinet Pharmacodyn (2007) 34:623–642