

Master 2 internship with possibility to pursue a PhD thesis

Modelling and inference of mRNA degradation

January 6, 2025

Scientific description and objective of the internship

Advances in high-throughput technologies in biology has opened up the possibility of simultaneously quantifying the amounts of components in the cell over time. The data account for the molecular responses of living organisms to perturbations, resulting from regulatory mechanisms that ensure adaptation and survival. Mechanistic modelling is essential to unravel these molecular mechanisms. Indeed, model estimation from high-throughput data provides parameters that have a biological interpretation.

However, the integration of high-throughput data with mechanistic knowledge is limited by the model nonlinearities and the availability of scalable computational approaches that are capable of disentangling biological and technical sources of variation. In the context of the study of the degradation of bacterial mRNAs, we have shown that combining mechanistic and statistical modelling by means of nonlinear mixed-effects modelling allows kinetic model parameters to be inferred from time-series transcriptomics data and new biological regulatory mechanisms to be uncovered [1,2]. The framework yields good estimation results, but several difficulties impede its extension to other high-throughput datasets.

The objective of the internship is to adapt the modelling and statistical framework to other high-throughput datasets taking into account additional biological processes and conditions. This work will involve modelling and inference using time-series transcriptomic datasets of the model organism *Escherichia coli* growing under different environmental conditions or subjected to genetic perturbations [3,4]. The work will be done in close collaboration with Muriel Coccagn-Bousquet and A. J. Carpousis (Toulouse Biotechnology Institute). Please note that there is a possibility to continue the work as a PhD student within the RECOM ANR project (funding available).

[1] T.A. Etienne, M. Coccagn-Bousquet & D. Ropers (2020). Competitive effects in bacterial mRNA decay. *Journal of Theoretical Biology*, 504, 110333.

[2] T.A. Etienne, C. Roux, E. Cinquemani, L. Girbal, M. Coccagn-Bousquet & D. Ropers (2022). A nonlinear mixed-effects approach for the mechanistic interpretation of time-series transcriptomics data. Preprint.

[3] T. Esquerre, S. Laguerre, C. Turlan, A.J. Carpousis, L. Girbal & M. Coccagn-Bousquet (2014). Dual role of transcription and transcript stability in the regulation of gene expression in *Escherichia coli* cells cultured on glucose at different growth rates. *Nucleic Acids Research*, 42(4), 2460-2472.

[4] L. Hamouche, L. Poljak & A.J. Carpousis (2021). Polyribosome-dependent clustering of membrane-anchored RNA degradosomes to form sites of mRNA degradation in *Escherichia coli*. *Mbio*, 12(5), 10-1128.

Mission and activities:

- Develop estimation strategies (simplification and/or reduction of mechanistic models of mRNA degradation, choosing random effects for the non-linear mixed effects models) to estimate degradation parameters from transcriptomic datasets

- Apply the different estimation strategies to a dataset obtained in the bacterium *E. coli* growing under different environmental conditions, assess the quality of model estimation, and interpret the estimation results

- Adapt the estimation procedure to a new transcriptomic dataset obtained in the bacterium *E. coli* subjected to genetic perturbations of the degradation machinery

Expected skills and knowledge:

Knowledge in statistics, model inference and dynamical systems

Programming language: R or Python

Interest in biological applications

Aptitude for teamwork

Good level of technical and scientific English, both spoken and written.

Additional information:

When: start in February-April 2025 (flexible).

How long: 4-6 months (flexible).

Where: [MICROCOSME](#) team, [Inria Centre at the University Grenoble Alpes](#).

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