

From modelling dynamical gene regulatory networks to system-level control of *E. coli* metabolism

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Laboratory

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Subjects

- 1.: gene regulation
- 2.: metabolism
- 3.: systems biology

Tools and Methodologies

- 1.: modelling
- 2.: networks
- 3.: theory

Summary of lab's interests

The UMR de Genetique Vegetale has a long-standing activity in "quantitative genetics", the sub-field of genetics focusing on multi-factorial traits. The organisms studied are either plants or model micro-organisms, namely *E. coli* and *S. cerevisiae*. The lab members mix methodological approaches with experimental measurements, with an interest in dissecting the genetic determinants of complex traits and their evolutionary origin. There is an in-house proteomics platform (Pappso, labeled IBSa) and across the street a metabolomics facility. The host team, Genetique Quantitative Fondamentale, is composed of modellers using mathematical, statistical and computational approaches. With the advent of network biology, there is a convergence between the methods of quantitative genetics and systems biology.

Summary of project

A key objective in modern biology is the «creation» of living organisms having predefined characteristics. These can range from a micro-organism's ability to produce biosynthetic compounds to a pet's having an economically advantageous phenotype such as non allergenic fur. Unfortunately in general such traits are multi-genic and are controlled by complex regulatory networks. The ability to modify at will organisms thus requires understanding the different molecular components, their regulatory mechanisms, and the effects of adding or removing new components. To date, the redesign of microorganisms to make products of interest has had a few successes. In the medium term, one can hope to do this kind of metabolic engineering to produce biofuels, bulk and fine chemicals, or pharmaceutical compounds. Ideally, a redesign should modify the metabolic flux distribution so the cells switch from growth, i.e., biomass production, to product synthesis, but in practice that goal has not been well achieved. And in fact we are even further away from being able to redesign realistic regulatory machineries, be-it for prokaryotes or eukaryotes.

The first part of this project will develop computational approaches for inferring dynamical models of genetic regulation. Following previous work in which putative interactions may or not be provided, we will use Markov Chain Monte Carlo to produce models (which means interaction graphs and the parameters determining the time dynamics of the molecular species) that have a good fit to the data. These data can come from multiple sources, but for our work we will mainly use

transcriptomics, proteomics, metabolomics, and low throughput observations from knock-downs and single cell measurements on reporter genes produced on *E. coli* by our collaborators in Grenoble (Hidde de Jong et al.). This data acquisition is part of an ANR contract in which we provide modeling expertise. Note that a true Bayesian treatment is not possible because of experimental limitations, but that a near Bayesian approach can be used via summary statistics to quantify the goodness of fit of any model. The result will be a large sample of « models » from which one can do data mining. Corresponding examples include (1) predictions of an interaction (if it is present in 95% of the models), (2) predictions of effects of genetic manipulations (for instance knock-outs or know-ins), (3) evolutionary insights of use for comparing different realizations of the regulatory control, etc.

The second part of the project will add the metabolic network to the previously constructed genetic regulatory system. Metabolic fluxes are usually treated by flux balance analysis in the steady state. A generalization, referred to as dynamic flux balance analysis, can be applied to our model system to understand the experimental measurements of our Grenoble collaborators. The goal is to provide a coarse-grained description of the coupled networks that takes into account among others the expression machinery. Within the ANR contract, our work task is to produce quantitative models of the redistribution of metabolic fluxes under various perturbing conditions. The research will incorporate flux dynamics, the near steady-state approximation, kinetics of transcription + translation, and coarse-grained approaches to regulation. The tools for this thesis are mathematical and computational, going from analytic equations to simulations. Strategies for combining this kind of global r egulation with classical metabolic engineering will be performed in silico.

Interdisciplinarity of the project

The thesis will consider networks of interacting genes and their targets along with the associated feedbacks. The networks of interest are molecular, with dynamics for transcription, translation and metabolism, and their understanding requires quantitative mathematical studies rooted in dynamical systems, structural analysis, control theory, etc. The topic definitely falls in "system" science but focused on the biological goal of understanding the functioning and regulation of cells driven by a significant number of different molecular species. The required technical know-how lies in mathematics, theoretical physics and computer science, while the object of study is at the heart of modern biology and its current extensions to systems biology. The environment is also clearly interdisciplinary: the thesis advisor is an ex theoretical physicist, while the host team/lab is at the interface between experimental biology and biological modelling. The hired Ph.D. student will be far better off seeing interdisciplinarity at work in the ED FdV than mingling with "one field only" students from our local ED.

Do you have an available funding for this project ?

ANR