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Université de Grenoble Alpes

Activity Report 2017

Project-Team IBIS

Modeling, simulation, measurement, and control of bacterial regulatory networks

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Computational Biology

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Project-Team IBIS

Creation of the Project-Team: 2009 January 01

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1. Personnel

Research Scientists

Hidde de Jong [Team leader, Inria, Senior Researcher, HDR]
Eugenio Cinquemani [Inria, Researcher]
Delphine Ropers [Inria, Researcher]

Faculty Members

Johannes Geiselmann [Univ Grenoble Alpes, Professor]
Stephan Lacour [Univ Grenoble Alpes, Associate Professor]
Yves Markowicz [Univ Grenoble Alpes, Associate Professor]
Michel Page [Univ Grenoble Alpes, Associate Professor]

Post-Doctoral Fellow

Marco Mauri [Inria, from Oct 2017]

PhD Student

Thibault Etienne [INRA]

Technical staff

Cyril Dutrieux [Inria, until Sep 2017]

Yannick Martin [Inria, until May 2017]
Tamas Muszbek [Inria, from Dec 2017]
Corinne Pinel [CNRS]
Ludowic Lancelot [Inria and Univ Grenoble Alpes, until Aug 2017]
Célia Boyat [Inria and Univ Grenoble Alpes]

Intern

Mathilde Lombardi [BSc student, IUT d'Avignon, from Feb 2017 until Jul 2017]

Administrative Assistants

Alexandra Fitzgerald [Inria]
Lydie Leon [Inria]

2. Overall Objectives

2.1. Overview

When confronted with changing environmental conditions, bacteria and other microorganisms have a remarkable capacity to adapt their functioning. The responses of bacteria to changes in their environment are controlled on the molecular level by large and complex networks of biochemical interactions involving genes, mRNAs, proteins, and metabolites. The study of bacterial regulatory networks requires experimental tools for mapping the interaction structure of the networks and measuring the dynamics of cellular processes. In addition, when dealing with such large and complex systems, we need mathematical modeling and computer simulation to integrate available biological data, and understand and predict the dynamics of the system under various physiological and genetic perturbations. The analysis of living systems through the combined application of experimental and computational methods has gathered momentum in recent years under the name of systems biology.

The first aim of the IBIS project-team is to apply such a systems-biology approach to gain a deeper understanding, on the mechanistic level, of the strategies that bacteria have developed to respond to changes in their environment. [1] In particular, we focus on the enterobacterium *Escherichia coli*, for which enormous amounts of genomic, genetic, biochemical and physiological data have accumulated over the past decades. A better understanding of the adaptive capabilities of *E. coli* to nutritional limitations or other environmental changes is an aim in itself, but also a necessary prerequisite for the second and most ambitious aim of the project: interfering with the cellular responses by specific perturbations or by rewiring the underlying regulatory networks. This does not only spawn fundamental research on the control of living matter, but may ultimately also lead to practical applications. Because *E. coli* is easy to manipulate in the laboratory, it serves as a model for many pathogenic bacteria and is widely used in biotechnology, for such diverse applications as the development of vaccines, the mass production of enzymes and other (heterologous) proteins, and the production of biofuels.

The aims of IBIS raise new questions on the interface of biology, applied mathematics, and computer science. In particular, the following objectives have structured the work of the project-team: (1) the analysis of the qualitative dynamics of gene regulatory networks, (2) the inference of gene regulatory networks from time-series data, (3) the analysis of integrated metabolic and regulatory networks, and (4) natural and engineered control of regulatory networks. Although these axes cover most of the work carried out in IBIS, some members have also made contributions to research projects on different topics. Since this usually represents a minor proportion of the overall research effort of the project-team, we will not describe this work in detail in the activity report. The publications resulting from these side-tracks have been included in the bibliography.

[1] The ibis was an object of religious veneration in ancient Egypt, particularly associated with the god Thoth. Thoth was seen, among other things, as a god of the measurement and regulation of events.

The challenges of the research programme of the IBIS team require a wide range of competences on the interface of (experimental) biology, applied mathematics, and computer science (Figure 1). Since no single person can be expected to possess all of these competences, the international trend in systems biology is to join researchers from different disciplines into a single group. In line with this development, the IBIS team is a merger of a microbiology and molecular genetics group on the one hand, and a bioinformatics and mathematical biology group on the other hand. In particular, the IBIS team is composed of members of the group of Johannes Geiselmann, formerly at the Laboratoire Adaptation et Pathogénicité des Microorganismes of the Univ Joseph Fourier (UJF, CNRS UMR 5163), and since September 2014 at the Laboratoire Interdisciplinaire de Physique (CNRS UMR 5588), and the members of the network modeling and simulation group formerly part of the HELIX project-team at Inria Grenoble - Rhône-Alpes, a group coordinated by Hidde de Jong. The two groups have established a fruitful collaboration, which has resulted in more than 60 peer-reviewed publications in journals, conferences, and books since 2000. [2]

Hidde de Jong is the head of the IBIS project-team and Johannes Geiselmann its co-director. The experimental component of IBIS is also part of the Laboratoire Interdisciplinaire de Physique, and Johannes Geiselmann continues to represent this group in the interactions with the laboratory and university administration.

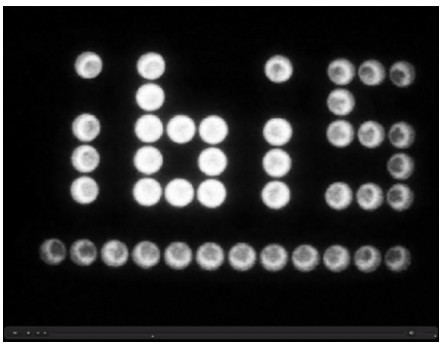


Figure 1. Display of the project-team name on a "bacterial billboard" (see http://team.inria.fr/ibis for the corresponding movie). A microplate containing a minimal medium (with glucose and acetate) is filmed during 36 hours. Wells contain E. coli bacteria which are transformed with a reporter plasmid carrying the luciferase operon (luxCDABE) under control of the acs promoter. This promoter is positively regulated by the CRP-cAMP complex. When bacteria have metabolized all the glucose, the cAMP concentration increases quickly and activates the global regulator CRP which turns on the transcription of the luciferase operon producing the light. The glucose concentration increases from left to right on the microplate, so its consumption takes more time when going up the gradient and the letters appear one after the other. The luciferase protein needs reductive power ($FMNH_2$) to produce light. At the end, when acetate has been depleted, there is no carbon source left in the medium. As a consequence, the reductive power falls and the bacterial billboard switches off. Source: Guillaume Baptist.

3. Research Program

3.1. Analysis of qualitative dynamics of gene regulatory networks

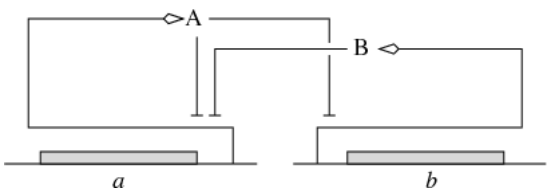
Participants: Hidde de Jong [Correspondent], Michel Page, Delphine Ropers.

[2] See http://team.inria.fr/ibis for a complete list.

The dynamics of gene regulatory networks can be modeled by means of ordinary differential equations (ODEs), describing the rate of synthesis and degradation of the gene products as well as regulatory interactions between gene products and metabolites. In practice, such models are not easy to construct though, as the parameters are often only constrained to within a range spanning several orders of magnitude for most systems of biological interest. Moreover, the models usually consist of a large number of variables, are strongly nonlinear, and include different time-scales, which makes them difficult to handle both mathematically and computationally. This has motivated the interest in qualitative models which, from incomplete knowledge of the system, are able to provide a coarse-grained picture of its dynamics.

A variety of qualitative modeling formalisms have been introduced over the past decades. Boolean or logical models, which describe gene regulatory and signalling networks as discrete-time finite-state transition systems, are probably most widely used. The dynamics of these systems are governed by logical functions representing the regulatory interactions between the genes and other components of the system. IBIS has focused on a related, hybrid formalism that embeds the logical functions describing regulatory interactions into an ODE formalism, giving rise to so-called piecewise-linear differential equations (PLDEs, Figure 2). The use of logical functions allows the qualitative dynamics of the PLDE models to be analyzed, even in high-dimensional systems. In particular, the qualitative dynamics can be represented by means of a so-called state transition graph, where the states correspond to (hyperrectangular) regions in the state space and transitions between states arise from solutions entering one region from another.

First proposed by Leon Glass and Stuart Kauffman in the early seventies, the mathematical analysis of PLDE models has been the subject of active research for more than four decades. IBIS has made contributions on the mathematical level, in collaboration with the BIOCORE and BIPOP project-teams, notably for solving problems induced by discontinuities in the dynamics of the system at the boundaries between regions, where the logical functions may abruptly switch from one discrete value to another, corresponding to the (in)activation of a gene. In addition, many efforts have gone into the development of the computer tool GENETIC NETWORK ANALYZER (GNA) and its applications to the analysis of the qualitative dynamics of a variety of regulatory networks in microorganisms. Some of the methodological work underlying GNA, notably the development of analysis tools based on temporal logics and model checking, which was carried out with the Inria project-teams CONVEX (ex-VASY) and POP-ART, has implications beyond PLDE models as they apply to logical and other qualitative models as well.



$$\dot{x}_a = \kappa_a \, s^-(x_a, \theta_a^2) \, s^-(x_b, \theta_b) - \gamma_a \, x_a$$

$$\dot{x}_b = \kappa_b \, s^-(x_a, \theta_a^1) - \gamma_b \, x_b$$

$$s^+(x, \theta) = \begin{cases} 1, & \text{if } x > \theta \\ 0, & \text{if } x < \theta \end{cases}$$

$$s^-(x, \theta) = 1 - s^+(x, \theta)$$

Figure 2. (Left) Example of a gene regulatory network of two genes (a and b), each coding for a regulatory protein (A and B). Protein B inhibits the expression of gene a, while protein A inhibits the expression of gene b and its own gene. (Right) PLDE model corresponding to the network in (a). Protein A is synthesized at a rate κ_a, if and only if the concentration of protein A is below its threshold θ_a^2 ($x_a < \theta_a^2$) and the concentration of protein B below its threshold θ_b ($x_b < \theta_b$). The degradation of protein A occurs at a rate proportional to the concentration of the protein itself ($\gamma_a \, x_a$).

3.2. Inference of gene regulatory networks from time-series data

Participants: Eugenio Cinquemani [Correspondent], Johannes Geiselmann, Hidde de Jong, Cyril Dutrieux, Stephan Lacour, Yannick Martin, Michel Page, Corinne Pinel, Delphine Ropers.

Measurements of the transcriptome of a bacterial cell by means of DNA microarrays, RNA sequencing, and other technologies have yielded huge amounts of data on the state of the transcriptional program in different growth conditions and genetic backgrounds, across different time-points in an experiment. The information on the time-varying state of the cell thus obtained has fueled the development of methods for inferring regulatory interactions between genes. In essence, these methods try to explain the observed variation in the activity of one gene in terms of the variation in activity of other genes. A large number of inference methods have been proposed in the literature and have been successful in a variety of applications, although a number of difficult problems remain.

Current reporter gene technologies, based on Green Fluorescent Proteins (GFPs) and other fluorescent and luminescent reporter proteins, provide an excellent means to measure the activity of a gene *in vivo* and in real time (Figure 3). The underlying principle of the technology is to fuse the promoter region and possibly (part of) the coding region of a gene of interest to a reporter gene. The expression of the reporter gene generates a visible signal (fluorescence or luminescence) that is easy to capture and reflects the expression of a gene of interest. The interest of the reporter systems is further enhanced when they are applied in mutant strains or combined with expression vectors that allow the controlled induction of any particular gene, or the degradation of its product, at a precise moment during the time-course of the experiment. This makes it possible to perturb the network dynamics in a variety of ways, thus obtaining precious information for network inference.

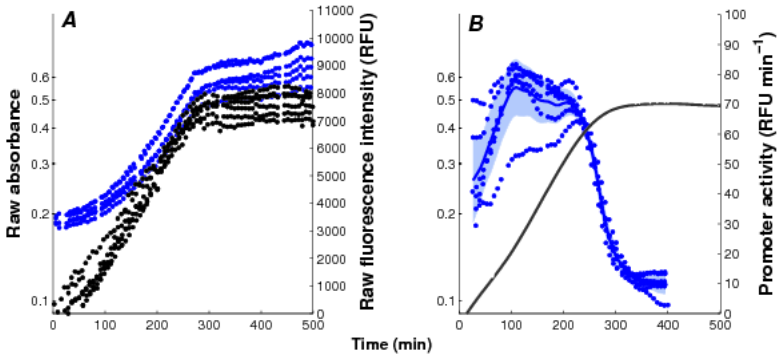


Figure 3. Monitoring of bacterial gene expression in vivo using fluorescent reporter genes (Stefan et al., PLoS Computational Biology, 11(1):e1004028, 2015). The plots show the primary data obtained in a kinetic experiment with E. coli cells, focusing on the expression of the motility gene tar in a mutant background. A: Absorbance (•, black) and fluorescence (•, blue) data, corrected for background intensities, obtained with the ΔcpxR strain transformed with the ptar-gfp reporter plasmid and grown in M9 with glucose. B: Activity of the tar promoter, computed from the primary data. The solid black line corresponds to the mean of 6 replicate absorbance measurements and the shaded blue region to the mean of the promoter activities ± twice the standard error of the mean.

The specific niche of IBIS in the field of network inference has been the development and application of genome engineering techniques for constructing the reporter and perturbation systems described above, as well as the use of reporter gene data for the reconstruction of gene regulation functions. We have developed an experimental pipeline that resolves most technical difficulties in the generation of reproducible time-series measurements on the population level. The pipeline comes with data analysis software that converts the primary data into measurements of time-varying promoter activities. In addition, for measuring gene expression on the single-cell level by means of microfluidics and time-lapse fluorescence microscopy, we have established collaborations with groups in Grenoble and Paris. The data thus obtained can be exploited for the structural and parametric identification of gene regulatory networks, for which methods with a solid

mathematical foundation are developed, in collaboration with colleagues at ETH Zürich and EPF Lausanne (Switzerland). The vertical integration of the network inference process, from the construction of the biological material to the data analysis and inference methods, has the advantage that it allows the experimental design to be precisely tuned to the identification requirements.

3.3. Analysis of integrated metabolic and gene regulatory networks

Participants: Eugenio Cinquemani, Hidde de Jong, Thibault Etienne, Johannes Geiselmann, Stephan Lacour, Yves Markowicz, Michel Page, Corinne Pinel, Delphine Ropers [Correspondent].

The response of bacteria to changes in their environment involves responses on several different levels, from the redistribution of metabolic fluxes and the adjustment of metabolic pools to changes in gene expression. In order to fully understand the mechanisms driving the adaptive response of bacteria, as mentioned above, we need to analyze the interactions between metabolism and gene expression. While often studied in isolation, gene regulatory networks and metabolic networks are closely intertwined. Genes code for enzymes which control metabolic fluxes, while the accumulation or depletion of metabolites may affect the activity of transcription factors and thus the expression of enzyme-encoding genes.

The fundamental principles underlying the interactions between gene expressions and metabolism are far from being understood today. From a biological point of view, the problem is quite challenging, as metabolism and gene expression are dynamic processes evolving on different time-scales and governed by different types of kinetics. Moreover, gene expression and metabolism are measured by different experimental methods generating heterogeneous, and often noisy and incomplete data sets. From a modeling point of view, difficult methodological problems concerned with the reduction and calibration of complex nonlinear models need to be addressed.

Most of the work carried out within the IBIS project-team specifically addressed the analysis of integrated metabolic and gene regulatory networks in the context of *E. coli* carbon metabolism (Figure 4). While an enormous amount of data has accumulated on this model system, the complexity of the regulatory mechanisms and the difficulty to precisely control experimental conditions during growth transitions leave many essential questions open, such as the physiological role and the relative importance of mechanisms on different levels of regulation (transcription factors, metabolic effectors, global physiological parameters, ...). We are interested in the elaboration of novel biological concepts and accompanying mathematical methods to grasp the nature of the interactions between metabolism and gene expression, and thus better understand the overall functioning of the system. Moreover, we have worked on the development of methods for solving what is probably the hardest problem when quantifying the interactions between metabolism and gene expression: the estimation of parameters from hetereogeneous and noisy high-throughput data. These problems are tackled in collaboration with experimental groups at Inra/INSA Toulouse and CEA Grenoble, which have complementary experimental competences (proteomics, metabolomics) and biological expertise.

3.4. Natural and engineered control of growth and gene expression

Participants: Célia Boyat, Eugenio Cinquemani, Cyril Dutrieux, Johannes Geiselmann [Correspondent], Hidde de Jong, Stephan Lacour, Ludowic Lancelot, Marco Mauri, Tamas Muszbek, Michel Page, Delphine Ropers.

The adaptation of bacterial physiology to changes in the environment, involving changes in the growth rate and a reorganization of gene expression, is fundamentally a resource allocation problem. It notably poses the question how microorganisms redistribute their protein synthesis capacity over different cellular functions when confronted with an environmental challenge. Assuming that resource allocation in microorganisms has been optimized through evolution, for example to allow maximal growth in a variety of environments, this question can be fruitfully formulated as an optimal control problem. We have developed such an optimal control perspective, focusing on the dynamical adaptation of growth and gene expression in response to envrionmental changes, in close collaboration with the BIOCORE project-team.

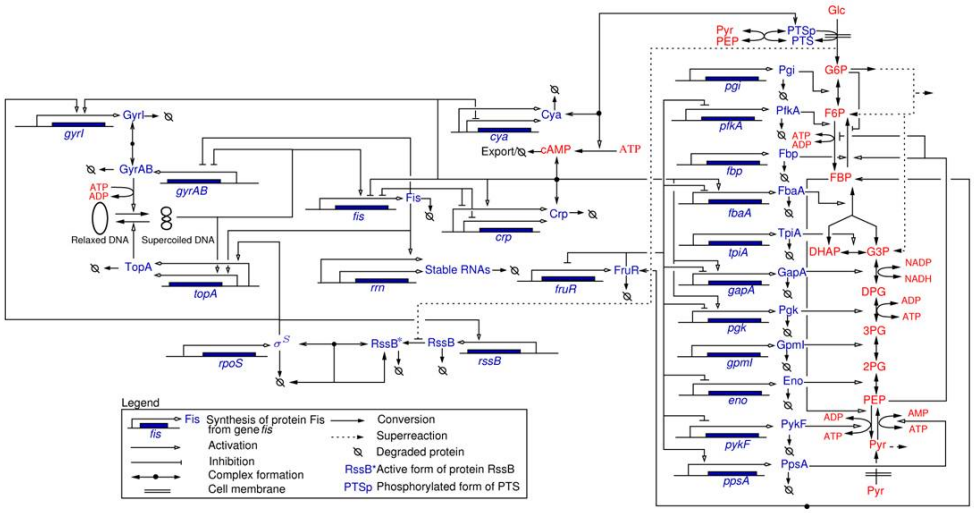


Figure 4. Network of key genes, proteins, and regulatory interactions involved in the carbon assimilation network in E. coli (Baldazzi et al., PLoS Computational Biology, 6(6):e1000812, 2010). The metabolic part includes the glycolysis/gluconeogenesis pathways as well as a simplified description of the PTS system, via the phosphorylated and non-phosphorylated form of its enzymes (represented by PTSp and PTS, respectively). The pentose-phosphate pathway (PPP) is not explicitly described but we take into account that a small pool of G6P escapes the upper part of glycolysis. At the level of the global regulators the network includes the control of the DNA supercoiling level, the accumulation of the sigma factor RpoS and the Crp·cAMP complex, and the regulatory role exerted by the fructose repressor FruR.

A complementary perspective consists in the use of control-theoretical approaches to modify the functioning of a bacterial cell towards a user-defined objective, by rewiring and selectively perturbing its regulatory networks. The question how regulatory networks in microorganisms can be externally controlled using engineering approaches has a long history in biotechnology and is receiving much attention in the emerging field of synthetic biology. Within a number of on-going projects, IBIS is focusing on two different questions. The first concerns the development of open-loop and closed-loop growth-rate controllers of bacterial cells for both fundamental research and biotechnological applications (Figure 5). Second, we are working on the development of methods for the real-time control of gene expression. These methods are obviously capital for the above-mentioned design of growth-rate controllers, but they have also been applied in the context of a platform for real-time control of gene expression in cell population and single cells, developed by the Inria project-team LIFEWARE, in collaboration with a biophysics group at Univ Paris Descartes.

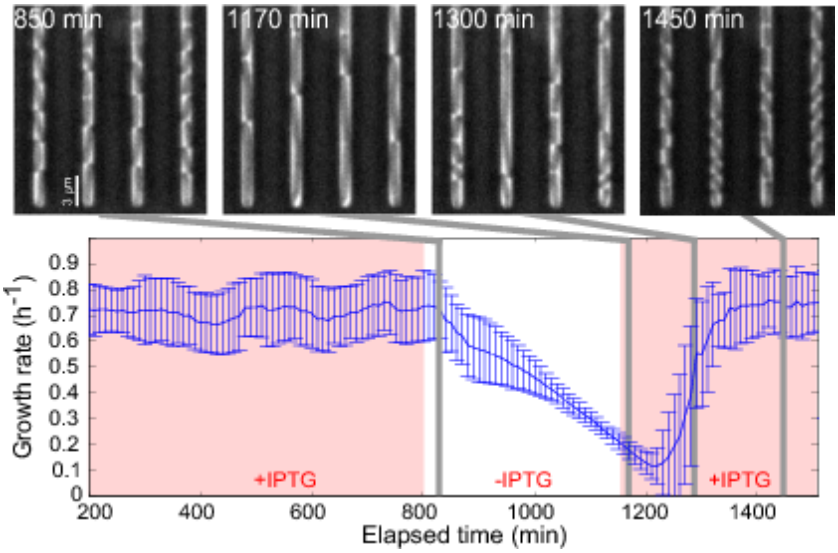


Figure 5. Growth arrest by external control of the gene expression machinery (Izard, Gomez Balderas et al., Molecular Systems Biology, 11:840, 2015). An E. coli strain in which an essential component of the gene expression machinery, the $\beta\beta'$ subunits of RNA polymerase, was put under the control of an externally-supplied inducer (IPTG), was grown in a microfluidics device and phase-contrast images were acquired every 10 min. The cells were grown in minimal medium with glucose, initially in the presence of 1 mM IPTG. 6 h after removing IPTG from the medium, the growth rate slows down and cells are elongated. About 100 min after adding back 1 mM IPTG into the medium, the elongated cells divide and resume normal growth. The growth rates in the plot are the (weighted) mean of the growth rates of 100 individual cells. The error bars correspond to $\pm$ one standard deviation. The results of the experiment show that the growth rate of a bacterial can be switched off in a reversible manner by an external inducer, based on the reengineering of the natural control of the expression of RNA polymerase.

4. Highlights of the Year

4.1. Highlights of the Year

Three new projects coordinated by IBIS started this year: the IPL COSY, the ADT CoSoft, and the ANR project Maximic (Section 8.2). A paper based on the PhD thesis of Manon Morin was published in *mBio*

this year [20]. The techniques used for the analysis of flux data were presented at ISMB/ECCB 2017 and published in a special issue of *Bioinformatics* [17]. Hidde de Jong organized a workshop on growth control in microorganisms, as a side event of the yearly meeting of the special interest group in systems and synthetic biology GDR BioSynSys, in La Grande Motte.

5. New Software and Platforms

5.1. WellFARE

KEYWORDS: Bioinformatics - Statistics - Data visualization - Data modeling
SCIENTIFIC DESCRIPTION: WellFARE is a Python library implementing linear inversion methods for the reconstruction of gene expression profiles from fluorescent or luminescent reporter gene data.
FUNCTIONAL DESCRIPTION: As input, WellFARE reads the primary data file produced by a 96-well microplate reader, containing time-series measurements of the absorbance (optical density) as well as the fluorescence and luminescence intensities in each well (if available). Various functions exist to analyze the data, in particular for detecting outliers, subtracting background, estimating growth rates, promoter activities and protein concentrations, visualizing expression profiles, synchronizing replicate profiles, etc. WellFARE is the computational core of the web application WellInverter.
NEWS OF THE YEAR: New version 2.0 with correction of several bugs.

- Participants: Delphine Ropers, Hans Geiselmann, Hidde De Jong, Michel Page, Valentin Zulkower and Yannick Martin
- Partner: UGA
- Contact: Hidde De Jong
- Publication: Robust reconstruction of gene expression profiles from reporter gene data using linear inversion
- URL: https://github.com/ibis-inria/wellfare

5.2. WellInverter

KEYWORDS: Bioinformatics - Statistics - Data visualization - Data modeling
SCIENTIFIC DESCRIPTION: WellInverter is a web application that implements linear inversion methods for the reconstruction of gene expression profiles from fluorescent or luminescent reporter gene data.
FUNCTIONAL DESCRIPTION: As input, WellInverter reads the primary data file produced by a 96-well microplate reader, containing time-series measurements of the absorbance (optical density) as well as the fluorescence and luminescence intensities in each well (if available). Various modules exist to analyze the data, in particular for detecting outliers, subtracting background, estimating growth rates, promoter activities and protein concentrations, visualizing expression profiles, synchronizing replicate profiles, etc. The computational core of the web application consists of the Python library WellFARE.
NEWS OF THE YEAR: New version developed this year, making the tool accessible to a broader audience of biologists and bioinformaticians. In particular, we have put in place a parallel computing architecture with a load balancer to distribute the analysis queries over several back-end servers, redesigned the graphical user interface, and developed a plug-in system for defining high-level routines for parsing data files produced by microplate readers from different manufacturers.

- Participants: Delphine Ropers, Hans Geiselmann, Hidde De Jong, Johannes Geiselmann, Michel Page, Valentin Zulkower and Yannick Martin
- Partner: UGA
- Contact: Hidde De Jong
- Publication: Robust reconstruction of gene expression profiles from reporter gene data using linear inversion
- URL: https://team.inria.fr/ibis/wellinverter/

5.3. FluoBacTracker

KEYWORDS: Bioinformatics - Biology - Biomedical imaging
SCIENTIFIC DESCRIPTION: FluoBacTracker is an ImageJ plugin allowing the segementation and tracking of growing bacterial cells from time-lapse microscopy movies. The segmentation and tracking algorithms used by FluoBacTracker have been developed by Lionel Moisan and colleagues at Université Paris Descartes.
FUNCTIONAL DESCRIPTION: FluoBacTracker has the following functionalities: 1) Select regions of interest in images of microcolonies 2) Denoise and renormalize the images 3) Identify each cells in each image (segmentation) 4) Follow cells through the whole movie (tracking), including the detection of cells washed out from a microfluidics channel 5) Detect divisions and construct cell lineage of the population
NEWS OF THE YEAR: Version 2 of FluoBacTracker also allows the analysis of microscopy of bacteria growing in a microfluidics device called "mother machine".

- Participants: Hugues Berry, Cyril Dutrieux, Hidde De Jong, Charles Kervrann, David Parsons and Magali Vangkeosay
- Partners: Université Descartes - UGA
- Contact: Hugues Berry
- URL: http://fluobactracker.inrialpes.fr

5.4. GNA

Genetic Network Analyzer
KEYWORDS: Model Checking - Bioinformatics - Gene regulatory networks - Qualitative simulation
SCIENTIFIC DESCRIPTION: Genetic Network Analyzer (GNA) is the implementation of methods for the qualitative modeling and simulation of gene regulatory networks developed in the IBIS project-team.
FUNCTIONAL DESCRIPTION: The input of GNA consists of a model of the regulatory network in the form of a system of piecewise-linear differential equations (PLDEs), supplemented by inequality constraints on the parameters and initial conditions. From this information, GNA generates a state transition graph summarizing the qualitative dynamics of the system. In order to analyze large graphs, GNA allows the user to specify properties of the qualitative dynamics of a network in temporal logic, using high-level query templates, and to verify these properties on the state transition graph by means of standard model-checking tools, either locally installed or accessible through a remote web server.

RELEASE FUNCTIONAL DESCRIPTION: (1) it supports the editing and visualization of regulatory networks, in an SBGN-compatible format, (2) it semi-automatically generates a prototype model from the network structure, thus accelerating the modeling process, and (3) it allows models to be exported in the SBML Qual standard.
NEWS OF THE YEAR: Use for the modeling of the osmotic stress response network in E. coli.

- Participants: François Rechenmann, Hidde De Jong and Michel Page
- Partner: UGA
- Contact: Hidde De Jong
- Publications: Genetic Network Analyzer: A Tool for the Qualitative Modeling and Simulation of Bacterial Regulatory Networks - Piecewise linear approximations to model the dynamics of adaptation to osmotic stress by food-borne pathogens
- URL: http://www-helix.inrialpes.fr/gna

6. New Results

6.1. Qualitative modeling of gene regulatory networks in food-borne pathogens

Bacteria are able to respond to a variety of environmental stresses, which poses food safety problems when these bacteria are food-borne pathogens. Addition of salt, one of the most ancient and common way of preserving food, subjects the bacteria to an osmotic stress to which some may survive. However, the molecular mechanisms of adaptation in food-born pathogens are largely unknown. As a first step towards better understanding these adaptation processes on the molecular level, Delphine Ropers and Aline Métris from the Institute for Food Research in Norwich (UK), invited researcher in IBIS last year, developed a qualitative model of the osmotic stress response in the model bacterium *Escherichia coli*. The qualitative dynamics of the network has been analyzed using the tool GENETIC NETWORK ANALYZER (GNA). The model has allowed to reproduce the behavior of *E. coli* cells adapting to an osmotic stress by including the regulatory mechanisms involved in the process. This work has been published in the *International Journal of Food Microbiology* [21]. It paves the way to modelling stress responses of other foodborne pathogens like *Salmonella* to stresses relevant for the food industry, for which much less is known.

6.2. Analysis of fluorescent reporter gene data

The use of fluorescent and luminescent reporter genes allows real-time monitoring of gene expression, both at the level of individual cells and cell populations (Section 3.2). In order to fully exploit this technology, we need methods to rapidly construct reporter genes, both on plasmids and on the chromosome, mathematical models to infer biologically relevant quantities from the primary data, and computer tools to achieve this in an efficient and user-friendly manner. For instance, in a typical microplate experiment, 96 cultures are followed in parallel, over several hours, resulting in 10,000-100,000 measurements of absorbance and fluorescence and luminescence intensities.

Valentin Zulkower, former PhD student in IBIS, developed novel methods for the analysis of reporter gene data obtained in microplate experiments, based on the use of regularized linear inversion. This allows a range of estimation problems in the analysis of reporter gene data, notably the inference of growth rate, promoter activity, and protein concentration profiles, to be solved in a mathematically sound and practical manner. The linear inversion methods, published in *Bioinformatics* in 2015 [12], in have been implemented in the Python package WELLFARE and integrated in the web application WELLINVERTER. Funded by a grant from the Institut Français de Bioinformatique (IFB), Yannick Martin has improved WellInverter by developing a parallel computational architecture with a load balancer to distribute the analysis queries over several back-end servers, a new graphical user interface, and a plug-in system for defining high-level routines for parsing data files produced by microplate readers from different manufacturers. This has resulted in a scalable and user-friendly web service providing a guaranteed quality of service, in terms of availability and response time. This web service has been deployed on the IFB cloud and on an Inria server, accompanied by extensive user documentation, online help, and a tutorial. A paper on WELLINVERTER is in preparation.

While the use of microplate readers results in population-level measurements of gene expression, for many applications it is mandatory to monitor gene expression over time on the level of individual cells. Several developments in the past decade have enormously extended the capabilities to achieve this, in particular the combination of fluorescence time-lapse microscopy for precisely quantifying gene expression in single cells and microfluidics technology for cultivating bacteria in confined spatial compartments and under well-controlled experimental conditions. One of the most wide-spread microfluidics devices is the so-called mother machine shown in Figure 5. A major problem is that functional software for image analysis (segmentation, tracking, lineage reconstruction, ...) adapted to the requirements of mother machine applications are still rare. IBIS has therefore collaborated with the BEAGLE project-team for the adaptation of their tool FLUOBACTRACKER to the analysis of time-lapse movies of fluorescent reporter expression and bacterial growth in microfluidics devices. This collaboration, which has also involved the SERPICO project-team, was supported by the Technology Transfer and Innovation department of Inria, in the framework of the Inria Hub program, and has allowed the hiring of Cyril Dutrieux as a software engineer in IBIS.

6.3. Analysis of dynamic metabolomics data

An important step in the study of intracellular metabolism is the quantification of growth rates as well as uptake and excretion rates of metabolites in growing cellular populations. Traditional approaches are based on steady-state experiments, where time-invariant growth rates and exchange fluxes are measured in different experimental conditions. Technological advances in metabolomics have made it possible to monitor the concentration of extracellular metabolites over time, thus paving the way for the study of metabolism in transient conditions. Recovering time-varying exchange and growth rates from time-lapse metabolimics data is a key aspect of this challenge.

We have investigated the reconstruction of exchange reaction and growth rates from time-lapse measurements of external metabolite concentrations and population growth. In particular we have focused on the case of exhaustion of specific substrates, entailing sudden metabolic reorganization of the cell such as diauxie shifts in *E. coli*. Such discontinuities in the metabolic dynamics make data analysis and rate recosntruction particularly challenging but also information-rich. We have developed a Bayesian method that explicitly accounts for these sudden changes and the correlated adaptation of growth in order to accurately estimate time-varying exchange reaction and growth rates, and tested the method on real data from batch and fed-batch cultures of *E. coli* and *L. lactis* obtained at INRA/INSA Toulouse. The method is based on a time-inhomogeneous Gaussian process characterization of the rate dynamics, and Kalman smoothing techniques for the solution of the regularized estimation problem. Method and results were presented at the joint 2017 ISMB-ECCB conference, and published in the corresponding special issue of *Bioinformatics* [17]. The software implementing the method in Matlab is available at https://team.inria.fr/ibis/rate-estimation-software/, and has also been used for the data analysis in another joint publication with INRA/INSA Toulouse [20]. Further developments of the method are under consideration.

6.4. Models of carbon metabolism in bacteria

Adaptation of bacterial growth to changes in environmental conditions, such as the availability of specific carbon sources, is triggered at the molecular level by the reorganization of metabolism and gene expression: the concentration of metabolites is adjusted, as well as the concentration and activities of enzymes, the rate of metabolic reactions, the transcription and translation rates, and the stability of proteins and RNAs. This reprogramming of the bacterial cell is carried out by i) specific interactions involving regulatory proteins or RNAs that specifically respond to the change of environmental conditions and ii) global regulation involving changes in the concentration of RNA polymerase, ribosomes, and metabolite pools that globally affect the rates of transcription, translation, and degradation of all RNAs and proteins. While these phenomena have been well studied in steady-state growth conditions, recent works by IBIS members and collaborators support the view that regulatory mechanisms of growth adaptation are best observed in dynamical conditions.

A first study concerns the second messenger cAMP in *E. coli* and its role in carbon catabolite repression, the mechanism by which bacterial cells select their preferred carbon source for growth. Studies performed in steady-state conditions have questioned the importance of cAMP, leading to a controversy on its physiological role, more than fifty years after its discovery. In a recently submitted journal paper, reporting work started during the PhD thesis of Valentin Zulkower and continued over the past two years, we argue that in order to properly assess the role of cAMP one should shift the focus from steady-state to dynamical conditions. We show, by a combination of fluorescent reporter gene assays and quantitative modeling, that a transient peak in the expression of cAMP-dependent genes leads to the accumulation of proteins necessary for growth on a variety of alternative carbon sources. In the long run, the expression of genes cognate to the alternative carbon source present in the environment is maintained by dedicated positive feedback circuits. Our results thus demonstrate that carbon catabolite repression and diauxic growth need to be understood from a dynamical perspective within the context of a hierarchical regulatory network.

A quantitative description and understanding of this complex network, cutting across metabolism, gene expression, and signalling, can be accessed through mathematical modelling only. In collaboration with Andreas Kremling, professor at TU München and former visiting scientist in the IBIS project-team, Hans

Geiselmann, Delphine Ropers and Hidde de Jong developed an ensemble of variants of a simple core model of carbon catabolite repression. The model variants, with two substrate assimilation pathways and four intracellular metabolites only, differ from one another in only a single aspect, each breaking the symmetry between the two pathways in a different manner. Interestingly, all model variants are able to reproduce the data from a reference diauxic growth experiment. For each of the model variants, we predicted the behaviour in two new experimental conditions. When qualitatively comparing these predictions with experimental data, a number of models could be excluded while other model variants are still not discriminable. The best-performing model variants are based on inducer inclusion and activation of enzymatic genes by a global transcription factor, but the other proposed factors may complement these well-known regulatory mechanisms. The model ensemble, which was described in a journal paper recently submitted for publication, offers a better understanding of the variety of mechanisms that have been proposed to play a role in carbon catabolite repression, but is also useful as an educational resource for systems biology.

The same focus on the dynamics of physiological processes has shaped a project on the post-transcriptional control of carbon central metabolism in *E. coli*. In the framework of the PhD thesis of Manon Morin, supported by a Contrat Jeune Scientifique INRA-Inria, the collaboration of Delphine Ropers with Muriel Cocaign-Bousquet and Brice Enjalbert at INRA/INSA Toulouse has demonstrated the key role played by the post-transcriptional regulatory system CSR in growth transitions. In a multi-scale analysis of several wild-type and mutant strains of the CSR system, a variety of experimental data have been acquired in relevant conditions, including growth parameters, gene expression levels and metabolite pools. Data integration through the estimation of fermentation fluxes and flux balance analysis, using the method described above (Section 6.3), have elucidated the role of post-transcriptional regulation in the dynamics of glycogen storage and consumption, as well as the key role of the latter compound for bacterial fitness, through the regulation of intracellular energy levels. A paper summarizing the work has been published in *mBio* [20].

The collaboration with INRA/INSA de Toulouse is continued in the context of the PhD thesis of Thibault Etienne, funded by an INRA-Inria PhD grant, with the objective of developing models able to explain how cells coordinate their physiology and the functioning of the transcription, translation, and degradation machineries following changes in the availability of carbon sources in the environment.

6.5. Stochastic modeling and identification of gene regulatory networks in bacteria

At the single-cell level, the processes that govern single-cell dynamics in general and gene expression in particular are better described by stochastic models. Modern techniques for the real-time monitoring of gene expression in single cells enable one to apply stochastic modelling to study the origins and consequences of random noise in response to various environmental stresses, and the emergence of phenotypic variability. The potential impact of single-cell stochastic analysis and modelling ranges from a better comprehension of the biochemical regulatory mechanisms underlying cellular phenotypes to the development of new strategies for the (computer assisted or genetically engineered) control of cell populations and even of single cells.

Work in IBIS on gene expression and interaction dynamics at the level of individual cells is addressed in terms of identification of intrinsic noise models from population snapshot data, on the one hand, and the inference of models focusing on cellular variability within isogenic populations from fluorescence microscopy gene expression profiles, on the other hand. Along with modelling and inference comes analysis of the inferred models in various respects, notably in terms of identifiability, single-cell state estimation and control. Other problems related with single-cell modelling and extracellular variability are considered in eukaryotic cells through external collaborations.

Concerning identification of intrinsic noise dynamics in single cells, previous results on the contribution of stochasticity to parameter identifiability have been revisited in the context of reconstruction of unknown networks. For the case of population snapshot meaurements, where the dynamics of the population statistics are observed by simple time-lapse experiments, we performed an analytical study of the additional information provided by variance measurements for the reconstruction of unknown first-order kinetics. Based on simulated

example, we showed that a tremendous improvement in network reconstruction is achieved relative to the utilization of population-average statistics alone, as addressed by deterministic modelling. These exciting yet preliminary results were published in the form of a paper in the proceedings of the *IFAC World Congress* [22] and will be further developed.

Reconstruction of promoter activity statistics from reporter gene population snapshot data has been further investigated, leading to a full-blown spectral analysis and reconstruction method for reporter gene systems. Building upon reults in previous conference papers, in the context of the ANR project MEMIP (Section 8.2), we have characterized reporter systems as noisy linear systems operating on a stochastic input (promoter activity), and developed an inversion method for nonparametric estimation of promoter dynamics, namely the autocovariance function, from the considered readouts. These theoretical and simulation results have been submitted for journal publication and are also available as an arXiv pre-print. The method will be further developed and applied to real data and case studies.

Modelling of heterogeneity in isogenic cell populations is also an active research direction. Still in the context of MEMIP, in collaboration with the INBIO team, we are considering generalizations of our achievements on Mixed-Effects modelling and inference on yeast, in order to account for different sources of noise and lineage effects. As an offspring of this work, a study of inter-individual variability of *E. coli* gene expression and growth rate in growth arrest-and-restart experiments has been carried out with BIOCORE. Results obtained so far are part of the PhD thesis of Stefano Casagrande.

6.6. Modelling bacterial growth

Various mathematical approaches have been used in the literature to describe the networks of biochemical reactions involved in microbial growth. With various levels of detail, the resulting models provide an integrated view of these reaction networks, including the transport of nutrients from the environment and the metabolism and gene expression allowing the conversion of these nutrients into biomass. The models hence bridge the scale between individual reactions to the growth of cell populations. In a review article published in the *Journal of the Royal Society Interface* [18], several IBIS members as well as colleagues from the BIOCORE project-team, discuss various models of microbial growth that are, at first sight, quite diverse. They have a different scope and granularity, make different simplifications, use different approaches to obtain predictions from the model structure and have their origin in different fields. In the review we derive a general framework for the kinetic modelling of microbial growth from a few basic hypotheses on the systems of biochemical reactions underlying microbial growth. Additional simplifying assumptions lead to the several families of approximate models of microbial growth found in the literature, including self-replicator models of bacterial growth developed by Nils Giordano in his PhD thesis and published in *PLoS Computational Biology* last year [5]. This reveals how the models are related on a deeper level and provides a sound basis for further modelling studies.

Analysing the dynamics of some of the network models mentioned above becomes quickly intractable, when mathematical functions are for instance given by complex algebraic expressions resulting from the mass balance of biochemical reactions. In a paper published in the *Bulletin of Mathematical Biology* [16], Edith Grac, former post-doc in Ibis, Delphine Ropers, and Stefano Casagranda and Jean-Luc Gouzé from the BIOCORE project-team, have studied how monotone system theory and time-scale arguments can be used to reduce high-dimension models based on the mass-action law. Applying the approach to an important positive feedback loop regulating the expression of RNA polymerase in *E. coli*, made it possible to study the stability of the system steady states and relate the dynamical behaviour of the system to observations on the physiology of the bacterium *E. coli*.

6.7. Growth control in bacteria and biotechnological applications

The ability to experimentally control the growth rate is crucial for studying bacterial physiology. It is also of central importance for applications in biotechnology, where often the goal is to limit or even arrest growth. Growth-arrested cells with a functional metabolism open the possibility to channel resources into

the production of a desired metabolite, instead of wasting nutrients on biomass production. The objective of the RESET project, supported in the framework of the Programme d'Investissements d'Avenir (Section 8.2), is to develop novel strategies to limit or completely stop microbial growth and to explore biotechnological applications of these approaches.

A foundation result for growth control in bacteria was published in the journal *Molecular Systems Biology* at the end of 2015 [6]. In that publication, we described an engineered *E. coli* strain where the transcription of a key component of the gene expression machinery, RNA polymerase, is under the control of an inducible promoter. By changing the inducer concentration in the medium, we can adjust the RNA polymerase concentration and thereby switch bacterial growth between zero and the maximal growth rate supported by the medium. The publication also presented a biotechnological application of the synthetic growth switch in which both the wild-type *E. coli* strain and our modified strain were endowed with the capacity to produce glycerol when growing on glucose. Cells in which growth has been switched off continue to be metabolically active and harness the energy gain to produce glycerol at a twofold higher yield than in cells with natural control of RNA polymerase expression. Remarkably, without any further optimization, the improved yield is close to the theoretical maximum computed from a flux balance model of *E. coli* metabolism. This work has been continued in several directions in the context of the RESET project by Célia Boyat. Moreover, extending work on self-replicator models of bacterial growth, we have studied the production of metabolites by means of the growth switch from an optimal control perspective, in a paper that is currently being prepared for publication.

In a review published in *Trends in Microbiology* this year [19], we have put the scientific results mentioned above in a broader context. As illustrated by the synthetic growth switch, reengineering the gene expression machinery allows modifying naturally evolved regulatory networks and thereby profoundly reorganizing the manner in which bacteria allocate resources to different cellular functions. This opens new opportunities for our fundamental understanding of microbial physiology and for a variety of applications. We describe how recent breakthroughs in genome engineering and the miniaturization and automation of culturing methods have offered new perspectives for the reengineering of the transcription and translation machinery in bacteria as well as the development of novel *in vitro* and *in vivo* gene expression systems. In our paper, we review different examples from the unifying perspective of resource reallocation, and discuss the impact of these approaches for microbial systems biology and biotechnological applications.

7. Bilateral Contracts and Grants with Industry

7.1. BGene

Participants: Johannes Geiselmann, Corinne Pinel.

BGene is a start-up company of Université Grenoble Alpes in the field of DNA engineering. BGene proposes efficient and custom-made modifications of bacterial genomes, leaving no scars or antibiotics resistance genes. The company has know-how and expertise at all stages of the development process, including the *in-silico* design of a desired construction, the choice of the appropriate genetic tools, and the delivery of the finished product. Former IBIS-member Caroline Ranquet and Johannes Geiselmann are co-founders of BGene, together with Marie-Gabrielle Jouan (Floralis, Université Grenoble Alpes). For more information on BGene, see http://www.bgene-genetics.com/.

7.2. Genostar

Participants: Hidde de Jong, Michel Page.

Genostar, an Inria start-up created in 2004, provides bioinformatics solutions for the comparative analysis of bacterial genomes, proteomes and metabolomes. Genostar's software suite performs the annotation of sets of genomic sequences, *i.e.*, the identification of the coding sequences and other features, followed by the prediction of the functions of the gene products. The modules which make up the software suite were originally developed within the Genostar consortium and the HELIX project team at Inria Grenoble - Rhône-Alpes. The software suite also includes the modeling and simulation tool GNA developed by members of IBIS. Unfortunately after the retirement of its CEO, former IBIS member François Rechenmann, Genostar ceased its activity.

8. Partnerships and Cooperations

8.1. Regional Initiatives

Project name	RNAfluo: Quantification d'ARN régulateurs in vivo
Coordinators	S. Lacour
IBIS participants	S. Lacour
Type	AGIR program, Université Grenoble Alpes (2016-2019)

8.2. National Initiatives

Project name	COSY: real-time COntrol of SYnthetic microbial communities
Coordinator	E. Cinquemani
IBIS participants	E. Cinquemani, H. de Jong, J. Geiselmann, M. Mauri, T. Muszbek, C. Pinel, D. Ropers
Type	Inria Project Lab (2017-2021)
Web page	https://project.inria.fr/iplcosy/

Project name	AlgeaInSilico: Prédire et optimiser la productivité des microalgues en fonction de leur milieu de croissance
Coordinator	O. Bernard
IBIS participants	H. de Jong, N. Giordano
Type	Inria Project Lab (2015-2019)
Web page	https://project.inria.fr/iplalgaeinsilico/

Project name	RESET – Arrest and restart of the gene expression machinery in bacteria: from mathematical models to biotechnological applications
Coordinator	H. de Jong
IBIS participants	C. Boyat, E. Cinquemani, J. Geiselmann, H. de Jong, S. Lacour, L. Lancelot, Y. Markowicz, C. Pinel, D. Ropers
Type	Bioinformatics call, Investissements d'Avenir program (2012-2017)
Web page	https://project.inria.fr/reset/

Project name	MEMIP – Modèles à effets mixtes de processus intracellulaires : méthodes, outils et applications
Coordinator	G. Batt
IBIS participants	E. Cinquemani, D. Ropers
Type	ANR project (2016-2020)

Project name	ENZINVIVO – Détermination in vivo des paramètres enzymatiques dans une voie métabolique synthétique
Coordinator	G. Truan
IBIS participants	J. Geiselmann, H. de Jong
Type	ANR project (2016-2020)

Project name	MAXIMIC – Optimal control of microbial cells by natural and synthetic strategies
Coordinator	H. de Jong
IBIS participants	C. Boyat, E. Cinquemani, J. Geiselmann, H. de Jong, C. Pinel, D. Ropers
Type	ANR project (2017-2021)

Project name	Analyse intégrative de la coordination entre stabilité des ARNm et physiologie cellulaire chez Escherichia coli
Coordinators	D. Ropers, M. Cocaign-Bousquet (Inra, LISBP)
IBIS participants	T. Etienne, D. Ropers
Type	Contrat Jeune Scientifique Inra-Inria (2016-2019)

Project name	A web application for the analysis of time-series fluorescent reporter gene data
Coordinator	H. de Jong
IBIS participants	E. Cinquemani, J. Geiselmann, Y. Martin, M. Page, D. Ropers, V. Zulkower (University of Edinburgh)
Type	IFB call for development of innovative bioinformatics services for life sciences (2016-2017)

Project name	FluoBacTracker – Adaptation et valorisation scientifique du logiciel FluoBacTracker
Coordinator	H. de Jong, H. Berry
IBIS participants	C. Dutrieux, H. de Jong, J. Geiselmann
Type	Inria Hub (2016-2017)

Project name	CoSoft – Control software for a system of mini-bioreactors
Coordinator	E. Cinquemani
IBIS participants	E. Cinquemani, H. de Jong, J. Geiselmann, T. Muszbek
Type	Inria Hub (2017-2018)

8.3. European Initiatives

8.3.1. Collaborations with Major European Organizations

Laboratoire d'Automatique at Ecole Polytechnique Fédérale de Lausanne (Switzerland), Giancarlo Ferrari-Trecate

Control theory and systems identification with applications to systems biology

Automatic Control Lab at ETH Zürich (Switzerland), John Lygeros

Control theory and systems identification with applications to systems biology

Computational Microbiology research group, Institute of Food Research, Norwich (United Kingdom), Aline Métris and József Baranyi

Mathematical modelling of survival and growth of bacteria

9. Dissemination

9.1. Research

9.1.1. Scientific events: organizing committees

9.1.1.1. Member of organizing committees

IBIS members	Conference, workshop, school	Date
Hidde de Jong	Workshop on microbial growth control and biotechnological applications, La Grande Motte	Oct 2017
Hidde de Jong	CompSysBio: Advanced Lecture Course on Computational Systems Biology, Aussois	Mar 2017
Delphine Ropers	Séminaire de Modélisation du Vivant (SeMoVi), Lyon and Grenoble	2016

9.1.2. Scientific events: selection committees

9.1.2.1. Chair of conference program committees

IBIS member	Conference, workshop, school	Role
Eugenio Cinquemani	European Control Conference (ECC 2017)	Associate editor

9.1.2.2. Member of conference program committees

IBIS member	Conference, workshop, program
Eugenio Cinquemani	ECC 2017
Hidde de Jong	ISMB/ECCB 2017, CMSB 2018, WML 2018
Delphine Ropers	JOBIM 2017

9.1.3. Journals

9.1.3.1. Member of editorial boards

IBIS member	Journal
Johannes Geiselmann	Frontiers in Microbiology (review editor)
Hidde de Jong	Journal of Mathematical Biology
Hidde de Jong	Biosystems
Hidde de Jong	ACM/IEEE Transactions on Computational Biology and Bioinformatics

9.1.4. Scientific evaluation and expertise

IBIS member	Organism	Role
Johannes Geiselmann	INRA	Member of scientific advisory committee Microbiologie, Adaptation, Pathogénie
Johannes Geiselmann	UMR5240 CNRS-UCBL-INSA-BayerCropScience	Member scientific council
Johannes Geiselmann	ARC1, Rhône-Alpes region	Member scientific committee
Hidde de Jong	Microbiology and Food Chain Department, Inra	Member scientific council
Hidde de Jong	HCERES	Member of evaluation committee of TAGC laboratory (UMR U1090), Marseille

9.1.5. Recruitment committees

IBIS member	Organism	Recruitment
Hidde de Jong	INRA	Chargés de recherche
Johannes Geiselmann	INSA de Lyon	Full professor
Delphine Ropers	Inria	Chargés de recherche CR1 (jury d'admissibilité)
Delphine Ropers	Inria Sophia-Antipolis	Chargés de recherche (jury d'admissibilité)
Delphine Ropers	INSA de Lyon	Assistant professor

9.1.6. Invited talks

Eugenio Cinquemani

Title	Event and location	Date
Reconstruction of promoter activity statistics from reporter protein population snapshot data	Workshop on "Modélisation stochastique et analyse statistique de l'expression génétique", Laboratoire de Mathématiques et Applications (LMA) de l'Université de Poitiers	Jan 2017
Modeling of stochastic gene expression	Tutorial at CompSysBio: Advanced Lecture Course on Computational Systems Biology, Aussois	Mar 2017
Toward automatic control of synthetic microbial communities	Journées Scientifiques Inria 2017, Sophia Antipolis – Méditerranée	Jun 2017

Hidde de Jong

Title	Event and location	Date
Analysis and control of bacterial regulatory networks	Seminar Systems Biology Institute, ETH Zürich, Switzerland	Feb 2017
Qualitative modeling and simulation of bacterial regulatory networks	Course at Instituto de Tecnologia Química e Biológica, Oeiras, Portugal	Feb 2017
Natural and synthetic control of resource allocation in bacteria	Seminar at Instituto de Tecnologia Química e Biológica, Oeiras, Portugal	Feb 2017
Integrated models of the cell: metabolism, gene expression, signalling	Tutorial at CompSysBio: Advanced Lecture Course on Computational Systems Biology, Aussois	Mar 2017
Presentation IBIS and IPL COSY	Réunion de suivi du Programme Transversal Microbiote, Inserm, Paris	Jun 2017
Natural and synthetic control of resource allocation in bacteria	Keynote talk at 3rd BeNeLuxFra Student Symposium, Lille	Jul 2017
Natural and synthetic control of resource allocation in bacteria	International Workshop on Control Engineering and Synthetic Biology, London	Jul 2017
Resource allocation in microorganisms: Some control-theoretical problems	Journée McTAO, Institut mathématique de Bourgogne, Dijon	Dec 2017
A dynamic analysis of carbon catabolite repression and diauxic growth in bacteria	6th network retreat of BEeSy, Saint Hugues de Biviers	Dec 2017

Johannes Geiselmann

Title	Event and location	Date
Growth rate control in Escherichia coli	Seminars in Molecular Biology, University of British Columbia, Vancouver, Canada	Jun 2017
Changing resource allocation and growth rate by a genetic control of transcription and DNA replication	Workshop growth rate control in bacteria, BioSynSys conference, Montpellier, France	Oct 2017
Engineering resource allocation and growth rate in Escherichia coli	International symposium on Systems, Synthetic and Chemical Biology, Kolkata, India	Dec 2017

Stephan Lacour

Title	Event and location	Date
NGS sequencing techniques in biology	Seminar Mechanobiology, UGA Phitem, Grenoble	Jan 2017
Direct versus indirect gene regulation by the stress response SigmaS factor	Seminar Institut de Biologie Structurale, Grenoble	Feb 2017
Modulation of curli production in Escherichia coli by non-coding RNA	Réseau National Biofilm (RNB), Clermont-Ferrand	Dec 2017

Delphine Ropers

Title	Event and location	Date

9.1.7. Research administration

IBIS member	Committee	Role
Eugenio Cinquemani	Inria Grenoble - Rhône-Alpes	Member Comité des Emplois Scientifiques (CES)
Eugenio Cinquemani	Inria Grenoble - Rhône-Alpes	Member Comité des Utilisateurs des Moyens Informatiques (CUMI)
Eugenio Cinquemani	Inria	Member Comité Administrative Paritaire (CAP)
Hidde de Jong	Inria Grenoble - Rhône-Alpes	Member scientific council
Hidde de Jong	Inria	Member working group on International Relations of Conseil d'Orientation Scientifique et Technique (COST)
Delphine Ropers	Inria	Member of Commission d'évaluation d'Inria
Delphine Ropers	Inria	Member of Groupe de travail plan stratégique
Delphine Ropers	Inria Grenoble - Rhône-Alpes	Référente chercheurs
Delphine Ropers	Inria Grenoble - Rhône-Alpes	Member of Comité des études doctorales (CED)

9.2. Teaching - Supervision - Committees

9.2.1. Teaching

Four members of the IBIS team are either full professor, associate professor or assistant professor at the Université Grenoble Alpes. They therefore have a full teaching service (at least 192 hours per year) and administrative duties related to the organization and evaluation of the university course programs on all levels (from BSc to PhD). Besides the full-time academic staff in IBIS, the following people have contributed to courses last year.

Eugenio Cinquemani

Master: Stochastic modelling of gene regulatory networks, M2, BIM, INSA de Lyon (6 h)

Master: Statistics for systems biology, M1, Master Approches Interdisciplinaires du Vivant, CRI/Université Paris Descartes (24 h, also in charge of 24 h of practicals)

Master: Modelling and identification of metabolic networks, M1, Phelma, INP Grenoble (4 h)

Hidde de Jong

Master: Modeling and simulation of gene regulatory networks, M2, BIM, INSA de Lyon (20 h)

Master: Integrated models of the cell: metabolism, gene expression, signalling, M2, ENS Paris (6 h)

Master: Integrated models of the cell: metabolism, gene expression, signalling, M2, Institut de Technologie et d'Innovation, Paris Sciences Lettres (PSL) (6 h)

Delphine Ropers

Master: Modelling in systems biology, M1, Phelma, INP Grenoble (16 h)

Master: Modeling and simulation of genetic regulatory networks, M1, Université Grenoble Alpes (9 h)

Master: Modeling and simulation of genetic regulatory networks, M2, INSA de Toulouse (4 h)

9.2.2. Supervision

PhD defended: **Stefano Casagranda**, Analysis and control of models of gene regulatory networks. Supervisors: Jean-Luc Gouzé (BIOCORE) and Delphine Ropers

PhD defended: **Nils Giordano**, Microbial growth control in shifting environments: Theoretical and experimental study of resource allocation in Escherichia coli. Supervisors: Hidde de Jong and Johannes Geiselmann

PhD defended: **Bernard Chelli Ponce de Leon**, Quantitative study of the effects of low DnaA concentrations in Escherichia coli, using the uhp pathway as an inducible expression system. Supervisors: Irina Mihalcescu (Université Grenoble Alpes) and Johannes Geiselmann

PhD in progress: **Thibault Etienne**, Analyse intégrative de la coordination entre stabilité des ARNm et physiologie cellulaire chez *Escherichia coli*. Supervisors: Delphine Ropers and Muriel Cocaign-Bousquet (INRA Toulouse)

PhD in progress: **Joël Espel**, RNA engineering: Design of the dynamical folding of RNA and of RNA switches. Supervisors: Alexandre Dawid (Université Grenoble Alpes) and Johannes Geiselmann

9.2.3. PhD thesis committees, PhD advisory committees, and habilitation committees

PhD thesis committees

IBIS member	Role	PhD student	University	Date
Eugenio Cinquemani	Invité	Stefano Casagranda	Université Nice Sophia Antipolis	Jun 2017
Hidde de Jong	Président	Bernard Chelli Ponce de Leon	Université de Grenoble	Mar 2017
Hidde de Jong	Directeur de thèse	Nils Giordano	Université de Grenoble	Mar 2017
Hidde de Jong	Rapporteur	Mathias Weyder	Université de Toulouse	Mar 2017
Johannes Geiselmann	Rapporteur	Stanislas Thiriet-Rupert	Université du Mans	Jan 2017
Johannes Geiselmann	Président	Defne Dalkara	Université de Grenoble	Jan 2017
Johannes Geiselmann	Directeur de thèse	Nils Giordano	Université de Grenoble	Mar 2017
Johannes Geiselmann	Directeur de thèse	Bernard Chelli Ponce de Leon	Université de Grenoble	Mar 2017
Johannes Geiselmann	Rapporteur	Lionel Uhl	Université de Marseille	Apr 2017
Johannes Geiselmann	Rapporteur	Zoran Marinkovic	Université Paris Diderot	Nov 2017
Stephan Lacour	Examinateur	Benjamin Diel	Université de Lyon	Sep 2017
Stephan Lacour	Examinateur	Sophie Bouillet	Université Aix-Marseille	Dec 2017
Delphine Ropers	Directrice de thèse	Stefano Casagranda	Université Nice Sophia Antipolis	Jun 2017
Delphine Ropers	Examinateur	Guillaume Madelaine	Université de Lille	Mar 2017

Habilitation (HDR) committees

IBIS member	Role	PhD student	University	Date
Hidde de Jong	Rapporteur	Elisabeth Rémy	Université Aix-Marseille	Avr 2017

PhD advisory committees

IBIS member	PhD student	University
Eugenio Cinquemani	Luis Pereira	Université Nice Sophia Antipolis
Stephan Lacour	Alice Berry	Université de Grenoble
Stephan Lacour	Simon Léonard	Université Claude Bernard de Lyon

9.2.4. Teaching adminstration

Yves Markowicz is director of the BSc department at Université Grenoble Alpes.

Michel Page is coordinator of the master Systèmes d'information et d'organisation at the Institut d'Adminstration des Entreprises (IAE), Université Grenoble Alpes.

Eugenio Cinquemani organizes a module on statistics in systems biology at CRI/Université Paris Descartes.

Delphine Ropers organizes a module on the mathematical modeling of biological systems at PHELMA, INP Grenoble.

Hidde de Jong organizes with Daniel Kahn a module on the modeling of genetic and metabolic networks at INSA de Lyon.

10. Bibliography

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