IN PARTNERSHIP WITH:
Université Joseph Fourier (Grenoble)

Activity Report 2015

Project-Team IBIS

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

IN COLLABORATION WITH: Laboratoire Interdisciplinaire de Physique

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Computational Biology

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Project-Team IBIS

Creation of the Project-Team: 2009 January 01

Keywords:

Computer Science and Digital Science:

3.1.1. - Modeling, representation
3.4.5. - Bayesian methods
6.1.1. - Continuous Modeling (PDE, ODE)
6.1.2. - Stochastic Modeling (SPDE, SDE)
6.2.1. - Numerical analysis of PDE and ODE
6.2.3. - Probabilistic methods
6.2.4. - Statistical methods
6.3.1. - Inverse problems
6.3.2. - Data assimilation
6.3.3. - Data processing
6.4.1. - Deterministic control

Other Research Topics and Application Domains:

1. - Life sciences
1.1.10. - Mathematical biology
1.1.11. - Systems biology
1.1.12. - Synthetic biology
1.1.2. - Molecular biology
1.1.5. - Genetics
1.1.6. - Genomics
1.1.9. - Bioinformatics
4.2.1. - Biofuels

IBIS is bilocated at the Inria Grenoble - Rhône-Alpes research center in Montbonnot and the Laboratoire Interdisciplinaire de Physique (CNRS UMR 5588) in Saint Martin d'Hères.

1. Members

Research Scientists

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Stéphan Lacour [Université Grenoble Alpes, Associate Professor]
Yves Markowicz [Université Grenoble Alpes, Associate Professor]
Michel Page [Université Grenoble Alpes, Associate Professor]

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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.

[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 aims of IBIS raise new problems 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 maintained a research activity in their domain of origin (automatic control, molecular biology of HIV, immunology, ...) or made a contribution to research projects on different topics (human cancer cell genomics, plant modeling, ...). 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.

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 Université 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. Both groups include researchers and technicians from other institutes, such as CNRS and the Université Pierre Mendès France (UPMF). 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.

3. Research Program

3.1. Analysis of qualitative dynamics of gene regulatory networks

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

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.

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

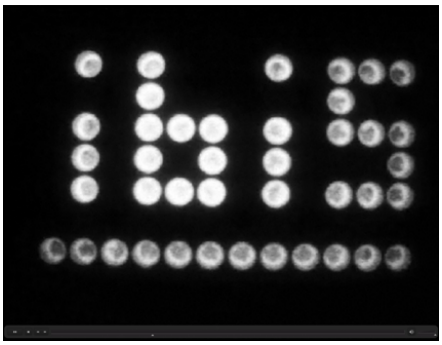


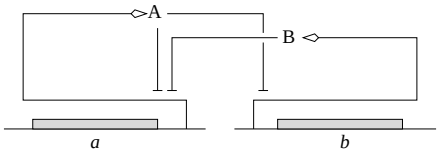
Figure 1. Display of the project-team name on a "bacterial billboard" (see http://ibis.inrialpes.fr for the corresponding movie). A microplate containing a minimal medium (with glucose and acetate) is filmed during 36 hours. Wells contain E. coli bacteria which are transformed with a reporter plasmid containing 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 more carbon source in the wells. As a consequence, the reductive power falls and the bacterial billboard switches off. Source: Guillaume Baptist.

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.

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

Participants: Eugenio Cinquemani [Correspondent], Johannes Geiselmann, Hidde de Jong, Stéphan Lacour, Michel Page, Corinne Pinel, Delphine Ropers, Valentin Zulkower.

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.



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

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

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

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

(a) (b)

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 ($\gamma_a \, x_a$).

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.

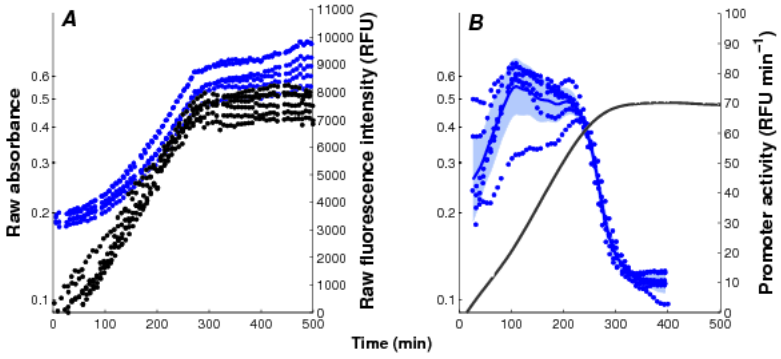


Figure 3. Monitoring of bacterial gene expression in vivo using fluorescent reporter genes (Stefan et al., PLoS Computational Biology, 11(1):e1004028, 2015). The plots show the primary data obtained in a kinetic experiment with E. coli cells, focusing on the expression of the motility gene tar in a mutant 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 (Sections 5.4 and 5.3). 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 (Switzerland) and the University of Pavia (Italy). 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, Johannes Geiselmann, Stéphan Lacour, Yves Markowicz, Manon Morin, Michel Page, Corinne Pinel, Stéphane Pinhal, Delphine Ropers [Correspondent], Valentin Zulkower.

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: Cindy Gomez Balderas, Eugenio Cinquemani, Johannes Geiselmann [Correspondent], Nils Giordano, Hidde de Jong, Stéphan Lacour, Delphine Ropers, Alberto Soria-Lopéz.

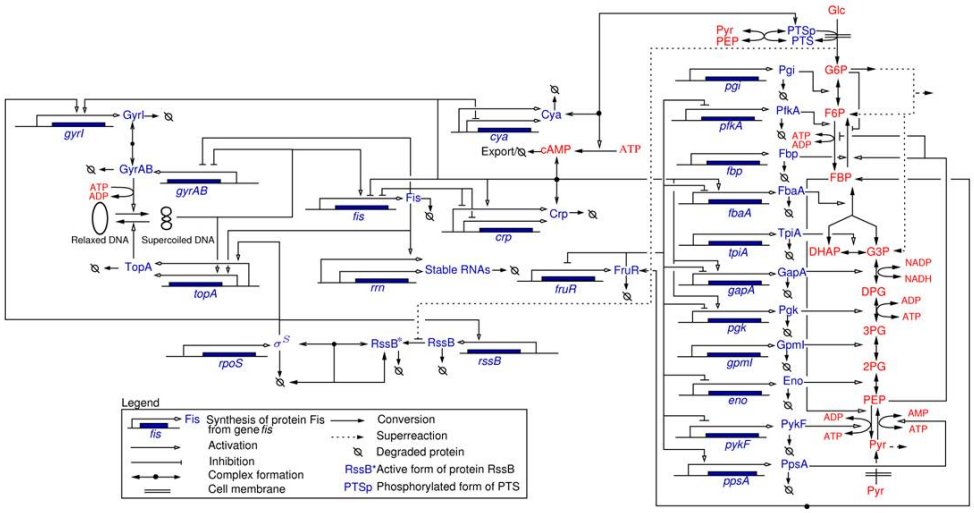


Figure 4. Network of key genes, proteins, and regulatory interactions involved in the carbon assimilation network in E. coli (Baldazzi et al., PLoS Computational Biology, 6(6):e1000812, 2010). The metabolic part includes the glycolysis/gluconeogenesis pathways as well as a simplified description of the 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.

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.

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 Université Paris Descartes.

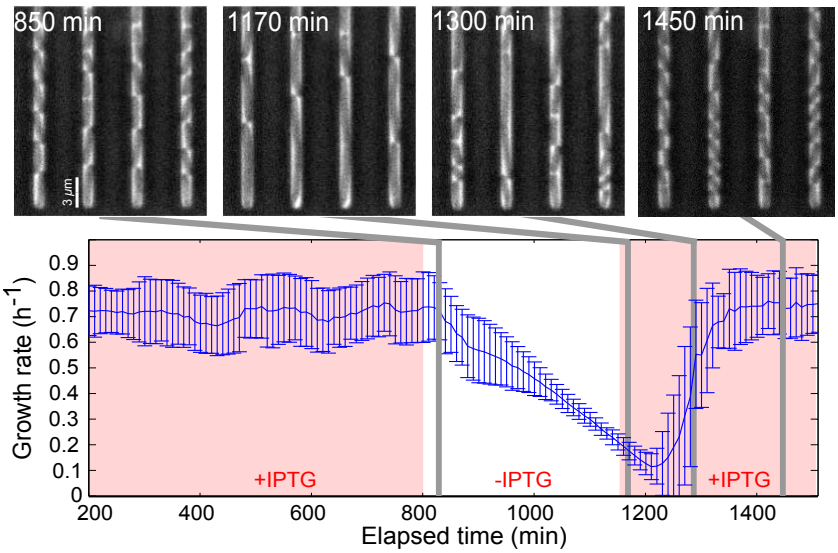


Figure 5. Growth arrest by external control of the gene expression machinery (Izard, Gomez Balderas et al., Molecular Systems Biology, 11:840, 2015). An E. coli strain in which an essential component of the gene expression machinery, the $\beta\beta'$ subunits of RNA polymerase, was put under the control 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

A paper based on the PhD thesis of Jérôme Izard and the post-doctoral work of Cindy Gomez Balderas was published in *Molecular Systems Biology* this year [18]. The paper describes foundational results for the RESET project (Section 8.2). A paper by Eugenio Cinquemani and colleagues from the LIFEWARE project-team and from the University of Pavia was accepted for *PLoS Computational Biology* this year [20], while a paper based on the PhD thesis of Valentin Zulkower was published in a special issue of *Bioinformatics* associated with the major bioinformatics conference ISMB/ECCB [24].

5. New Software and Platforms

5.1. Genetic Network Analyzer (GNA)

KEYWORDS: Bioinformatics - Gene regulatory networks - Qualitative simulation - Model checking
GENETIC NETWORK ANALYZER (GNA) is the implementation of methods for the qualitative modeling and simulation of gene regulatory networks developed in the IBIS project. 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. GNA is currently distributed by the company Genostar, but remains freely available for academic research purposes. The current version is GNA 8.7.1. In comparison with the previously distributed versions, GNA 8.7.1 has the following additional functionalities: (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.

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- URL: http://www-helix.inrialpes.fr/gna

5.2. WellFARE

KEYWORDS: Bioinformatics - Statistics - Data visualization - Data modeling
WELLFARE is a Python library implementing linear inversion methods for the reconstruction of gene expression profiles from fluorescent or luminescent reporter gene data. 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.

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- Contact: Hidde de Jong
- URL: https://github.com/ibis-inria/wellfare

5.3. WellInverter

KEYWORDS: Bioinformatics - Statistics - Data visualization - Data modeling
WELLINVERTER is a web application that implements linear inversion methods for the reconstruction of gene expression profiles from fluorescent or luminescent reporter gene data. 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.

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5.4. WellReader

WELLREADER is a program for the analysis of gene expression data obtained by means of fluorescent and luminescent reporter genes. WELLREADER reads data files in an XML format or in a format produced by microplate readers, and allows the user to detect outliers, perform background corrections and spline fits, compute promoter activities and protein concentrations, and compare expression profiles across different conditions. WELLREADER has been written in MATLAB and is available under an LGPL licence, both as source code (M files) and compiled code (platform-specific binary files).

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- URL: http://ibis.inrialpes.fr/article957.html

6. New Results

6.1. Inference of bacterial regulatory networks from 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. Over the past few years, we put into place an experimental platform and data analysis software, notably the WELLREADER program (Section 5.4), to allow biologists to make the most out of the information contained in reporter gene expression data. An invited review on the analysis of fluorescent reporter gene data was published in the proceedings of the Third International Workshop on Hybrid Systems Biology (HSB 14) [25].

Valentin Zulkower, in the framework of his PhD thesis, has developed novel methods for the analysis of reporter gene data, 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. We have evaluated the validity of the approach using *in-silico* simulation studies, and observed that the methods are more robust and less biased than indirect approaches usually encountered in the experimental literature based on smoothing and subsequent processing of the primary data, like in WELLREADER. We have applied the methods to the analysis of fluorescent reporter gene data acquired in kinetic experiments with *Escherichia coli*. The methods were shown capable of reliably reconstructing time-course profiles of growth rate, promoter activity, and protein concentration from weak and noisy signals at low population volumes. Moreover, they captured critical features of those profiles, notably rapid changes in gene expression during growth transitions. The linear inversion methods have been implemented in the Python package WELLFARE, and integrated by Michel Page in the web application WELLINVERTER (Section 5.3). This work was presented at the major bioinformatics conference ISMB/ECCB 2015 and published in the special issue of *Bioinformatics* associated with the conference [24]. The Institut Français de Bioinformatique (IFB) accepted a proposal to extend WellInverter into a scalable and user-friendly web service providing a guaranteed quality of service, in terms of availability and response time. This web service will be deployed on the IFB platform and accompanied by extensive user documentation, online help, and a tutorial.

Over the years, the above tools have been used in several studies in IBIS directed at the experimental mapping of gene regulatory networks in *E. coli*. An example is the motility network of *E. coli*, studied by Diana Stefan in the context of her PhD thesis. The main thrust of this work lies in clarifying and solving methodological issues in the automated inference of quantitative models of gene regulatory networks from time-series gene expression data, also called reverse engineering in the bioinformatics literature. The application of existing reverse engineering methods is commonly based on implicit assumptions on the biological processes under study. First, the measurements of mRNA abundance obtained in transcriptomics experiments are taken to be representative of protein concentrations. Second, the observed changes in gene expression are assumed to be solely due to transcription factors and other specific regulators, while changes in the activity of the gene expression machinery and other global physiological effects are neglected. While convenient in practice, these assumptions are often not valid and bias the reverse engineering process. In her PhD thesis, Diana Stefan systematically investigated, using a combination of models and experiments, the importance of this bias and possible corrections. She measured with the help of fluorescent reporter genes the activity of genes involved in the FliA-FlgM module of the *E. coli* motility network. From these data, protein concentrations and global physiological effects were estimated by means of kinetic models of gene expression. The results indicate that correcting for the bias of commonly-made assumptions improves the quality of the models inferred from the data. Moreover, it was shown by simulation that these improvements are expected to be even stronger for systems in which protein concentrations have longer half-lives and the activity of the gene expression machinery varies more strongly across conditions than in the FliA-FlgM module. The approach proposed in this study is broadly applicable when using time-series transcriptome data to learn about the structure and dynamics of regulatory networks. The paper describing the work was published in *PLoS Computational Biology* [23].

In addition to reporter gene data, a variety of other experimental data can be used for the mapping of gene regulatory networks. For example, using Chromatin Immunoprecipitation-sequencing (ChIP-seq) experiments, Stéphan Lacour and colleagues have identified a large number of target promoters of the sigma factor σ^S during the transition from exponential to stationary phase. Sigma factors are accesory subunits of RNA polymerase, allowing the recognition of specific promoter sequences by the transcriptional machinery, and σ^S is known to specifically accumulate in a variety of stress conditions. The study, published in *Scientific Reports* [21], has confirmed the importance of σ^S for redirecting RNA polymerase to promoters that drive the expression of genes necessary for the survival of *E. coli* after nutrient exhaustion. Furthermore, the results highlight the role of σ^S in the regulation of several noncoding RNAs.

6.2. Models of carbon metabolism in bacteria

All free-living bacteria have to adapt to a changing environment. Specific regulatory systems respond to particular stresses, but the most common decision bacteria have to make is the choice between alternative carbon sources, each sustaining a specific, maximal growth rate. Many bacteria have evolved a strategy that consists in utilizing carbon sources sequentially, in general favouring carbon sources that sustain a higher growth rate. As long as a preferred carbon source is present in sufficient amounts, the synthesis of enzymes necessary for the uptake and metabolism of less favourable carbon sources is repressed. This phenomenon is called Carbon Catabolite Repression (CCR) and the most salient manifestation of this regulatory choice is diauxic growth, a phenomenon discovered by Jacques Monod more than 70 years ago. Although this system is one of the paradigms of the regulation of gene expression in bacteria, the underlying mechanisms remain controversial. CCR involves the coordination of different subsystems of the cell - responsible for the uptake of carbon sources, their breakdown for the production of energy and precursors, and the conversion of the latter to biomass.

The complexity of this integrated system, with regulatory mechanisms cutting across metabolism, gene expression, signaling and subject to global physical and physiological constraints, has motivated important modeling efforts over the past four decades, especially in the enterobacterium Escherichia coli. Different hypotheses concerning the dynamic functioning of the system have been explored by a variety of modeling approaches. In an article in *Trends in Microbiology* [19], which was initiated during the sabbatical of Andreas Kremling in Grenoble in 2013, we have reviewed these studies and summarized their contributions to the quantitative understanding of CCR, focusing on diauxic growth in *E. coli*. Moreover, we have proposed a highly simplified representation of diauxic growth that makes it possible to bring out the salient features of the models proposed in the literature and confront and compare the explanations they provide. In parallel, specific aspects of CCR, in particular a better understanding of the role of the signalling molecule cyclic adenosine monophosphate (cAMP) in the dynamic regulation of promoters during growth transitions in *E. coli*, have been studied in the context of the PhD thesis of Valentin Zulkower, using both models and experimental data.

Beside CCR and the multiple regulatory systems controlling the metabolism of *E. coli*, the involvement of post-transcriptional regulation is uncertain. The post-transcriptional factor CsrA is stated as being the only regulator essential for the use of glycolytic substrates, but its impact on the functioning of central carbon metabolism has not been demonstrated. In the framework of the PhD thesis of Manon Morin, supported by a Contrat Jeune Scientifique INRA-Inria, the collaboration of Delphine Ropers, Muriel Cocaign-Bousquet and Brice Enjalbert from LISBP at INSA Toulouse has resulted in a multi-scale analysis of a wild-type strain and its isogenic mutant attenuated for CsrA. A variety of experimental data has been acquired for these two strains in relevant conditions, including growth parameters, gene expression levels, metabolite pools, enzyme activities and metabolic fluxes. Data integration, metabolic flux analysis and regulation analysis revealed the pivotal role of post-transcriptional regulation for reshaping carbon metabolism. In particular, the work has shed light on *csrA* essentiality and has provided an explanation for the glucose-phosphate stress observed in the mutant strain. A paper summarizing the work has been submitted for publication in a microbiology journal.

6.3. 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.

In the context of the response of yeast cells to osmotic shocks, in collaboration with the LIFEWARE project-team and colleagues from Université Paris Descartes and University of Pavia (Italy), Eugenio Cinquemani has investigated the use of mixed effects-modelling and identification techniques to characterize individual cell dynamics in isogenic cell populations. Mixed-effects models are hierarchical models where parametric response profiles of individuals is subject to inter-individual parameter variability following a common population distribution. Starting from identification approaches in pharmacokinetics, we have developed and applied inference methods to microfluidics data, with a focus on the response of budding yeast to osmotic shocks. First results presented at conference in 2013 and the identification and validation work performed with Andres Gonzales, who visited IBIS for a few months in 2014 during his PhD at the University of Pavia, have been finalized into a journal article recently accepted for publication in *PLoS Computational Biology* [20].

Started with a study of the arabinose uptake dynamics in *E. coli*, work on identification and state estimation for single-cell intrinsic noise models of gene networks has focused on the reconstruction of promoter activity profiles from fluorescent reporter data. In the single-cell stochastic context, given population snapshots of fluorescence levels at subsequent experimental instants, the problem becomes that of inferring promoter activity statistics over a cell population such as mean, variance or even higher-order moments from analogous statistics of the reporter output. This nontrivial extension of the deterministic deconvolution of promoter activity from population-average data requires knowledge of the stochastic reporter dynamics and of the relation between promoter and fluorescence statistical moments. In two conference papers, Eugenio Cinquemani investigated identifiability and identification of the kinetic parameters of the stochastic reporter dynamics [28] and proposed parametric and nonparametric methods for the reconstruction of the desired promoter activity statistics [27], [28], demonstrating their effectiveness *in silico*. Further developments of these methods and application to experimental data for addressing relevant biological questions will be the subject of future journal publications.

In parallel, collaboration of Eugenio Cinquemani with Marianna Rapsomaniki, post-doctoral researcher at at IBM Zurich Research Lab (Switzerland), Zoi Lygerou at the University of Patras (Greece) and John Lygeros at ETH Zurich (Switzerland) has been devoted to the analysis of data from Fluorescence Recovery After Photobleaching (FRAP) experiments and the inference of kinetic parameters of protein dynamics in single eukaryotic cells. As an alternative to current approximate analytical methods, we have explored inference methods based on simulation of biological processes in realistic environments at a particle level. We introduced and demonstrated a new method for the inference of kinetic parameters of protein dynamics, where a limited number of *in-silico* FRAP experiments is used to construct a mapping from FRAP recovery curves to the parameters sought. Parameter estimates from experimental data are then computed by applying the mapping to the observed recovery curves, at virtually no additional price for any number of experiments, along with the application of a bootstrap procedure for determining identifiability of the parameters and confidence intervals for their estimates. After validation on synthetic data, the method was successfully applied to the analysis of the nuclear proteins Cdt1, PCNA and GFPnls in mammalian cells, also sheding light on cell-to-cell variability of the protein kinetics. Method and results have been published in *Bioinformatics* this year [22].

6.4. 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* this year [18]. In this publication, which is based on the PhD thesis of Jérôme Izard and post-doctoral work of Cindy Gomez Balderas, we describe 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. We have shown that our synthetic growth switch functions in a medium-independent and reversible way, and we have provided evidence that the switching phenotype arises from the ultrasensitive response of the growth rate to the concentration of RNA polymerase. In parallel, Delphine Ropers in collaboration with Jean-Luc Gouzé and Stefano Casagrande of the BIOCORE team are developing a quantitative model of the gene expression machinery to account for this surprising observation.

The publication in *Molecular Systems Biology* also presents a biotechnological application of the growth switch in which both the wild-type *E. coli* strain and our modified strain are 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. The synthetic growth switch is thus a promising tool for gaining a better understanding of bacterial physiology and for applications in synthetic biology and biotechnology. We submitted a patent for such applications at the European Patent Office.

Whereas the synthetic growth switch has been designed for biotechnological purposes, the question can be asked how resource allocation is organized in wild-type strains that have naturally evolved. Recent work has shown that coarse-grained models of resource allocation can account for a number of empirical regularities relating the the macromolecular composition of the cell to the growth rate. Some of these models hypothesize control strategies enabling microorganisms to optimize growth. While these studies focus on steady-state growth, such conditions are rarely found in natural habitats, where microorganisms are continually challenged by environmental fluctuations. The aim of the PhD thesis of Nils Giordano is to extend the study of microbial growth strategies to dynamical environments, using a self-replicator model. In a recently submitted paper, we have formulated dynamical growth maximization as an optimal control problem that can be solved using Pontryagin's Maximum Principle. We compare this theoretical gold standard with different possible implementations of growth control in bacterial cells. This study has been carried out in collaboration with Jean-Luc Gouzé and Francis Mairet of the BIOCORE project-team.

7. Bilateral Contracts and Grants with Industry

7.1. BGene

Participants: Johannes Geiselmann, Hidde de Jong, Corinne Pinel.

BGene is a start-up company of Université Joseph Fourier 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 Joseph Fourier). Corinne Pinel works part-time at BGene, and Johannes Geiselmann and Hidde de Jong are members of its scientific advisory board. For more information on BGene, see http://www.bgene-genetics.com/.

7.2. Genostar

Participants: Hidde de Jong, Michel Page, François Rechenmann.

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 (Section 5.1). Genostar offers a comprehensive service line-up that spans genome sequencing, read assembly, annotation, and comparison. Genostar thus works with trusted subcontractors, each specialized in state-of-the-art sequencing technologies. François Rechenmann is CEO of the company. For more information, see http://www.genostar.com.

8. Partnerships and Cooperations

8.1. Regional Initiatives

Project name	Séminaire grenoblois des systèmes complexes
Coordinators	S. Achard, O. François, A. Maignan, E. Prados, S. Rafai, D. Ropers
IBIS participants	D. Ropers
Type	Funding by Institut des Systèmes Complexes de Lyon (IXXI)
Web page	http://www.ixxi.fr/?page_id=114&lang=fr

8.2. National Initiatives

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-)
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	E. Cinquemani, J. Geiselmann, C. Gomez Balderas, H. de Jong, S. Lacour, Y. Markowicz, C. Pinel, D. Ropers
Type	Bioinformatics call, Investissements d'Avenir program (2012-2017)
Web page	https://project.inria.fr/reset/

Project name	Fonction du système de régulation post-transcriptionnel CSR dans la dynamique de l'adaptation métabolique chez la bactérie modèle Escherichia coli
Coordinators	M. Cocaign-Bousquet (Inra, LISBP), B. Enjalbert (INSA, LISBP), D. Ropers
IBIS participants	M. Morin, D. Ropers
Type	Contrat Jeune Scientifique Inra-Inria (2012-2015)
Web page	http://www.inra.fr/les_hommes_et_les_femmes/rejoignez_nous/completer_sa_formation/le_recrutement_de_doctorants/cjs__1/inra_inria

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, M. Page, D. Ropers, V. Zulkower (University of Edinburgh)
Type	IFB call for development of innovative bioinformatics services for life sciences (2016-2017)

8.3. European Initiatives

8.3.1. Collaborations with Major European Organizations

Computer Engineering & Systems Science Department of University of Pavia (Italy), 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

8.4. International Research Visitors

8.4.1. Visits of International Scientists

Invited professor	Alberto Soria-Lopéz (Centro de Investigación y de Estudios Avanzados (Cinestav) of Instituto Politécnico Nacional (IPN), Mexico)
Subject	Development of an automatically-controlled system of multiplexed mini-bioreactors

Visiting scientist	Aline Métris (Institute of Food Research (IFR), Norwich, UK)
Subject	Comparative analysis of metabolic networks of Escherichia coli and Salmonella

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, Johannes Geiselmann	BEeSy Conference on Perspectives in Environmental and Systems Biology, Grenoble	April 2015
Hidde de Jong	CompSysBio: Advanced Lecture Course on Computational Systems Biology, Aussois	April 2015
Delphine Ropers	Séminaires de l'IXXI, Grenoble	2015
Delphine Ropers	Séminaire de Modélisation du Vivant (SeMoVi), Lyon and Grenoble	2015

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) 2015 and 2016	Associate editor
Hidde de Jong	International Conference on Intelligent Systems in Molecular Biology (ISMB) jointly held with European Conference on Computational Biology (ECCB) 2015 and ISMB 2016	Area chair

9.1.2.2. Member of conference program committees

IBIS member	Conference, workshop, program
Hidde de Jong	CMSB 2015, HSB 2015, FOSBE 2016

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	BGene	Member scientific advisory board
Johannes Geiselmann	ANR	Member of selection committee
Johannes Geiselmann	INRA	Member of scientific advisory committee Microbiology 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	International Human Frontier Science Program (HFSP)	Member selection and review committees
Hidde de Jong	Microbiology and Food Chain Department, Inra	Member scientific council
Hidde de Jong	BGene	Member scientific advisory board
Delphine Ropers	IXXI, Complex Systems Institute in Lyon	Member scientific board

9.1.5. Recruitment committees

IBIS member	Organism	Recruitment
Johannes Geiselmann	INSA de Lyon	Professor
Delphine Ropers	Inria	Chargés de recherche (jury d'admission)
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	Presentation at 54th IEEE Conference on Decision and Control (CDC), Osaka, Japan	December 2015
Reconstructing statistics of promoter switching from reporter protein population snapshot data	Presentation at 4th International Workshop on Hybrid Systems Biology (HSB), Madrid, Spain	September 2015

Hidde de Jong

Title	Event and location	Date
Global physiological effects and the analysis of gene regulatory networks	Invited talk at Lorentz center workshop Integrated cell models, Leiden, the Netherlands	January 2015
Modeling gene regulatory networks by means of piecewise-linear models	Invited talk during Spring school on Sliding mode control: theory and applications, Aussois	June 2015
Integrated models of the cell: metabolism, gene expression, signalling	Tutorial at CompSysBio: Advanced Lecture Course on Computational Systems Biology, Aussois	March 2015
Analysis and control of bacterial regulatory networks	Seminar Centre for Research and Interdisciplinarity (CRI), INSERM, Paris, with Johannes Geiselmann and Delphine Ropers	June 2015
Accounting for global physiological effects in the analysis of gene regulatory networks	Seminar BrisSynBio, University of Bristol, UK	February 2015
Global physiological effects in the analysis of gene regulatory networks	Invited talk ETH Systems biology student retreat, Reichenau, Germany	September 2015

Johannes Geiselmann

Title	Event and location	Date
Analysis and control of bacterial regulatory networks	Seminar Centre for Research and Interdisciplinarity (CRI), INSERM, Paris, with Hidde de Jong and Delphine Ropers	June 2015
A synthetic growth switch and its biotechnological application	Presentation at BioSynSys Conference, Paris	September 2015
Control of bacterial growth	Seminar ENS Cachan	December 2015

Nils Giordano

Title	Event and location	Date
Understanding regulatory strategies for dynamical resource allocation in microorganisms	Presentation at CompSysBio (Advanced Lecture Course on Computational Systems Biology), Aussois	April 2015
Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies	Invited presentation at Séminaire de Modélisation du Vivant (SeMoVi), Grenoble	October 2015
Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies	Poster at Journée Annuelle des Doctorants de l'Ecole Doctorale CSV, Grenoble	October 2015

Stéphan Lacour

Title	Event and location	Date
Characterization of the Escherichia coli sigmaS core regulon by Chromatin Immunoprecipitation-sequencing (ChIP-seq) analysis: regulation of ncRNA by the alternative sigmaS factor	Regulating with RNA in Bacteria and Archaea Conference, Cancun, Mexico	December 2015

Delphine Ropers

Title	Event and location	Date
Analysis and control of bacterial regulatory networks	Seminar Centre for Research and Interdisciplinarity (CRI), INSERM, Paris, with Hidde de Jong and Johannes Geiselmann	June 2015
Adaptation of E. coli growth to environmental cues: global control of gene expression and post-transcriptional regulation	CEA Grenoble	November 2015

9.1.7. Research administration

IBIS member	Committee	Role
Eugenio Cinquemani	Inria Grenoble - Rhône-Alpes	Member Commission des Emplois Scientifiques
Eugenio Cinquemani	Comité des Utilisateurs des Moyens Informatiques (CUMI), Inria Grenoble - Rhône-Alpes	Member
Johannes Geiselmann	Department of Biology, Université Joseph Fourier	Member scientific council
Hidde de Jong	Grenoble - Rhône-Alpes research centre, Inria	Member scientific council
Hidde de Jong	Conseil d'Orientation Scientifique et Technique (COST), Inria	Member working group on International Relations
Delphine Ropers	Référente chercheurs, Inria Grenoble - Rhône-Alpes	
Delphine Ropers	Commission de Formation Permanente, Inria Grenoble - Rhône-Alpes	Member
Delphine Ropers	Inria	Member of Commission d'évaluation

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: Identification of dynamical models of genetic networks, M2, BIM, INSA de Lyon (4 h)

Master: Statistics for biologists, M1, Master Approches Interdisciplinaires du Vivant, CRI/Université Paris Descartes (24 h)

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, with Nils Giordano, M2, ENS Paris (8 h)

Nils Giordano

Master: Integrated models of the cell: metabolism, gene expression, signalling, with Hidde de Jong, M2, ENS Paris (8 h)

Master: Génétique des populations et biologie de la conservation, M1, Université Grenoble Alpes (6 h)

Bachelor: La bio-informatique : de l'analyse du génome à la modélisation, L2, Université Grenoble Alpes (24 h)

Bachelor: Génétique prokaryote, L2, Université Grenoble Alpes (40 h)

Bachelor: Génétique des populations, L2-L3, Université Grenoble Alpes (27 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 (7.5 h)

Master: Modeling and simulation of genetic regulatory networks, M2, INSA de Toulouse (5 h)

François Rechenmann

E-learning: MOOC Bioinformatics: Genomes and Algorithms (http://www.inria.fr/actualite/actualites-inria/mooc-bioinformatique-genomes-et-algorithmes)

9.2.2. Supervision

PhD: **Manon Morin**, Rôle du régulateur post-transcriptionnel CSR dans l'adaptation métabolique de la bactérie modèle *Escherichia coli*, November 2015. Supervisors: Muriel Cocaign-Bousquet (INRA) and Delphine Ropers

PhD: **Stéphane Pinhal**, Adaptation d'*E. coli* à la croissance sur acétate : une approche pluridisciplinaire, Université Grenoble Alpes, March 2015. Supervisors: Johannes Geiselmann, Delphine Ropers, and Hidde de Jong

PhD: **Valentin Zulkower**, Etude de la dynamique des mécanismes de la répression catabolique : des modèles mathématiques aux données expérimentales, Université Grenoble Alpes, March 2015. Supervisors: Hidde de Jong, Johannes Geiselmann, and Delphine Ropers

PhD in progress: **Stefano Casagranda**, Analysis and control of cell growth models. Supervisors: Jean-Luc Gouzé (BIOCORE) and Delphine Ropers

PhD in progress: **Nils Giordano**, Régulation de la croissance chez *Escherichia coli* : étude théorique et expérimentale à l'aide de modèles coûts-bénéfices. Supervisors: Hidde de Jong and Johannes Geiselmann

PhD in progress: **Bernard Chielli Ponce de Leon**, Stochasticity of gene expression in strains of *E. coli* with a controlled growth rate and number of chromosomes. Supervisors: Irina Mihalcescu (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
Johannes Geiselmann	Membre	Stéphane Pinhal	Université Grenoble Alpes	March 2015
Johannes Geiselmann	Membre	Valentin Zulkower	Université Grenoble Alpes	March 2015
Johannes Geiselmann	Rapporteur	Marie Carquet	Université Paul Sabatier, Toulouse	March 2015
Johannes Geiselmann	Membre	Marie-Cecilia Duvernoy	Université Grenoble Alpes	November 2015
Johannes Geiselmann	Membre	Christopher Swale	Université Paul Grenoble Alpes	November 2015
Johannes Geiselmann	Rapporteur	Aleksandra Delplanque	Université Paris-Saclay	December 2015
Hidde de Jong	Rapporteur	Thomas Todd	University of Bristol, UK	February 2015
Hidde de Jong	Rapporteur	Thomas Duigou	Université Paris Sud	May 2015
Hidde de Jong	Rapporteur	Abhishekh Gupta	Tampere University of Technology, Finland	June 2015
Hidde de Jong	Président	Adrien Richard	Université Paris Descartes	December 2015
Hidde de Jong	Invité	Stéphane Pinhal	Université Grenoble Alpes	March 2015
Hidde de Jong	Membre	Valentin Zulkower	Université Grenoble Alpes	March 2015
Stéphan Lacour	Examinateur	Xuejiao Jiang	INSA de Lyon	September 2015
Delphine Ropers	Membre	Stéphane Pinhal	Université Grenoble Alpes	March 2015
Delphine Ropers	Membre	Valentin Zulkower	Université Grenoble Alpes	March 2015
Delphine Ropers	Examinateur	Ismail Belgacem	Université de Nice-Sophia Antipolis	March 2015
Delphine Ropers	Membre	Manon Morin	Université de Toulouse	November 2015

habilitation (HDR) committees

IBIS member	Role	PhD student	University	Date
Johannes Geiselmann	Membre	Gilles Curien	Université Grenoble Alpes	February 2015

PhD advisory committees

IBIS member	PhD student	University
Eugenio Cinquemani	Artemis Llamosi	Université Paris Descartes
Johannes Geiselmann	Jean-Baptiste Lugagne	Université Paris Descartes
Stéphan Lacour	Alexandre Duprey	INSA de Lyon
Delphine Ropers	Alice Julien-Laferrière	Université de Lyon
Delphine Ropers	Martin Wannagat	Université de Lyon

9.2.4. Teaching adminstration

Yves Markowicz is director of the BSc department at Université Joseph Fourier.

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

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.

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