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Activity Report 2016

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

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.

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
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Other Research Topics and Application Domains:

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

1. Members

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Faculty Members

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Corinne Pinel [CNRS, Assistant engineer]
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Yannick Martin [Inria, since June 2016]
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Visiting Scientists

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Aline Métris [Institute of Food Research, Norwich, UK, from September 2016 until December 2016]

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Others

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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 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.

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.

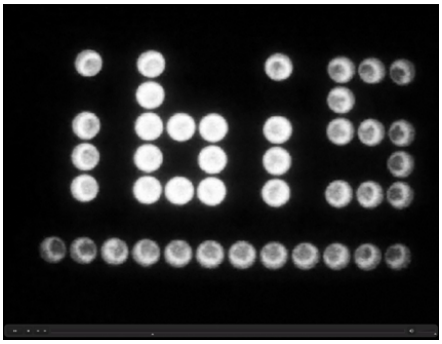


Figure 1. Display of the project-team name on a "bacterial billboard" (see http://team.inria.fr/ibis for the corresponding movie). A microplate containing a minimal medium (with glucose and acetate) is filmed during 36 hours. Wells contain E. coli bacteria which are transformed with a reporter plasmid 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.

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

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.

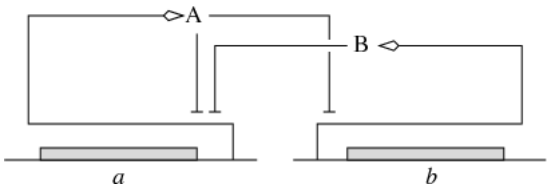
A variety of qualitative modeling formalisms have been introduced over the past decades. Boolean or logical models, which describe gene regulatory and signalling networks as discrete-time finite-state transition systems, are probably most widely used. The dynamics of these systems are governed by logical 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.

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, 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.



$$\dot{x}_a = \kappa_a \, s^-(x_a, \theta_a^2) \, s^-(x_b, \theta_b) - \gamma_a \, x_a$$
$$\dot{x}_b = \kappa_b \, s^-(x_a, \theta_a^1) - \gamma_b \, x_b$$
$$s^+(x, \theta) = \begin{cases} 1, & \text{if } x > \theta \\ 0, & \text{if } x < \theta \end{cases}$$
$$s^-(x, \theta) = 1 - s^+(x, \theta)$$

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 ($\gamma_a \, x_a$).

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.

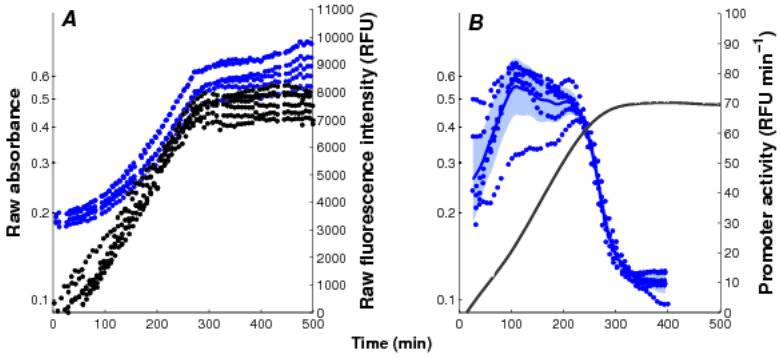


Figure 3. Monitoring of bacterial gene expression in vivo using fluorescent reporter genes (Stefan et al., PLoS Computational Biology, 11(1):e1004028, 2015). The plots show the primary data obtained in a kinetic experiment with E. coli cells, focusing on the expression of the motility gene tar in a mutant 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 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, Aline Métris, 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], Nils Giordano, Hidde de Jong, Stephan Lacour, Ludowic Lancelot, Delphine Ropers, Alberto Soria-Lopéz.

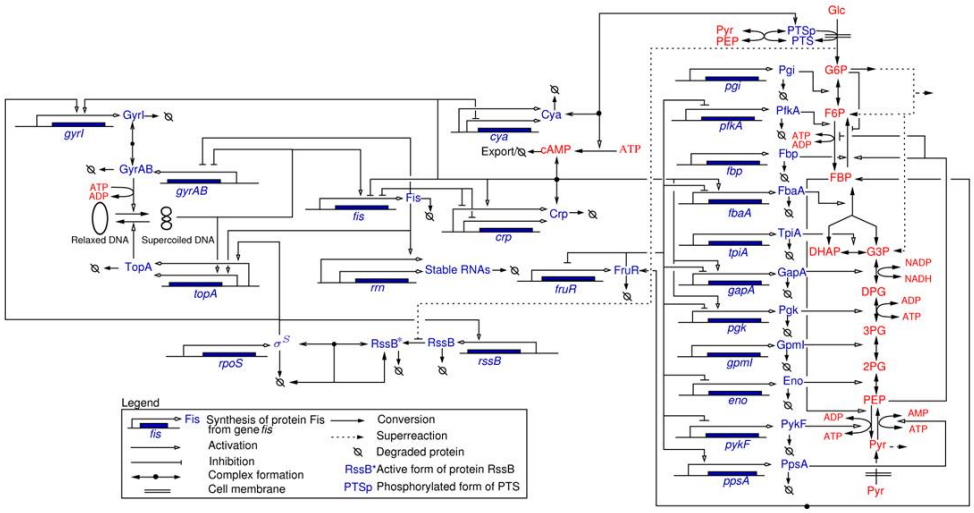


Figure 4. Network of key genes, proteins, and regulatory interactions involved in the carbon assimilation network in E. coli (Baldazzi et al., PLoS Computational Biology, 6(6):e1000812, 2010). The metabolic part includes the glycolysis/gluconeogenesis pathways as well as a simplified description of the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

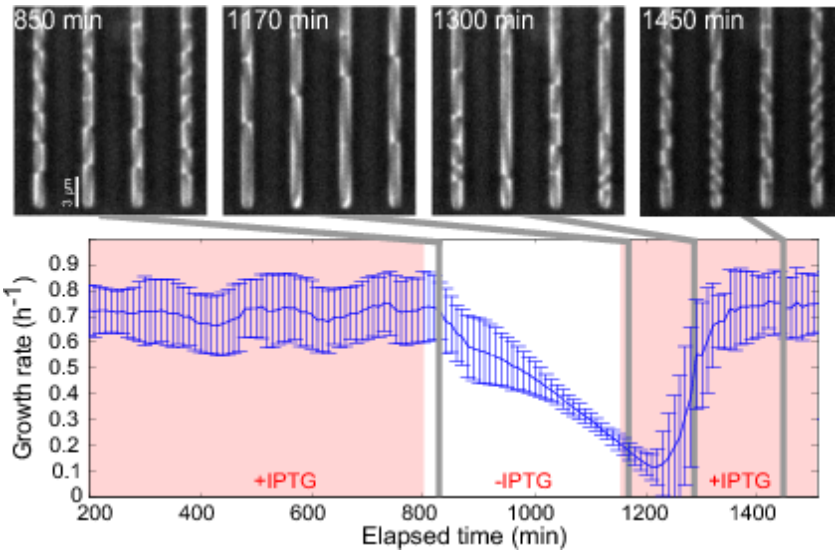


Figure 5. Growth arrest by external control of the gene expression machinery (Izard, Gomez Balderas et al., Molecular Systems Biology, 11:840, 2015). An E. coli strain in which an essential component of the gene expression machinery, the $\beta\beta'$ subunits of RNA polymerase, was put under the control 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 Manon Morin was published in *Molecular Microbiology* this year [14]. Furthermore, two papers appeared in *PLoS Computational Biology*, one by Eugenio Cinquemani and colleagues from the LIFEWARE project-team and the University of Pavia [13], and one describing results from the PhD thesis of Nils Giordano, in collaboration with colleagues from the BIOCORE project-team [12]. Eugenio Cinquemani co-organized the Fifth International Conference on Hybrid Systems Biology (HSB 2016) (http://hsb2016.imag.fr/) in Grenoble.

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 a tool 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 8.7.2. In comparison with the previously distributed versions, GNA 8.7.2 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.

- Participants: Johannes Geiselmann, Hidde de Jong, Yannick Martin, Michel Page, Delphine Ropers, Valentin Zulkower
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- 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).

- Participants: Johannes Geiselmann, Hidde de Jong, Michel Page, Delphine Ropers
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- URL: http://ibis.inrialpes.fr/article957.html

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 this year, have developed a qualitative model of the osmotic stress response in the model bacterium *Escherichia coli* for which more information is available in the literature. 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* [15] and in *Data in Brief* [16]. 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.

The tool used for the qualitative modeling and simulation of the regulatory mechanism underlying osmotic stress is GENETIC NETWORK ANALYZER (GNA). This tool describes the dynamics of gene regulatory networks by means of PLDE models, as described in Section 5.1. GNA has been integrated with the other bioinformatics tools distributed by Genostar (http://www.genostar.com/). Version 8.7.2 of GNA was released by IBIS and Genostar this year and has been deposited at the Agence pour la Protection des Programmes (APP). Some bugs have been corrected in the new version and the program has been adapted to the latest versions of Java and the software platform of Genostar. Version 8.7.2 supports the SBML standard and is also capable of exporting its models to the newly-developed standard for qualitative models, SBML Qual. This standard has been elaborated by the community of developers of logical and related modeling tools (CoLoMoTo), in which the GNA developers participate.

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. This work was presented at the major bioinformatics conference ISMB/ECCB and published in the special issue of *Bioinformatics* associated with the conference last year. The linear inversion methods have been implemented in the Python package WELLFARE and integrated in the web application WELLINVERTER (Section 5.3). Funded by the Institut Français de Bioinformatique (IFB), Yannick Martin is currently extending 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.

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 software for image analysis (segmentation, tracking, lineage reconstruction, ...) adapted to the requirements of mother machine applications are still missing. IBIS therefore collaborates 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 is 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. 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, much less is known about adaptation during growth transitions. In particular, only very few data are available on changes in the concentration and activity of the transcription and translation machineries and almost no data exost for the dynamic response of the degradation machinery.

In the framework of the PhD thesis of Manon Morin, supported by a Contrat Jeune Scientifique INRA-Inria (2012-2015), the collaboration of Delphine Ropers with Muriel Cocaign-Bousquet and Brice Enjalbert at INRA/INSA de Toulouse has allowed to disentangle the role of post-transcriptional regulation from other regulatory interactions in the dynamic adaptation of central carbon metabolism in *E. coli*. In a multi-scale analysis of a wild-type strain and its isogenic mutant attenuated for the protein CsrA, a variety of experimental data have been acquired 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 shaping 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 published in *Molecular Microbiology* this year [14]. A follow-up study conducted with various mutant strains of the carbon storage regulator system has 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. A paper summarizing the work is being prepared for publication.

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.

6.4. 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. Results were described in a publication in *PLoS Computational Biology* [13]. A study of statistical

validation methods for mixed-effects and alternative stochastic modelling paradigms has been presented at the *IFAC Conference on Foundations of Systems Biology in Engineering (FOSBE)* in Magdeburg [19]. In collaboration with the project-team BIOCORE at Inria Sophia-Antipolis - Méditerranée, the approach is now being investigated for the joint modelling of growth and gene expression in *E. coli*, based on single-cell microfluidics data from growth arrest-and-restart experiments. Further challenges stemming from this activity toward modelling and identification of extrinsic noise in individual cells are part of the recently started ANR project MEMIP (Section 8.2).

Work on identification and state estimation for single-cell gene network dynamics has been focused on the reconstruction of promoter activity profiles from fluorescent reporter data. In a stochastic, intrinsic noise modelling context, Eugenio Cinquemani addressed the problem of inferring promoter activity statistics over a cell population, such as mean and variance, from analogous statistics of the reporter output, as obtained from so-called population snapshot data. This nontrivial extension of the deterministic promoter activity deconvolution problem from population-average data is the first, crucial step toward reconstruction of promoter activity regulation and inference of stochastic network models. Earlier results, concerning parameter identifiability of stochastic promoter activity models and reconstruction of promoter activity distributions in the special case of single-switch systems, were further developed in a contribution to the HSB conference this year [18]. The relationship between the spectrum of the promoter process (cross-correlation function) and the mean-variance profiles of fluorescent reporter readouts was derived and demonstrated on examples, laying down the bases for a full-blown observability analysis and the development of spectrum estimation methods.

The collaboration of Eugenio Cinquemani with Marianna Rapsomaniki (IBM Zurich Research Lab, Switzerland), Zoi Lygerou (University of Patras, Greece) and John Lygeros (ETH Zurich, Switzerland) is moving on to applications of joint work published in *Bioinformatics* last year. Deployment of the methods developed into an efficient cluster-based software for the inference of protein kinetics in single cells from Fluorescence Recovery After Photobleaching (FRAP) experiments is under study. Exploitation of the same methods for the simulation and analysis of more general biochemical processes in single cells is part of the ongoing research efforts.

6.5. 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* last year. 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 is being continued in several directions in the context of the RESET project by Célia Boyat. In order to further explore the possibility of transferring this technology to biotechnology companies, we participated in the Challenge Out of Labs (http://www.linksium.fr/lancez-vous/resultat-challenge-out-of-labs/) organized by Linksium, the local

incubator for technology transfer and start-up building. The presentation by Hans Geiselmann was selected for further development by Linksium.

In a review recently accepted for publication in *Trends in Microbiology* [11], 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.

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 collaboration with the BIOCORE project-team, we formulate 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. We find that simple control strategies enabling growth-rate maximization at steady state are suboptimal for transitions from one growth regime to another, for example when shifting bacterial cells to a medium supporting a higher growth rate. A near-optimal control strategy in dynamical conditions is shown to require information on several, rather than a single physiological variable. Interestingly, this strategy has structural analogies with the regulation of ribosomal protein synthesis by ppGpp in *E. coli*. It involves sensing a mismatch between precursor and ribosome concentrations, as well as the adjustment of ribosome synthesis in a switch-like manner. Our results show how the capability of regulatory systems to integrate information about several physiological variables is critical for optimizing growth in a changing environment. A paper describing the above results was published in *PLoS Computational Biology* this year [12].

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 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). 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	RNAfluo: Quantification d'ARN régulateurs in vivo
Coordinators	S. Lacour
IBIS participants	S. Lacour
Type	AGIR program, Université Grenoble Alpes

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 (2015-2019)
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	Analyse intégrative de la coordination entre stabilité des ARNm et physiologie cellulaire chez Escherichia coli
Coordinators IBIS participants Type	D. Ropers, M. Cocaign-Bousquet (Inra, LISBP) T. Etienne, D. Ropers Contrat Jeune Scientifique Inra-Inria (2016-2019)

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

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

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

8.4. International Research Visitors

8.4.1. Visits of International Scientists

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

Invited researcher Subject	Aline Métris (Institute of Food Research (IFR), Norwich, UK) 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
Eugenio Cinquemani	Fifth International Workshop on Hybrid Systems Biology (HSB 2016), Grenoble	October 2017
Hidde de Jong	CompSysBio: Advanced Lecture Course on Computational Systems Biology, Aussois	March 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 2016)	Associate editor
Eugenio Cinquemani	Fifth International Workshop on Hybrid Systems Biology (HSB 2016)	Program chair
Hidde de Jong	International Conference on Intelligent Systems in Molecular Biology (ISMB 2016)	Area chair

9.1.2.2. Member of conference program committees

IBIS member	Conference, workshop, program
Eugenio Cinquemani	HSB 2016, SASB 2016
Hidde de Jong	ISMB 2016, ECCB 2016, HSB 2016, FOSBE 2016
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	BGene	Member scientific advisory board
Johannes Geiselmann	ANR	Member of selection committee
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	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
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	Université Pierre et Marie Curie, Paris	Full professors in systems biology, applied to microbiology and to physiology
Delphine Ropers	Inria Lille	Chargés de recherche (jury d'admissibilité)
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	Seminar at Control theory and systems biology laboratory, D-BSSE, Basel, Switzerland	January 2016
Identifying variability of gene expression dynamics from time-course data	Seminar at IBM Research Center, Zurich, Switzerland	January 2016
Reconstruction of promoter activity statistics from reporter protein population snapshot data	Seminar at Automatic control laboratory, ETH Zurich, Switzerland	January 2016
Inference of regulatory networks from time-series reporter gene data: The case of promoter regulation in the E. coli motility network	Invited talk at workshop on Static Analysis in Systems Biology (SASB 2016), Edinburgh, UK	September 2016
On observability and reconstruction of promoter activity statistics from reporter protein mean and variance profiles	Presentation at 5th International Workshop on Hybrid Systems Biology (HSB 2016), Grenoble	October 2016

Hidde de Jong

Title	Event and location	Date
Natural and synthetic control of growth rate and gene expression in bacteria	Seminar Centre de Biologie Intégrative de Toulouse	February 2016
Natural and synthetic control of resource allocation in bacteria	Seminar MIRA institute, University of Twente, the Netherlands	July 2016
A synthetic growth switch based on controlled expression of RNA polymerase	Presentation at 17th International Conference on Systems Biology (ICSB 2016), Barcelona, Spain	October 2016
Natural and synthetic control of resource allocation in bacteria	Journée Biologie des systémes BiLille, Lille	November 2016

Johannes Geiselmann

Title	Event and location	Date
Growth control in bacteria	Seminar at CPBS Montpellier	June 2016

Nils Giordano

Title	Event and location	Date
Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies	Talk during annual meeting of working group GT-BIOSS, Lyon	July 2016

Stephan Lacour

Title	Event and location	Date
Direct versus indirect gene regulation by the stress response SigmaS factor	Seminar Institut de Biologie Structurale, Grenoble	February 2016
Identification of novel curli regulators in Escherichia coli	Poster at Biofilms7, Porto, Portugal	June 2016
Quantification of non-coding RNAs in bacterial cells using a Broccoli aptamer	Poster at 8th Bordeaux RNA Club Symposium & Aptamers in Bordeaux	June 2016

Aline Métris

Title	Event and location	Date
What does it take for a foodborne pathogen to survive a pinch of salt? Bioinformatics and systems biology approaches to model food safety	Invited researcher seminar Inria Grenoble - Rhône-Alpes	December 2016
Modèles et –omics pour mieux comprendre la réponse des pathogènes alimentaires au stress osmotique	INRA Avignon	December 2016

Delphine Ropers

Title	Event and location	Date
Adaptation of E. coli growth to environmental cues: global control of gene expression and post-transcriptional regulations	Institute for Food Research, Norwich, UK	March 2016
Adaptation of E. coli growth to environmental cues: global control of gene expression and post-transcriptional regulations	Journées INRA-Inria, Mallemort	October 2016

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)
Johannes Geiselmann	Department of Biology, Université Grenoble Alpes	Member scientific council
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 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)

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)

Nils Giordano

Bachelor: La bio-informatique : de l'analyse du génome à la modélisation, L2, Université Grenoble Alpes (9 h)

François Rechenmann

E-learning: MOOC Bioinformatique : algorithmes et génomes (https://www.fun-mooc.fr/courses/inria/41003S02/session02/about)

French language version of Bioinformatics MOOC published last year, including the possibility to run the algorithms by means of a dedicated Python notebook (in collaboration with Thierry Parmentelat from Inria Sophia-Antipolis - Méditerranée).

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 (6 h)

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

9.2.2. Supervision

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

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
Hidde de Jong	Rapporteur	Jetse Scholma	University of Twente, the Netherlands	July 2016
Hidde de Jong	Rapporteur	Jean-Baptiste Lugagne	Université Paris Descartes	December 2016
Hidde de Jong	Président	José Morales Morales	Université de Grenoble	December 2016
Hidde de Jong	Rapporteur	Sébastien Raguideau	AgroParisTech	December 2016
Johannes Geiselmann	Président	Jessica Penin	Université de Grenoble	April 2016
Johannes Geiselmann	Rapporteur	Minyeong Yoo	Université Paul Sabatier Toulouse	May 2016
Johannes Geiselmann	Président	Ramachandran Boopathi	ENS de Lyon	May 2016
Johannes Geiselmann	Rapporteur	Ayyappasamy Sudalaiyadum Perumal	Université de Montpellier	June 2016
Stéphan Lacour	Examinateur	Simon Léonard	Université de Lyon	September 2016
Stéphan Lacour	Examinateur	Alice Berry	Université de Grenoble	November 2016

Habilitation (HDR) committees

IBIS member	Role	PhD student	University	Date
Hidde de Jong	Examinateur	Morgan Magnin	Université de Nantes	Avril 2016
Johannes Geiselmann	President	Jan Bednar	Université de Grenoble	December 2015

PhD advisory committees

IBIS member	PhD student	University
Johannes Geiselmann	Jean-Baptiste Lugagne	Université Paris Descartes

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.

9.3. Science education

Delphine Ropers gave a course on bacteria and antibiotic resistance at the primary school Ecole Bizanet in Grenoble (December 2016).

10. Bibliography

Major publications by the team in recent years

[1] G. BAPTIST, C. PINEL, C. RANQUET, J. IZARD, D. ROPERS, H. DE JONG, J. GEISELMANN. *A genome-wide screen for identifying all regulators of a target gene*, in "Nucleic Acids Research", 2013, vol. 41, n° 17, 11 p. , http://hal.inria.fr/hal-00857345

[2] S. BERTHOUMIEUX, M. BRILLI, H. DE JONG, D. KAHN, E. CINQUEMANI. *Identification of metabolic network models from incomplete high-throughput datasets*, in "Bioinformatics", 2011, vol. 27, n° 13, pp. i186-i195

[3] S. BERTHOUMIEUX, M. BRILLI, D. KAHN, H. DE JONG, E. CINQUEMANI. *On the identifiability of metabolic network models*, in "Journal of Mathematical Biology", 2013, vol. 67, n° 6-7, pp. 1795-1832, http://hal.inria.fr/hal-00762620

[4] S. BERTHOUMIEUX, H. DE JONG, G. BAPTIST, C. PINEL, C. RANQUET, D. ROPERS, J. GEISELMANN. *Shared control of gene expression in bacteria by transcription factors and global physiology of the cell*, in "Molecular Systems Biology", January 2013, vol. 9, n° 1, 11 p. [*DOI :* 10.1038/MSB.2012.70], http://hal.inria.fr/hal-00793352

[5] J. IZARD, C. GOMEZ-BALDERAS, D. ROPERS, S. LACOUR, X. SONG, Y. YANG, A. B. LINDNER, J. GEISELMANN, H. DE JONG. *A synthetic growth switch based on controlled expression of RNA polymerase*, in "Molecular Systems Biology", November 2015, vol. 11, n° 11, 16 p. , https://hal.inria.fr/hal-01247993

[6] A. KREMLING, J. GEISELMANN, D. ROPERS, H. DE JONG. *Understanding carbon catabolite repression in Escherichia coli using quantitative models*, in "Trends in Microbiology", 2015, vol. 23, n° 2, pp. 99-109, https://hal.inria.fr/hal-01103556

[7] C. PEANO, J. WOLF, J. DEMOL, E. ROSSI, L. PETITI, G. DE BELLIS, J. GEISELMANN, T. EGLI, S. LACOUR, P. LANDINI. *Characterization of the Escherichia coli σ(S) core regulon by Chromatin Immunoprecipitation-sequencing (ChIP-seq) analysis*, in "Scientific Reports", 2015, vol. 5, 15 p. [*DOI :* 10.1038/SREP10469], https://hal.inria.fr/hal-01217828

[8] M. A. RAPSOMANIKI, E. CINQUEMANI, N. N. GIAKOUMAKIS, P. KOTSANTIS, J. LYGEROS, Z. LYGEROU. *Inference of protein kinetics by stochastic modeling and simulation of fluorescence recovery after photobleaching experiments*, in "Bioinformatics", 2015, vol. 31, n° 3, pp. 355-362 [*DOI :* 10.1093/BIOINFORMATICS/BTU619], https://hal.inria.fr/hal-01096966

[9] D. STEFAN, C. PINEL, S. PINHAL, E. CINQUEMANI, J. GEISELMANN, H. DE JONG. *Inference of quantitative models of bacterial promoters from time-series reporter gene data*, in "PLoS Computational Biology", 2015, vol. 11, n° 1, e1004028, https://hal.inria.fr/hal-01097632

[10] V. ZULKOWER, M. PAGE, D. ROPERS, J. GEISELMANN, H. DE JONG. *Robust reconstruction of gene expression profiles from reporter gene data using linear inversion*, in "Bioinformatics", 2015, vol. 31, n° 12, pp. i71-i79, https://hal.inria.fr/hal-01217800

Publications of the year

Articles in International Peer-Reviewed Journals

[11] H. DE JONG, J. GEISELMANN, D. ROPERS. *Resource reallocation in bacteria by reengineering the gene expression machinery*, in "Trends in Microbiology", 2017, https://hal.inria.fr/hal-01420729

[12] N. GIORDANO, F. MAIRET, J.-L. GOUZÉ, J. GEISELMANN, H. DE JONG. *Dynamical allocation of cellular resources as an optimal control problem: Novel insights into microbial growth strategies*, in "PLoS Computational Biology", March 2016, vol. 12, n° 3, e1004802 [*DOI :* 10.1371/JOURNAL.PCBI.1004802], https://hal.inria.fr/hal-01332394

[13] A. LLAMOSI, A. GONZALEZ, C. VERSARI, E. CINQUEMANI, G. FERRARI-TRECATE, P. HERSEN, G. BATT. *What population reveals about individual cell identity: Single-cell parameter estimation of models of gene expression in yeast*, in "PLoS Computational Biology", February 2016, vol. 12, n° 2, e1004706 [*DOI :* 10.1371/JOURNAL.PCBI.1004706], https://hal.inria.fr/hal-01248298

[14] M. MORIN, D. ROPERS, F. LETISSE, S. LAGUERRE, J.-C. J.-C. PORTAIS, M. COCAIGN-BOUSQUET, B. ENJALBERT. *The post-transcriptional regulatory system CSR controls the balance of metabolic pools in upper glycolysis of Escherichia coli*, in "Molecular Microbiology", January 2016, vol. 100, n° 4, pp. 686-700 [*DOI :* 10.1111/MMI.13343], https://hal.inria.fr/hal-01418224

[15] A. MÉTRIS, S. GEORGE, D. ROPERS. *Piecewise linear approximations to model the dynamics of adaptation to osmotic stress by food-borne pathogens*, in "International Journal of Food Microbiology", 2017, vol. 240, pp. 63-74 [*DOI :* 10.1016/J.IJFOODMICRO.2016.06.022], https://hal.inria.fr/hal-01417975

[16] D. ROPERS, A. MÉTRIS. *Data for the qualitative modeling of the osmotic stress response to NaCl in Escherichia coli*, in "Data in Brief", September 2016, vol. 9, pp. 606-612 [*DOI :* 10.1016/J.DIB.2016.09.028], https://hal.inria.fr/hal-01417966

Invited Conferences

[17] S. CASAGRANDA, D. ROPERS, J.-L. GOUZÉ. *Model simplification and process analysis of biological models*, in "The 5th International Symposium on Positive Systems (POSTA)", Rome, Italy, September 2016, https://hal.inria.fr/hal-01412049

International Conferences with Proceedings

[18] E. CINQUEMANI. *On observability and reconstruction of promoter activity statistics from reporter protein mean and variance profiles*, in "Fifth International workshop on Hybrid Systems Biology - HSB 2016", Grenoble, France, E. CINQUEMANI, A. DONZÉ (editors), Hybrid Systems Biology, Springer, October 2016, vol. 9957, pp. 147-163 [*DOI :* 10.1007/978-3-319-47151-8], https://hal.inria.fr/hal-01399934

[19] A. M. GONZALEZ-VARGAS, E. CINQUEMANI, G. FERRARI-TRECATE. *Validation Methods for Population Models of Gene Expression Dynamics*, in "6th IFAC Conference on Foundations of Systems Biology in Engineering - FOSBE 2016", Magdeburg, Germany, October 2016, https://hal.inria.fr/hal-01399921

Books or Proceedings Editing

[20] E. CINQUEMANI, A. DONZÉ (editors). *Hybrid Systems Biology: 5th International Workshop, HSB 2016, Grenoble, France, October 20-21, 2016, Proceedings*, Lecture Notes in Bioinformatics, Springer, Grenoble, France, 2016, n^{o} 9957 [*DOI :* 10.1007/978-3-319-47151-8], https://hal.inria.fr/hal-01399942

Research Reports

[21] A. M. GONZALEZ-VARGAS, E. CINQUEMANI, G. FERRARI-TRECATE. *Validation methods for population models of gene expression dynamics*, Inria Grenoble - Rhône-Alpes, July 2016, n^{o} RR-8938, 17 p. , https://hal.inria.fr/hal-01349030