IN PARTNERSHIP WITH:
Université Joseph Fourier (Grenoble)

Activity Report 2013

Project-Team IBIS

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

IN COLLABORATION WITH: Laboratoire Adaptation et Pathogénie des Microorganismes (LAPM)

RESEARCH CENTER
Grenoble - Rhône-Alpes

THEME
Computational Biology

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Project-Team IBIS

Keywords: Computational Biology, Systems Biology, Microbiology, Regulatory Networks, System Analysis And Control

IBIS is bilocated at the Inria Grenoble - Rhône-Alpes research center in Montbonnot and the Laboratoire Adaptation et Pathogénie des Microorganismes (UMR 5163) at the Institut Jean Roget in La Tronche.

Creation of the Project-Team: 2009 January 01.

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2. Overall Objectives

2.1. Overview

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

The aims of IBIS raise new 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. 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 at the Laboratoire Adaptation et Pathogénicité des Microorganismes of the Université Joseph

Fourier (UJF, CNRS UMR 5163), and 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. [1]

Hidde de Jong is the head of the IBIS project-team and Johannes Geiselmann is the co-director. The experimental component of IBIS also remains part of the Laboratoire Adaptation et Pathogénicité des Microorganismes, and Johannes Geiselmann continues to represent this group in the interactions with the laboratory and university administration.

Figure 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****. Here Thoth is shown in human form with the face of an ibis. (Sources: http://en.wikipedia.org/wiki/Ibis, http://en.wikipedia.org/wiki/Thoth, and http://www.shoarns.com).*

2.2. Highlights of the Year

A paper based on the PhD thesis of Sara Berthoumieux was accepted for *Molecular Systems Biology* this year [4] and selected as an Editor's choice in *Science* (http://ibis.inrialpes.fr/article1040.html).

The start-up company BGene, created by Johannes Geiselmann and former IBIS member Caroline Ranquet, together with Marie-Gabrielle Jouan (Floralis, Université Joseph Fourier), obtained an Emergence award in the 2013 Oséo Concours d'entreprises innovantes (http://www.grain-incubation.com/oseo-start-ups-laureates-categorie-emergence/). BGene is active in the field of DNA engineering (Section 6.2).

3. Research Program

3.1. Analysis of qualitative dynamics of gene regulatory networks

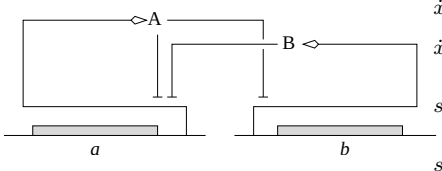
Participants: Johannes Geiselmann, Hidde de Jong [Correspondent], Michel Page, Delphine Ropers.

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

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

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

First proposed by Leon Glass and Stuart Kauffman in the early seventies, the mathematical analysis of PLDE models has been the subject of active research for more than four decades. IBIS has made contributions on the mathematical level, in collaboration with the BIOCORE project-team, 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.



(a)

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

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

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

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

(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 ($\gamma_a \, x_a$).

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

Participants: Eugenio Cinquemani [Correspondent], Johannes Geiselmann, Hidde de Jong, Julien Demol, Stéphan Lacour, Michel Page, Corinne Pinel, Delphine Ropers, Alberto Soria-Lopéz, Diana Stefan, Claire Villiers, 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.

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.

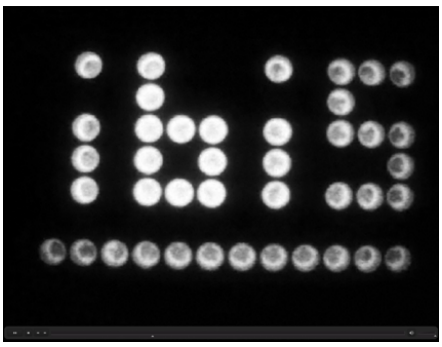


Figure 3. Playful illustration of the principle of reporter genes (see http://ibis.inrialpes.fr for the corresponding movie). A microplate containing a minimal medium (with glucose and acetate) is filmed during 36 hours. Wells contain E. coli bacteria which are transformed with a reporter plasmid containing 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.

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 (Section 4.2). 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, Johannes Geiselmann, Hidde de Jong, Michel Page, Stéphan Lacour, Yves Markowicz, Manon Morin, Corinne Pinel, Stéphane Pinhal, Delphine Ropers [Correspondent], Diana Stefan, Claire Villiers, 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 regulatory networks

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

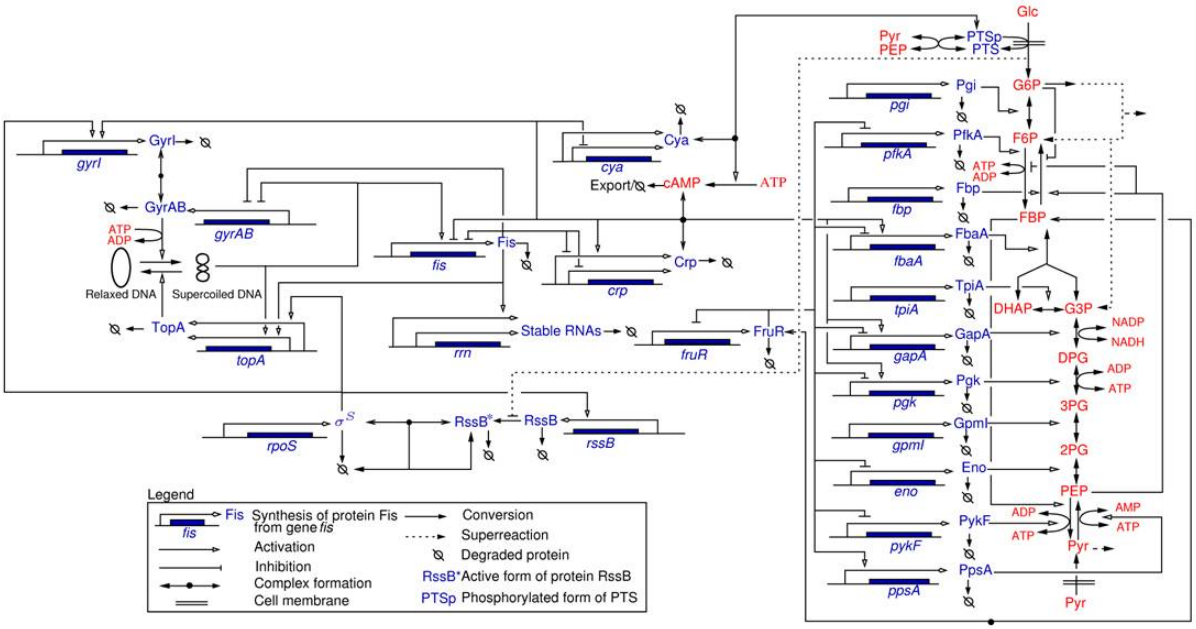


Figure 4. Network of key genes, proteins, and regulatory interactions involved in the carbon assimilation network in E. coli (Baldazzi et al., PLoS Computational Biology, 6(6):e1000812, 2010). The metabolic part includes the glycolysis/gluconeogenesis pathways as well as a simplified description of the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

In the previously-described objectives, we have focused on identifying complex regulatory networks and gaining a better understanding of how the network dynamics underlies the observable behavior of the cell. Based on the insights thus obtained, a complementary perspective consists in changing 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 growth-rate controllers of bacterial cells. Since the growth rate is the most important physiological parameter in microorganisms, a better understanding of the molecular basis of growth-rate control and the engineering of open-loop and closed-loop growth-rate controllers is of major interest for both fundamental research and biotechnological applications. Second, we are working on the development of methods with a solid foundation in control theory 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 CONTRAINTES, in collaboration with a biophysics group at Université Paris Descartes.

4. Software and Platforms

4.1. Genetic Network Analyzer (GNA)

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

Keywords. 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 8.5. In comparison with the previously distributed versions, GNA 8.5 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 [6]. For more information, see http://www-helix.inrialpes.fr/gna.

4.2. WellReader

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

Keywords. Gene expression, reporter gene data

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). For more information, see: http://ibis.inrialpes.fr/article957.html.

5. New Results

5.1. Analysis of gene regulatory networks by means of piecewise-linear (PL) models

GENETIC NETWORK ANALYZER (GNA) is a tool for the qualitative modeling and simulation of the dynamics of gene regulatory networks by means of PLDE models, as described in Section 4.1. GNA has been integrated with the other bioinformatics tools distributed by Genostar (http://www.genostar.com/). Version 8.5 of GNA was released by IBIS and Genostar this year. This version is an update of version 8.0, 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 8.5 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, and has been described in detail in a paper published in *BMC Systems Biology* [6].

The predictions obtained with the help of GNA are purely qualitative, describing the dynamics of the network by means of a state transition graph. While a qualitative analysis is appropriate for certain problems, the absence of precise quantitative predictions may not be desirable in others, such as the analysis of a limit cycle or the design of a controller for a synthetic network. The quantitative study of PLDE models of gene regulatory networks is hindered by the fact that the step functions describing the logic of regulatory interactions lead to discontinuities in the right-hand side of the PLDE models (Section 3.1). This has motivated extensions of the PLDE models based on differential inclusions and Filippov solutions. As of now, no numerical simulation tool for the simulation of these Filippov extensions is available.

In collaboration with Vincent Acary and Bernard Brogliato of the BIPOP project-team, we have shown how tools developed for the simulation of nonsmooth mechanical, electrical and control systems can be adapted for this purpose, in a paper published in *Physica D* [2]. We have presented a method for the numerical analysis of one proposed extension, called Aizerman–Pyatnitskii (AP)-extension, by reformulating the PLDE models as mixed complementarity systems (MCSs). This allows the application of powerful methods developed for this class of nonsmooth dynamical systems, in particular those implemented in the SICONOS PLATFORM developed by BIPOP. We have also shown that under a set of reasonable biological assumptions, putting constraints on the right-hand side of the PLDE models, AP-extensions and classical Filippov extensions are equivalent. This means that the proposed numerical method is valid for a range of different solution concepts. We have illustrated the practical interest of our approach through the numerical analysis of three well-known networks developed in the field of synthetic biology.

5.2. 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 4.2), to allow biologists to make the most out of the information contained in reporter gene expression data. A web-based version of WELLREADER is currently in preparation. Valentin Zulkower has analyzed the measurement models underlying WELLREADER, work was presented at the *Journées Ouvertes Biologie, Informatique et Mathématiques (JOBIM'13)* [13] and submitted for publication.

The above tools have been used in a series of studies directed at the experimental mapping of gene regulatory networks in *E. coli*. A first example, which was carried out in the framework of the PhD thesis of former IBIS member Guillaume Baptist, concerns the development of a new screening methodology for identifying all genes that control the expression of a target gene through genetic or metabolic interactions. The screen combines mutant libraries with luciferase reporter constructs. Instead of a static picture of gene expression, this method allows dynamical monitoring in different environmental conditions. Mutants with interesting phenotypes can thus be selected based on multiple criteria, and the expression dynamics of the target gene can be extensively characterized. The method has been applied to the identification of the direct and indirect regulators of the gene *acs* in *Escherichia coli*. We confirmed known genetic regulators of the gene and identified new regulatory influences, many of which involve metabolic intermediates or metabolic sensing. An analysis of mutants involved in glycolysis and glucose transport demonstrates that the classical model of catabolite repression in *E. coli* needs to be amended. A paper describing the above work was published in *Nucleic Acids Research* this year [3].

A second example is a study, led by Stéphan Lacour in collaboration with Akira Ishihama and Hiroshi Ogasawara in Japan, on the lifestyle adaptation of *E. coli*. The study concerns the switch between swimming motility and biofilm formation in response to changes in environmental growth conditions. The stationary phase sigma factor RpoS is an important regulator of this switch since it stimulates adhesion and represses flagellar biosynthesis. By measuring the dynamics of gene expression, we show that RpoS inhibits the transcription of the flagellar sigma factor, FliA, in exponential growth phase. RpoS also partially controls the expression of CsgD and CpxR, two transcription factors important for bacterial adhesion. We have demonstrated that these two regulators repress the transcription of *fliA*, *flgM* and *tar*, and that this regulation is dependent on the growth medium. CsgD binds to the flgM and fliA promoters around their -10 promoter element, strongly suggesting direct repression. The results show that CsgD and CpxR also affect the expression of other known modulators of cell motility. An updated structure of the regulatory network controlling the choice between adhesion and motility was proposed in the paper based on this work, published in the *Journal of Bacteriology* [7].

A third study, published in *Research in Microbiology* [8], also focuses on the alternative sigma factor RpoS. The small protein Crl increases the interaction between RpoS and RNA polymerase and thereby activates certain RpoS-dependent promoters. However, the growth-phase dependence of the interaction of Crl with different forms of polymerase remains unknown. We have used 41 GFP transcriptional fusions to study the dynamics of gene regulation by RpoS and Crl during growth transition from exponential to stationary phase in *Escherichia coli*. This has confirmed that RpoS can regulate gene expression in exponential phase, both positively and negatively. Crl slightly stimulates transcription by RpoS in exponential phase and controls a subset of RpoS-dependent genes in stationary phase. Growth temperature strongly affects induction of specific promoters by RpoS, whereas its impact on gene regulation by Crl is much less significant. In addition, we have identified five new genes regulated by Crl (*ada*, *cbpA*, *glgS*, *sodC* and *flgM*), and demonstrated that Crl improves promoter binding and opening by RpoS-containing RNA polymerase at the *hdeA* promoter. The study also shows that Crl is a cognate enhancer of RpoS activity under different growth conditions, since its deletion has no effect on genes transcribed by other sigma factors.

In the framework of the PhD thesis of Diana Stefan, a network inference method developed by Eugenio Cinquemani and colleagues, first published in *Bioinformatics* in 2010, has been applied to reporter gene data from the network regulating motility of *E. coli*, described above. The results are currently being prepared for publication.

5.3. Models of carbon metabolism in bacteria

Kinetic models capture the dynamics of the large and complex networks of biochemical reactions that endow bacteria with the capacity to adapt their functioning to changes in the environment. In collaboration with Matteo Brilli and Daniel Kahn (Inra and Université Claude Bernard in Lyon), we previously developed an approximate model of central metabolism of *E. coli*, using linlog kinetics, and estimated the parameter values from metabolomics, transcriptome, proteomics data sets, as described in an article published in *Bioinformatics*

in 2011. The results of this study revealed the fundamental role played by the identifiability of the model parameters, an issue often overlooked in systems biology. This prompted us for a thorough investigation of the concepts of structural identifiability (in presence of perfect, idealized data), practical identifiability (in presence of noisy and limited amounts of data), and the relations between the two. In addition, we looked into the implications of this analysis for the reduction of nonidentifable to identifiable models. While having a solid mathematical basis, the study was tailored to the actual experimental practice, and resulted in a practical model reduction method that improves upon our previous approach in case of large measurement noise. This study, and the results from its application to both *in-silico* case studies and state-of-the-art datasets, were reported in a paper that appeared in the *Journal of Mathematical Biology* this year [4]. Although the theoretical development has focused on linlog models and related classes of approximate kinetic models, it is important to note that the results also bear on more general classes of nonlinear models of metabolism.

A second line of work is based on the use of classical kinetic models that are, in comparison with the above-mentioned linlog models, much reduced in scope (the focus is on the metabolic and genetic regulation of the glycolysis pathway) and granularity (individual reactions are lumped together). The models, developed by Delphine Ropers, are being calibrated using experimental data from IBIS group and the group of Jean-Charles Portais at Inra/INSA in Toulouse, and will be used to understand some key mechanisms in the adaptation of *E. coli* to the exhaustion of glucose. The PhD thesis of Manon Morin, in the framework of a collaboration supported by a Contrat Jeune Scientifique Inra-Inria, will further develop these research directions. In the framework of their PhD theses, Stéphane Pinhal and Valentin Zulkower also study specific aspects of carbon metabolism, using both models and experimental data. In parallel, we collaborate with Myriam Ferro at CEA in Grenoble to investigate how state-of-the-art measurements of the absolute concentrations of enzymes in *E. coli* can be integrated with other high-throughput data sets and kinetic models. The first results of this collaboration were accepted for publication in *Molecular and Cellular Proteomics* early 2014.

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

At the single-cell level, the processes that govern gene expression are often 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 control of cell populations and even of single cells. General modeling paradigms, such as the Chemical Master Equation, exist for the description of stochastic dynamics at the single-cell level. However, due to the complexity of the interactions, current studies have often preferred to focus on specific cases of interest by *ad-hoc* modeling and analysis. In addition, theoretical and practical challenges inherent in the inference of stochastic models from biological experimental data have limited the development of general identification approaches.

Work in IBIS on the probabilistic modeling of gene expression and interaction dynamics at the level of individual cells is centered around two main challenges. On the one hand, we address identification from microscopy data and analysis of the arabinose uptake dynamics in *E. coli* upon glucose exhaustion. Starting from a reduced arabinose uptake model, Eugenio Cinquemani and Michel Page are working on methods for the estimation of unknown stochastic model parameters from statistical population snapshot data collected by fluorescence microscopy experiments. Analysis of the model focuses on the problem of model-based real-time single-cell state estimation, with feedback control applications in mind, in collaboration with Alfonso Carta (BIOCORE). Based on a stochastic model reflecting switch-like dynamics in the form of sigmoidal reaction rates, taking a Chemical Master Equation model with cell-dependent parameters as a gold standard desdcription of the system, a Chemical Langevin Equation approximation is proposed as a convenient approximation of the model for observer design purposes. On top of this model approximation, a so-called Square-Root Unscented Kalman filter (SRUKF) is designed. Based on simulations of a realistically tuned model, SRUKF is found to perform as good as much heavier particle filters based on the gold-standard model.

Results were presented at the *European Control Conference (ECC)* in 2013 [11], where we also showed that including extrinsic noise effects explicitly in the estimation process allows one to improve the knowledge of the hidden states.

On the other hand, we investigate the use mixed effects-modelling and identification techniques to characterize single-cell profiles 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. In collaboration with Gregory Batt (CONTRAINTES) and Giancarlo Ferrari-Trecate (University of Pavia, Italy), we are adapting and applying existing procedures from pharmacokinetics to the context of microfluidic data, with focus on the budding yeast response to osmolarity shocks. The first results of the work were presented at the *European Control Conference (ECC)* this year [12]. Rigorous model identification and validation steps are performed on data from real-time control experments performed in Pascal Hersen's lab at Université Paris Descartes, for both mixed-effects modelling and for the competing method of moment-based identification. Results show the tendency of mixed-effects modelling to avoid overfitting for this system, trading fitting performance for validation performance and hence predictive capabilities. The work is being further developed and the collaboration tightened by the ongoing visit of Andres Gonzalez, PhD candidate at the University of Pavia, to CONTRAINTES and IBIS. A first journal publication is in preparation, which will be followed by extensions and refinements of the method.

In parallel, work concerning the study of noise propagation in gene regulatory networks is carried out in collaboration with Irina Mihalcescu (Université Joseph Fourier). Finally, collaboration of Eugenio Cinquemani with Marianna Rapsomaniki, PhD student affiliated with Zoi Lygerou (University of Patras, Greece) and John Lygeros (ETH Zürich, Switzerland), has been devoted to the analysis of data from Fluorescence Recovery After Photobleaching (FRAP) experiments. It has given rise to a novel method for reconstructing physical diffusion and immobilization parameters at the level of single cells. The method has been applied to nuclear species of mammalian cells and results are part of a journal paper under revision.

5.5. Shared control of gene expression by global physiological effects and specific regulators

Gene expression is controlled by the joint effect of (1) the global physiological state of the cell, in particular the activity of the gene expression machinery, and (2) DNA-binding transcription factors and other specific regulators. While many studies have focused on networks of transcription factors, the analysis of the relative contributions of both transcription factors and global effects of the physiological state has received relatively little attention thus far.

In the framework of the PhD thesis of former IBIS member Sara Berthoumieux, we have developed a model-based approach to distinguish between these two effects using time-resolved measurements of promoter activities. We have demonstrated the strength of the approach by analyzing a circuit involved in the regulation of carbon metabolism in *E. coli*, consisting of two pleiotropic regulators of the cell (Crp and Fis), the gene *acs* encoding the enzyme acetyl-CoA synthetase (Acs), and the signaling metabolite cyclic AMP (cAMP) which activates Crp. *acs* is strongly expressed in the absence of glucose and is thus an excellent indicator of the transcriptional response of carbon metabolism to a growth-phase transition.

Our results show that the transcriptional response of the network is controlled by the physiological state of the cell and the signalling metabolite cAMP. The (surprising) absence of a strong regulatory effect of transcription factors suggests that they are not the main coordinators of gene expression changes during growth transitions, but rather that they complement the effect of global physiological control mechanisms. This change of perspective has important consequences for the interpretation of transcriptome data and the design of biological networks in biotechnology and synthetic biology. An article presenting the above results was published in *Molecular Systems Biology* this year [5] and selected as an Editor's choice in *Science* (http://ibis.inrialpes.fr/article1040.html).

In the above-mentioned work, the activity of the gene expression machinery was indirectly measured, by monitoring the activity of a constitutive gene, that is, a gene whose expression does not depend on any specific regulators but only on the activity of the gene expression machinery. There exists a huge literature on the molecular mechanisms coupling the activity of the gene expression machinery to changes in the nutritional quality of the environment, but a quantitative and dynamic picture of this very complicated regulatory system is still missing. Delphine Ropers and Edith Grac as well as Nils Giordano are developing models to achieve this, from bottom-up and top-down perspectives, respectively.

5.6. Control of regulatory networks in bacteria

A bacterial cell adapts its growth rate to the environment, notably to the availability of nutrients providing the molecular building blocks and the energy required for growth. Upon a change in the environment, the global physiology of the cell is adjusted in parallel with the adaptation of the growth rate. In the context of the PhD thesis of former IBIS member Jérôme Izard, we have studied the relation between the gene expression machinery, the global physiology of the cell, and the growth rate from a different perspective. Our aim was to change the mechanisms regulating the activity of the gene expression machinery in such a way so as to be able to externally control the growth rate of the cell.

More precisely, we have engineered an *E. coli* strain in which the transcription of an essential component of the global gene expression machinery, RNA polymerase, is under the tight control of an inducible promoter. By adjusting the inducer concentration in the medium we can adjust the RNA polymerase concentration and thereby reversibly tune the growth rate of the bacterium between zero and the maximal growth rate. The growth arrest is completely reversed when RNA polymerase is provided again. The analysis of the transcriptome at growth rates restricted by the concentration of RNA polymerase confirms that the concentration of RNA polymerase is the major determinant of changes in gene expression patterns. Our modified *E. coli* strain provides a novel way of setting growth rate in a tunable, reversible, modular, and medium-independent way. The strain, described in a paper submitted for publication, opens new perspectives for studying the mechanisms of growth control as well as for developing biotechnological applications, the subject of the post-doctoral fellowship of Cindy Gomez Balderas-Barillot. We have submitted a patent proposing such applications, which underlies the technology transfer activities undertaken in the recently-started Reset project (Section 7.2).

6. Bilateral Contracts and Grants with Industry

6.1. Genostar

Participant: 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 4.1). 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.

6.2. BGene

Participant: Johannes Geiselmann.

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). BGene obtained an Emergence award in the 2013 Oséo Concours d'entreprises innovantes (see http://www.grain-incubation.com/oseo-start-ups-laureates-categorie-emergence/ for the press release). For more information on BGene, see http://www.bgene-genetics.com/.

7. Partnerships and Cooperations

7.1. Regional initiatives

Project name	Identification structurelle et paramétrique des réseaux de régulation bactériens
Coordinator	E. Cinquemani
IBIS participants	E. Cinquemani, J. Geiselmann, H. de Jong, D. Stefan
Type	Funding PhD grant, Cluster ISLE, Région Rhône-Alpes
Web page	http://cluster-isle.grenoble-inp.fr/

Project name	Motilité ou adhésion : comment les entérobactéries choisissent entres ces deux états physiologiques déterminants pour la virulence
Coordinator	S. Lacour
IBIS participants	J. Demol, J. Geiselmann, S. Lacour, C. Pinel
Type	Grant, Cluster Infectiologie, Région Rhône-Alpes

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

Project name	Séminaire de modélisation du vivant
Coordinators	O. Gandrillon
IBIS participants	D. Ropers
Type	Funding by GdR BIM
Web page	http://cgphimc.univ-lyon1.fr/CGphiMC/Semovi/Semovi.php

7.2. National initiatives

Project name	ColAge – Lifespan control in bacteria: Natural and engineering solutions
Coordinator	H. Berry
IBIS participants	E. Cinquemani, J. Geiselmann, H. de Jong, S. Lacour, C. Pinel, D. Ropers
Type	Inria-Inserm Project Lab (2009-2013)
Web page	http://colage.saclay.inria.fr

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
Type	Inria Project Lab (2013-)

Project name	GeMCo – Model reduction, experimental validation, and control for the gene expression machinery in *E. coli*
Coordinator	M. Chaves
IBIS participants	E. Cinquemani, J. Geiselmann, C. Gomez Balderas-Barillot, E. Grac, H. de Jong, S. Lacour, C. Pinel, D. Ropers
Type	ANR Blanc (2010-2014)
Web page	http://www-sop.inria.fr/members/Madalena.Chaves/ANR-GeMCo/main.html

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-Barillot, E. Grac, H. de Jong, S. Lacour, Y. Markowicz, C. Pinel, D. Ropers
Type	Bioinformatics call, Investissements d'Avenir program (2012-2016)
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 (2012-2016)
Web page	http://www.inra.fr/les_hommes_et_les_femmes/rejoignez_nous/completer_sa_formation/le_recrutement_de_doctorants/cjs__1/inra_inria

7.3. International projects

Project name	French bioinformatics contribution to ICGC
Coordinator	G. Thomas
IBIS participants	F. Rechenmann
Type	International Cancer Genome Consortium (ICGC)
Web page	http://www.icgc.org/

The goal of ICGC (International Cancer Genome Consortium) is to obtain a comprehensive description of genomic, transcriptomic and epigenomic changes in 50 different cancer types. In France, INCa (French National Cancer Institute) contributes to this project and focuses on two types of cancer. The main idea is to sequence the human genome of normal and tumoral cells of a large set of patients and to compare these genomic sequences to identify the mutations which may explain the development of the cancers. Bioinformatics is clearly involved in the management, the analysis and the visualization of the huge sets of data and results. Bioinformatics of the French contribution is carried out at Lyon, in the context of the Synergie Lyon Cancer Foundation. Until this year, François Rechenmann was part of the bioinformatics team and contributed to the organization of the data management and analysis workflow, under the leadership of prof. Gilles Thomas.

7.4. International collaborations

IBIS has strong collaborations with the group of Giancarlo Ferrari-Trecate at the Computer Engineering & Systems Science Department of the University of Pavia (Italy) and the group of John Lygeros at the Automatic Control Lab at ETH Zürich (Switzerland). This collaboration started with the FP6 project Hygeia, in which the above groups and IBIS (then HELIX) participated. Over the years, it has resulted in a dozen of co-authored papers and the co-supervision of a PhD thesis by Hidde de Jong and Giancarlo Ferrari-Trecate. Eugenio Cinquemani was a post-doctoral fellow at ETH in the framework of the Hygeia project, and joined the IBIS group as a research scientist in the fall of 2009. Andres Gonzales-Vargas, PhD student of Giancarlo Ferrari-Trecate, will spend six months in IBIS in 2014.

7.5. International research visitors

Invited professor	Andreas Kremling (Technische Universität Münich)
Subject	Modeling of carbon catabolite repression in *E. coli*

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

8. Dissemination

8.1. Editorial, animation, and reviewing activities

Eugenio Cinquemani

Type	Journal, conference, agency
Associate Editor	European Control Conference (ECC) 2014

Hidde de Jong

Type	Journal, conference, agency
Member Editorial Board	Journal of Mathematical Biology
Member Editorial Board	ACM/IEEE Transactions on Computational Biology and Bioinformatics
Member Editorial Board	Biosystems
Member Program Committee	CMSB 13, IEEE BIBM 13, JOBIM 13, HSB 14
Member Scientific Advisory Board	Microbiology and Food Chain Department, Inra
Member Review and Selection Committees	International Human Frontier Science Program (HFSP)
Member Promotion Committee	Senior research scientists, Inra
Member PhD Committee	Mathieu Trauchessec (CEA/Metabolic Explorer and Université Joseph Fourier)
Member PhD Advisory Committee	Caroline Baroukh (Inria/Inra and Université de Montpellier 2)
Coordinator (with C. Ambroise and F. Molina)	Working group on Transcriptome, protéome, modélisation, inférence et analyse des réseaux biologiques of GDR CNRS 3003 Bioinformatique moléculaire
Advisor	Grenoble team for iGEM 2013 competition
Project reviews	ANR, IDEX Saclay, Institut Pasteur, CNRS, NWO

Johannes Geiselmann

Type	Journal, conference, agency
Member Scientific Council	Department of Biology, Université Joseph Fourier
Member PhD Committee	Khady Sall (CEA and Université Joseph Fourier)
Member PhD Advisory Committee	Xuejiao Jiang (INSA de Lyon)
Advisor	Grenoble team for iGEM 2013 competition
Project reviews	ANR, CNRS

Stéphane Pinhal

Type	Journal, conference, agency
Advisor	Grenoble team for iGEM 2013 competition
Co-organizer	Journée des doctorants du LAPM

Delphine Ropers

Type	Journal, conference, agency
Member Organization Committee	SeMoVi (Séminaire de Modélisation du Vivant)
Member PhD Committee	Claire Villiers (Université Joseph Fourier)
Advisor	Grenoble team for iGEM 2013 competition

8.2. Other administrative activities

Eugenio Cinquemani is member of the Comité des Utilisateurs des Moyens Informatiques (CUMI) and of the Commission des Emplois Scientifiques at Inria Grenoble - Rhône-Alpes.

Hidde de Jong is member of the working group on International Relations of the Conseil d'Orientation Scientifique et Technique (COST) of Inria.

Johannes Geiselmann is head of the Control of Gene Expression group in the Laboratoire Adaptation et Pathogénie des Microorganismes (UMR 5163) and adjunct-director of the laboratory.

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

François Rechenmann is CEO of Genostar. Until 2013, he has been leader of the editorial committee of the Interstices website (http://interstices.info). In addition, he has been commissioned by the Director of Inria Grenoble - Rhône-Alpes to help and to coach PhD students, in the research center, who encounter problems of various sorts during their thesis.

Michel Page is coordinator of the master Systèmes d'information et d'organisation at the Institut d'Adminstration des Entreprises (IAE), Université Pierre Mendès-France, Grenoble. Moreover, he is head of the ICT service center at IAE.

Delphine Ropers represents Inria Grenoble - Rhône-Alpes in the scientific board of IXXI, the Complex Systems Institute in Lyon (http://www.ixxi.fr). She is also member of the Commission de Formation Permanente at Inria Grenoble - Rhône-Alpes.

8.3. Seminars, presentations, and PhD thesis defenses

Eugenio Cinquemani

Title	Event and location	Date
On identifiability and identification of metabolic network models	Seminar GIPSA Lab, Grenoble	April 2013
Mixed-effects modelling of biochemical reaction networks: Two applications on two systems	BCM seminar, TIMC-IMAG, Grenoble	May 2013
State estimation for gene networks with intrinsic and extrinsic noise: Models and approaches on a case study	HYCON2-AD3 Workshop on Biological and Medical Systems, Paris	June 2013
Identification of biological systems	Seminar PhD school on Systems Biology, Bertinoro (Italy)	July 2013

Hidde de Jong

Title	Event and location	Date
Shared control of gene expression in bacteria by transcription factors and global physiological state	Invited talk at Network Biology Symposium, Institut Pasteur, Paris (France)	October 2013

Johannes Geiselmann

Title	Event and location	Date
Adaptation of bacteria to their environment: dominance of the global physiological state of the cell and only a minor role for specific transcription factors	Talk at conference of the French Society of Microbiology, Lille	February 2013
Synthetic biology, an emerging technology	Talk at conference Biologie de synthèse : potentiels et défis, Nimes	March 2013
Shared control of gene expression in bacteria by transcription factors and the global physiology of the cell	Talk at ESF Research Conference on Bacterial Networks, Pultusk (Pologne)	March 2013
The global physiological state controls bacterial regulatory networks: a new design paradigm for biotechnology	Talk at World Congress of Industrial Biotechnology, Nanjing (China)	April 2013
Growth rate and gene expression	Talk at ST-FLOW, University of Birmingham, Birmingham (UK)	September 2013
Growth-rate control in Escherichia coli	Talk at SynBio 2013, Heidelberg (Germany)	December 2013

Nils Giordano

Title	Event and location	Date
Dynamic optimisation of resource allocation in microorganisms	Poster presentation at Journée des doctorants du LAPM, Grenoble	October 2013

Stéphane Pinhal

Title	Event and location	Date
Inhibition de la croissance d'E. coli par l'acétate lors d'une croissance sur glucose	Poster presentation at Journée des doctorants du LAPM, Grenoble	October 2013

Delphine Ropers

Title	Event and location	Date
Mathématiques pour la biologie : quand les gènes jouent la montre	Programme 2012-2013 "Informatique au lycée" - Initiation, Villard-de-Lans	April 2013
Mathématiques pour la biologie : quand les gènes jouent la montre	Programme 2012-2013 "Informatique au lycée" - Approfondissement, Montbonnot	May 2013
Global control of gene expression in Escherichia coli	Keynote speaker at International Conference on Predictive Modelling in Food (ICPMF8), Paris	September 2013
Global control of gene expression in Escherichia coli	Invited talk at meeting ANR Stochagène	September 2013
Régulation globale et contrôle de la croissance chez E. coli	BEesy annual meeting, Saint Hugues de Biviers	November 2013

Diana Stefan

Title	Event and location	Date
Structural and parametric identification of bacterial regulatory networks A case study on the gene network regulating motility in E. coli	Poster presentation at Journée des doctorants du LAPM, Grenoble	October 2013

Valentin Zulkower

Title	Event and location	Date
Quantitative comparison of one-step and two-step models of gene expression	Oral presentation at Journées Ouvertes Biologie, Informatique et Mathématiques (JOBIM'13), Toulouse	July 2013
Carbon catabolite repression in E. coli	Poster presentation at EMS Autumn School on Computational Aspects of Gene Regulation, Bedlewo (Poland)	October 2013

8.4. Popular science writing

The members of IBIS are actively involved in the dissemination of research results in systems biology and bioinformatics to a wider, non-specialist audience. François Rechenmann has been leader of the editorial committee of the Interstices (http://interstices.info). Interstices offers pedagogic presentations of research themes and activities in the computer science domain, including at its interface with life sciences. François Rechenmann also contributed an article to *Texte et documents dans la classe (TDC)* this year, in the special issue on "Les mathématiques de la terre".

8.5. Teaching

Four members of the IBIS team are either full professor, associate professor or assistant professor at the Université Joseph Fourier or the Université Pierre Mendès-France in Grenoble. 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

Subject	Year	Location	Hours
Identification of dynamical models of genetic networks	5	INSA de Lyon	4
Statistics for biologists	5	Master Approches Interdisciplinaires du Vivant, Centre de Recherches Interdisciplinaires/Université Paris Descartes	20

Hidde de Jong

Subject	Year	Location	Hours
Modeling and simulation of genetic regulatory networks	5	INSA de Lyon	20
Modeling and simulation of genetic regulatory networks	5	ENS Paris	8

Nils Giordano

Subject	Year	Location	Hours
Modeling and simulation of genetic regulatory networks	5	ENS Paris	8
Génétique Procaryote	2	Université Joseph Fourier	16
Génétique des Populations	2	Université Joseph Fourier	18

Stéphane Pinhal

Subject	Year	Location	Hours
Génétique microbienne	2	Université Joseph Fourier	34
Eau en sciences	1	Université Joseph Fourier	17

Delphine Ropers

Subject	Year	Location	Hours
Modeling and simulation of genetic regulatory networks	4	Université Joseph Fourier	7.5
Modeling and simulation of genetic regulatory networks	5	INSA de Toulouse	4

Diana Stefan

Subject	Year	Location	Hours
Project Signal, Image, Communication, Multimédia	3	INPG Phelma	36

Valentin Zulkower

Subject	Year	Location	Hours
Calcul matriciel	3	Polytech' Grenoble	41

Hidde de Jong organized with Daniel Kahn a module on the modeling of genetic and metabolic networks at INSA de Lyon. Delphine Ropers is preparing a module on the mathematical modeling of biological systems at PHELMA, INP Grenoble.

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